CrossMark

Natural history of *Mycobacterium avium* complex lung disease in untreated patients with stable course

Ji An Hwang[1,3], Sunyoung Kim[2,3], Kyung-Wook Jo[1] and Tae Sun Shim[1]

Affiliations: [1]Dept of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea. [2]Dept of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea. [3]These authors contributed equally to this work.

Correspondence: Tae Sun Shim, Dept of Pulmonary and Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea. E-mail: shimts@amc.seoul.kr

ABSTRACT   Little is known about the long-term natural history of *Mycobacterium avium* complex lung disease (MAC-LD) in untreated patients with stable course.

The aim of this study was to investigate the natural course of untreated stable MAC-LD, with a focus on factors associated with clinical deterioration, spontaneous sputum conversion and prognosis.

Of 488 patients diagnosed with MAC-LD between 1998 and 2011, 305 patients (62.5%) showed progressive MAC-LD resulting in treatment initiation within 3 years of diagnosis and 115 patients (23.6%) exhibited stable MAC-LD for at least 3 years with a median follow-up duration of 5.6 years. Patients with stable MAC-LD were more likely to have higher body mass index and less systemic symptoms at initial diagnosis compared with patients with progressive MAC-LD, while positive sputum acid-fast bacilli smear, fibrocavitary type and more extensive disease in radiological findings were more associated with progressive MAC-LD. Of the untreated patients with stable MAC-LD, 51.6% underwent spontaneous sputum conversion, with younger age, higher body mass index and negative sputum acid-fast bacilli smear at initial diagnosis found to be predictors of this occurrence.

Advanced age, fibrocavitary type and abnormal pulmonary function were negative prognostic factors for survival in patients with stable MAC-LD.

Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous organisms in the environment. Of the NTM-related pulmonary diseases, *Mycobacterium avium* complex lung disease (MAC-LD) is the most common, with the incidence and prevalence increasing in many countries [1–4].

MAC organisms consist of two main species, *i.e. M. avium* and *Mycobacterium intracellulare*, and two radiological types of MAC-LD have been described. The fibrocavitary (FC) type usually develops in middle-aged male smokers and accompanies apical fibrocavitary lesions. If left untreated, it can progress within a relatively short time period, leading to extensive lung destruction and respiratory failure [1, 5]. In contrast, the nodular bronchiectatic (NB) type occurs predominantly in post-menopausal, nonsmoking females with frequent involvement in the right middle lobe or lingula and tends to have much slower progression than the FC type [1, 6]. Generally, immediate treatment initiation is recommended for FC cases or extensive disease due to the possibility of rapid lung destruction. However, when the course of disease is stationary or demonstrates slow progression, treatment can be deferred at the discretion of the attending physician, considering the potential benefits and risks of treatment, until definite aggravation of disease is observed [1, 7].

To date, many indicators have been suggested to evaluate treatment efficacy for MAC-LD, such as sputum culture conversion rate, relapse rate and mortality [5], and many clinical studies have been conducted to determine the course of disease and identify prognostic factors in treated patients with MAC-LD [8–15]. However, little is known about the long-term natural history of MAC-LD in untreated patients with stable disease.

Our present study aimed to investigate the natural course of stable MAC-LD in untreated patients, with a focus on factors associated with clinical deterioration resulting in treatment initiation, spontaneous sputum conversion and prognosis.

Methods

Study subjects

We identified a total of 488 patients with MAC-LD, newly diagnosed between January 1998 and December 2011 at Asan Medical Center (a 2700-bed tertiary referral hospital in Seoul, Korea), based on the 2007 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) diagnostic criteria for NTM lung disease [1]. Patients with a history of previous NTM lung disease were excluded and all patients enrolled were free from HIV infection. This study was approved by the Institutional Review Board of Asan Medical Center. Due to the retrospective nature of the study, the requirement for informed consent was waived.

Clinical assessment

Baseline clinical characteristics at the time of diagnosis were obtained by medical chart review, including age, body mass index (BMI), smoking status, previous history of pulmonary tuberculosis (TB), comorbidities, presence of symptoms, sputum acid-fast bacilli (AFB) smear, mycobacterial culture and pulmonary function test results.

Radiological assessment

Radiological abnormalities were classified into three categories according to computed tomography (CT) findings at the time of diagnosis: NB, FC and unclassifiable types. Radiological findings of the NB type were bronchiectasis and small centrilobular nodules predominantly in the right middle lobe or lingula of the left upper lobe, while the FC type exhibited apical fibrocavitary lesions [1, 6]. Cases in which the FC and NB types were both found were considered as FC type, as described previously [9]. Other CT findings in which consolidations were present or a specific type could not be determined due to the presence of underlying disease were designated as unclassifiable.

Microbiological assessment

Expectorated sputum or bronchoscopic samples were examined by Ziehl–Neelsen stain. The results of smear microscopy were reported semiquantitatively and a positive smear was defined as one with >1 AFB per 100 high-power fields [16]. AFB were cultured in solid Ogawa medium (Korean Institute of Tuberculosis, Osong, Korea) and using the liquid MGIT (mycobacteria growth indicator tube) system (Becton Dickinson, Sparks, MD, USA). Cultured isolates were identified as NTM using duplex PCR (Seegene, Seoul, Korea). NTM species were identified using a PCR-restriction fragment length polymorphism method, based on the *rpoB* gene [17].

Routine practice for airway hygiene in patients with MAC-LD

Encouraging sputum expectoration with active coughing or with postural drainage was a basic treatment policy of our respiratory clinic for all patients with MAC-LD. However, active bronchial hygiene therapies using nebulised hypertonic saline or inhaled adrenergic agents were not applied for patients with MAC-LD, and inhaled antibiotics were not available in Korea, except for nebulised colistin (nebulised colistin was not applied for patients with MAC-LD).

Study design

Of the 488 patients diagnosed during the 14-year period, 305 patients were started on treatment with macrolide-containing regimen within 3 years of initial diagnosis due to the progression of MAC-LD and were therefore defined as the progressive group. Of the remaining 183 patients, after excluding 68 untreated patients who had a follow-up duration of <3 years, 115 patients who were stable for at least 3 years after initial diagnosis without evidence of clinical or radiological deterioration were designated as the stationary group. The stationary group comprised 93 untreated patients and 22 patients started on treatment after a stable period of at least 3 years from diagnosis (figure 1). Baseline characteristics at the time of diagnosis were compared between the two groups and factors associated with disease progression resulting in treatment initiation within 3 years of diagnosis were determined.

To elucidate the clinical course of stable MAC-LD, we further investigated the sputum culture conversion rate during the follow-up period in the stationary group. The mean±SD number of sputum cultures was 19±15 in the 115 subjects in the stationary group. Sputum conversion was defined as three consecutive negative cultures spanning at least a 2-month period, with the time of conversion defined as the date of the first negative culture. As patients in this group were not treated, sputum culture conversion was designated as "spontaneous sputum conversion". If the patients demonstrated improvement of symptoms without worsening of radiological findings and could not expectorate sputum even after hypertonic saline induction, sputum was considered to be converted. Patients in the stationary group were followed through December 2014 or until death before December 2014. Survival data were collected from medical records and/or direct telephone interview.

Statistical analyses

Parametric data are presented as mean±standard deviation and nonparametric data as median (interquartile range (IQR)). Categorical variables are expressed as either the percentage of the total or number as appropriate. Numeric data were compared using the t-test, and categorical variables were compared using the Chi-squared test or Fisher's exact test. Cumulative rates for spontaneous sputum conversion or survival were estimated using the Kaplan–Meier method. Cox proportional hazard regression analyses were performed to identify predictors of clinical deterioration leading to treatment initiation, spontaneous sputum conversion and mortality in the
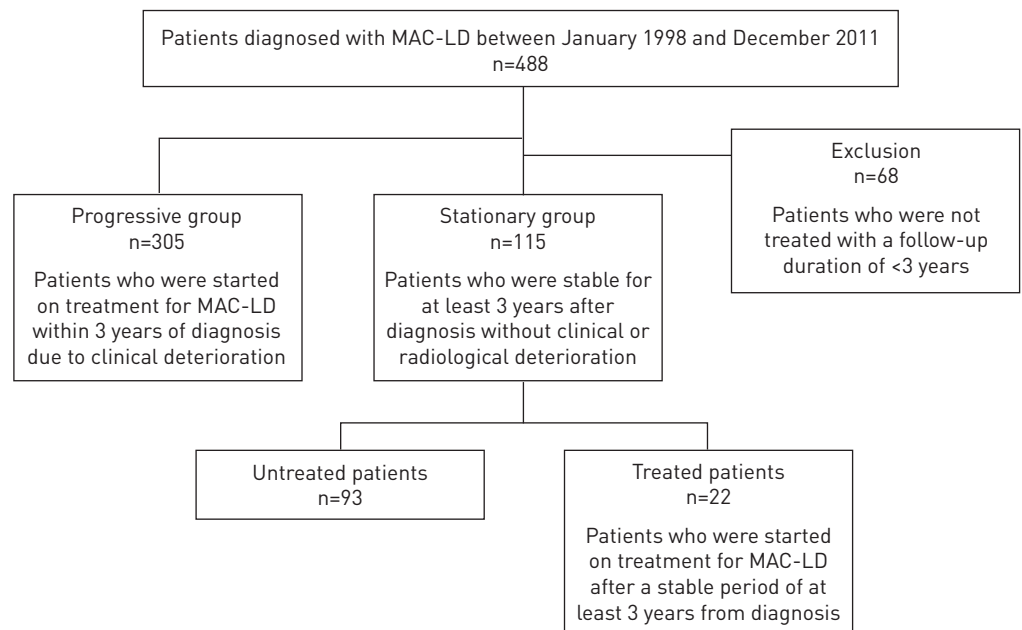

FIGURE 1 Flow chart of patients diagnosed with *Mycobacterium avium* complex lung disease (MAC-LD) between January 1998 and December 2011.

untreated stationary group. In all tests, two-sided p-values <0.05 were considered significant. All statistical analyses were performed using SPSS version 18.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics

Baseline patient characteristics are summarised in table 1. The median (range) age was 62 (21–89) years and the median (IQR) follow-up duration for all patients was 3.6 (2.2–5.4) years. Of the 420 patients, 305 (72.6%) patients received treatment for MAC-LD within 3 years of initial diagnosis (progressive group), while 115 (27.4%) patients belonged to the stationary group. The median (IQR) follow-up durations for the progressive and stationary groups were 3.0 (1.8–4.1) and 5.6 (4.8–6.6) years, respectively.

There were no differences in age, sex, smoking status, comorbidities such as diabetes mellitus, malignancy, chronic liver disease or chronic kidney disease, use of immunosuppressants and pulmonary symptoms such as cough, sputum, haemoptysis or dyspnoea between the two groups. However, patients in the

TABLE 1 Clinical characteristics of the 420 patients diagnosed with *Mycobacterium avium* complex lung disease (MAC-LD)

	Progressive group	Stationary group	p-value
Subjects	305	115	
Age years	60.8±11.5	62.1±11.5	0.284
Male	161 (52.8)	54 (47.0)	0.286
BMI kg·m^{-2}	20.2±2.9	22.1±3.6	<0.001
Smoker	144 (47.2)	53 (46.1)	0.837
Past history of pulmonary TB[#]	154 (52.7)	42 (41.2)	0.044
Comorbidities	270 (88.5)	110 (95.7)	0.026
Diabetes mellitus	34 (11.1)	12 (10.4)	0.835
Malignancy	62 (20.3)	17 (14.8)	0.195
COPD	59 (19.3)	33 (28.7)	0.039
Bronchiectasis	168 (55.1)	86 (74.8)	<0.001
Chronic interstitial pneumonia	25 (8.2)	14 (12.2)	0.210
Other chronic lung disease[¶]	4 (1.3)	0 (0)	0.579
Chronic liver disease	13 (4.3)	2 (1.7)	0.375
Chronic kidney disease	4 (1.3)	0 (0)	0.579
Use of immunosuppressant[+]	17 (5.6)	10 (8.7)	0.245
Symptoms	275 (90.2)	103 (89.6)	0.855
Cough	172 (56.4)	54 (47.0)	0.084
Sputum	162 (53.1)	66 (57.4)	0.433
Dyspnoea	77 (25.2)	29 (25.2)	0.995
Haemoptysis	78 (25.6)	30 (26.1)	0.915
Fever	20 (6.6)	1 (0.9)	0.017
Fatigue	38 (12.5)	3 (2.6)	0.002
Weight loss	41 (13.4)	9 (7.8)	0.113
Positive AFB smear	189 (62.0)	35 (30.4)	<0.001
Causative organisms			0.001
Mycobacterium avium	134 (43.9)	72 (62.6)	0.001
Mycobacterium intracellulare	171 (56.1)	43 (37.4)	0.001
Radiological types			<0.001
Fibrocavitary	134 (43.9)	14 (12.2)	<0.001
Nodular bronchiectatic	152 (49.8)	83 (72.2)	<0.001
Unclassifiable	19 (6.2)	19 (16.5)	0.001
Radiological extent: no. of lobes[§]	3.1±1.3	2.3±1.0	<0.001
Spirometry results			
FVC % pred	78.1±18.8	84.1±17.2	0.008
FEV1 % pred	77.2±23.5	77.1±22.8	0.968
FEV1/FVC %	73.0±15.3	68.1±16.2	0.010

Data are presented as n, mean±SD or n (%), unless otherwise stated. BMI: body mass index; TB: tuberculosis; COPD: chronic obstructive lung disease; AFB: acid-fast bacilli; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s. [#]: progressive group n=292, stationary group n=102; [¶]: chronic thromboembolic pulmonary hypertension (n=2), primary pulmonary hypertension (n=1) and pneumoconiosis (n=1); [+]: patients who were prescribed immunosuppressants at the time of diagnosis; [§]: radiological extent was estimated and expressed as the number of lobes presumed to have been infiltrated by MAC organisms in computed tomography at the time of diagnosis. p<0.05 was considered significant.

stationary group were more likely to have higher BMI, chronic obstructive pulmonary disease, bronchiectasis, positive cultures for *M. avium*, NB type, less extensive radiological lobar involvement and higher forced vital capacity (FVC) at diagnosis than those in the progressive group. In contrast, previous history of pulmonary TB, systemic symptoms such as fatigue or fever, sputum AFB smear positivity, *M. intracellulare* isolation and FC type were more frequent in the progressive group.

In contrast to the progressive group in which all patients were treated, only 22 (19.1%) patients in the stationary group were started on treatment for MAC-LD after at least 3 years of stable disease. The median (IQR) intervals from diagnosis to treatment were 2.7 (0.7–8.0) months for the progressive group and 65 (53–75) months for the stationary group.

NTM and bacterial cultures during follow-up

As the disease progressed, sputum specimens for NTM culture were more frequently collected in the progressive group than in the stationary group (26±15 *versus* 19±15; p<0.001). The number of positive sputum cultures was also significantly higher in the progressive group compared with the stationary group (12±10 *versus* 10±8; p=0.004).

Additional analyses revealed no difference between the two groups in terms of the proportion of patients who underwent more than one sputum bacterial culture (progressive *versus* stationary group: 72.8% *versus* 73.9%; p=0.816) and the proportion of patients who were administered antibiotics for the treatment of respiratory bacterial infection during the follow-up periods (20.7% *versus* 21.7%; p=0.808). The mean±SD numbers of sputum bacterial cultures during follow-up periods were 6±11 and 7±13 in the progressive and stationary group, respectively (p=0.45).

No significant difference was noted between the two groups in terms of the frequency and spectrum of isolated bacterial organisms. The most frequently isolated organism was *Pseudomonas aeruginosa* in 16.2% and 20% of the patients in the progressive and stationary group, respectively, followed by *Staphylococcus aureus* (10.4% *versus* 10.6%) and *Klebsiella pneumoniae* (9.5% *versus* 9.4%). In addition, *Enterobacter* spp. (5.9%), *Haemophilus influenza* (4.5%), *Acinetobacter baumannii* (3.2%) and *Streptococcus pneumoniae* (2.7%) were isolated with lower frequencies in the progressive group, and *Streptococcus pneumoniae* (7.1%), *Haemophilus influenzae* (7.1%), *Acinetobacter baumannii* (4.7%), *Moraxella catarrhalis* (3.5%), *Stenotrophomonas maltophilia* (3.5%) and *Enterobacter* spp. (2.4%) were isolated in the stationary group.

Predictors of disease progression necessitating antibiotic treatment

Cox proportional hazard regression analyses were conducted to determine factors associated with clinical deterioration leading to treatment initiation within 3 years of diagnosis in the total patients (table 2). Multivariate analysis revealed that patients with older age or higher BMI were less likely to receive treatment during the follow-up period (age: hazard ratio (HR) 0.987, 95% CI 0.975–0.999; p=0.04; BMI: HR 0.926, 95% CI 0.882–0.973; p=0.002), while patients with systemic symptoms such as fever, fatigue or weight loss (HR 1.490, 95% CI 1.095–2.028; p=0.011) or sputum AFB smear positivity (HR 1.811, 95% CI 1.350–2.428; p<0.001) were more likely to be treated. Patients with the FC type (HR 2.102, 95% CI 1.519–2.908; p<0.001) or more extensive disease (number of involved lobes: HR 1.178, 95% CI 1.050–1.322; p=0.005) also tended to undergo clinical deterioration necessitating treatment more frequently than those without.

In subgroup analysis performed to identify risk factors for deterioration of MAC-LD in the stationary group, chronic interstitial pneumonia as a comorbidity was the sole factor associated with the progression of MAC-LD resulting in treatment initiation in multivariate analysis (HR 4.642, 95% CI 1.541–13.979; p=0.006).

Spontaneous sputum conversion

Spontaneous negative conversion of sputum cultures occurred in 48 (51.6%) patients among the 93 untreated patients in the stationary group. Cumulative rates for spontaneous sputum conversion were 21.5%, 33.3% and 40.9% at 1, 2 and 3 years from diagnosis, respectively. The median (IQR) time from diagnosis to spontaneous sputum conversion was 41.8 (13.7–64) months. When further analyses were performed to identify predictors of sputum conversion in the untreated stationary group, age, BMI, sputum AFB smear positivity and transient anti-TB medication (⩾1 month) at the time of diagnosis were significantly associated in multivariate analysis (table 3). Namely, as age decreases or BMI increases, patients were more likely to undergo spontaneous sputum conversion (age: HR 0.973, 95% CI 0.948–0.999; p=0.043; BMI: HR 1.101, 95% CI 1.007–1.205; p=0.035). Conversely, patients with a positive sputum AFB smear tended to experience culture conversion less frequently than those with a negative smear (HR 0.377, 95% CI 0.156–0.912; p=0.03). Transient anti-TB medication (⩾1 month) at the time of MAC-LD diagnosis increased the probability of experiencing culture conversion (HR 3.769, 95% CI 1.505–9.435; p=0.005).

TABLE 2 Predictors of disease progression resulting in treatment initiation within 3 years of diagnosis of *Mycobacterium avium* complex lung disease (MAC-LD) in a total of 466 patients[#]

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age years	0.990 (0.980–1.001)	0.072	0.987 (0.975–0.999)	0.040
Male	0.976 (0.767–1.243)	0.846		
BMI kg·m^{-2}	0.890 (0.856–0.925)	<0.001	0.926 (0.882–0.973)	0.002
Smoker	0.887 (0.695–1.133)	0.337		
Past history of pulmonary TB	1.269 (0.991–1.624)	0.059	0.987 (0.746–1.306)	0.928
Presence of comorbidity[¶]	0.911 (0.714–1.162)	0.452		
Presence of systemic symptom[+]	1.560 (1.191–2.045)	0.001	1.490 (1.095–2.028)	0.011
Positive sputum AFB smear	2.298 (1.795–2.941)	<0.001	1.811 (1.350–2.428)	<0.001
Causative organism		0.001		0.364
Mycobacterium avium	1		1	
Mycobacterium intracellulare	1.512 (1.186–1.928)		0.869 (0.642–1.177)	
Radiological type: fibrocavitary	2.695 (2.099–3.460)	<0.001	2.102 (1.519–2.908)	<0.001
Involved lobes	1.384 (1.260–1.519)	<0.001	1.178 (1.050–1.322)	0.005
FVC % pred	0.991 (0.984–1.998)	0.011	1.001 (0.994–1.009)	0.712

HR: hazard ratio; BMI: body mass index; TB: tuberculosis; AFB: acid-fast bacilli; FVC: forced vital capacity. [#]: analysed after excluding 22 patients who were started on treatment for MAC-LD after at least 3 years of stable period from diagnosis and including 68 patients who were not treated with a follow-up duration of <3 years to reduce selection bias (n=466); [¶]: bronchiectasis was not included in the comorbidities because nonfibrocavitary type (mostly nodular bronchiectatic type) significantly overlapped with the presence of bronchiectasis; [+]: systemic symptoms included fever, fatigue or weight loss at the time of diagnosis. p<0.05 was considered significant.

Mortality in the stationary group

Death from any cause occurred in 16 (17.2%) patients over a median (range) follow-up duration of 6.4 (3.6–12.1) years in the untreated stationary group. Cumulative rates for all-cause mortality were 9.2% and 45% at 5 and 10 years from diagnosis, respectively. Causes of death included chronic interstitial pneumonia progression (18.8%), nonpulmonary malignancy (18.8%), pneumonia (12.5%), lung cancer

TABLE 3 Predictors of spontaneous sputum conversion in the untreated stationary group of 93 patients

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age years	0.969 (0.945–0.994)	0.015	0.973 (0.948–0.999)	0.043
Male	1.087 (0.612–1.929)	0.776	0.885 (0.484–1.621)	0.693
BMI kg·m^{-2}	1.108 (1.018–1.205)	0.017	1.101 (1.007–1.205)	0.035
Nonsmoker	0.961 (0.542–1.704)	0.892		
Presence of comorbidity[#]	1.309 (0.730–2.345)	0.366		
Positive sputum AFB smear	0.536 (0.259–1.110)	0.093	0.377 (0.156–0.912)	0.030
Causative organism		0.817		
Mycobacterium avium	1			
Mycobacterium intracellulare	0.932 (0.514–1.691)			
Radiological type: nodular bronchiectatic	1.246 (0.634–2.450)	0.524		
Involved lobes	1.012 (0.770–1.329)	0.934		
FVC % pred <80%	1.165 (0.655–2.072)	0.604		
Transient anti-TB medication (≥1 month)[¶]	2.091 (0.974–4.490)	0.059	3.769 (1.505–9.435)	0.005

HR: hazard ratio; BMI: body mass index; AFB: acid-fast bacilli; FVC: forced vital capacity; TB: tuberculosis. [#]: bronchiectasis was not included in the comorbidities because nodular bronchiectatic type significantly overlapped with the presence of bronchiectasis; [¶]: a few patients were transiently administered anti-TB medication before isolation of nontuberculous mycobacteria due to radiological findings indistinguishable from those of pulmonary TB or positive sputum AFB smear at the onset of disease; this was regarded as a potential confounder and input into multivariate analysis to determine predictors of spontaneous sputum conversion. p<0.05 was considered significant.

(12.5%), cardiovascular problems (12.5%) and unknown causes (25%). Death from MAC-LD itself did not occur in any patient during the overall follow-up period.

Prognostic factors for survival in the untreated stationary group

When Cox proportional hazard regression analyses were conducted to determine prognostic factors for survival in the untreated stationary group, older age, FC type and abnormal FVC at initial diagnosis were significantly associated with mortality (age: HR 1.094, 95% CI 1.024–1.167; p=0.007; FC type: HR 3.700, 95% CI 1.225–11.174; p=0.02; FVC % pred <80%: HR 3.325, 95% CI 1.029–10.743; p=0.045) (table 4). Additional analyses revealed that chronic interstitial pneumonia and use of immunosuppressants were independent prognostic factors of poor survival among the comorbid conditions in the untreated stationary group (chronic interstitial pneumonia: HR 35.369, 95% CI 7.571–165.229; p<0.001; use of immunosuppressants: HR 6.430, 95% CI 1.191–34.725; p=0.031).

Discussion

We investigated 488 patients with MAC-LD to evaluate the natural course of MAC-LD and found that patients with stable disease without clinical deterioration were more likely to have a higher BMI and less systemic symptoms at initial diagnosis than those with progressive disease. However, positive sputum AFB smear, FC type and more extensive disease on radiology were associated with the progressive course of MAC-LD. About half of the untreated patients with stable MAC-LD course underwent spontaneous sputum conversion, and younger age, higher BMI, negative sputum AFB smear and transient anti-TB medication at diagnosis were predictors of spontaneous sputum conversion. Meanwhile, older age, FC type and abnormal pulmonary function at diagnosis were associated with poor survival in those patients.

To date, there have been several studies that evaluated factors associated with deterioration of MAC-LD. LEE et al. [18] stated that 48% of their 265 patients demonstrated progressive disease on serial CT over a mean observation period of 32 months, and the presence of cavities and/or consolidation at initial CT were independent predictors of clinical deterioration of MAC-LD. Although their study showed a correlation between the presence of cavities and sputum smear positivity, sputum smear positivity was not associated with disease progression [18]. However, according to the study by KOH et al. [14], factors associated with treatment initiation in MAC-LD included sputum AFB smear positivity, FC type and age, which is consistent with the findings of our present study. Older patients are less likely to receive treatment than younger patients, which probably reflects poor tolerability or adherence to the current treatment regimen for MAC-LD in older patients. While *M. intracellulare* infection was not related to deterioration of MAC-LD after adjusting for confounders in our study, it was an independent risk factor for unfavourable treatment response in their study [14]. Prior studies have also suggested that *M. intracellulare* is more virulent with more frequent association with the FC type than *M. avium* [12, 19]. Further studies are needed to assess the difference in virulence *in vivo* according to different MAC species.

TABLE 4 Prognostic factors for all-cause mortality in the untreated stationary group of 93 patients

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age years	1.097 (1.031–1.167)	0.003	1.094 (1.024–1.167)	0.007
Male	2.135 (0.737–6.181)	0.162		
BMI kg·m^{-2}	0.927 (0.797–1.077)	0.321		
Smoker	1.946 (0.662–5.715)	0.226		
Presence of comorbidity [#]	1.347 (0.451–4.023)	0.594		
Positive sputum AFB smear	1.416 (0.483–4.151)	0.526		
Spontaneous sputum conversion	0.626 (0.217–1.806)	0.386		
Causative organism		0.130		
Mycobacterium avium	1			
Mycobacterium intracellulare	2.164 (0.797–5.876)			
Radiological type: fibrocavitary	5.356 (1.833–15.652)	0.002	3.700 (1.225–11.174)	0.020
Involved lobes n⩾4	1.297 (0.283–5.942)	0.738		
FVC % pred <80%	4.418 (1.409–13.849)	0.011	3.325 (1.029–10.743)	0.045

HR: hazard ratio; BMI: body mass index; AFB: acid-fast bacilli; FVC: forced vital capacity. [#]: bronchiectasis was not included in the comorbidities because nonfibrocavitary type (mostly nodular bronchiectatic type) significantly overlapped with the presence of bronchiectasis. p<0.05 was considered significant.

Our study demonstrated that higher BMI has a protective effect on the progression of MAC-LD, lowering the risk of disease progression by 7.4% per unit increase in BMI. This is in line with the findings of a previous study by Yamazaki et al. [7], in which older age and lower BMI were associated with aggravation of MAC-LD, along with higher serum inflammatory markers. Although they included patients after at least a 12-month observation period without treatment, total follow-up duration varied widely, ranging from 12 to 42 months, and the durations were not specified according to each group (deteriorated versus not deteriorated group), making it difficult to discern how long the stability of MAC-LD was maintained in the "not deteriorated group". However, our study included only patients who had not experienced disease progression for at least 3 years in the stationary group, with a median follow-up duration of 5.6 years, thus clarifying the differences in the clinical characteristics between the progressive and stationary groups.

Our present data showed that the presence of systemic symptoms such as fever or fatigue at the onset of disease was significantly associated with subsequent disease progression. To the best of our knowledge, this is the first study to demonstrate a close correlation between systemic symptoms and clinical course of MAC-LD. We speculate that the manifestation of these systemic symptoms reflects systemic inflammatory responses triggered by MAC infection, suggesting more active advanced disease. This is supported by the fact that an elevation in inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate was significantly associated with MAC-LD progression, further impacting the degree of sputum conversion and MAC-specific mortality [7, 9, 20]. It has been found that many pro- or anti-inflammatory cytokines are activated to varying degrees in severe, advanced MAC infection [21–23].

Our current analysis further indicated that the more extensive the disease at initial diagnosis, the more likely a subsequent clinical deterioration becomes, which is in accordance with the findings of a previous study by Kim et al. [24]. However, despite the long duration of follow-up, their study included a considerable proportion of treated patients in both deteriorated and nondeteriorated groups, thus making it difficult to exclude the possibility that treatment for MAC-LD influenced the course of the disease.

In our subgroup analyses, it was revealed that chronic interstitial pneumonia as a comorbidity was the sole predictive factor of the need for antibiotics for MAC-LD after at least a 3-year stable period. This implies that patients with chronic interstitial pneumonia tend to receive treatment for concurrent MAC-LD as chronic interstitial pneumonia gradually progresses. Patients with chronic interstitial pneumonia show structural lung damage such as honeycombing cysts or reticulation as the disease progresses to end-stage. One prior study stated that characteristic radiological findings associated with MAC-LD encompass consolidation with or without cavities in these changed structures, suggesting impaired local immunity in the damaged lung [25]. In addition, chronic interstitial pneumonia patients are often treated with immunosuppressants or have other immune-related conditions such as connective tissue diseases. This possibly increases the risk of reactivation of dormant mycobacterial infections, including TB and NTM, and predisposes patients to various opportunistic infections, which can often accelerate clinical deterioration, leading to increased mortality in these patients [26–28]. This may explain our current findings, emphasising the importance of treatment for concurrent MAC-LD as patients with chronic interstitial pneumonia exhibit a gradually deteriorating course.

Our present study also revealed that half of the untreated patients with stable MAC-LD experienced spontaneous sputum conversion, with positive predictors including younger age, higher BMI, negative sputum AFB smear and transient anti-TB medication at the time of diagnosis. As some of our patients exhibited radiological findings indistinguishable from those of pulmonary TB or sputum AFB smear positivity at the onset of disease, they transiently received anti-TB medication in advance of MAC-LD diagnosis. However, when we adjusted for those confounders in multivariate analysis, all of the above-mentioned factors were still significant. Previous studies showed that factors associated with culture response in treated MAC patients included presence of cavities and sputum smear positivity [10, 13, 29]. Similarly, these factors influenced time to smear or culture conversion in patients with pulmonary TB [30–32], suggesting a common association between initial mycobacterial load and treatment response. However, we demonstrated that sputum smear positivity also affects culture conversion in untreated patients with stable MAC-LD, while the presence of cavities was not related.

Although one previous study reported that being severely underweight (BMI <16 kg·m^{-2}) was associated with increased risk of delayed culture conversion in patients with multidrug-resistant TB [33], no other studies have proven the relationship between BMI and culture conversion in MAC-LD. In that regard, our study has clinical significance in demonstrating for the first time that host predisposing factors such as age or BMI are relatively more important than microbiological factors in stable MAC-LD patients with low mycobacterial burden.

Little is known regarding the prognosis of untreated stable MAC-LD. In our present study, all-cause mortality for the stationary group was 17.2%, with no MAC-specific deaths, which was lower than the

mortality rate seen for treated patients in previous studies [8, 9, 11]. According to previous studies, factors that determine prognosis in MAC-LD include mycobacterial virulence and host predisposing factors [34, 35]. With regard to mycobacterial virulence, specific serotypes or genotypes with specific variable numbers of tandem repeats and *Mycobacterium xenopi* infection are associated with a poor prognosis in MAC-LD [8, 36–38]. Among MAC species, conflicting data exist regarding the difference in virulence between *M. avium* and *M. intracellulare* [14, 39], although our study showed no difference in terms of disease progression or prognosis in stable MAC-LD. We speculate that host predisposing factors such as old age or reduced FVC were of more importance than mycobacterial virulence factors in predicting the prognosis of stable MAC-LD with presumable low virulence or mycobacterial burden. Previous studies including treated MAC-LD patients revealed that old age, male sex and comorbidities were common negative prognostic factors [8, 9]. In our study, chronic interstitial pneumonia was only associated with poor prognosis among comorbidities in stable MAC-LD, although comorbidities as a whole were not related. Also, abnormal FVC was predictive of poor prognosis. While one prior study suggested an association of lung function with health-related quality of life in patients with MAC-LD [40], our current study is the first to demonstrate an association between reduced lung function and mortality in MAC-LD. Although chronic interstitial pneumonia progression strongly correlates with reduced lung volume, abnormal FVC was still an independent prognostic factor for poor survival, even after excluding chronic interstitial pneumonia patients from the analysis. Decreased FVC or FC type may indicate reduced pulmonary function in itself and reflect structural lung damage, which predisposes frequent pulmonary infection afterwards with ultimately poor prognosis. However, further studies are warranted to verify the above hypothesis.

Several limitations of our retrospective study should be noted. First, as this study was conducted at a single tertiary referral centre, it is not representative of the national population. Second, the number of study patients may have been underestimated as patients who were not treated with a follow-up duration of <3 years were excluded from the analyses. Therefore, factors with clinical significance in reality may have proven insignificant in the analyses with reduced statistical power. However, we believe that there were no apparent differences in clinical features between included and excluded patients except for follow-up duration. In addition, regarding spontaneous sputum conversion and prognosis in the stationary group, factors meaningful in univariate analyses were still significant after adjusting for confounders in multivariate analyses despite the limited number of patients.

Nonetheless, considering that many previous studies included considerable proportions of patients with possible MAC-LD who only satisfied microbiological criteria, our present study is notable because we only included patients with definite MAC-LD based on the 2007 ATS/IDSA diagnostic criteria, who had been regularly followed up with clinical and microbiological assessments for a relatively long duration of time. Furthermore, our findings have clinical significance in demonstrating for the first time the natural history of MAC-LD in untreated patients with stable course.

In summary, patients with stable MAC-LD had higher BMI and less systemic symptoms at initial diagnosis, and were less likely to have sputum smear positivity, FC type or extensive disease, compared with patients with progressive MAC-LD. Spontaneous sputum conversion occurred in half of them, and older age, FC type and abnormal pulmonary function were predictive of poor survival in these patients.

References
1   Griffith DE, Aksamit T, Brown-Elliott BA, *et al.* An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; 175: 367–416.
2   Hoefsloot W, van Ingen J, Andrejak C, *et al.* The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. *Eur Respir J* 2013; 42: 1604–1613.
3   Winthrop KL, McNelley E, Kendall B, *et al.* Pulmonary nontuberculous mycobacterial disease prevalence and clinical features: an emerging public health disease. *Am J Respir Crit Care Med* 2010; 182: 977–982.
4   Russell CD, Claxton P, Doig C, *et al.* Non-tuberculous mycobacteria: a retrospective review of Scottish isolates from 2000 to 2010. *Thorax* 2014; 69: 593–595.
5   Field SK, Fisher D, Cowie RL. *Mycobacterium avium* complex pulmonary disease in patients without HIV infection. *Chest* 2004; 126: 566–581.
6   Reich JM, Johnson RE. *Mycobacterium avium* complex pulmonary disease presenting as an isolated lingular or middle lobe pattern. The Lady Windermere syndrome. *Chest* 1992; 101: 1605–1609.
7   Yamazaki Y, Kubo K, Takamizawa A, *et al.* Markers indicating deterioration of pulmonary *Mycobacterium avium-intracellulare* infection. *Am J Respir Crit Care Med* 1999; 160: 1851–1855.
8   Andréjak C, Thomsen VØ, Johansen IS, *et al.* Nontuberculous pulmonary mycobacteriosis in Denmark: incidence and prognostic factors. *Am J Respir Crit Care Med* 2010; 181: 514–521.

9   Hayashi M, Takayanagi N, Kanauchi T, *et al.* Prognostic factors of 634 HIV-negative patients with *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med* 2012; 185: 575–583.

10   Ito Y, Hirai T, Maekawa K, *et al.* Predictors of 5-year mortality in pulmonary *Mycobacterium avium-intracellulare* complex disease. *Int J Tuberc Lung Dis* 2012; 16: 408–414.

11   Jenkins PA, Campbell IA, Banks J, *et al.* Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in treating opportunist mycobacterial lung diseases and an assessment of *Mycobacterium vaccae* immunotherapy. *Thorax* 2008; 63: 627–634.

12   Griffith DE, Brown-Elliott BA, Langsjoen B, *et al.* Clinical and molecular analysis of macrolide resistance in *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med* 2006; 174: 928–934.

13   Lam PK, Griffith DE, Aksamit TR, *et al.* Factors related to response to intermittent treatment of *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med* 2006; 173: 1283–1289.

14   Koh WJ, Jeong BH, Jeon K, *et al.* Clinical significance of the differentiation between *Mycobacterium avium* and *Mycobacterium intracellulare* in *M. avium* complex lung disease. *Chest* 2012; 142: 1482–1488.

15   Griffith DE, Brown BA, Cegielski P, *et al.* Early results (at 6 months) with intermittent clarithromycin-including regimens for lung disease due to *Mycobacterium avium* complex. *Clin Infect Dis* 2000; 30: 288–292.

16   Koh WJ, Kwon OJ, Jeon K, *et al.* Clinical significance of nontuberculous mycobacteria isolated from respiratory specimens in Korea. *Chest* 2006; 129: 341–348.

17   Lee H, Park HJ, Cho SN, *et al.* Species identification of mycobacteria by PCR-restriction fragment length polymorphism of the *rpoB* gene. *J Clin Microbiol* 2000; 38: 2966–2971.

18   Lee G, Lee KS, Moon JW, *et al.* Nodular bronchiectatic *Mycobacterium avium* complex pulmonary disease. Natural course on serial computed tomographic scans. *Ann Am Thorac Soc* 2013; 10: 299–306.

19   Tomioka H, Saito H, Sato K, *et al.* Comparison of the virulence for mice of *Mycobacterium avium* and *Mycobacterium intracellulare* identified by DNA probe test. *Microbiol Immunol* 1993; 37: 259–264.

20   Kuroishi S, Nakamura Y, Hayakawa H, *et al.* Mycobacterium avium complex disease: prognostic implication of high-resolution computed tomography findings. *Eur Respir J* 2008; 32: 147–152.

21   González-Pérez M, Mariño-Ramírez L, Parra-López CA, *et al.* Virulence and immune response induced by *Mycobacterium avium* complex strains in a model of progressive pulmonary tuberculosis and subcutaneous infection in BALB/c mice. *Infect Immun* 2013; 81: 4001–4012.

22   Rocco JM, Irani VR. Mycobacterium avium and modulation of the host macrophage immune mechanisms. *Int J Tuberc Lung Dis* 2011; 15: 447–452.

23   Ghassemi M, Andersen BR, Roebuck KA, *et al.* Mycobacterium avium complex activates nuclear factor kappaB via induction of inflammatory cytokines. *Cell Immunol* 1999; 191: 117–123.

24   Kim SJ, Park J, Lee H, *et al.* Risk factors for deterioration of nodular bronchiectatic *Mycobacterium avium* complex lung disease. *Int J Tuberc Lung Dis* 2014; 18: 730–736.

25   Hwang HJ, Kim MY, Shim TS, *et al.* Nontuberculous mycobacterial pulmonary infection in patients with idiopathic interstitial pneumonias: comparison with patients without idiopathic interstitial pneumonias. *J Comput Assist Tomogr* 2014; 38: 972–978.

26   Selman M, King TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med* 2001; 134: 136–151.

27   Saydain G, Islam A, Afessa B, *et al.* Outcome of patients with idiopathic pulmonary fibrosis admitted to the intensive care unit. *Am J Respir Crit Care Med* 2002; 166: 839–842.

28   Churg A, Müller NL, Silva CI *et al.* Acute exacerbation (acute lung injury of unknown cause) in UIP and other forms of fibrotic interstitial pneumonias. *Am J Surg Pathol* 2007; 31: 277–284.

29   Ito Y, Hirai T, Fujita K, *et al.* The influence of environmental exposure on the response to antimicrobial treatment in pulmonary *Mycobacterial avium* complex disease. *BMC Infect Dis* 2014; 14: 522.

30   Wang JY, Lee LN, Yu CJ, *et al.* Factors influencing time to smear conversion in patients with smear-positive pulmonary tuberculosis. *Respirology* 2009; 14: 1012–1019.

31   Su WJ, Feng JY, Chiu YC, *et al.* Role of 2-month sputum smears in predicting culture conversion in pulmonary tuberculosis. *Eur Respir J* 2011; 37: 376–383.

32   Visser ME, Stead MC, Walzl G, *et al.* Baseline predictors of sputum culture conversion in pulmonary tuberculosis: importance of cavities, smoking, time to detection and W-Beijing genotype. *PLoS One* 2012; 7: e29588.

33   Putri FA, Burhan E, Nawas A, *et al.* Body mass index predictive of sputum culture conversion among MDR-TB patients in Indonesia. *Int J Tuberc Lung Dis* 2014; 18: 564–570.

34   Field SK, Cowie RL. Lung disease due to the more common nontuberculous mycobacteria. *Chest* 2006; 129: 1653–1672.

35   Glassroth J. Pulmonary disease due to nontuberculous mycobacteria. *Chest* 2008; 133: 243–251.

36   Maekura R, Okuda Y, Hirotani A, *et al.* Clinical and prognostic importance of serotyping *Mycobacterium avium-Mycobacterium intracellulare* complex isolates in human immunodeficiency virus-negative patients. *J Clin Microbiol* 2005; 43: 3150–3158.

37   Kikuchi T, Watanabe A, Gomi K, *et al.* Association between mycobacterial genotypes and disease progression in *Mycobacterium avium* pulmonary infection. *Thorax* 2009; 64: 901–907.

38   Andréjak C, Lescure FX, Douadi Y, *et al.* Non-tuberculous mycobacteria pulmonary infection: management and follow-up of 31 infected patients. *J Infect* 2007; 55: 34–40.

39   Boyle DP, Zembower TR, Reddy S, *et al.* Comparison of clinical features, virulence, and relapse among *Mycobacterium avium* complex species. *Am J Respir Crit Care Med* 2015; 191: 1310–1317.

40   Mehta M, Marras TK. Impaired health-related quality of life in pulmonary nontuberculous mycobacterial disease. *Respir Med* 2011; 105: 1718–1725.