RESEARCH ARTICLE

Differences in the clinical characteristics of chronic pulmonary aspergillosis according to spirometric impairment

Myoung Kyu Lee[1], Sae Byol Kim[2], Beomsu Shin●[3]*

1 Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea,
2 Division of Pulmonology, Department of Internal Medicine, Myongji Hospital, Jecheon, South Korea,
3 Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Republic of Korea

* bsshin83@gmail.com

Abbreviations: BMI, body mass index; CPA, chronic pulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FVC, forced vital capacity; FEV_1,

Abstract

The clinical features by declining lung function remain uncharacterized in chronic pulmonary aspergillosis (CPA) patients. We investigated the clinical characteristics of CPA patients based on spirometric impairments (restrictive spirometric pattern [RSP] and obstructive spirometric pattern [OSP]) and their severity. We retrospectively analyzed medical records of CPA patients who underwent pulmonary function tests from March 2017 to February 2020. We used Global Lung Initiative 2012 equations with lower limit of normal. The clinical characteristics of patients with RSP were compared to those with OSP. Additionally, RSP patients' characteristics were analyzed according to forced vital capacity (FVC) tertile, and OSP patients' characteristics were analyzed according to forced expiratory volume in 1 second (FEV_1) tertile. Among the 112 patients with CPA (52 [46%] with RSP and 60 [54%] with OSP), body mass index (BMI) was significantly lower in patients with RSP than in those with OSP (17.6 kg/m^2 versus 20.3 kg/m^2; $P = 0.003$), and non-tuberculous mycobacterial disease was more frequently observed in patients with RSP than in those with OSP (28.8% versus 11.7%; $P = 0.004$). Additionally, for patients with RSP, younger age and bilateral pulmonary lesions were more frequently observed in the first tertile group than in the other groups (P for trend: 0.025 and 0.001, respectively). For patients with OSP, low BMI, paracavitary infiltrates, and elevated WBC count were more frequently observed in the first tertile group than in the other groups (P for trend: < 0.001, 0.011, and 0.041, respectively). Differences in the clinical features of CPA patients were identified according to heterogeneous spirometric patterns and their severity. Further studies are needed to investigate the clinical significance of these findings.

Introduction

Chronic pulmonary aspergillosis (CPA) is a progressively destructive disease caused by *Aspergillus* infection that results in inflammation and damage to the lung parenchyma and pleura

forced expiratory volume in 1 second; ILD, interstitial lung disease; LLN, lower limit of normal; NSP, normal spirometric pattern; OSP, obstructive spirometric pattern; PFT, pulmonary function test; NTM, non-tuberculous mycobacterial disease; RSP, restrictive spirometric pattern.

[1]. CPA usually occurs in non-immunocompromised patients with pre-existing pulmonary diseases such as tuberculous destroyed lung, non-tuberculous mycobacterial disease (NTM), emphysema, bronchiectasis, and sarcoidosis [2, 3]. *Aspergillus* species grow in places where there are structural problems in the lungs [4]. While the progression of CPA is not fully understood, it is known that differences in the progression occur depending on the patient's immune status, the condition of the underlying lung disease, and the severity of *Aspergillus* infection [5].

Abnormal spirometric results obtained from chronic lung disease may manifest in one of two forms, an obstructive spirometric pattern (OSP) or a restrictive spirometric pattern (RSP) [6]. Furthermore, pulmonary diseases with OSP are subdivided based on the forced expiratory volume in 1 second (FEV_1), and those with RSP are subdivided based on the forced vital capacity (FVC) for the objective evaluation of clinical features and prognosis [7, 8]. Previous studies have demonstrated that spirometry was a useful method for measuring and monitoring chronic lung disease, which is divided into obstructive lung disease (e.g., chronic obstructive pulmonary disease [COPD] and bronchiectasis) and restrictive lung disease (e.g., interstitial lung disease [ILD] and sarcoidosis) [6].

However, unlike other chronic lung diseases, the clinical implication of spirometry results is not known in patients with CPA [9]. Therefore, we aimed to evaluate the clinical characteristics according to the spirometric patterns and severity of FVC or FEV_1.

Materials and methods

Study population

Data were collected from consecutive patients with CPA who underwent PFT at the Wonju Severance Christian Hospital (an 866-bed, university-affiliated, tertiary referral hospital in Wonju, South Korea) between March 2017 and February 2020 and were retrospectively analyzed.

Diagnosis of CPA

The diagnosis of CPA required a clinical decision by the combination of clinical, radiological, and microbiological parameters as follows: (1) compatible chronic respiratory symptoms including at least cough, sputum, breathlessness, or hemoptysis sustained for at least three months; (2) compatible chest radiological findings, including a cavity containing one or more aspergillomas or irregular intraluminal material with evidence of radiological progression (e.g., expansion of the cavity size, new cavities, or increasing paracavitary infiltrates); and (3) positive serum anti-Aspergillus antibodies (*Aspergillus fumigatus* IgG ELISA kit; IBL International, Hamburg, Germany) or positive *Aspergillus* species cultures from respiratory samples [1, 10]. Simple aspergilloma and subacute invasive aspergillosis were excluded from the present study [11]. All patients were observed for cavitary lesions on the chest CT in the present study. Finally, 183 patients with chronic cavitary pulmonary aspergillosis were recruited.

Pulmonary function test

Spirometry was performed by trained technicians using a Vmax 22 apparatus (CareFusion, Yorba Linda, CA, USA) according to recommendations set by the American Thoracic Society/ European Respiratory Society guidelines [12]. The absolute values for FVC and FEV_1 were measured and the percentage of predicted values for FVC, FEV_1, and the lower limit of normal (LLN; values below the fifth percentile in healthy, non-smoking subjects [z-score of −1.64]) were calculated using a reference equation obtained from the Global Lung Initiative (GLI)

2012 recommendation [13]. A normal spirometric pattern (NSP) was defined as a post-bronchodilator $FEV_1/FVC \geq LLN$ and $FVC \geq LLN$. RSP was defined as a post-bronchodilator $FEV_1/FVC \geq LLN$ and $FVC < LLN$. OSP was defined as a post-bronchodilator $FEV_1/FVC < LLN$. For the statistical analysis, the severity of RSP was classified according to the FVC tertile: tertile 1 was an FVC < 49% of the predicted value, tertile 2 was 49% $\leq$ FVC < 63% of predicted value, and tertile 3 was an FVC $\geq$ 63% of the predicted value. The severity of OSP was classified according to the FEV_1 tertile: tertile 1 was an $FEV_1 < 38\%$ of the predicted value, tertile 2 was 38% $\leq FEV_1 < 54\%$ of the predicted value, and tertile 3 was an $FEV_1 \geq 54\%$ of the predicted value.

Data collection

Clinical data were collected from electrical health records. All information for patients included demographic data, comorbidities, respiratory symptoms, image findings, and laboratory parameters was collected retrospectively. "Breathlessness" represents a modified Medical Research Council dyspnea score ≥ 2 [14]. "Bilateral lung lesions" was defined as a case with compatible radiological findings of *Aspergillus* in both lungs.

Ethics approval

This study was conducted in accordance with the amended Declaration of Helsinki. The Institutional Review Board for Human Research at Yonsei University Wonju Severance Christian Hospital (CR-320141) and the Institutional Review Board at the Samsung Changwon Hospital (SMC202010007) approved the study. As this study was a retrospective evaluation, written informed consent from each patient was waived. All data collected from each patient were de-identified prior to analysis.

Statistical analysis

All data are expressed as median and interquartile range for continuous and ordinal variables, or as numbers and percentages for categorical variables. Continuous and categorical variables were analyzed by Mann–Whitney U test and Chi-square or Fisher's exact test, respectively. To test for linear trends, subjects were grouped into tertiles of the observed FVC (% predicted) in RSP and FEV_1 (% predicted) in OSP. The statistical significance level was set at a *P*-value of < 0.05. All statistical analyses were performed using SPSS version 26.0 (IBM Co., Armonk, NY, USA) statistical software.

Results

Patient characteristics

A total of 183 patients were recruited. After excluding the patients who did not undergo pulmonary function test (PFT) (n = 48) or had NSP (n = 23), 112 patients were included in the study. The patients were further classified into RSP (n = 52, 46%) and OSP (n = 60, 54%) according to the spirometric patterns (Fig 1). The clinical characteristics of study participants are shown in Table 1. The median age of participants was 65 years and 87% of the participants were men. Seventy-six (68%) patients were current or ex-smokers. The main underlying diseases were tuberculous destroyed lung (n = 86, 77%), emphysema (n = 35, 31%), or NTM (n = 22, 20%). The most common respiratory symptoms were breathlessness (n = 66, 59%), cough (n = 56, 50%), sputum (n = 51, 46%), and hemoptysis (n = 34, 30%). All participants had at least one of the following imaging findings: paracavitary infiltration (n = 97, 87%),
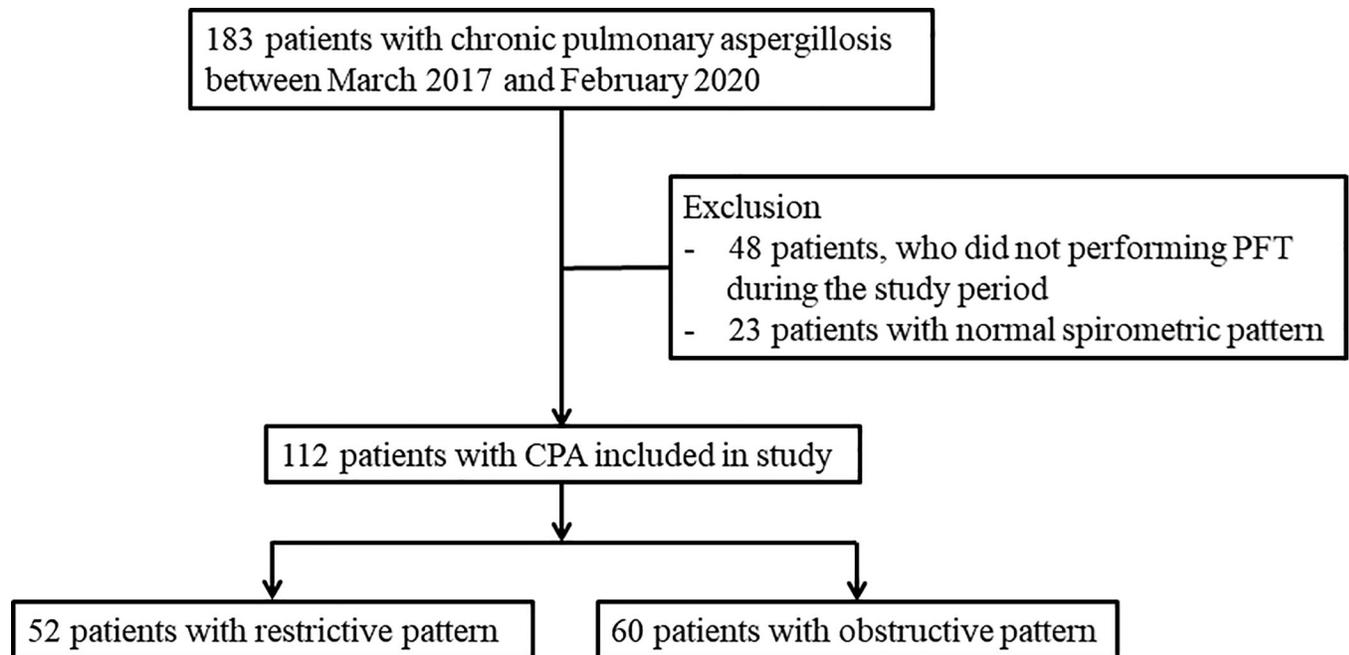
Fig 1. Flow chart of the study population in the study. PFT, pulmonary function test; CPA, chronic pulmonary aspergillosis.

https://doi.org/10.1371/journal.pone.0260274.g001

mycetoma (n = 44, 39%), or consolidation (n = 17, 15%). Bilateral pulmonary lesions were observed in 29 (26%) patients.

Compared to the participants with OSP, the participants with RSP were more likely to have a lower body mass index (BMI) (17.6 kg/m^2 versus 20.3 kg/m^2; P = 0.003) and to have NTM (29% versus 12%; P = 0.031), but were less likely to have emphysema (17% versus 43%; P = 0.004). There were no significant differences in other clinical characteristics including pulmonary symptoms, chest CT findings, and laboratory findings between the two groups.

Pulmonary function tests

PFT results are shown in Table 2. The median FVC and FEV_1 were 2.12 L (62%) and 1.33 L (55%), respectively. The median FVC and FEV_1 with RSP were 2.03 L (56%) and 1.78 L (71%), respectively, and the median FVC and FEV_1 with OSP were 2.34 L (68%) and 1.05 L (46%), respectively.

Clinical characteristics according to the spirometric patterns

Compared to the participants with RSP in FVC tertiles 2–3 (% predicted), those in tertile 1 were more likely to be younger (P for trend, 0.025) and have bilateral pulmonary lesions (P for trend, 0.001) (Table 3). However, there were no statistic differences in the trends for comorbidities, pulmonary symptoms, and laboratory findings among the three FVC tertile groups.

Compared to participants with OSP in FEV_1 tertiles 2–3 (% predicted), those in tertile 1 were more likely to have lower BMI (P for trend, < 0.001), paracavitary infiltrates (P for trend, 0.011), and higher average WBC counts (P for trend, 0.041) (Table 4). However, there were no statistic differences in trends for comorbidities and pulmonary symptoms among the three FEV_1 tertile groups.

Table 1. Patient characteristics according to spirometric patterns[§].

	Total	Restrictive spirometric pattern[§]	Obstructive spirometric pattern[§]	P value
	(N = 112)	(n = 52)	(n = 60)	
Age, years	65 (56–73)	64 (50–76)	65 (57–72)	0.966
Sex, male	87 (77.7)	42 (80.8)	45 (75.0)	0.503
Body mass index, kg/m^2	19.5	17.6	20.3	**0.003**
	(16.8–21.8)	(16.3–20.6)	(17.4–22.5)	
Smoking history				
Ex or current smoker	76 (67.9)	32 (61.5)	44 (73.3)	0.225
Underlying lung disease*				
Previous history of pulmonary tuberculosis	86 (76.8)	41 (78.8)	45 (75.0)	0.660
Non-tuberculous mycobacterial disease	22 (19.6)	15 (28.8)	7 (11.7)	**0.031**
Emphysema	35 (31.3)	9 (17.3)	26 (43.3)	**0.004**
Bronchiectasis	16 (14.3)	8 (15.4)	8 (13.3)	0.792
Interstitial lung disease	3 (2.7)	3 (5.8)	0	0.097
Previous history of thoracic malignancy	3 (2.7)	2 (3.8)	1 (1.7)	0.596
Other comorbidities*				
Diabetes mellitus	14 (12.5)	5 (9.6)	9 (15.0)	0.568
Chronic hepatic insufficiency	10 (8.9)	3 (5.8)	7 (11.7)	0.334
Chronic renal insufficiency	1 (0.9)	0	1 (1.7)	> 0.999
Rheumatic disease	4 (3.6)	1 (1.9)	3 (5.0)	0.622
Previous history of extra-thoracic malignancy	12 (10.7)	5 (9.6)	7 (11.7)	0.769
Chronic pulmonary symptoms*				
Cough	56 (50.0)	28 (53.8)	28 (46.7)	0.570
Sputum	51 (45.5)	23 (44.2)	28 (46.7)	0.850
Breathlessness[†]	66 (58.9)	31 (59.6)	35 (58.3)	> 0.999
Hemoptysis	34 (30.4)	16 (30.8)	18 (30.0)	> 0.999
Chest computed tomographic findings*				
Cavitation	112 (100)	52 (100)	60 (100)	NA
Consolidation	17 (15.2)	6 (11.5)	11 (18.3)	0.430
Mycetoma	44 (39.3)	23 (44.2)	21 (35.0)	0.339
Paracavitary infiltrates	97 (86.6)	47 (90.4)	50 (83.3)	0.405
Bilateral pulmonary lesions	29 (25.9)	10 (19.2)	19 (31.7)	0.194
Laboratory findings				
White blood cells/μl	7,690	8,075	7,360	0.524
	(5,900–9,740)	(5,605–9,465)	(6,160–9,990)	
C-reactive protein, mg/dL	2.86	3.65	1.90	0.108
	(0.54–7.81)	(1.24–8.09)	(0.40–6.18)	
Albumin, g/dL	3.8	3.8	3.8	0.216
	(3.3–4.2)	(3.1–4.2)	(3.5–4.2)	

The data are presented as median (interquartile range) or number (%).

[§] Spirometric pattern was defined as follows: (1) restrictive spirometry pattern was defined as a post-bronchodilator $FEV_1/FVC \geq LLN$ and a FVC < LLN; (2) obstructive spirometry pattern was defined as a post-bronchodilator $FEV_1/FVC < LLN$.

* Cases are duplicated.

[†] "Breathlessness" represents a modified Medical Research Council dyspnea score ≥ 2.

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

https://doi.org/10.1371/journal.pone.0260274.t001

Table 2. Pulmonary function tests.

	Total	Restrictive spirometric pattern[§]	Obstructive spirometric pattern[§]
	(N = 112)	(n = 52)	(n = 60)
FVC, L	2.12 (1.61–2.81)	2.03 (1.56–2.41)	2.34 (1.61–3.10)
FVC, % predicted	62 (48–76)	56 (43–68)	68 (53–87)
FEV_1, L	1.33 (1.00–1.89)	1.78 (1.25–2.05)	1.05 (0.80–1.41)
FEV_1, % predicted	55 (40–77)	71 (50–81)	46 (35–65)

The data are presented as median (interquartile range) or number (%).

[§] Spirometric pattern was defined as follows: (1) restrictive spirometry pattern was defined as a post-bronchodilator $FEV_1/FVC \geq$ LLN and a FVC < LLN; (2) obstructive spirometry pattern was defined as a post-bronchodilator $FEV_1/FVC <$ LLN.

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; LLN, lower limit of normal.

Discussion

CPA is a slowly progressive respiratory syndrome with obscure pathogenesis, complex methods of diagnosis, and limited therapeutic response [15, 16]. Thus, CPA can result in very diverse clinical outcomes. Until now, a pulmonologist can predict the condition and progress of the chronic lung diseases through PFT and imaging modalities [8, 17, 18]. However, the role of spirometry is not clear in patients with CPA [19, 20]. All participants in this study were classified based on pulmonary function results. Unlike other chronic diseases, patients with CPA have heterogeneous spirometric patterns. This was thought to be accompanied by various underlying diseases and the extent of lung damage caused by *Aspergillus* species, which are ubiquitous airborne molds [21–23].

In this study, the proportion of CPA patients with NTM was higher in patients with RSP than in those with OSP. This was due to the higher proportion of NTM patients with fibrocavitary form than those with nodular bronchiectatic form [24]. Conversely, the proportion of CPA patients with emphysema was higher in patients with OSP than in those with RSP [25]. Additionally, the BMI in the present study participants was in the normal range, but we found that CPA patients with RSP had a lower BMI than those with OSP. This was also considered to be due to the differences in the frequency of underlying diseases.

Among CPA patients with RSP (N = 52), the proportion of younger patients became higher as the FVC decreased. In the present study, the most common underlying lung disease in those patients is previous pulmonary tuberculosis (n = 41). The age was significantly lower in tuberculous destroyed lung patients with RSP in FVC tertile 1 compared to those in tertiles 2–3 (56 years versus 66 years; *P* = 0.025) (S1 Table). Additionally, although this was not statistically significant, the proportion of female participants with RSP in FVC in tertile 1 was higher than those in tertiles 2–3. The median age of women was 55 years while the median age of men was 68 years in the present study, with statistical significance (*P* < 0.001) (S2 Table). Although there are limitations in the interpretation due to the small number of patients included in our study, we were able to identify specific groups with decreased lung function among heterogeneous CPA patients. Further research is needed to investigate the differences in clinical features and prognosis for each group. The results also showed that the lower FVC, the higher frequency of bilateral lesions, which was an independent risk factor for CPA relapse [26]. This was thought to be because bilateral lesions themselves lead to FVC reduction.

Among CPA patients with OSP, on the other hands, the proportion of patients with lower BMI became higher as the FEV_1 decreased. Previous research confirmed that only severe COPD was associated with underweight [27]. The study also confirmed that the lower FEV_1, the higher frequency of paracavitary infiltrates with elevated WBC counts. These findings may

Table 3. RSP[§] patients' characteristics by tertile of FVC (% predicted).

FVC	Tertile 1	Tertile 2	Tertile 3	*P* for trend
(% predicted)	< 49	49 ≤–< 63	≥ 63	
	(n = 16)	(n = 19)	(n = 17)	
Age, years	56 (47–67)	68 (60–77)	68 (52–79)	**0.025**
Sex, male	12 (75.0)	16 (84.2)	14 (82.4)	0.825
Body mass index, kg/m^2	17.3	17.3	19.3	0.051
	(15.2–21.2)	(16.4–19.3)	(16.9–22.1)	
Smoking history				
Ex or current smoker	9 (56.3)	11 (57.9)	12 (70.6)	0.723
Underlying lung disease*				
Previous history of pulmonary tuberculosis	14 (87.5)	13 (68.4)	14 (82.4)	0.401
Non-tuberculous mycobacterial disease	2 (12.5)	6 (31.6)	7 (41.2)	0.187
Emphysema	2 (12.5)	4 (21.1)	3 (17.6)	0.900
Bronchiectasis	3 (18.8)	3 (15.8)	2 (11.8)	0.895
Interstitial lung disease	0	2 (10.5)	1 (5.9)	0.766
Previous history of thoracic malignancy	1 (6.3)	1 (5.3)	0	0.756
Other comorbidities*				
Diabetes mellitus	1 (6.3)	1 (5.3)	3 (17.6)	0.502
Chronic hepatic insufficiency	2 (12.5)	0	1 (5.9)	0.192
Chronic renal insufficiency	0	0	0	NA
Rheumatic disease	1 (6.3)	0	0	0.308
Previous history of extra-thoracic malignancy	0	3 (15.8)	2 (11.8)	0.353
Chronic pulmonary symptoms*				
Cough	7 (43.8)	10 (52.6)	11 (64.7)	0.504
Sputum	6 (37.5)	8 (42.1)	9 (52.9)	0.733
Breathlessness[†]	9 (56.3)	12 (63.2)	10 (58.8)	0.939
Hemoptysis	6 (37.5)	5 (26.3)	5 (29.4)	0.810
Chest computed tomographic findings*				
Cavitation	16 (100)	19 (100)	17 (100)	NA
Consolidation	3 (18.8)	1 (5.3)	2 (11.8)	0.415
Mycetoma	8 (50.0)	7 (36.8)	8 (47.1)	0.778
Paracavitary infiltrates	16 (100)	17 (89.5)	14 (82.4)	0.302
Bilateral pulmonary lesions	8 (50.0)	1 (5.3)	1 (5.9)	**0.001**
Laboratory findings				
White blood cells/μl	7,275	8,610	7,135	0.454
	(5,643–9,213)	(5,773–10,310)	(5,093–9,143)	
C-reactive protein, mg/dL	7.94	2.67	3.49	0.055
	(3.52–12.23)	(0.59–9.23)	(0.78–4.62)	
Albumin, g/dL	3.5	4.0	3.9	0.794
	(3.1–4.1)	(3.2–4.4)	(3.0–4.1)	

The data are presented as median (interquartile range) or number (%).

[§] Restrictive spirometry pattern was defined as a post-bronchodilator FEV$_1$/FVC ≥ LLN and a FVC < LLN.

* Cases are duplicated.

[†] "Breathlessness" represents a modified Medical Research Council dyspnea score ≥ 2.

RSP, restrictive spirometry pattern; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

Table 4. OSP§ patients' characteristics by tertile of FEV$_1$ (% predicted).

FEV$_1$	Tertile 1	Tertile 2	Tertile 3	P for trend
(% predicted)	< 38	38 ≤–< 54	≥ 54	
	(n = 18)	(n = 22)	(n = 20)	
Age, years	63 (58–71)	61 (55–68)	72 (59–78)	0.134
Sex, male	14 (77.8)	14 (63.6)	17 (85.0)	0.319
Body mass index, kg/m^2	17.2	20.3	21.9	< **0.001**
	(15.2–19.9)	(19.4–22.0)	(20.2–24.6)	
Smoking history				
Ex or current smoker	13 (72.2)	15 (68.2)	16 (80.0)	0.711
Underlying lung disease*				
Previous history of pulmonary tuberculosis	14 (77.8)	17 (77.3)	14 (70.0)	0.868
Non-tuberculous mycobacterial disease	4 (22.2)	1 (4.5)	2 (10.0)	0.233
Emphysema	9 (50.0)	8 (36.4)	9 (45.0)	0.721
Bronchiectasis	1 (5.6)	4 (18.2)	3 (15.0)	0.568
Interstitial lung disease	0	0	0	NA
Previous history of thoracic malignancy	0	0	1 (5.0)	0.633
Other comorbidities*				
Diabetes mellitus	3 (16.7)	5 (22.7)	1 (5.0)	0.287
Chronic hepatic insufficiency	2 (11.1)	3 (13.6)	2 (10.0)	> 0.999
Chronic renal insufficiency	0	1 (4.5)	0	> 0.999
Rheumatic disease	0	1 (4.5)	2 (10.0)	0.634
Previous history of extra-thoracic malignancy	1 (5.6)	3 (13.6)	3 (15.0)	0.687
Chronic pulmonary symptoms*				
Cough	10 (55.6)	10 (45.5)	8 (40.0)	0.653
Sputum	10 (55.6)	11 (50.0)	7 (35.0)	0.444
Breathlessness†	14 (77.8)	13 (59.1)	8 (40.0)	0.066
Hemoptysis	3 (16.7)	7 (31.8)	8 (40.0)	0.298
Chest computed tomographic findings*				
Cavitation	18 (100)	22 (100)	20 (100)	NA
Consolidation	4 (22.2)	3 (13.6)	4 (20.0)	0.770
Mycetoma	6 (33.3)	8 (36.4)	7 (35.0)	> 0.999
Paracavitary infiltrates	18 (100)	19 (86.4)	13 (65.0)	**0.011**
Bilateral pulmonary lesions	4 (22.2)	10 (45.5)	5 (25.0)	0.238
Laboratory findings				
White blood cells/μl	9,445	7,785	6,650	**0.041**
	(6,295–12,100)	(7,267–8,878)	(5,230–7,630)	
C-reactive protein, mg/dL	4.85	0.69	1.43	0.080
	(1.59–10.32)	(0.38–3.09)	(0.40–8.73)	
Albumin, g/dL	3.6	4.1	3.8	0.227
	(3.2–3.8)	(3.8–4.4)	(3.3–4.2)	

The data are presented as median (interquartile range) or number (%).

§ Obstructive spirometry pattern was defined as having a post-bronchodilator FEV$_1$/FVC < LLN.

* Cases are duplicated.

† "Breathlessness" represents a modified Medical Research Council dyspnea score ≥ 2.

OSP, obstructive spirometry pattern; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

indicate that paracavitary infiltrates by *Aspergillus* are associated with inflammatory aggravation, which could lead to the deterioration of FEV_1.

Lastly, the spirometric results of CPA treatment response used in previous studies were based on FVC and FEV_1 without categorization by spirometric patterns [14, 19, 28]. Our study showed that spirometric results categorized by spirometric patterns may be a viable alternative for monitoring the disease progression of CPA.

The current study had some limitations. First, this study was a retrospective analysis of patients from a single referral center and the sample size was relatively small, which might have led to selection bias. Second, not all patients underwent regular screening tests for CPA, mainly due to the low level of attention from pulmonologists and the complexity of the diagnostic method. Therefore, some CPA cases might have been missed. Third, PFT was not performed in all patients diagnosed with CPA during the study period. This is because it has not been recommended as a mandatory assessment in the previous guideline [1]. Spirometry might have been conducted more frequently in CPA patients with breathlessness, and these results could have affected the clinical characteristics. However, the present data would reflect real-world clinical practice.

Conclusions

This study identified the difference in clinical features of the patients with CPA according to a variety of spirometric patterns, which possibly reflects the complexities of the patients with CPA. Further large-scale studies are required to evaluate the prognosis and mortality of CPA according to spirometric patterns.

Supporting information

S1 Table. Tuberculosis destroyed lung patients' age by tertile of FVC (% predicted). The data are presented as median (interquartile range). FVC, forced vital capacity.
(DOCX)

S2 Table. RSP$^\$$ patients' age by tertile of FVC (% predicted) according to the sex. The data are presented as median (interquartile range). $^\$$ Restrictive spirometry pattern was defined as a post-bronchodilator FEV_1/FVC $\geq$ LLN and a FVC $<$ LLN. RSP, restrictive spirometry pattern; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; LLN, lower limit of normal.
(DOCX)

S1 Data.
(XLSX)

Author Contributions

Conceptualization: Beomsu Shin.

Data curation: Sae Byol Kim.

Formal analysis: Beomsu Shin.

Investigation: Myoung Kyu Lee, Sae Byol Kim.

Methodology: Myoung Kyu Lee, Beomsu Shin.

Project administration: Beomsu Shin.

Writing – original draft: Myoung Kyu Lee, Beomsu Shin.

Writing – review & editing: Myoung Kyu Lee, Sae Byol Kim, Beomsu Shin.

References

1. Denning DW, Cadranel J, Beigelman-Aubry C, Ader F, Chakrabarti A, Blot S, et al. Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. Eur Respir J. 2016; 47: 45–68. https://doi.org/10.1183/13993003.00583-2015 PMID: 26699723.

2. Fukushima K, Kitada S, Abe Y, Yamamoto Y, Matsuki T, Kagawa H, et al. Long-Term Treatment Outcome of Progressive Mycobacterium Avium Complex Pulmonary Disease. J Clin Med. 2020; 9: https://doi.org/10.3390/jcm9051315 PMID: 32370226.

3. Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. Eur Respir J. 2011; 37: 865–872. https://doi.org/10.1183/09031936.00054810 PMID: 20595150.

4. Gago S, Denning DW, Bowyer P. Pathophysiological aspects of Aspergillus colonization in disease. Med Mycol. 2019; 57: S219–s227. https://doi.org/10.1093/mmy/myy076 PMID: 30239804.

5. Bongomin F, Harris C, Foden P, Kosmidis C, Denning DW. Innate and Adaptive Immune Defects in Chronic Pulmonary Aspergillosis. J Fungi (Basel). 2017;3: https://doi.org/10.3390/jof3020026 PMID: 29371544.

6. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005; 26: 948–968. https://doi.org/10.1183/09031936.05.00035205 PMID: 16264058.

7. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017; 195: 557–582. https://doi.org/10.1164/rccm.201701-0218PP PMID: 28128970.

8. Ley B, Collard HR, King TE Jr., Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011; 183: 431–440. https://doi.org/10.1164/rccm.201006-0894CI PMID: 20935110.

9. Lee MK, Kim SB, Lee JH, Lee SJ, Kim SH, Lee WY, et al. Association between airflow limitation and prognosis in patients with chronic pulmonary aspergillosis. J Thorac Dis. 2021; 13: 681–688. https://doi.org/10.21037/jtd-20-1815 PMID: 33717541.

10. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016; 63: e1–e60. https://doi.org/10.1093/cid/ciw326 PMID: 27365388.

11. Sehgal IS, Dhooria S, Muthu V, Prasad KT, Agarwal R. An overview of the available treatments for chronic cavitary pulmonary aspergillosis. Expert Rev Respir Med. 2020: 1–13. https://doi.org/10.1080/17476348.2020.1750956 PMID: 32249630.

12. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019; 200: e70–e88. https://doi.org/10.1164/rccm.201908-1590ST PMID: 31613151.

13. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012; 40: 1324–1343. https://doi.org/10.1183/09031936.00080312 PMID: 22743675.

14. Al-Shair K, Atherton GT, Harris C, Ratcliffe L, Newton PJ, Denning DW. Long-term antifungal treatment improves health status in patients with chronic pulmonary aspergillosis: a longitudinal analysis. Clin Infect Dis. 2013; 57: 828–835. https://doi.org/10.1093/cid/cit411 PMID: 23788240.

15. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. Thorax. 2015; 70: 270–277. https://doi.org/10.1136/thoraxjnl-2014-206291 PMID: 25354514.

16. Setianingrum F, Rautemaa-Richardson R, Shah R, Denning DW. Clinical outcomes of patients with chronic pulmonary aspergillosis managed surgically. Eur J Cardiothorac Surg. 2020: https://doi.org/10.1093/ejcts/ezaa137 PMID: 32386208.

17. Leivseth L, Brumpton BM, Nilsen TI, Mai XM, Johnsen R, Langhammer A. GOLD classifications and mortality in chronic obstructive pulmonary disease: the HUNT Study, Norway. Thorax. 2013; 68: 914–921. https://doi.org/10.1136/thoraxjnl-2013-203270 PMID: 23611880.

18. Labaki WW, Martinez CH, Martinez FJ, Galbán CJ, Ross BD, Washko GR, et al. The Role of Chest Computed Tomography in the Evaluation and Management of the Patient with Chronic Obstructive

Pulmonary Disease. Am J Respir Crit Care Med. 2017; 196: 1372–1379. https://doi.org/10.1164/rccm.201703-0451PP PMID: 28661698.

19. Sehgal IS, Dhooria S, Choudhary H, Aggarwal AN, Garg M, Chakrabarti A, et al. Monitoring treatment response in chronic pulmonary aspergillosis: role of clinical, spirometric and immunological markers. Clin Microbiol Infect. 2019; 25: 1157.e1151–1157.e1157. https://doi.org/10.1016/j.cmi.2019.01.007 PMID: 30685498.

20. Godet C, Laurent F, Bergeron A, Ingrand P, Beigelman-Aubry C, Camara B, et al. CT Imaging Assessment of Response to Treatment in Chronic Pulmonary Aspergillosis. Chest. 2016; 150: 139–147. https://doi.org/10.1016/j.chest.2016.02.640 PMID: 26905365.

21. Denning DW. Chronic forms of pulmonary aspergillosis. Clin Microbiol Infect. 2001; 7 Suppl 2: 25–31. https://doi.org/10.1111/j.1469-0691.2001.tb00006.x PMID: 11525215.

22. Uzunhan Y, Nunes H, Jeny F, Lacroix M, Brun S, Brillet PY, et al. Chronic pulmonary aspergillosis complicating sarcoidosis. Eur Respir J. 2017; 49: https://doi.org/10.1183/13993003.02396-2016 PMID: 28619957.

23. de Vallière S, Barker RD. Residual lung damage after completion of treatment for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2004; 8: 767–771. PMID: 15182148.

24. Jhun BW, Jung WJ, Hwang NY, Park HY, Jeon K, Kang ES, et al. Risk factors for the development of chronic pulmonary aspergillosis in patients with nontuberculous mycobacterial lung disease. PLoS One. 2017; 12: e0188716. https://doi.org/10.1371/journal.pone.0188716 PMID: 29190796.

25. Barberán J, García-Pérez FJ, Villena V, Fernández-Villar A, Malmierca E, Salas C, et al. Development of Aspergillosis in a cohort of non-neutropenic, non-transplant patients colonised by Aspergillus spp. BMC Infect Dis. 2017; 17: 34. https://doi.org/10.1186/s12879-016-2143-5 PMID: 28056830.

26. Bongomin F, Otu A, Harris C, Foden P, Kosmidis C, Denning DW. Risk factors for relapse of chronic pulmonary aspergillosis after discontinuation of antifungal therapy. Clinical Infection in Practice. 2020; 5: 100015.

27. Eriksson B, Backman H, Bossios A, Bjerg A, Hedman L, Lindberg A, et al. Only severe COPD is associated with being underweight: results from a population survey. ERJ Open Res. 2016; 2: https://doi.org/10.1183/23120541.00051-2015 PMID: 27730201.

28. Lee JG, Lee CY, Park IK, Kim DJ, Chang J, Kim SK, et al. Pulmonary aspergilloma: analysis of prognosis in relation to symptoms and treatment. J Thorac Cardiovasc Surg. 2009; 138: 820–825. https://doi.org/10.1016/j.jtcvs.2009.01.019 PMID: 19660294.