



Association between airflow limitation and prognosis in patients with chronic pulmonary aspergillosis

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Background: Previous studies have shown that reduced levels of lung function, characterized by forced expiratory volume in 1 second (FEV₁), are associated with higher respiratory events and mortality in general population and some chronic lung diseases. Chronic pulmonary aspergillosis (CPA) is a destructive, fatal lung disease caused by *Aspergillus* infection in non-immunocompromised patients with suboptimal pulmonary function. However, there is limited information on the status and features of CPA according to FEV₁.

Methods: We performed a retrospective observational study to investigate the FEV₁ and airflow limitation in patients with CPA between March 2017 and February 2019 at a tertiary hospital in South Korea.

Results: Of the 144 CPA patients, 104 underwent spirometry, demonstrating median forced vital capacity (FVC) and FEV₁ of 2.35 L (68%) and 1.43 L (62%), respectively. Among them, 56 patients had airflow limitation on PFT, with median FVC, and FEV₁ of 2.47 L (73%) and 1.11 L (47%), respectively. Low body mass index (BMI) (20.1 *vs.* 22.1 kg/m²; P=0.011), breathlessness (60% *vs.* 20%; P=0.002), and bilateral pulmonary lesions (33.3% *vs.* 4%; P=0.006) were more common in patients with moderate to very severe airflow limitation than in those with normal to mild airflow limitation.

Conclusions: Moderate to very severe airflow limitation was observed in 43.3% of patients with CPA. Additionally, low BMI, breathlessness, and bilateral pulmonary lesions contributing to poor prognosis were more common in patients with moderate to very severe airflow limitation than in those with normal to mild airflow limitation. Our findings suggest that airflow limitation can be associated with the prognosis of CPA. Further investigations are needed to demonstrate the clinical significance of this association.

Keywords: Pulmonary aspergillosis; spirometry; pulmonary disease; chronic obstructive; prognosis

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Introduction

Chronic pulmonary aspergillosis (CPA) is a progressively destructive pulmonary disease (1). CPA is usually seen in immunocompetent patients with underlying structural lung diseases, such as a tuberculous destroyed lung, emphysema, or bronchiectasis caused by *Aspergillus* infection (1).

Treatment of CPA is difficult. Although some patients may consider surgical treatment, surgery is usually avoided due to reduced lung function and extensiveness of disease burden (2). Accordingly, antifungal therapy is considered the main treatment for disease control (3). However, anti-CPA chemotherapy response is often slow and disease progression is common in patients who discontinue

pharmacotherapy (1,4). Thus, outcomes are generally poor because of insufficient defense mechanisms in patients as well as the aforementioned limitations in treatment (5). It has been shown that the mortality rate in patients with CPA can range from 50% to 80% over 5 years (6-9).

In connection with the prognosis of CPA, previous studies have been focused on host factors associated with high mortality risk. The following several factors have been identified: low body mass index (BMI), high Charlson index score, and previous history of systemic corticosteroids or pulmonary non-tuberculous mycobacterial disease (PNTM) (9-11).

Spirometry measures respiratory functions and is used in a well-established predictor of mortality in general population (12,13). Among parameters, forced expiratory volume in 1 second (FEV_1) is an independent predictor of respiratory outcomes such as respiratory hospitalization and mortality in some chronic lung diseases (14,15). However, there are few studies about clinical characteristics of CPA patients concentrated on FEV_1 and airflow limitation (16). Therefore, we aimed to investigate the status and features of airflow limitation and severity of airflow limitation in patients with CPA. We present the following article in accordance with the STROBE guidelines checklist (available at <http://dx.doi.org/10.21037/jtd-20-1815>).

Methods

Study population

Data were collected from consecutive patients with CPA who underwent a pulmonary function test (PFT) at Wonju Severance Christian Hospital (an 866-bed, university-affiliated, tertiary referral hospital in Wonju, South Korea) between March 2017 and February 2019 and were retrospectively analyzed. A total of 144 patients with newly diagnosed CPA was recruited. Among them, 40 patients were excluded without PFT results. Finally, 104 patients were included in the study and classified into normal ($n=14$), restrictive ($n=34$), and obstructive ($n=56$) patterns according to PFT. Additionally, we divided the patients with normal and obstructive patterns into two groups according to airflow limitation: patients with normal to mild airflow limitation (Group A, $n=25$) and those with moderate to very severe airflow limitation (Group B, $n=45$). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board for Human Research at

Yonsei University Wonju Severance Christian Hospital (CR-319144) and individual consent for this retrospective analysis was waived.

Diagnosis of CPA

During the study period, diagnosis of CPA was based on clinical, radiologic, and microbiological findings (1). Such a diagnosis was associated with the following: (I) compatible chronic respiratory symptoms including at least cough, sputum, breathlessness, or hemoptysis; (II) compatible chest radiological findings including a cavitary lesion with evidence of paracavitary infiltrates, or expansion of cavity size over time; and (III) positive serum anti-*Aspergillus* antibodies (*Aspergillus fumigatus* IgG ELISA kit; IBL International, Hamburg, Germany) or positive cultures of *Aspergillus* species from a respiratory sample (i.e., sputum, transtracheal aspirate, or bronchial aspiration fluid). Simple aspergilloma was excluded from the diagnosis of CPA.

PFT

Spirometry was performed using a Vmax 22 apparatus (CareFusion, Yorba Linda, CA, USA) in accordance with American Thoracic Society/European Respiratory Society guidelines (17). Absolute values of forced vital capacity (FVC) and FEV_1 were measured and percentage of predicted values for FVC and FEV_1 were calculated using a reference equation obtained through a representative Korean sample (18). Normal spirometric pattern (NSP) was defined as $FEV_1/FVC \geq 0.7$ and $FVC \geq 80\%$ predicted. Restrictive spirometric pattern (RSP) was defined as $FEV_1/FVC \geq 0.7$ and $FVC < 80\%$ predicted. Obstructive spirometric pattern (OSP) or airflow limitation was defined as $FEV_1/FVC < 0.7$. Furthermore, we classified patients into mild ($FEV_1 \geq 80$), moderate ($50 \leq FEV_1 < 80$), severe ($30 \leq FEV_1 < 50$), and very severe ($FEV_1 < 30$) airflow limitation based on FEV_1 (% predicted) (19,20). Patients with airflow limitation were considered to have chronic obstructive pulmonary disease (COPD) in the present study, even though we did not perform a post-bronchodilator test (21).

Data collection

The following data were collected from electronic health record including demographic data, comorbidities, respiratory or systemic symptoms, laboratory measurements,

Table 1 Patients characteristics

Characteristics	N=104
Age, years	68 [56–76]
Sex, male	83 (79.8)
Body mass index, kg/m ²	19.8 [17.2–22.5]
Smoking history	
Ex or current smoker	76 (73.1)
Underlying lung disease*	
Previous history of pulmonary tuberculosis	80 (76.9)
Pulmonary non-tuberculous mycobacterial disease	17 (16.3)
Emphysema	35 (33.7)
Bronchiectasis	9 (8.7)
Interstitial lung disease	3 (2.9)
Previous history of thoracic malignancy	3 (2.9)
Other comorbidities*	
Diabetes mellitus	16 (15.4)
Chronic heart disease	16 (15.4)
Chronic liver disease	9 (8.7)
Chronic kidney disease	2 (1.9)
Rheumatic disease	4 (3.8)
Previous history of extra-thoracic malignancy	12 (11.5)
Chronic pulmonary symptoms*	
Cough	46 (44.2)
Sputum	41 (39.4)
Breathlessness [†]	54 (51.9)
Hemoptysis	36 (34.6)
Chest computed tomographic findings*	
Cavitation	104 (100.0)
Consolidation	21 (20.2)
Mycetoma	43 (41.3)
Paracavitary infiltrates	83 (79.8)
Bilateral pulmonary lesions	23 (22.1)
Albumin, g/dL	3.8 [3.2–4.1]

The data are presented as median [interquartile change] or number (%). *, cases are duplicated; [†], “Breathlessness” represents a modified Medical Research Council dyspnea score ≥ 2 .

radiological findings including computed tomography (CT), and survival time. “Breathlessness” represents a modified Medical Research Council dyspnea score ≥ 2 (22).

Statistical analysis

The data are presented as medians and interquartile ranges for continuous variables and as numbers (percentages) for categorical variables. To compare categorical variables, the Chi-square or Fisher’s exact test was used. The Mann-Whitney U-test was used to compare continuous variables. Overall survival after diagnosis of CPA was estimated using the Kaplan-Meier method followed by the log-rank test for comparison between the two groups. The data were analyzed using SPSS version 23.0 (IBM Co., Chicago, IL, USA). We considered all variables with $P < 0.05$ as statistically significant.

Results

Patient characteristics

The clinical characteristics of the eligible patients are presented in *Table 1*. The median age was 68 years, and 80% of the patients were male. The median BMI was 20 kg/m². Seventy-six (73%) patients were current or ex-smokers. The median albumin was 3.8 g/dL. The underlying lung diseases included previous pulmonary tuberculosis (n=80, 77%), emphysema (n=35, 34%), and PNTM (n=17, 16%). The underlying extra-pulmonary diseases consisted of diabetes mellitus (n=16, 15%), chronic heart disease (n=16, 15%), and previous history of extra-thoracic malignancy (n=12, 12%).

The most common respiratory symptoms were breathlessness (n=54, 52%), cough (n=46, 44%), sputum (n=41, 39%), and hemoptysis (n=36, 35%). The chest radiological findings revealed a cavitory lesion in all patients. Additionally, all patients possessed at least one of the following radiologic findings at presentation: consolidation (n=21, 20%), mycetoma (n=43, 41%), or paracavitary infiltration including pleural thickening (n=83, 80%). In addition, bilateral pulmonary lesions were observed in 23 (22%) patients.

Lung function tests

The PFT results are presented in *Table 2*. The median FVC and FEV₁ were 2.35 L (68%) and 1.43 L (62%),

respectively. Among the previously defined 56 (54%) patients with airflow limitation, the severity was classified as mild (n=11, 20%), moderate (n=15, 27%), severe (n=21, 38%), and very severe (n=9, 16%) according to FEV₁. Among these patients, the median FEV₁ values were 1.92 L (94%), 1.49 L (64%), 1.00 L (42%), and 0.60 L (24%), respectively. The PFT results of these patients with airflow limitation are additionally presented in Table 3.

Clinical characteristics according to airflow limitation

The clinical characteristics of the two groups (normal to

mild *vs.* moderate to very severe airflow limitation) are described in Table 4. BMI was significantly lower in patients with moderate to very severe airflow limitation (Group B) compared to those with normal to mild airflow limitation (Group A) (20.1 *vs.* 22.1 kg/m²; P=0.011). Breathlessness was significantly higher in group B compared to group A (60% *vs.* 20%; P=0.002). Bilateral pulmonary infiltrates were also frequently observed in group B compared to group A (33.3% *vs.* 4%; P=0.006). On the other hand, the surgery was performed only in group A (48% *vs.* 0%; P=0.042). Apart from the above results, there were no differences in characteristics between the two groups including age, sex, smoking history, underlying lung disease, other comorbidities, chronic pulmonary symptoms, and antifungal therapy.

Survival

The median follow-up period was 15 months (range, 8–26 months). The overall survival rates after diagnosis of CPA in the two groups are shown in Figure 1. Survival rates at 1 year and 1.5 years were 94.7% and 94.7%, respectively. Finally, the survival rate tended to be higher in patients with normal to mild airflow limitation (94.7%) than in those with moderate to very severe airflow limitation (86.5%, P=0.345).

Discussion

We investigated the clinical characteristics of patients with CPA with regard to airflow limitation extent as measured by FEV₁. Fifty-six (54%) patients demonstrated airflow limitation on PFT, and more than half of them had severe

Table 2 Pulmonary function test

Variables	N=104
FVC, L	2.35 [1.62–3.03]
FVC, % predicted	68 [49–87]
FEV ₁ , L	1.43 [0.98–2.06]
FEV ₁ , % predicted	62 [42–87]
Spirometric pattern*	
Normal	14 (13.5)
Restrictive	34 (32.7)
Obstructive	56 (53.8)

The data are presented as median [interquartile change] or number (%). *, spirometric pattern was defined as follows: (I) normal spirometric pattern was defined as FEV₁/FVC ≥0.7 and FVC ≥80% predicted; (II) restrictive spirometric pattern was defined as FEV₁/FVC ≥0.7 and FVC <80% predicted; (III) obstructive spirometric pattern was defined as FEV₁/FVC <0.7. FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second.

Table 3 Pulmonary function test according to airflow limitation severity*

Variables	Airflow limitation [†] (N=56)			
	Mild (n=11)	Moderate (n=15)	Severe (n=21)	Very severe (n=9)
FVC, L	3.03 [2.58–3.86]	2.99 [2.43–3.43]	2.10 [1.48–2.78]	1.61 [1.07–2.14]
FVC, % predicted	105 [95–115]	77 [74–89]	55 [48–74]	41 [32–59]
FEV ₁ , L	1.92 [1.59–2.43]	1.49 [1.37–1.91]	1.00 [0.82–1.11]	0.60 [0.55–0.69]
FEV ₁ , % predicted	94 [88–108]	64 [51–69]	42 [35–47]	24 [23–26]

The data are presented as median [interquartile change]. *, airflow limitation severity was defined as follows: (I) mild airflow limitation was defined as FEV₁/FVC <0.7 and FEV₁ ≥80% predicted; (II) moderate airflow limitation was defined as FEV₁/FVC <0.7 and 50% ≤ FEV₁ <80% predicted; (III) severe airflow limitation was defined as FEV₁/FVC <0.7 and 30% ≤ FEV₁ <50% predicted; (IV) very severe airflow limitation was defined as FEV₁/FVC <0.7 and FEV₁ <30% predicted; [†], “Airflow limitation” was defined using the FEV₁/FVC <0.7. FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second.

Table 4 Comparisons of clinical characteristics between the two groups

Characteristics	Normal to mild airflow limitation* (N=25)	Moderate to very severe airflow limitation† (N=45)	P value
Age, years	74 [57–79]	67 [56–72]	0.122
Sex, male	21 (84.0)	35 (77.8)	0.756
Body mass index, kg/m ²	22.1 [19.6–24.6]	20.1 [16.9–22.0]	0.011
Smoking history			
Ex or current smoker	18 (72.0)	35 (77.8)	0.772
Underlying lung disease‡			
Previous history of pulmonary tuberculosis	20 (80.0)	35 (77.8)	>0.999
Pulmonary non-tuberculous mycobacterial disease	3 (12.0)	7 (15.6)	>0.999
Emphysema	9 (36.0)	20 (44.4)	0.614
Bronchiectasis	2 (8.0)	3 (6.7)	>0.999
Interstitial lung disease	1 (4.0)	0	0.357
Previous history of thoracic malignancy	0	1 (2.2)	>0.999
Other comorbidities‡			
Diabetes mellitus	8 (32.0)	5 (11.1)	0.052
Chronic heart disease	3 (12.0)	8 (17.8)	0.735
Chronic liver disease	2 (8.0)	5 (11.1)	>0.999
Chronic kidney disease	0	1 (2.2)	>0.999
Rheumatic disease	0	3 (6.7)	0.548
Previous history of extra-thoracic malignancy	2 (8.0)	4 (8.9)	>0.999
Chronic pulmonary symptoms‡			
Cough	10 (40.0)	19 (42.2)	>0.999
Sputum	7 (28.0)	21 (46.7)	0.203
Breathlessness§	5 (20.0)	27 (60.0)	0.002
Hemoptysis	12 (48.0)	15 (33.3)	0.306
Chest computed tomographic findings‡			
Cavitation	25 (100.0)	45 (100.0)	NA
Consolidation	6 (24.0)	9 (20.0)	0.765
Mycetoma	11 (44.0)	16 (35.8)	0.609
Paracavitary infiltrates	17 (68.0)	37 (82.2)	0.236
Bilateral pulmonary lesions	1 (4.0)	15 (33.3)	0.006
Albumin, g/dL	4.1 [3.5–4.5]	3.8 [3.5–4.1]	0.100
Treatments			
Antifungal therapy	12 (48.0)	23 (51.1)	>0.999
Surgery	3 (12.0)	0	0.042

The data are presented as median [interquartile change] or number (%). *, normal to mild airflow limitation was defined as FEV₁/FVC ≥0.7 and FVC ≥80% predicted, and FEV₁/FVC <0.7 and FEV₁ ≥80% predicted; †, moderate to very severe airflow limitation was defined as FEV₁/FVC <0.7 and FEV₁ <80% predicted; ‡, cases are duplicated; §, “Breathlessness” represents a modified Medical Research Council dyspnea score ≥2. FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second.

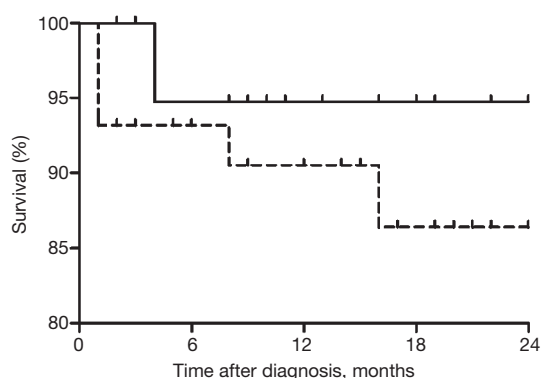


Figure 1 The Overall survival rate after the diagnosis of CPA in patients with normal to mild airflow limitation (solid line) and patients with moderate to very severe airflow limitation (dotted line) ($P=0.345$, log-rank test). Normal to mild airflow limitation was defined as $FEV_1/FVC \geq 0.7$ and $FVC \geq 80\%$ predicted, and $FEV_1/FVC < 0.7$ and $FEV_1 \geq 80\%$ predicted. Moderate to very severe airflow limitation was defined as $FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ predicted. CPA, chronic pulmonary aspergillosis; FVC, forced vital capacity; FEV_1 , forced expiratory volume in 1 second.

to very severe airflow limitation. Additionally, we found that low BMI, breathlessness, and bilateral pulmonary lesions associated with poor prognosis are common in patients with moderate to very severe airflow limitation than in those with normal to mild airflow limitation.

CPA is a chronic pulmonary disease with a poor prognosis (22). The majority of CPA patients die from respiratory failure (23,24). However, surgery and pharmacotherapy are still challenging; a recent study comparing voriconazole and itraconazole failed to demonstrate improved survival (11).

Several studies have been conducted to identify host-related factors that may affect the overall survival rate at patients with CPA (9-11). In the present study, patients with moderate to very severe airflow limitation were likely to have low BMI, breathlessness, and bilateral lung involvement by *Aspergillus* infection. Past studies have confirmed that these factors are associated with poor prognosis (6,10).

The FEV_1 , which is an indicator of the level of airflow limitation, is associated with mortality at chronic lung diseases such as lung cancer and COPD (14,25). However, there was no data on the clinical aspects related to FEV_1 impairment in CPA patients. In the present study, when the study population was classified based on FEV_1 , 43% of

patients had Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade ≥ 2 . When patient selection was restricted to those with airflow limitation, 80% of patients had a GOLD grade ≥ 2 . In 2011, the prevalence of COPD in South Korea was 13.2%, and of the prevalence of mild, moderate, and severe COPD was 5.8%, 6.9%, and 0.5%, respectively (26). Compared to those results, the ratio of GOLD ≥ 3 grade in our results was significantly higher. The frequency of use of corticosteroids was increased in patients with GOLD ≥ 3 (27). Inhaled or systemic treatment with corticosteroids is one of the risk factors for CPA (28). This was thought to be due to accelerated structural changes caused by combined *Aspergillus* infection and impaired immune function. In addition, 33% of patients in this study demonstrated a RSP on PFT. Traditionally, a RSP was associated with interstitial lung disease and space-occupying lesions (29). A recent study comparing patients with and without a RSP reported poor prognosis in patients with a RSP (30). However, there has been no research on the effect of a RSP on prognosis in CPA patients.

There is even no specific mention of PFT examination at the time of diagnosis or during the follow-up period in the recently published clinical CPA guideline (1). Periodic PFT measurements for monitoring of disease may be considered in patients with substantially impaired pulmonary function due to underlying lung diseases and CPA itself. Physicians may also consider the use of bronchodilators, a fundamental treatment for patients with COPD due to the subsequent improvement in lung function, dyspnea, and health status (31,32). There are no studies on whether the usage of bronchodilators improves respiratory symptoms and prognosis in patients with CPA. However, Yum *et al.* has shown that the bronchodilator medication in the tuberculous destroyed lung, which is the most common structural lung disease in CPA, may achieve improved lung functions (33).

The current study had several limitations. First, this study was a retrospective analysis of patients from a single institution, and the sample size was small, so selection bias was inevitable. Second, not all patients underwent regular screening tests for CPA, mainly due to the low level of attention from respiratory physicians and the complexity of the diagnostic method. Therefore, some CPA cases might have been missed. Third, COPD was defined by a pre-bronchodilator test that may have misclassified some patients. However, all participants had structural lung disease, and more than half of them demonstrated severe or very severe airflow limitation. Thus, these patients likely

had COPD. Finally, the prognosis of these patients could not be addressed in this study because of the small sample size and short duration of follow up. Further well-designed prognosis-related studies are needed.

In conclusion, we showed that 43.3% of the CPA patients had moderate to very severe airflow limitation in the present study. Moreover, there were several poor prognostic factors such as low BMI, breathlessness, and bilateral pulmonary lesions, which were more common in CPA patients with moderate to very severe airflow limitation than in those with normal to mild airflow limitation. This study suggests that physicians may be considered the assessment of airflow limitation severity as a more precise prediction of prognosis in the clinical course of CPA. Prospective studies are needed to confirm the correlation between lung function decline and prognosis in these patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE guideline checklist, available at <http://dx.doi.org/10.21037/jtd-20-1815>

Data Sharing Statement: Available at <http://dx.doi.org/10.21037/jtd-20-1815>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-1815>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board for Human Research at Yonsei University Wonju Severance Christian Hospital (CR-319144) and individual consent for this retrospective analysis was waived.

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