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Original Article

Risk stratification for the development of chronic pulmonary aspergillosis in patients with *Mycobacterium avium* complex lung disease

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ABSTRACT

Background: The number of patients with pulmonary nontuberculous mycobacterial disease complicated by chronic pulmonary aspergillosis (CPA) has been increasing. Additionally, CPA is reportedly associated with mortality in patients with *Mycobacterium avium* complex lung disease (MAC-LD). In the present study, we aimed to identify risk factors for developing CPA and stratify the risk for CPA development in patients with MAC-LD.

Methods: We retrospectively examined 361 patients newly diagnosed with MAC-LD. Risk factors for CPA development were examined using multivariate Cox proportional hazards regression analyses. A risk stratification system was established using the risk factors and receiver operating characteristic curve analyses.

Results: CPA developed in 20 (5.5%) of the 361 patients. Independent risk factors for CPA development included the presence of pulmonary emphysema, baseline steroid use, a serum albumin level <3.5 g/dL, and the presence of MAC-LD cavities. A 4-point scoring system was established to stratify patients into low-risk (0–1 point) and high-risk (2–4 points) groups. The 5-year incidence rates of CPA were 2.2% and 31% in the low- and high-risk groups, respectively ($P < 0.001$).

Conclusions: We identified independent predictors of CPA development and established a simple risk stratification system for identifying patients with MAC-LD who were at a high risk of developing CPA.

1. Introduction

The *Mycobacterium avium* complex (MAC), which consists of *M. avium* and *M. intracellulare*, is the most common etiology of pulmonary disease caused by nontuberculous mycobacteria (NTM) [1,2]. MAC causes chronic lung infection in immunocompetent and immunocompromised patients, and the incidences of this infection have been on the rise, in recent times, worldwide [2–4].

Chronic pulmonary aspergillosis (CPA) is a slowly progressing, destructive lung disease caused by *Aspergillus* spp., which complicates many other respiratory disorders [5]. Although the treatment for CPA involves the use of long-term antifungal agents, the prognosis is generally poor [6,7]. In recent times, the number of patients with NTM lung disease complicated by CPA has been on the rise [8–10]. In such cases, physicians often have difficulty determining the treatment regimen owing to potential drug interactions. Several studies have reported that coexisting CPA is associated with mortality in patients with MAC lung disease (MAC-LD) [11,12]. However, the risk factors for CPA development in patients with MAC-LD remain unclear. Furthermore, to our knowledge, there have been no studies that have attempted to stratify the risk for CPA development. Therefore, the aim of the present study was to examine the risk factors for CPA. Based on these identified risk factors, we established a convenient risk stratification system for determining the risk of CPA development in patients with MAC-LD. We believe that our risk stratification system will help physicians identify MAC-LD patients who are at a high risk of developing CPA.

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2. Material and methods

2.1. Patients

The data of patients who were newly diagnosed with MAC-LD, between December 2005 and January 2012, at Kurashiki Central Hospital in Japan were retrospectively reviewed. All the patients met the diagnostic criteria for MAC-LD, based on the guidelines by the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) [2]. Patients who developed simple aspergilloma (SA) were excluded from the analysis because the clinical characteristics and outcomes of SA differ widely from those of other types of CPA. None of the patients had been diagnosed with an infection caused by an *Aspergillus* species prior to the diagnosis of MAC-LD.

2.2. Study design

This was a retrospective cohort study. Clinical data including age, sex, smoking history, body mass index (BMI), complications, baseline steroid use, immunosuppressants use, laboratory data, bacteriological data, radiographic features, and treatment history were collected from the patients' medical records. Baseline clinical parameters were obtained within 2 months of the diagnosis of MAC-LD. Patients were followed through August 2015. The survival time was measured from the date of MAC-LD diagnosis until the date of death or censoring. The radiographic features of MAC-LD were classified into the following four patterns using computed tomography (CT) images of the chest: nodular/bronchiectatic (NB), fibrocavitary (FC), FC + NB, and unclassifiable [13]. In addition, the presence or absence of cavities caused by MAC-LD was recorded. All chest CT images were independently reviewed by four pulmonologists and discrepancies in their readings were resolved by a consensus. Respiratory samples were processed using Ziehl-Neelsen staining, solid medium culture (2% Ogawa medium), and the liquid-based BACTEC 960 system (Becton Dickinson Co., USA). MAC isolates were identified using the DNA-DNA hybridization for the genetic identification of mycobacteria, DDH Mycobacterium (KYOKUTO Pharmaceutical Industrial Co. Ltd., Tokyo, Japan). Cultures using 2% Ogawa medium were quantitated on a scale of 0−4+, as follows: 0, solid medium growth with 0 colonies; 1+, 1−199 colonies; 2+, 200−499 colonies; 3+, 500−2000 colonies; and 4+, >2000 colonies [14]. Baseline steroid use was defined as a daily dose of >10 mg or a cumulative dose of >700 mg of prednisone, in accordance with a report on the association between corticosteroid therapy and infectious complications [15].

The main objectives of this study included the identification of risk factors for CPA and the stratification of risk of CPA development in patients with MAC-LD. CPA was diagnosed based on the presence of a combination of the following characteristics: compatible clinical symptoms; radiological findings such as the new appearance of or increase in pericavitary infiltration, pleural thickening, or fungus ball; and isolation of *Aspergillus* species from respiratory samples or positive findings in the serum *Aspergillus* precipitin test (*Aspergillus* immunodiffusion system; Mercia Diagnostics Ltd., Surry, UK). These criteria are consistent with the definition of CPA provided in the guidelines of the European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society [5].

This study was approved by the ethics committee of Kurashiki Central Hospital (Institutional Review Board number: 2091) and was performed in accordance with the Declaration of Helsinki.

2.3. Statistical analysis

The categorical baseline characteristics are summarized using frequencies and percentages, whereas the continuous variables are expressed as the mean ± the standard deviation. We compared baseline characteristics between patients who developed CPA and those who did not, using Fisher's exact tests (categorical variables) or the Mann-Whitney *U* test (continuous variables). To assess the risk factors for CPA-development, each variable was entered into a univariate Cox proportional hazard analysis. All the variables that were significant in the univariate analysis were entered into a multivariate Cox proportional hazard regression analysis, wherein a stepwise backward procedure was used to derive a final model.

Variables identified as independent predictors of CPA in the regression analyses were then used to construct a score-based risk stratification system. A receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive performance of the scoring model and to determine the optimal cut-off point for identifying a high-risk group for CPA development. The cumulative incidence of CPA was estimated using a Kaplan-Meier analysis. The incidence rates of CPA for each risk group (low risk and high risk) were compared using a log-rank test. Differences were considered significant at $P < 0.05$. All statistical analyses were performed using

Table 1
Characteristics of the study participants.

Characteristic	Total (n = 361)		
	Non-CPA n = 341	CPA n = 20	*P* value
Age, years	71.1 ± 9.8	73.4 ± 9.5	0.325
Female	204 (59.8)	12 (60.0)	1.000
Smoking status (ex or current)	120 (35.2)	7 (35.0)	1.000
BMI, kg/m^2	19.7 ± 3.2	16.6 ± 3.6	<0.001
Complications			
Respiratory disease			
Previous pulmonary tuberculosis	29 (8.5)	3 (15.0)	0.405
Pulmonary emphysema	33 (9.7)	5 (25.0)	0.047
Interstitial pneumonia	23 (6.8)	2 (10.0)	0.640
Asthma	11 (3.2)	1 (5.0)	0.503
Systemic disease			
Diabetes mellitus	36 (10.6)	5 (25.0)	0.063
Rheumatoid arthritis	18 (5.3)	2 (10.0)	0.305
Malignancy	71 (20.8)	6 (30.0)	0.397
Steroid use	25 (7.4)	4 (19.0)	0.066
Immunosuppresants use[a]	16 (4.7)	3 (15.0)	0.080
Laboratory data			
Albumin, g/dL	3.90 ± 0.62	3.17 ± 0.64	<0.001
Hb, g/dL	12.4 ± 1.90	11.7 ± 1.03	0.023
Bacteriological examinations			
Culture score ≥2+	66 (19.7)	8 (40.0)	0.044
Positive smear result	42 (12.6)	4 (20.0)	0.311
MAC-LD cavity	70 (20.5)	13 (65.0)	<0.001
Radiographic features			0.002
FC	28 (8.2)	7 (35.0)	
NB	291 (85.3)	11 (55.0)	
FC + NB	8 (2.3)	0 (0.0)	
Unclassifiable	14 (4.1)	2 (10.0)	
Treatment for MAC	185 (54.3)	12 (60.0)	0.652
5-year mortality rate, %	19.3	59.1	<0.001[b]
Death throughout the study period	59 (17.3)	15 (75.0)	<0.001
Cause of death			<0.001
Pneumonia	9/59 (15.5)	5/15 (33.3)	
Progression of MAC	3/59 (5.2)	3/15 (20.0)	
Pulmonary aspergillosis	0/59 (0.0)	4/15 (26.7)	
Other pulmonary diseases	20/59 (34.5)	2/15 (13.3)	
Non-pulmonary diseases	20/59 (34.5)	0/15 (0.0)	
Unknown causes	6/59 (10.3)	1/15 (6.7)	

CPA, chronic pulmonary aspergillosis; BMI, body mass index; Hb, hemoglobin; MAC-LD, *Mycobacterium avium* complex lung disease; FC, fibrocavitary disease; NB, nodular/bronchiectatic disease; MAC, *Mycobacterium avium* complex.
Data are presented as n (%) or as the mean ± standard deviation.
[a] Immunosuppressants include methotrexate, cyclosporin, azathioprine, cyclophosphamide, tacrolimus, mizoribine.
[b] Analyzed by log-rank test.

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