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Clinical characteristics of patients with *Aspergillus* species isolation from respiratory samples: Comparison of chronic pulmonary aspergillosis and colonization

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ABSTRACT

Background: With advancements in anti-fungal drugs, it has become more important to correctly diagnose chronic pulmonary aspergillosis (CPA); however, it is not easy to distinguish CPA from colonization when *Aspergillus* species are isolated from respiratory samples. The aim of the study was to clarify the particular clinical characteristics of patients with CPA vs. those with colonization.
Methods: We retrospectively reviewed the medical records of 110 patients with *Aspergillus* species isolation from respiratory samples, to analyze and compare the differences between CPA and colonization of the *Aspergillus* species.
Results: The median age of all analyzed was 71 years (range: 31–92 years); 64 were female (58%). The most frequently cultured *Aspergillus* species was *Aspergillus fumigatus* (48.3%), followed by *A. niger* (29.2%). Thirty patients (27.4%) were diagnosed with CPA, vs. 75 (68.2%) with colonization and 5 (4.5%) with allergic bronchopulmonary aspergillosis. Compared with the colonization group, the CPA group included more males (CPA vs. colonization: 49.3% vs. 13.3%) and subjects with a low body mass index (18.45 kg/m^2 vs. 21.09 kg/m^2). As for the underlying pulmonary diseases, the patients with CPA showed a significantly higher prevalence of sequelae of pulmonary tuberculosis (40% vs. 8%) and a history of thoracic surgery (43% vs. 13%) than those with colonization. Asthma was less frequent in the CPA group than in the colonization group (0% vs. 20%). We found no significantly important underlying extrapulmonary diseases.
Conclusions: Patients with CPA display clinical characteristics distinct from those seen in subjects with colonization.

Abbreviations: CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis; IPA, invasive pulmonary aspergillosis; SD, standard deviation; Asp, *Aspergillus*; COPD, chronic obstructive pulmonary disease; BMI, body mass index.

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1. Introduction

Aspergillus species, which are commonly found in humid solid, water, and other materials, can cause a variety of illnesses in humans. We inhale several hundred spores per day and, although these spores are generally cleared from the body without resulting in disease in most people, some are affected by several *Aspergillus* species that can cause pulmonary diseases, such as allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis (CPA) and simple aspergilloma [1], even if they are not immunocompromised.

When isolating *Aspergillus* species from respiratory samples, it is important to confirm whether the isolates simply indicate colonization, meaning that the species are a component of the normal flora and are not pathogenic. In this study, we reviewed the characteristics of patients seen in our hospital, in whom *Aspergillus* species were isolated from respiratory samples, to clarify the differences in clinical characteristics between CPA and colonization.

2. Patients and methods

2.1. Study design

We retrospectively reviewed the laboratory data of a series of consecutive samples from which *Aspergillus* species were isolated between January 2002 and December 2011 at the NTT Medical Center Tokyo, Tokyo, Japan. Only patients with *Aspergillus* species isolates from respiratory samples, without hematological malignancy, were included in this study. The subjects' electronic medical records were reviewed to obtain clinical and demographic data, including gender; age; category of pulmonary aspergillosis; laboratory data (white blood cell count, serum albumin, and *Aspergillus* antigen levels, and [1–3] *beta*-D glucan titer); underlying pulmonary diseases; comorbidities; treatment; and survival rates. The study protocol was reviewed and approved by the Ethics Committee of NTT Medical Center Tokyo on May 17, 2012 (approval number 12-116).

The patients were categorized into the following 5 groups based on their diagnosis: (1) CPA; (2) simple aspergilloma; (3) invasive pulmonary aspergillosis (IPA); (4) ABPA; and (5) colonization [2]. Since there is no definitive definition of CPA [3], in this study, a diagnosis of CPA was given when all of the following criteria were met: (1) isolation of *Aspergillus* species from respiratory samples; (2) the presence of clinical symptoms, such as weight loss, malaise, coughing, hemosputum, increased sputum, dyspnea, and fever; and (3) radiological findings, such as the new appearance or the enlargement of paracavitary infiltration, adjacent pleural thickening, fungus ball, or niveau formation [4]. Immunocompromised patients expressing neutropenia with respiratory symptoms and radiological findings, such as the halo sign, the air-crescent sign, and consolidation with cavitary lesions within the previous month were categorized as having IPA [5]. Radiological findings were determined by 2 physicians (S.O. and K.U.) who specialize in respiratory medicine. If these 2 physicians had different findings, they discussed it in order to come to an agreement. The diagnosis of ABPA was made by the physician in charge, although patients diagnosed with ABPA were confirmed to have a history of asthma, an elevated serum total immunoglobulin E level, and central bronchiectasis on chest computed tomography [6]. Colonization was defined as the lack of radiological or clinical findings suggestive of the above 3 categories in patients.

The (1-3) *beta*-D glucan assays were conducted using a product manufactured by MP Biomedicals, Inc (Santa Ana, Calif). The *Aspergillus* antigen tests were performed using the Platelia *Aspergillus* AG EIA device (Siemens Healthcare, Erlangen, Germany); the cut-off value for *Aspergillus* antigens was set at ≥ 0.5.

2.2. Statistical analysis

The data are expressed as either the mean (standard deviation [SD]) or the median (range). Non-categorical variables were compared using the *t* test. Categorical variables were expressed as percentages and compared using the Chi-square test. A *P* value of <0.05 was considered statistically significant, and survival rates were analyzed according to the Kaplan–Meier method using the log-rank test. The data were analyzed using the StatView version 5.0J software package (Statistical Analysis Systems, Cary, NC).

3. Results

Fig. 1 shows a diagram of the study cohort. Of the 368 samples with *Aspergillus* species isolates, 188 were respiratory samples obtained from 125 patients. Fifteen patients were excluded due to hematological malignancy, for a total of 110 patients included in the study.

Table 1 shows the patient characteristics. The median age (range) was 71 years (range: 31–92 years); 64 (58%) were male. The samples were mostly of sputum (85 samples [77%]), followed by bronchoalveolar lavage fluid (23 samples [21%]) and lung biopsy specimens (2 samples [2%]). The most commonly isolated *Aspergillus* species were *Aspergillus fumigatus* (48.3%), followed by *Aspergillus niger* (29.2%), *Aspergillus*

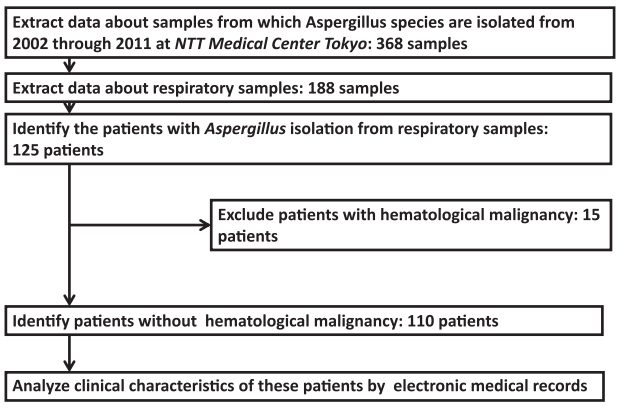

Fig. 1 – Flow chart of the study.

Table 1 – Patient characteristics.

Total number of patients	110
Age, median (range)	71(31–92)
Gender, *n* (%)	
Female	46(42)
Male	64(58)
Samples, *n* (%)	
Sputum	85(77)
Bronchoalveolar lavage fluid	23(21)
Other	2(2)
Aspergillus species, *n* (%)	
A. fumigatus	58(48.3)
A. niger	35(29.2)
A. flavus	10(8.3)
A. terreus	3(2.5)
A. nidulans	1(0.8)
A. spp.	13(10.6)
Categories of Aspergillosis, *n*(%)	
CPA	30(27.4)
Simple aspergilloma	0(0)
ABPA	5(4.5)
IPA	0(0)
Colonization	75(68.2)

Abbreviations: CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis; IPA: invasive pulmonary aspergillosis.

flavus (8.3%), *Aspergillus terreus* (2.5%), and *Aspergillus nidulans* (0.8%); 13 species were unidentified.

In the pulmonary aspergillosis category, 30 patients (27%) were classified as having CPA and 5 were classified as having ABPA, with no cases of simple aspergilloma or IPA. The remainder of the patients (68.2%) was classified as having colonization.

The characteristics of the CPA and the colonization groups are shown in Table 2. The proportion of males was significantly higher in the CPA group than in the colonization group (CPA: 86.7%; colonization: 49.3% [$P=0.001$]). The body mass index (BMI) was significantly lower in the CPA group than in the colonization group (CPA: 18.45 ± 3.08 kg/m^2; colonization: 21.09 ± 4.30 kg/m^2 [$P=0.004$]).

The distribution of the underlying pulmonary diseases differed between the CPA and the colonization groups (Table 2). In particular, sequelae of tuberculosis and a history of thoracic surgery were significantly more prevalent in the CPA group than in the colonization group. Additionally, there tended to be more cases of chronic obstructive pulmonary disease (COPD) in the CPA group, but fewer cases of either pulmonary non-tuberculous mycobacteria infection or bronchial asthma in this group. In contrast, the prevalence of extrapulmonary comorbidities was not significantly different between the 2 groups. Further, the levels of serum albumin were significantly lower in the CPA group than in the colonization group (CPA: 3.05 ± 0.64 g/dl; colonization: 3.49 ± 0.78 g/dl [$P=0.010$]); however, there were no significant differences in the levels of serum total protein (CPA: 6.74 ± 0.87 g/dl; colonization: 6.89 ± 0.83 g/dl [$P=0.467$]); serum creatinine (CPA: 0.75 ± 0.30 mg/dl; colonization: 0.75 ± 0.30 mg/dl [$P=0.465$]); C-reactive protein (CPA: 6.96 ± 7.21 mg/dl; colonization: 6.58 ± 8.02 mg/dl [$P=0.829$]); or white blood cell count (CPA: 8067 ± 3989 cells/μl; colonization: 8348 ± 4659 cells/μl [$P=0.772$]) between the groups.

The treatments for comorbidities, including the use of systemic steroids, inhaled corticosteroids, cytotoxic chemotherapy, molecular targeted therapy, and immunosuppressive therapy, did not differ between the 2 groups.

Table 2 – Characteristics of the patients with chronic pulmonary aspergillosis and colonization.

	CPA ($n=30$)	Colonization ($n=75$)	*P* value
Age, median (range)	72 (45–89)	72 (38–92)	0.644
Gender: male, *n* (%)	26 (86.7)	37 (49.3)	0.001
BMI (kg/m^2), mean±SD	18.45±3.08	21.09±4.30	0.004
Sample: sputum, *n* (%)	22 (73.3)	60 (80.0)	>0.999
Aspergillus species, *n*			
A. fumigatus	19	35	0.123
A. niger	8	27	0.360
A. flavus	1	8	0.225
A. terreus	1	2	0.853
A. nidulans	0	1	0.525
A. spp.	4	8	0.698
Underlying pulmonary disease, *n* (%)			
Bronchial asthma	0 (0)	11 (15)	0.027
COPD	9 (30)	8 (11)	0.015
Interstitial pneumonia	6 (20)	9 (12)	0.29
PNTM	3 (10)	25 (33)	0.015
Sequelae of tuberculosis	12 (40)	6 (8)	<0.001
Lung cancer	2 (7)	4 (5)	0.79
Bronchiectasis	0 (0)	2 (3)	0.367
Thoracic surgery	13 (43)	10 (13)	<0.001
None	0 (0)	15 (20)	0.008
Comorbidities, *n* (%)			
Cancer	10 (33)	16 (21)	0.198
Autoimmune	1 (3)	4 (5)	0.604
Kidney	1 (3)	3 (4)	0.872
Cerebrovascular	0 (0)	6 (8)	0.11
Heart	1 (3)	9 (12)	0.171
Liver	1 (3)	4 (5)	0.664
Diabetes	2 (7)	13 (17)	0.158
None	1 (3)	8 (11)	0.255
Laboratory data, mean±SD			
Total protein (g/dL)	6.74±0.87	6.89±0.83	0.467
Albumin (g/dL)	3.05±0.64	3.49±0.78	0.01
Creatinine (mg/dL)	0.75±0.30	0.79±0.25	0.465
CRP (mg/dL)	6.96 ±7.21	6.58±8.02	0.829
WBC (cells/μL)	8067±3989	8348±4659	0.772
Comorbidities treatment, *n* (%)			
Systemic steroid therapy	5 (17)	15 (20)	0.694
Inhaled corticosteroid	4 (13)	9 (12)	0.851
Cytotoxic chemotherapy	3 (10)	5 (7)	0.56
Molecular target therapy	0 (0)	5 (7)	0.147
Immunosuppressive therapy	3 (10)	1 (1)	0.036

CPA, chronic pulmonary aspergillosis; BMI, body mass index; SD, standard deviation; COPD, chronic obstructive pulmonary disease; PNTM, pulmonary nontuberculous mycobacterial infection; CRP, C-reactive protein; WBC, white blood count.

Table 3 shows the characteristics of CPA group. The patients with CPA all demonstrated symptoms that indicated *Aspergillus* infection. Elevation of inflammatory markers was apparent, and most were challenged with antibiotics.

The positive rates seen in the serum *Aspergillus* antigen test was higher in the CPA group (64%) than in the colonization group (14%) (Fig. 2A) ($P=0.023$). In contrast, there were no significant differences in the results of the (1-3) *b*-D glucan assays between the groups (Fig. 2B) (CPA: 6.75±7.19 pg/ml; colonization: 5.88±4.52 pg/ml [$P=0.641$]).

The patients with CPA demonstrated a poor prognosis. The median survival time after the isolation of *Aspergillus* species was 1126 days in the CPA group, whereas the median survival time was not reached in the colonization group during our observation period (Fig. 3) ($P=0.007$, log-rank test).

Table 3 – Clinical characteristics of patients with chronic pulmonary aspergillosis.

	($n=30$) (%)
Symptoms	
Cough	16 (53)
Sputum/hemosputum	9 (30)
Fever	14 (47)
Weight Loss	1 (3)
Dyspnea	5 (17)
No appearance of the above symptoms	0
Radiological findings	30 (100)
Enlargement of cavitary lesion	12 (40)
Infiltration of cavitary lesion	11 (37)
Fungus-ball like formation	6 (20)
Pleural thickening	6 (20)
Formation of niveau	5 (17)
Elevation of inflammatory markers	30 (100)
Use of antibiotics before treatment for CPA	25 (83)
(No response to antibiotics)	25 (83)

CPA, chronic pulmonary aspergillosis.

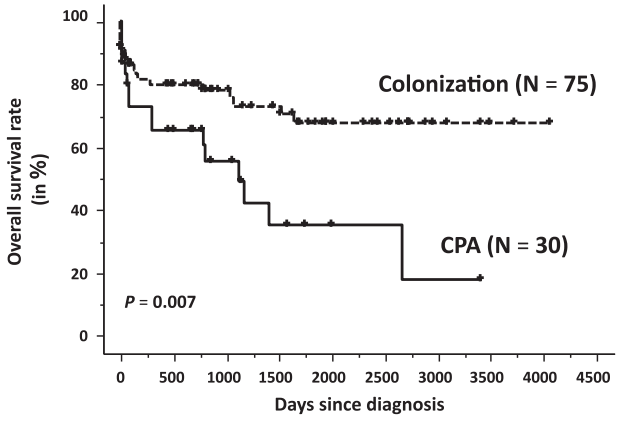

Fig. 3 – Overall survival rates of the patients with chronic pulmonary aspergillosis (CPA) and those with colonization from the day of isolation of the *Aspergillus* species. The patients with CPA showed a poorer prognosis than those with colonization (median survival time for CPA: 1126 days; colonization: not reached [$P=0.007$]).

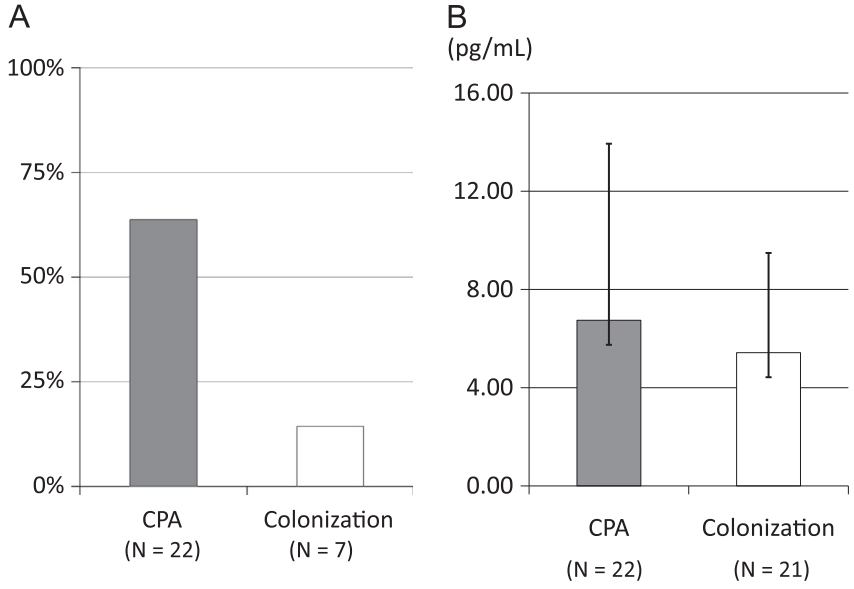

Fig. 2 – Rates of positivity for serum *Aspergillus* antigens (A) and serum beta D-glucan (B) in patients with chronic pulmonary aspergillosis (CPA) and with colonization. More patients with CPA showed positivity for serum *Aspergillus* antigens than seen in those with colonization; 14 (63.6%) of 22 patients with CPA and 1 (14.3%) of 7 patients with colonization exhibited positive findings for serum *Aspergillus* antigens ($P=0.023$). The mean values of serum beta D-glucan did not differ between the patients with CPA and those with colonization (mean±standard deviation: 6.75±7.19 vs. 5.88±4.52 [$P=0.641$]).

4. Discussion

In this study, we reviewed the clinical characteristics of 110 patients with *Aspergillus* species isolates obtained from respiratory samples. The most frequently isolated *Aspergillus* species was *A. fumigatus*, followed by *A. niger* and *A. flavus*. Approximately 25% of the patients with *Aspergillus* isolates from respiratory samples were diagnosed with CPA. The patients with CPA exhibited malnutrition and a different distribution of underlying pulmonary diseases, as well as a poorer prognosis.

In particular, the patients with CPA had different demographic characteristics from those in the colonization group. Males were more prevalent in the CPA group than in the colonization group, and the patients with CPA had significantly lower BMI values and serum albumin levels.

The underlying pulmonary diseases differed between the CPA and the colonization groups. The CPA group had a higher prevalence of COPD, sequelae of tuberculosis, and history of thoracic surgery, similar to the results of earlier studies [7,8]. Gender differences in these underlying diseases might explain why there were more men in CPA group than the colonization group; gender differences in CPA might also be explained by smoking status. However, our results cannot demonstrate this connection, as smoking status was not included in our study due to insufficient data in the medical records. On the other hand, our results differ from those of other studies, in that pulmonary non-tuberculous mycobacteria infection was less frequently seen in the patients with CPA [7,8]. Kunst et al. demonstrated that patients with bronchiectasis and non-tuberculous mycobacteria had a higher prevalence of *Aspergillus*-related lung disease [9]. Non-tuberculous mycobacteria infection is unusually destructive, and causes cavities that provide a favorable environment for the *Aspergillus* species. In our study, pulmonary non-tuberculous mycobacteria infections were less frequently seen than in other studies. One possible reason may be that our patients showed less severe non-tuberculous mycobacteria infection and thus pulmonary destruction was mild. We did not find any patients with asthma in the CPA group. Other studies have shown patients with comorbid asthma in CPA, but it was not a frequent underlying pulmonary disease [7]. That may be because asthma does not cause pulmonary destruction. Unlike the positive correlations observed with some underlying pulmonary diseases, CPA is not significantly related to extrapulmonary comorbidities. The high prevalence of pulmonary aspergillosis seen in the patients with a history of tuberculosis, COPD, and thoracic surgery in this study suggests that early intervention is required for cases in which *Aspergillus* species are isolated from respiratory samples. In addition, further research is necessary to elucidate the proper timing of initiating treatment in patients with *Aspergillus* species isolated from respiratory samples without these risk factors.

The rate of positivity for serum *Aspergillus* antigens was higher in the CPA group; however, the serum *b*-D glucan titers showed no relationship to CPA. This observation suggests that the serum *Aspergillus* antigen level is more useful than the *b*-D glucan titer in determining whether the isolation of *Aspergillus* simply reflects colonization. A study by Kitasato et al. showed a rate of positivity for serum *Aspergillus* antigens of 50%, for a cut-off index ≥ 0.5 [10]. Our result is higher than this result. Kitasato et al. also showed a rate of positivity for *b*-D glucan for CPA at the time of diagnosis of 15.4% (≥ 20 pg/ml as positive). In the current study, we did not set a cut-off value for the *b*-D glucan titer. However, if we had set a cut-off index of $\geqq 11$ (the cut-off index for the kit used in this study), the rate of positivity would have been 13.6%. It is difficult to compare the 2 studies, as we used different methods to measure the *b*-D glucan titer. Further, the *b*-D glucan assay shows high values for infection with *Aspergillus* as well as other fungi, such as *Candida*. Therefore, in cases in which the *b*-D glucan titer is high, it is necessary to take into consideration the possibility that the isolation of *Aspergillus* species may simply be due to colonization, and thus other fungal infections may be present.

Finally, the findings for overall survival rates indicated the poor prognosis of patients with CPA. Although long-term treatment is required in CPA [11], its poor prognosis indicates the need to diagnose the disease in affected patients at an early stage and promptly initiate treatment. For patients with pulmonary comorbidities, such as sequelae of tuberculosis, in whom *Aspergillus* species are isolated from respiratory samples, it is useful to carefully perform other tests, such as those for serum *Aspergillus* antigens, in order to diagnose CPA appropriately.

Since our study was set in a Japanese hospital, it is also important to confirm that our study conformed to Japanese physicians' diagnoses of CPA. Japanese physicians diagnose CPA using the 2014 Guidelines for Management of Deep-seated Mycoses, created by the Committee for Guidelines for Management of Deep-seated Mycoses [2]. According to these guidelines, those with pulmonary comorbidities, such as sequelae of tuberculosis, pulmonary nontuberculous mycobacterial infection, thoracic surgery, interstitial pneumonia, bronchiectasis, COPD, diabetes, radiological findings of cavitary lesion, and medical history of aspergillosis or pneumonia are categorized as patient at high risk for CPA. These patients were suspected of having CPA when they displayed the following 4 signs: (1) clinical symptoms of cough, weight loss, sputum, dyspnea and fever that continues more than 1 month; (2) radiological findings of cavitary lesion enlargement, cavitary lesion infiltration, fungus ball formation, pleural thickening, and niveau formation; (3) no response to antibiotic treatment; and (4) elevation of C-reactive protein or white blood cell count. Clinical diagnoses are made either when patients are positive for serum *Aspergillus*-precipitating antibody or receive a pathological diagnoses of aspergillosis, with the definitive diagnosis occurring when the *Aspergillus* species are isolated from respiratory samples.

In our study, although the serum *Aspergillus*-precipitating antibody was not examined, our definition of CPA was based on the isolation of the species, as well as other conditions in line with the Japanese guidelines.

Our study did have some limitations. First, the design was retrospective. Hence, treatment for CPA was chosen by the treating physician, and the results for overall survival would have differed depending on treatment with different antifungal agents. Second, our results are based on a relatively small number of patients. Third, we did not perform *Aspergillus*-precipitating antibody tests, because they are not covered by insurance in Japan. The *Aspergillus*-precipitating antibody tests are reported to be more sensitive than the serum *Aspergillus* antigen tests [12]. In the present study, we

studied patients who had evidence of *Aspergillus* species isolated from respiratory samples. The patients were categorized as having either simple aspergilloma, IPA, ABPA, or CPA according to their clinical presentation, including radiological findings. Colonization was a diagnosis of exclusion if the patients lacked the clinical features of these 4 diagnoses. Since we included clinical symptoms for our diagnosis of CPA in our definition, the early or the stable state of CPA in patients without clinical symptoms might be initially categorized into the colonization group. In such cases, *Aspergillus*-precipitating antibody test might be much more useful in detecting CPA in these patients.

Our study is valuable in that the results are based on the isolation of the *Aspergillus* species. This technique allowed us to compare the characteristics of patients with aspergillosis and those with colonization. In most of previous studies of CPA, the diagnosis of CPA was based on the clinical diagnosis obtained from radiographic and serum *Aspergillus* examinations [13]. Comparing the characteristics of patients with aspergillosis vs. colonization is not possible in such cases. Our results are also valuable for giving physicians some indications to differentiate CPA from colonization in cases where the *Aspergillus* species are isolated from respiratory samples.

5. Conclusions

We herein demonstrated that patients with CPA have clinical characteristics distinct from those seen in individuals with colonization. In particular, the patients with CPA exhibited a shorter survival times than those with colonization. For cases in which *Aspergillus* species are isolated from respiratory samples, especially in patients with malnutrition and/or a history of tuberculosis, emphysema, or thoracic surgery, it is important to promptly diagnose and treat these patients with anti-fungal medications.

Conflict of interest

The authors have no conflicts of interest.

Acknowledgments

None.

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