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MAJOR ARTICLE

Microbiological Persistence in Patients With *Mycobacterium avium* Complex Lung Disease: The Predictors and the Impact on Radiographic Progression

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Background. Persistent growth of *Mycobacterium avium* complex (MAC) in the lungs indicates continuous infection in MAC lung disease (MAC-LD), but its clinical significance has not been investigated. We aimed to evaluate the predictors of persistent culture-positivity for MAC (MAC-PP) and its impact on radiographic deterioration in MAC-LD.

Methods. Patients with MAC-LD at multiple medical centers from 2011 to 2016 were enrolled retrospectively. Microbiological persistence of MAC-LD was defined as MAC-PP exceeding 1 year, in contrast with the negative-conversion group. The outcome was radiographic progression, namely, increased number of involved lung areas or cavitary formation.

Results. Among 126 patients with MAC-LD, 75 (60%) were in the MAC-PP group; these patients had a higher proportion of radiographic progression (54%) than patients in the negative-conversion group (odds ratio [OR], 3.318; 95% confidence interval, 1.146–9.612). Independent predictors of MAC-PP were low body mass index (BMI), radiographic nodular-bronchiectatic (NB) pattern, and increase in the highest grade of acid-fast bacilli smear (AFS). Patients with BMI <21 kg/m^2, NB pattern, and positive AFS had an OR of 17.7 for MAC-PP, and those with ≥2 of the factors had a 4.5-fold increased OR for MAC-PP relative to the comparison group. Other than MAC-PP, the highest AFS grade and no anti-MAC treatment were correlated with radiographic progression.

Conclusion. Microbiological persistence in patients with MAC-LD is not uncommon and leads to an increased risk of radiographic progression. The predictors of MAC-PP are low BMI, NB pattern, and high AFS grade; if these risk factors are present, anti-MAC treatment should be seriously considered.

Keywords. body mass index (BMI); nontuberculous *Mycobacterium* (NTM); *Mycobacterium avium* complex (MAC); predictor; microbiological persistence.

Although the incidence rate of tuberculosis has continuously declined worldwide, the incidence of nontuberculous mycobacterial lung disease (NTM-LD) has been increasing in the past 2 decades [1–4]. This finding cannot be explained simply by improved diagnostic methods or surveillance bias, so the clinical importance of NTM-LD is increasing [1]. *Mycobacterium avium* complex (MAC) is the major causative pathogen of NTM infection, and MAC lung disease (MAC-LD) is prevalent in both immunocompromised and immunocompetent patients [5, 6].

Because MAC-LD is indolent in nature, clinical observation might be considered, but about 22% and 53% of patients with MAC-LD reportedly present with radiographic deterioration at follow-up after 5 and 10 years, respectively [7]. Of the untreated patients who had MAC-LD with the nodular-bronchiectatic (NB) radiographic form, nearly half showed radiographic deterioration and needed treatment after a mean follow-up of 2.7 years [8]. In particular, some patients might have a rapid lethal course [9], and the 5-year mortality rate could be as high as 28% [10]. Therefore, the predictors of poor outcome need to be investigated.

Risk factors for the disease progression of MAC-LD include the presence of a fibrocavitary pattern in radiography and certain microbiological characteristics, such as *Mycobacterium intracellulare* subspecies and positive acid-fast bacilli smear (AFS) in sputum samples [11]. In addition to these initial characteristics, subsequent radiographic deterioration is an evident indicator of MAC-LD progression [12, 13]. In contrast, microbiological persistence, meaning that MAC persistently grows in the airways and lungs, might be an indicator for monitoring MAC biological activity. Such monitoring is also easy for clinicians to perform and more specific than chest imaging. However, the clinical impact of microbiological persistence of MAC-LD on radiographic progression and the predictors of that have rarely been studied, especially in patients without anti-MAC treatment.

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In the past, a microbiological change in a subsequent culture follow-up was a marker of clinical response to therapy and recurrence [12, 14]. A decline in the sputum culture semiquantitative score within the first few months after therapy is predictive of long-term sputum conversion status and early radiographic improvement [15]. Therefore, we aimed to study the persistent positivity of MAC (MAC-PP) in MAC-LD to understand its impact on radiographic progression and to prioritize the targeted population for anti-MAC therapy.

METHODS

Design, Setting, and Patients

The present study was conducted in 2 tertiary referral medical centers in northern Taiwan, National Taiwan University Hospital (NTUH) and Taipei Veterans General Hospital (TVGH). This multicenter study was approved by institutional review boards (IRB Nos. 201408068RINC, 2014-09-008BC, and 2016-07-006BC). From January 2011 to December 2015 at NTUH, and from September 2012 to March 2016 at TVGH, patients listed in the microbiological database as having ≥2 separated MAC-positive sputum cultures within a 12-month interval were selected, and their medical records and follow-up microbiological reports were reviewed. Patients were excluded from this study if they tested positive for human immunodeficiency virus (HIV), had no microbiological follow-up after the initial year, or were found not to have MAC pulmonary infection at screening.

Definition and Measurements

Mycobacterial cultures were performed, and the NTM species were identified using conventional biochemical methods in NTUH [16] and a molecular diagnostic biochip in TVGH [17]. Patients with ≥2 MAC-positive sputum samples were assessed for MAC-LD according to the diagnostic guidelines suggested by the American Thoracic Society (ATS) [12]. The patients whose sputum cultures tested positive for MAC but did not fulfill the ATS criteria of MAC-LD were classified as MAC-colonization and not enrolled. For enrolled patients, the index date was defined as the date of collection of the first MAC-positive sputum sample.

We reviewed the medical charts and recorded clinical characteristics, including age, sex, body mass index (BMI), smoking, comorbid conditions, radiographic findings, AFS grade of sputum sample (AFS grade) [18], *Mycobacterium* culture results, and treatment for MAC-LD. Chest radiographic and computed tomographic findings, if extant, were reviewed by 2 pulmonologists, and radiographic findings, including fibrocavitary and NB patterns, were recorded. In addition, radiographic scores were interpreted as described elsewhere [19]. The main outcome measured was radiographic progression, defined as an increased number of involved lung segments or cavitary formation at follow-up imaging after the initial year. MAC-PP was defined as the continuous presence of culture positivity for MAC in respiratory samples for >1 year after the index date. Negative conversion (MAC-NC) was defined as the presence of ≥2 negative sputum cultures collected after a positive culture for MAC and no sputum culture isolating MAC thereafter.

Statistical Analysis

For continuous variables, a Student *t* test was used to compare differences between groups if the variables were normally distributed, and a Mann-Whitney *U* test if they were nonnormally distributed. A χ^2 or Fisher exact test, where appropriate, was used to analyze intergroup differences of percentages. Logistic regression analysis was used to identify variables associated with MAC-PP or radiographic progression (see the details in the Supplementary material). Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and *P* values were calculated. In addition, receiver operating characteristic curve analysis and the Youden index were used to investigate the optimal cutoff point of continuous variables [20]. To avoid anti-MAC treatment as a confounder in assessing predictors of MAC-PP, a subgroup analysis was performed in patients without initial anti-MAC treatment [8]. All statistical analyses were performed using SPSS software, version 18.0 (SPSS).

RESULTS

Patient Enrollment

The flowchart of enrollment is provided in Figure 1. From 2011 to 2016, a total of 450 patients with ≥2 sputum samples culture-positive for MAC within a 12-month interval were identified from a microbiological database. After sequential exclusion of patients with incomplete data, HIV infection, no follow-up microbiological study, or MAC colonization, we enrolled a total of 126 patients with an MAC-LD diagnosis and with follow-up for analysis. The mean age of the enrolled patients was 67.4 years, and 46% of them were male. More than two-thirds of the study patients (72%) had NB patterns on initial images. Within the initial year, half of them presented ≥1 AFS-positive sputum. Overall, the 126 patients with MAC-LD had 507 culture-positive sputum samples in the first year after the index date. Only 15 (12%) received anti-MAC treatment for MAC-LD in the initial year. Twenty patients received transient antituberculosis medication (≥1 month) shortly before MAC-LD was diagnosed, and 1 patient was coinfected by *Mycobacterium tuberculosis* and MAC.

Variables Associated With Persistent Positivity of *Mycobacterium avium* Complex

Based on the sequential sputum culture results during follow-up, MAC-PP was defined in 75 patients (60%) (Table 1). Patients with MAC-PP had lower BMI (19.4 vs 21.1 kg/m^2; $P = .01$) and higher rates of NB radiographic patterns, AFS grades, and more positive cultures for MAC within the initial year than those with MAC-NC. Table 2 presents the results of univariate logistical

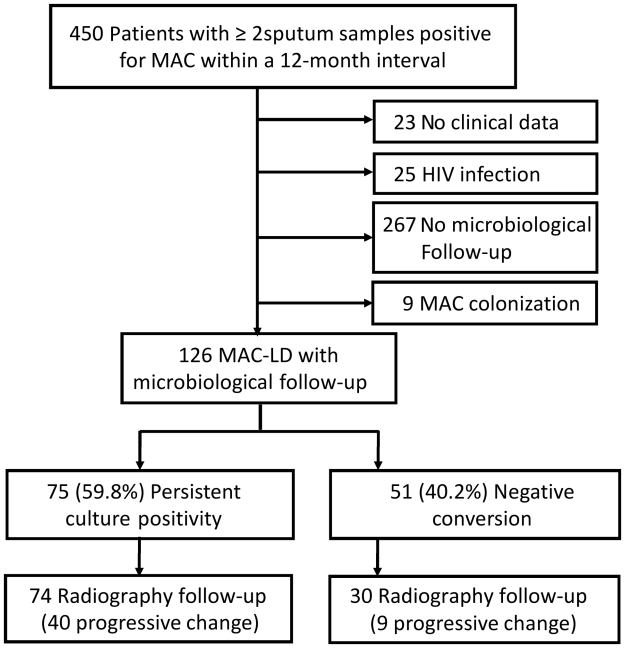

Figure 1. Flow chart of this study. Abbreviations: HIV, human immunodeficiency virus; LD, lung disease; MAC, *Mycobacterium avium* complex.

regression, and variables with a *P* values <.10 were entered into the multivariate analysis. In the multivariate model, the 3 independent predictors retained for MAC-PP were low BMI (1-kg/m^2 decrease; adjusted OR, 1.179; 95% CI, 1.031–1.348), presence of NB pattern (6.396; 2.259–18.113), and the highest AFS grade within the initial year (1-grade increase, 1.928; 1.224–3.035).

Synergistic Effect of 3 Predictors on the Risk of Persistent Positivity of *Mycobacterium avium* Complex

The 115 patients with MAC-LD who had BMI data were classified into 4 subgroups according to low BMI (<21 kg/m^2), presence of NB pattern at baseline, and AFS positivity in the initial year. The risk for MAC-PP increased significantly for those with 2 risk factors (OR adjusted by age and sex, 9.748; 95% CI, 1.029–92.370) and for those with all 3 factors (17.733; 1.585–198.398), compared with those with none of the factors (Figure 2). Receiver operating characteristic curve analysis showed that the optimal cutoff point for predicting MAC-PP was ≥2 risk factors (sensitivity, 81%; specificity, 53%; area under curve, 0.708 [95% CI, .610–.807]). Patients with ≥2 factors had a 4.5-fold increased risk for MAC-PP compared with those with <2 factors (OR adjusted for age and sex, 4.520; 95% CI, 1.901–10.748). Patients with all 3 factors had the highest specificity (89%) but low sensitivity (31%).

Correlation Between Persistent Positivity of *Mycobacterium avium* Complex and Radiographic Progression

Among the study participants, 104 patients had radiographic follow-up data; of them, 74 (99%) were in the MAC-PP group and 30 (59%) were in the MAC-NC group. Overall, 49 (47%) patients had radiographic progression. Among them, 38 (78%) had increased extent in existing area, 8 (16%) had new lung segment involvement, 2 (4%) had new cavity formation, and 1 (2%) had both new lung segment involvement and cavity formation. Specifically, radiographic progression was noted in 40 patients (54%) in the MAC-PP group and in only 9 (30%) in the MAC-NC group (*P* = .03). Patients with MAC-PP had a higher risk of radiographic progression than those with MAC-NC (crude OR, 2.745; 95% CI, 1.111–6.785; *P* = .03). This risk difference remained statistically significant after adjustments for age, sex, BMI, and initial NB pattern (adjusted OR, 3.318; 95% CI, 1.146–9.612; *P* = .03).

Particularly, in terms of early indicators other than MAC-PP, when anti-MAC treatment in the initial year, hemoptysis, age, sex, BMI, initial NB pattern, and the highest AFS grade were entered into a multivariate analysis using the forward selection method, the predictors of radiographic progression that were retained in the model were anti-MAC treatment (adjusted OR, 0.126; 95% CI, .025–.064; *P* = .01) and the highest AFS grade (1.474; 1.004–2.163; *P* = .047).

Association Between Initial Anti-*Mycobacterium avium* Complex (MAC) Treatment and Persistent Positivity of MAC

The characteristics of the patients with MAC-LD with or without anti-MAC treatment in the initial year are provided in Table 3. Those with anti-MAC treatment were younger (56.7 vs 68.8 years; *P* = .001) and had a higher proportion of AFS positivity in the initial year (80% vs 46%; *P* = .02) than those without anti-MAC treatment. Anti-MAC treatment was not associated with MAC-PP for the whole population. For the AFS-positive subgroup (n = 63), patients with anti-MAC treatment (n = 12) had a lower rate of MAC-PP development than those without (33% vs 76%; *P* = .007). The factors correlated with lower MAC-PP in the positive AFS subgroup were anti-MAC treatment (adjusted OR, 0.139; 95% CI, .031–.624; *P* = .01) and BMI (0.812; .665–.992; *P* = .04) in the multivariate analysis. In contrast, for the AFS-negative subgroup (n = 63), only 3 patients had anti-MAC treatment, which was not statistically associated with MAC-PP (*P* > .99).

Subgroup Analysis for Patients With *Mycobacterium avium* Complex (MAC) Lung Disease Without Anti-MAC Treatment

For patients with MAC-LD who did not receive anti-MAC treatment in the initial year (n = 111), low BMI (1-kg/m^2 decrease; adjusted OR, 1.226; 95% CI, 1.036–1.451; *P* = .02), presence of NB pattern (10.101; 2.701–37.808; *P* = .001), and increase in the highest AFS grade (1-grade increase; 3.375; 1.703–6.689; *P* < .001) were still independent predictors of MAC-PP. Fifteen (14%) of them received transient antituberculosis medication empirically, but this was not associated with MAC-PP (OR, 1.882; 95% CI, .558–6.340; *P* = .31). Moreover, in the untreated subgroup with radiographic follow-up (n = 91), patients in the MAC-PP group had an adjusted OR of 3.498 (95% CI,

Table 1. Clinical Characteristics of Patients With MAC Lung Disease According to Serial Follow-up of Sputum Culture

Characteristic	Patients, No. (%)[a] All	Persistent MAC Positivity (n = 75)	Negative Conversion (n = 51)	*P* Value
Age, mean (SD), y	67.4 (13.7)	65.7 (13.2)	69.8 (15.0)	.06
Male sex, No. (%)	58 (46)	31 (41)	27 (53)	.21
BMI, mean (SD), kg/m^2 (n = 115)	20.1 (3.5)	19.4 (3.3)	21.1 (3.6)	.01
BMI <21 kg/m^2	76 (66)	52 (74)	24 (53)	.03
Symptoms[b]				
Cough	88 (70)	57 (76)	31 (61)	.08
Shortness of breath	45 (36)	26 (35)	19 (37)	.85
Hemoptysis	25 (20)	16 (21)	9 (18)	.66
Constitutional	23 (18)	12 (16)	11 (22)	.48
Comorbid condition				
Cancer	38 (30)	25 (33)	13 (25)	.43
Diabetes mellitus	12 (10)	6 (8)	6 (12)	.55
COPD	21 (17)	12 (16)	9 (18)	>.99
History of tuberculosis disease	23 (18)	15 (20)	8 (16)	.64
Radiographic pattern				
NB	91 (72)	60 (80)	31 (61)	.02
Fibrocavitary	16 (13)	11 (15)	5 (10)	.59
Radiographic score, median (IQR)	3 (2–5)	3 (2–5)	3 (2–5)	.81
Highest AFS grade in initial year, median (IQR)	1 (0–2)	1 (0–2)	0 (0–1)	.03
Initial-year AFS positivity	63 (50)	43 (57)	20 (39)	.07
Low-grade (≤2) positive	45 (36)	29 (39)	16 (31)	.45
High-grade (≥3) positive	18 (14)	14 (19)	4 (8)	.12
Positive cultures in initial year, median (IQR), No.	2 (3–5)	3 (3–7)	2 (2–4)	.001
Anti-MAC treatment within initial year	15 (12)	7 (9)	8 (16)	.40
Transient antituberculosis medication (≥1 mo)	20 (16)	13 (17)	7 (14)	.63

Abbreviations: AFS, acid-fast bacilli smear (of sputum sample); BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MAC, *Mycobacterium avium* complex; NB, nodular-bronchiectatic; SD, standard deviation.

[a]Data represent No. (%) of patients unless otherwise specified.

[b]Two patients had all 4 symptoms, 8 had 3 symptoms, 33 had 2 symptoms, and the remaining 83 had only 1 symptom.

1.036–11.811; $P = .04$) for radiographic progression compared with those in the MAC-NC group, after adjustments for age, sex, BMI, and initial NB pattern.

DISCUSSION

In the present study, we found that nearly two-thirds of patients with MAC-LD had MAC-PP for >1 year. Patients with MAC-PP had a significantly higher risk for radiographic progression than did those with MAC-NC. Moreover, we identified the independent predictors for MAC-PP to be low BMI, radiographic NB pattern, and high AFS grade. Furthermore, BMI <21 kg/m^2, NB pattern at baseline, and AFS positivity in the initial year among patients with MAC-LD led to high specificity (89%) for microbiological persistence, and ≥2 of the factors denoted an adequate sensitivity of 81%. Within the first year, the highest AFS grade and no anti-MAC treatment in patients with MAC-LD were correlated with radiographic progression.

Because of the indolent course of MAC-LD, as well as the potential side effects and long course of the multidrug regimen for MAC-LD, a diagnosis of MAC-LD according to the ATS guidelines does not indicate the initialization of anti-MAC therapy in every individual, although nearly half of patients with MAC-LD eventually require treatment [7, 12, 21]. In the present study, only 12% of these patients were prescribed anti-MAC medication within the first year by a clinician, but nearly half exhibited disease progression at follow-up chest radiography. The apparent difference between the rate of early treatment and subsequent radiographic progression may indicate that disease awareness and timely management of MAC-LD need to be improved. Hence, it is imperative to identify further predictors of disease progression.

The persistence of MAC in respiratory specimens might imply a vicious cycle of active airway infection, inflammation, and then airway destruction leading to impaired clearance [22]. In addition, MAC-PP in MAC-LD might influence respiratory physiology. A prospective study reported in 2016 demonstrated

Table 2. Univariate and Multivariate Logistical Regression Analysis for Potential Predictors of Sputum Culture Persistently Positive for MAC

	Univariate		Multivariate Analysis[a]	
Variable	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age (y)	0.977 (.951–1.004)	.10	Entered but not retained	…
Male sex	0.626 (.306–1.282)	.20	…	…
BMI (1-kg/m^2 decrease)	1.159 (1.029–1.305)	.02	1.179 (1.031–1.348)	.02
Cancer	1.462 (.662–3.226)	.35	…	…
Cough	2.043 (0.944–4.424)	.07	Entered but not retained	
Shortness of breath	0.894 (.426–1.874)	.77	…	…
Hemoptysis	1.266 (.511–3.136)	.61	…	…
Constitutional symptoms	0.693 (.279–1.719)	.43	…	…
Diabetes mellitus	0.652 (.198–2.149)	.48	…	…
COPD	0.889 (.344–2.295)	.81	…	…
History of tuberculosis disease	0.344 (.523–3.451)	.54	…	…
Transient antituberculosis medication (≥1 mo)	1.318 (.486–3.571)	.59	…	…
NB pattern	2.581 (1.162–5.729)	.02	6.396 (2.259–18.113)	<.001
Fibrocavitary pattern	1.581 (.514–4.861)	.42	…	…
Radiographic score	0.986 (.880–1.105)	.81	…	…
Highest AFS grade in the initial year	1.429 (1.028–1.995)	.03	1.928 (1.224–3.035)	.005
Initial-year AFS positivity	2.083 (1.009–4.300)	.047	Entered but not retained	…
Number of positive cultures within the initial year	1.279 (1.068–1.531)	.007	Entered but not retained	
MAC treatment within the initial year	0.553 (.187–1.636)	.28	…	…

Abbreviations: AFS, acid-fast bacilli smear (of sputum sample); BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MAC, *Mycobacterium avium* complex; NB, nodular-bronchiectatic; OR, odds ratio.

[a]Variables with a *P* value <.10 in the univariate analysis were entered into the multivariate logistical analysis with forward stepwise regression. The factors which were entered into the analysis but not retained in the final model of multivariate analysis were labeled as "Enter but not retained."

that patients with NTM-LD in whom sputum culture conversion was not achieved during 1 year of treatment had greater declines in pulmonary function than those who were treated successfully [23]. Importantly, our study found that patients with MAC-PP had a 3-fold OR for radiographic progression compared with those without MAC-PP. To this end, our finding indicates that MAC-PP might precede disease progression and might be a practicable indicator for seriously considering the initiation of anti-MAC therapy after 1 year of follow-up.

To predict clinical deterioration that required early anti-MAC treatment, the majority of previous studies have focused on investigating the risk factors for radiographic progression in patients with MAC-LD, but little is known about the impact of related factors on their microbiological outcomes. Although the persistence of MAC in sputum could be used for guidance in anti-MAC treatment, the culture turn-around time and observation of the clinical course are time consuming. Thus, predicting microbiology outcomes might facilitate clinical decision making at the early stage. In our study, for both the whole population and the untreated subgroup, the significant predictors of MAC-PP included low BMI, NB radiographic pattern at baseline, and high AFS grade in the initial year. All 3 factors were correlated with

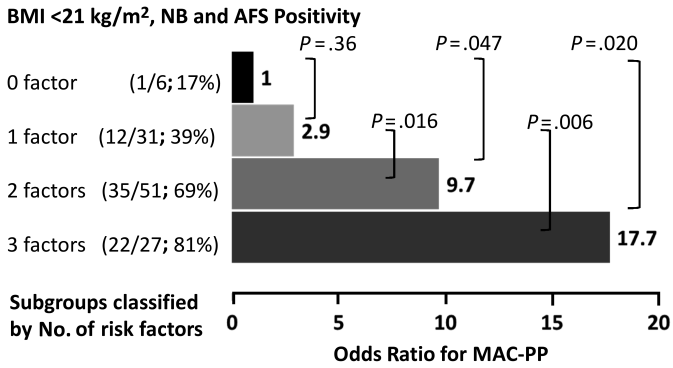

Figure 2. The risk of persistent culture-positivity for *Mycobacterium avium* complex (MAC-PP) stratified by body mass index (BMI), nodular-bronchiectatic (NB) pattern at baseline, and acid-fast bacilli smear (AFS) positivity in the initial year. All patients with BMI data (n = 115) were classified into 4 subgroups by the number of risk factors (baseline BMI <21 kg/m^2, NB pattern, and AFS positivity during the initial year). The rates of MAC-PP events among patients at risk (No. of events/No. of patients) are presented in the comparative subgroups. The odds ratios for MAC-PP are shown after adjustment for age and sex.

Table 3. Characteristics and Outcomes in Patients with MAC Lung Disease With or Without Anti-MAC Treatment During the Initial Year

Variable	Patients, No. (%)[a]		*P* value
	With Treatment (n = 15)	Without Treatment (n = 111)	
Age, mean (SD), y	56.7 (10.2)	68.8 (13.5)	.001
Male sex	7 (47)	51 (46)	>.99
BMI, mean (SD), kg/m^2 (n = 115)	21.1 (4.2)	19.9 (3.4)	.21
BMI <21 kg/m^2	9 (60)	67 (67)	.77
Symptoms			
Cough	8 (53)	80 (72)	.23
Shortness of breath	6 (40)	39 (35)	.78
Hemoptysis	4 (27)	21 (19)	.50
Constitutional	3 (20)	20 (18)	>.99
Comorbid condition			
Cancer	3 (20)	35 (32)	.40
Diabetes mellitus	0 (0)	12 (11)	.36
COPD	1 (7)	20 (18)	.46
History of tuberculosis disease	2 (13)	21 (19)	.74
Transient antituberculosis medication (≥1 mo)	5 (33)	15 (14)	.06
Radiographic pattern			
NB	10 (67)	81 (73)	.76
Fibrocavitary	2 (13)	14 (13)	>.99
Radiographic score, median (IQR)	4 (3–6)	3 (2–5)	.49
Highest AFS grade in initial year, median (IQR)	2 (1–2)	0 (0–1)	.053
Initial-year AFS positivity	12 (80)	51 (46)	.02
No. of positive cultures in initial year, median (IQR)	4 (3–7)	3 (2–5)	.20

Continuous data are expressed as mean ± standard deviation or median (interquartile and categorical data as number.

Abbreviations: AFS, acid-fast bacilli smear of sputum sample; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MAC, *Mycobacterium avium* complex; NB, nodular-bronchiectatic; SD, standard deviation.

[a]Data represent No. (%) of patients unless otherwise specified.

microbiological persistence specifically and might suggest anti-MAC treatment in the absence of contraindications.

In addition, the present study demonstrated a synergistic effect of BMI <21 kg/m^2, NB pattern, and AFS positivity on the risk of MAC-PP. This was especially true in patients with ≥2 of the significant factors; such patients might require regular follow-up to monitor for clinical progression. Among the factors, low BMI and positive AFS were also predictive of MAC-PP in untreated patients, as reported in a recent study [24]. In particular, the highest AFS grade was a predictor for not only microbiological but also radiographic outcomes in the present study. Thus, it may be worthwhile to consider early-stage therapies for patients with these risk factors of MAC-PP to improve their clinical outcomes.

The present study demonstrated that a leaner body morphotype is associated with susceptibility to persistent NTM-LD. Actually, slenderness has been reported as a risk factor for NTM-LD and correlates with low leptin, a deficiency that affects immune modulation [25, 26]. The imbalance of leptin and adiponectin in patients with low BMI might favor persistent MAC infection of the lungs [24, 26–28]. Particularly, as reported in a MAC-LD study with 4.7-year follow-up, low BMI itself was significantly associated with poor long-term outcomes, including MAC-specific mortality [29]. In addition, previous research has shown that the radiographic NB pattern is typically found in patients with NTM-LD [30–32]. Notably, for patients with MAC-LD with an NB pattern, initial extensive involvement of lung segments was independently associated with subsequent radiographic deterioration [33].

Bronchiectasis is an important underlying LD and contributes to subsequent culture positivity at follow-up [34, 35]. The present study showed that the NB pattern also favored microbiological persistence in MAC-LD. Moreover, the third independent factor for persistent MAC-LD was positivity of sputum AFS, which represented the MAC bacilli load and could directly predict the microbiological outcome. This finding may be supported by a study demonstrating that a positive sputum smear is a predictor of the progression to the initiation of anti-MAC therapy in patients with MAC-LD [11].

In this study, anti-MAC treatment for MAC-LD in the initial year was not associated with a decreased risk of MAC-PP for 1 year. This negative finding may be explained by the fact that the number of patients receiving treatment was too small, especially in AFS-negative patients (n = 3). In addition, the treatment regimens were not standardized, nor was the drug susceptibility of MAC checked in the study hospitals in this retrospective study design; therefore, the treatment response might be biased [5, 15, 36, 37]. However, because anti-MAC treatment led to a reduced

risk of MAC-PP in the AFS-positive subgroup, such treatment might reduce the mycobacterial loads in the airway and preferentially lead to MAC-NC, though future large scale studies will be needed to validate this assumption.

The present study has several limitations that must be acknowledged. First, its sample size was relatively small. Second, in contrast to the patients with MAC-PP, a high proportion of those with MAC-NC (41%) had no radiographic follow-up, which may be a potential confounder of the association between MAC-PP and radiographic progression. In addition, the anti-MAC treatment effect and long-term outcomes, including pulmonary function and mortality of patients with MAC-LD, could not be fully recovered because the study design was observational and retrospective. Further prospective studies are warranted to comprehensively investigate the correlation between MAC-PP and outcomes. Third, this study was conducted in Taiwan, a tuberculosis-prevalent area in Asia. Notably, one-seventh of patients with MAC-LD received transient antituberculosis medication before tuberculosis was ruled out, although this was not associated with subsequent MAC-PP or MAC-NC in the present study. Whether the findings in the present study can be generalized to areas of low tuberculosis incidence or to non-Asian populations is uncertain. Finally, we could not assess the risk difference among MAC subspecies, because no subspecies identification data were available.

In conclusion, 60% of the patients with MAC-LD in this study had microbiological persistence at follow-up. Compared with patients with MAC-NC, those with MAC-PP had an adjusted OR of 3.318 for radiographic progression. Independent predictors for MAC-PP were low BMI, NB radiographic pattern, and high AFS grade. If patients with MAC-LD have BMI <21 kg/m^2, NB pattern at baseline, and AFS positivity in the initial year, the risk of MAC-PP is significantly increased, and treatment for MAC-LD should be considered. Further studies are warranted to investigate the association between MAC-PP and the risk of poor long-term outcomes in patients with MAC-LD.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. S.W. P, C. C. S, and Y. J. C. collected data. S. W. P, C C. S., J. Y. F., J. Y. W., and Y. J. C. analyzed data and wrote the manuscript. C. J. Y. and W. J. S. were responsible for coordinating the study.

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