의학석사 학위논문

공동형 *Mycobacterium avium* complex 폐질환에서 치료결과에 따른 생존분석

Differences in mortality risk based on therapeutic outcomes in cavitary-type *Mycobacterium avium* complex pulmonary disease

울산대학교 대학원

의 학 과

이 주 광

공동형 *Mycobacterium avium* complex 폐질환에서 치료결과에 따른 생존분석

지 도 교 수 조 경 욱

이 논문을 의학석사 학위 논문으로 제출함

2023 년 6 월

울산대학교 대학원

의 학 과

이 주 광

이주광의 의학석사 학위 논문을 인준함

심사위원　　심 태 선　　인

심사위원　　조 경 욱　　인

심사위원　　김 호 철　　인

울 산 대 학 교　대 학 원

2023 년 6 월

국문요약

연구배경: 현재까지 공동형 *Mycobacterium avium* complex 폐질환에서 치료 후 객담 음전 여부와 사망률 사이의 관계가 명확히 보고되어 있지 않다. 이에 본 연구에서는 공동형 *Mycobacterium avium* complex 폐질환에서 치료 결과에 따라서 사망률의 유의한 차이가 있는지 알아보고자 하였다.

연구 방법: 2002 년부터 2020 년 사이에 마크로라이드를 포함한 약제로 6 개월 이상 치료받은 351 명의 공동형 *Mycobacterium avium* complex 폐질환 환자들을 후향적으로 분석하였다. 351 명 중 105 명은 섬유공동형이었고, 나머지 246 명은 공동-결절기관지확장형이었다. 치료 종료 시기에 객담 음전 여부에 따라 총 사망률을 비교하였고, 조기발견오류(immortal time bias) 를 배제하기 위해 랜드마크 분석(landmark analysis)를 함께 시행하였다.

연구결과: 치료 기간의 중앙값은 14.7 개월이었고, (사분위수 13.4-16.8 개월) 전체 환자 중 69.8% (245/351) 에서 치료 종료 시 객담 음전이 되었으며 30.2% (106/351)에서는 객담 음전이 되지 않았다. 객담 음전이 된 군에서 추적기간의 중앙값은 4.4 년 (사분위수 2.3-8.3 년), 객담 음전이 되지 않은 군에서는 3.1 년 (사분위수 2.1-4.8 년) 이었다. 총 사망률은 객담 음전이 된 군에서 5.3%, 객담 음전이 되지 않은 군에서 35.8%로 유의한 차이가 있었고, (P<0.001), 5 년간의 누적 사망률 역시 객담 음전이 된 군에서 낮았다 (20.0% vs 38.4%). 다변량 콕스 분석 결과 객담 음전을 달성하지 못한 경우 조정 위험률(adjusted hazard ratio) 5.73, (95% 신뢰구간 2.86-11.50)로 사망률 증가와 유의한 관련이 있었다. 또한 2 년을 기준으로 랜드마크 분석을 시행했을 때에도 객담 음전을 달성하지 못한 환자들에서 유의하게 사망률이 높았다 (P<0.001).

연구결론: 공동형 *Mycobacterium avium* complex 폐질환 환자에서 객담 음전이 되지 않는 경우 객담 음전을 달성한 사람들에 비해서 사망률이 유의하게 높다.

Contents

Abstract 3

List of tables and figures 4

Introduction 5

Methods 6

Study participants 6

Radiological and microbiological evaluation 8

Treatment regimen and outcome analysis 10

Statistical analysis 10

Results 11

Participants 11

Mortality rate according to the achievement of culture conversion 14

Multivariate analysis of all-cause mortality 15

Subgroup analysis according to the radiologic type 17

Landmark analysis 22

Subgroup analysis: severe BACES score 24

Discussion 24

Conclusion 27

References 28

Abstract

Background: The relationship between the outcome of treatment and mortality in individuals with cavitary type *Mycobacterium avium* complex pulmonary disease is not well understood. This study aimed to evaluate the influence of achieving culture conversion on mortality in patients with cavitary *Mycobacterium avium* complex pulmonary disease.

Methods: A retrospective analysis was conducted on 351 patients who received a macrolide-containing regimen for at least six months between 2002 and 2020 at a tertiary referral center in South Korea. Of these patients, 105 had fibrocavitary disease and 246 had cavitary nodular bronchiectatic disease. The primary outcome analyzed was all-cause mortality during the follow-up period, categorized based on whether culture conversion was achieved at the completion of treatment.

Results: The median treatment duration was 14.7 months [interquartile range (IQR) 13.4–16.8], and 69.8% (245/351) of patients achieved culture conversion, while 30.2% (106/351) did not. The follow-up period had a median duration of 4.4 years (IQR 2.3–8.3) for patients with culture conversion and 3.1 years (IQR 2.1–4.8) for patients without culture conversion. Among those with and without culture conversion, the all-cause mortality rates were 5.3% and 35.8% (P<0.001), respectively, with lower 5-year cumulative mortality rate for patients who achieved culture conversion (20.0% vs. 38.4%). Cox analysis indicated a significant association between non-achievement of culture conversion and higher mortality (adjusted hazard ratio 5.73, 95% confidence interval 2.86–11.50). Furthermore, the impact of treatment outcome on mortality was particularly evident in the 2-year landmark analysis, where patients without culture conversion had a significantly higher mortality rate compared to those with culture conversion.

Conclusion: In individuals with cavitary *Mycobacterium avium* complex pulmonary disease, the mortality rate was considerably higher in patients who did not achieve culture conversion compared to those who did.

List of tables and figures

Table 1. Detailed classification of non-standard regimens comprising ≥6 months of macrolide treatment in 185 patients with cavitary Mycobacterium avium complex pulmonary disease 12

Table 2. Clinical characteristics, treatment modality, and mortality rate of 351 patients with cavitary Mycobacterium avium complex pulmonary disease based on culture conversion status at treatment completion 13

Table 3. Extended Cox model of of mortality-associated risk factors in 351 patients with cavitary Mycobacterium avium complex pulmonary disease 16

Table 4. Clinical characteristics, treatment modality, and the mortality rate 105 patients of fibrocavitary type Mycobacterium avium complex pulmonary disease according to culture conversion at the end of treatment at treatment completion 18

Table 5. Clinical characteristics, treatment modality, and the mortality rate of 246 patients of cavitary nodular bronchiectatic type Mycobacterium avium complex pulmonary disease according to culture conversion at the end of treatment 19

Table 6. Effect of nonachievement of culture conversion at treatment completion on mortality according to the radiologic classification 20

Table 7. Landmark analysis at 2 years of mortality-associated risk factors in 289 patients with cavitary Mycobacterium avium complex pulmonary disease 23

Figure 1. Flowchart of the screening and selection of the study population 7

Figure 2. Radiologic findings of fibrocavitary type Mycobacterium avium complex pulmonary disease in a representative patient, a 69-year-old woman with a history of pulmonary tuberculosis. 8

Figure 3. Radiologic findings of a representative patient, a 55-year-old woman with cavitary nodular bronchiectatic type Mycobacterium avium complex pulmonary disease. 9

Figure 4. Simon–Makuch estimate of the cumulative mortality rate of Mycobacterium avium complex pulmonary disease according to the achievement of culture conversion at treatment completion in 351 patients with cavitary Mycobacterium avium complex pulmonary disease 15

Figure 5-A. Kaplan–Meier plot of the cumulative mortality rate of Mycobacterium avium complex pulmonary disease according to the achievement of culture conversion at treatment completion in patients with fibrocavitary type 21

Figure 5-B. Kaplan–Meier plot of the cumulative mortality rate of Mycobacterium avium complex pulmonary disease according to the achievement of culture conversion at treatment completion in patients with cavitary nodular bronchiectatic type. 21

Figure 6. Kaplan–Meier curves according to achievement of culture conversion from the 2-year landmark analysis of 289 patients who survived for 2 years after treatment initiation 22

Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous organisms that are prevalent in the environment, such as in water or soil (1). Certain NTM species have specific habitats, such as *M. simiae* in particular aquifers*, M. fortuitum* in pedicure baths, and *M. immunogenum* in metalworking fluids (2).

In general, NTM rarely cause disease in humans unless there is an underlying impairment in the host's defence mechanisms, such as in cases of HIV or bronchiectasis, or if there is direct entry into the body through inoculation. Human-to-human transmission of NTM is rare and mostly limited to cases of cystic fibrosis (2-4).

Considering that exposure to NTM is widespread but the occurrence of disease is uncommon, it can be inferred that the natural defence mechanisms of healthy individuals are generally effective in preventing NTM from causing significant illness. However, when otherwise healthy individuals develop substantial NTM disease, it is highly likely that they possess specific susceptibility factors that enable the establishment, multiplication, and pathogenicity of NTM (5).

Among more than 200 distinct NTM species, the *Mycobacterium avium* complex (MAC) is recognized as the predominant causative agent of NTM associated pulmonary disease (NTM-PD) in East Asia and North America (6). MAC encompasses a range of mycobacterial species, including *M. intracellulare, M. avium* (with four subspecies), and several other less commonly found species such as *M. chimaera.*

NTM-PD can develop in individuals with pre-existing lung conditions like bronchiectasis, chronic obstructive pulmonary disease, cystic fibrosis, as well as in individuals with no apparent lung abnormalities (3, 4). Symptoms of NTM-PD are diverse and not specific, as patients may experience a combination of respiratory and systemic symptoms, which can be associated with underlying lung conditions (4).

In worldwide, including in United States and South Korea, the occurrence and prevalence of NTM pulmonary infections, often associated with bronchiectasis, are rising among elderly individuals (7, 8). Among patients with cystic fibrosis, who frequently have bronchiectasis, the prevalence of clinical NTM infection ranges from 3% to 15%, with higher rates observed in older patients (2, 9).

One of the most serious aspects of NTM-PD is the increased mortality rate of the afflicted patients. Based on an analysis of a population-based cohort in South Korea between 2002 and 2017, Lee et al. reported that the 6-, 10-, and 14-year survival probabilities of the patients with NTM disease was significantly lower than that of the general population or those with tuberculosis (10). A study in Japan found that NTM mortality increased consistently between 1997 and 2016 (11).

One of the factors that can predict the NTM-PD mortality rate is the radiologic classification: among the three major radiologic types of NTM-PD [fibrocavitary (FC), cavitary nodular bronchiectatic (C-NB), and non-cavitary nodular bronchiectatic (NC-NB)] (12-14), Jhun et al. clearly identified significantly higher mortality rates in patients with FC and C-NB types than in those with the NC-NB type (15). Furthermore, the presence of cavitary lesions is an important factor that has been consistently associated with mortality (16-18). Therefore, due to poor prognosis and rapid progression, prompt treatment is recommended in clinical C-NB or FC type patients (4, 19).

On the other hand, for NC-NB cases, the current recommendations involve observation without treatment, unless clinical symptoms or radiological findings emerge. This approach is justified by research indicating that NC-NB cases generally exhibit slower progression compared to FC and C-NB types, and often remain stable for extended durations (4, 20, 21). Additionally, it has been observed that patients with MAC pulmonary disease who do not receive antimicrobial treatment may experience spontaneous conversion. A previous study reported that around 50% of patients with MAC-PD achieved sputum conversion without intervention (22).

For patients with tuberculosis, particularly those infected with a multidrug-resistant strain, a more effective treatment regimen could decrease the mortality rate (23-25). This lower mortality risk is believed to be achieved by a higher culture conversion rate (25, 26). However, in patients with NTM-PD, mortality differences according to the treatment outcome remain unelucidated (10, 27). In particular, although patients with cavitary lesion have a higher mortality rate (15-18), it is unclear whether achievement of culture conversion at treatment completion could affect the mortality rate of cavitary NTM-PD.

Therefore, we aimed to elucidate this issue by investigating the impact of treatment outcome on the mortality rate in patients with cavitary MAC-PD, which is the NTM-PD caused by the most common causative organism in South Korea

Methods

Study participants

The participants in this study were selected retrospectively from Asan Medical Center, a referral hospital in Seoul, Republic of Korea, which has a capacity of 2,700 beds. Between 2002 and 2020, a total of 464 patients diagnosed with cavitary MAC-PD (including FC and C-NB types) who had received a macrolide-containing treatment regimen at least once were identified. This included 144 patients with FC type disease and 320 patients with C-NB type disease. Initially, patients with macrolide-resistant

MAC isolates and those with a treatment duration of less than 6 months were excluded from the study. A minimum treatment duration of 6 months was considered necessary to accurately assess the impact of treatment outcomes on mortality rates. Additionally, the study aimed to evaluate mortality differences based on the final treatment outcome, irrespective of the specific treatment regimen used. Therefore, eligibility for the study was not limited to patients receiving a standard treatment regimen (i.e., macrolide, ethambutol, rifampin, and injectable aminoglycoside), but included participants treated with any regimen that included a macrolide. Consequently, patients who initiated non-standard regimens (e.g., standard regimen plus clofazimine) or did not adhere to a standard regimen (e.g., discontinuation of ethambutol/rifampin due to adverse events) were included. After excluding patients who underwent lung resection, the final study population consisted of patients who received a macrolide-containing regimen for at least 6 months (Figure 1). Data from these patients' medical records were retrospectively analyzed in December 2022.

The study protocol was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No. 2022-1424). Due to the retrospective nature of the study, the requirement for informed consent was waived by the IRB.

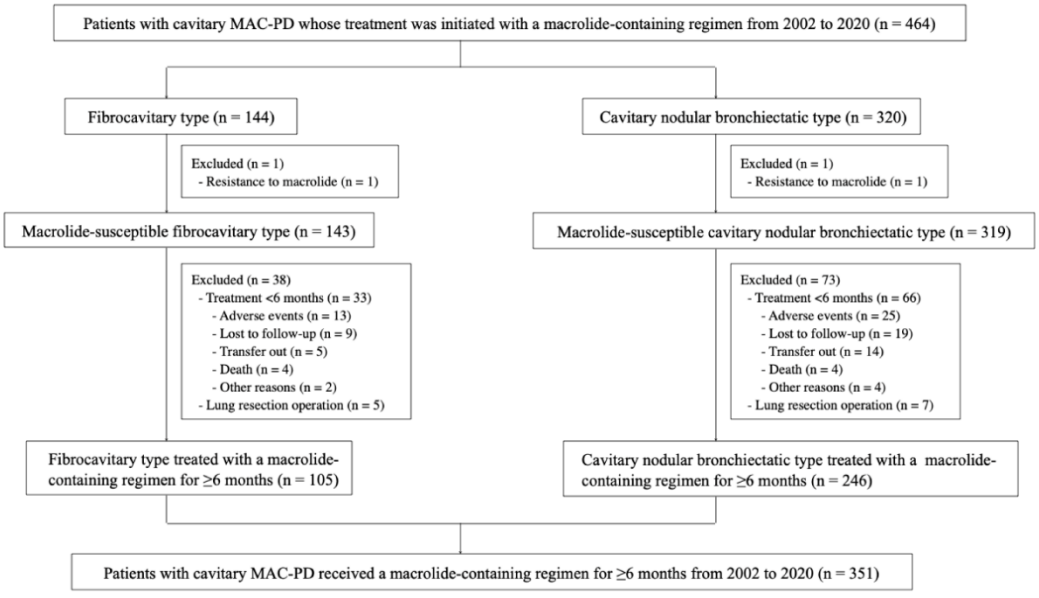


Figure 1. Flowchart of the screening and selection of the study population

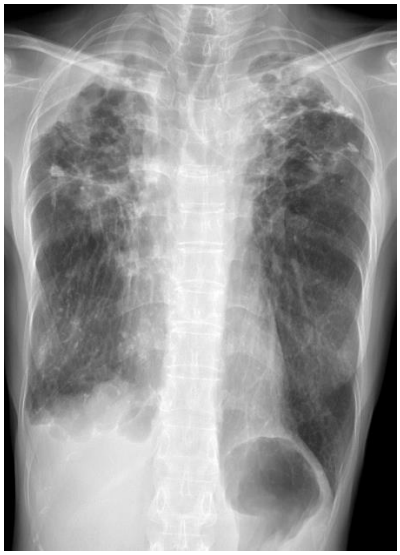
Abbreviations: MAC-PD, Mycobacterium avium complex pulmonary disease.

Radiological and microbiological evaluation

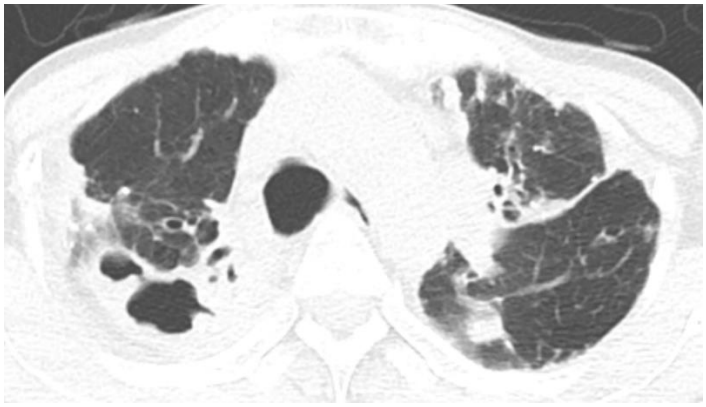
Two pulmonologists and one radiologist evaluated the chest computed tomography scans taken at the beginning of the treatment to assess the radiological findings. Based on these findings, the participants were categorized into the FC) and C-NB types, as previously described. (28, 29). The typical presentation of the FC and C-NB types is shown in the Figure 2 and 3.

Expectorated sputum specimen or samples obtained through bronchoscopy were cultured in both solid (Ogawa medium; Korean Institute of Tuberculosis, Republic of Korea) and liquid (BACTEC 960 Mycobacterial Growth Indicator Tube; Becton Dickinson, Sparks, MD, USA) media. AFB smears were made using Ziehl–Neelsen staining. Positive liquid cultures and colonies on solid medium were subjected to polymerase chain reaction assay using Seeplex tuberculosis detection (Seegen, Seoul, Republic of Korea) to differentiate the *M. tuberculosis* complex from NTM. The NTM species were identified using reverse-blot hybridization of the *rpoB* gene (GenoType *Mycobacterium* CM/AS; HAIN Life Science, Germany).

Figure 2. Radiologic findings of fibrocavitary type *Mycobacterium avium* complex pulmonary disease in a representative patient, a 69-year-old woman with a history of pulmonary tuberculosis.

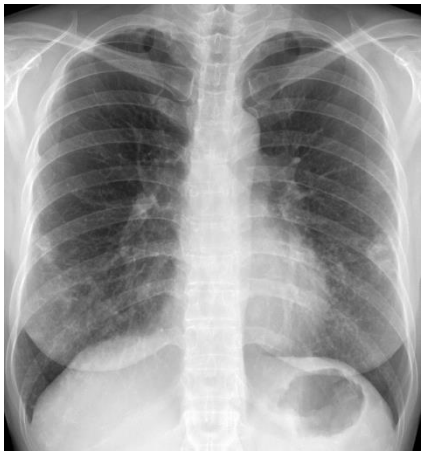


(A) Bilateral upper lobe fibrosis with volume loss, pleural thickening, and right upper lobe cavitary change is noted in the chest X-ray.

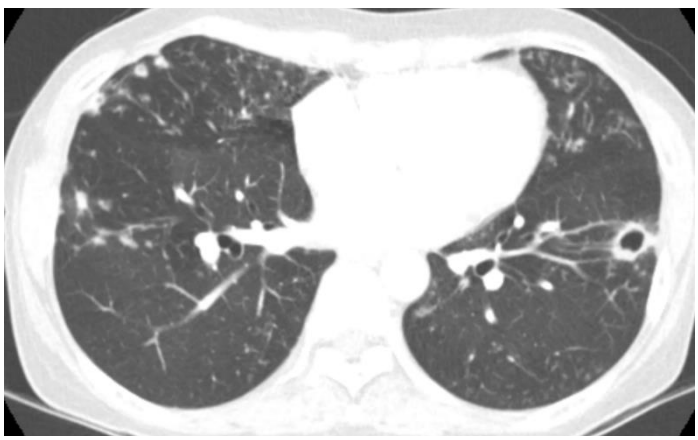


(B) Chest computed tomography findings. Multifocal bronchiectatic change and parenchymal distortion in the bilateral upper lobe as well as a large, thick-walled cavity in the right upper lobe.

Figure 3. Radiologic findings of a representative patient, a 55-year-old woman with cavitary nodular bronchiectatic type *Mycobacterium avium* complex pulmonary disease.



(A) A simple chest X-ray shows infiltration in the middle and lower lung fields and small cavitary lesions in bilateral lung fields.



(B) Chest computed tomography shows multiple small nodules with tree-in-bud apperance, and bronchiectasis located mainly in the lingular segment of the left and right middle lobes as well as a small, thin-walled cavitary lesion in the left lower lobe.

Treatment regimen and outcome analysis

The attending physician determined the treatment modality and regimen for each participant without following a predefined protocol. However, the majority of participants were treated as follows: for patients who achieved culture conversion, the treatment was continued for at least 1 year after the conversion. If patients continued to have positive cultures even after receiving treatment for ≥6 months, the treatment was typically discontinued after more than 1 year without any regimen augmentation.

Patients were asked to provide expectorated sputum samples at intervals of at least 1 month until the sputum culture conversion results were confirmed as negative. After achieving negative sputum cultures, additional samples were collected at intervals of 2- or 3- months until the completion of treatment. If a patient was unable to produce sputum even after induction, it was considered as a conversion to a negative status (30).

The treatment outcome was evaluated based on the achievement of sputum culture conversion at the completion of treatment. Culture conversion was defined according to a previous consensus statement, requiring at least three consecutive negative sputum cultures collected at least 4 weeks apart during the treatment of MAC-PD (31). The analysis included both all-cause mortality and MAC-specific mortality during the follow-up period, categorized based on the culture conversion status at treatment completion. The duration of follow-up was calculated from the initiation of treatment, and since all patients received a minimum of 6 months of treatment, they all had a follow-up duration of at least 6 months.

Statistical analysis

To compare continuous variables, we employed either the Student's *t*-test or the Mann-Whitney *U*-test, while categorical variables were compared using either the chi-square test or Fisher's exact test. The Simon-Makuch method was utilized to analyze the cumulative mortality rates of MAC-PD patients, treating the achievement of culture conversion as a time-dependent covariate. Cox regression analyses were conducted to estimate the hazard ratios (HR) of mortality, considering culture conversion as a time-dependent covariate and other variables as time-independent covariates. The multivariate analysis included variables selected through backward elimination, and age was included in the analysis. The HR with a 95% confidence interval (CI) was calculated. We examined the interaction effect between culture conversion and the radiologic type to compare the impact of culture conversion based on the

radiologic type. Additionally, landmark analysis was performed to address immortal time bias related to the time required for culture conversion. In the landmark method, a fixed time after treatment initiation was selected as the landmark, and only patients with MAC-PD who were alive at that specific timepoint were included in the analysis. These patients were divided into two groups based on whether they achieved culture conversion at the designated timepoint. Hence, the landmark method disregards treatment responses occurring after the landmark timepoint and any cases with mortality prior to that timepoint. The Kaplan-Meier method with a log-rank test was utilized to estimate the conditional mortality probability for the landmark analysis. All statistical tests were two-sided, and a significance level of $p<0.05$ was considered statistically significant. The statistical analyses were conducted using SPSS version 24.0 (IBM Corp., Chicago, Ill., USA) and R (version 3.6.1; R Foundation for Statistical Computing).

Results

Participants

After the eligibility screening process, a total of 351 patients with cavitary MAC-PD were included in the study, consisting of 105 patients with the FC type and 246 patients with the C-NB type (Figure 1). The median duration of treatment for these patients was 14.7 [interquartile range (IQR), 13.4–16.8] months. Among the study cohort, 47.3% (166/351) received standard treatment regimens, while 52.7% received non-standard treatments with various regimens. The detailed classification of non-standard regimens can be found in Table 1. At the completion of treatment, 69.8% (245/351) of patients achieved culture conversion, while 30.2% (106/351) did not. Table 2 presents the clinical characteristics, radiologic findings, treatment regimens, baseline pulmonary function, and mortality rate according to the achievement of culture conversion. Significant differences were observed between the groups in baseline characteristics such as age, sex, history of tuberculosis/NTM treatment, AFB smear positivity, and the size/number of cavities. Baseline pulmonary function parameters showed a trend of being higher in the culture conversion group, although the difference did not reach statistical significance.

TABLE 1 Detailed classification of non-standard regimens comprising ≥6 months of macrolide treatment in 185 patients with cavitary *Mycobacterium avium* complex pulmonary disease

Classification of non-standard regimens	N
Treatment regimen comprising three-drug oral antibiotics* only, without injectable aminoglycosides	n = 90
Adverse event-related discontinuation of ethambutol during the treatment period	n = 32
Initial regimen did not include ethambutol or rifampin	n = 25
Initial treatment regimen comprising standard therapy† plus clofazimine or moxifloxacin	n = 20
Adverse event-related discontinuation of rifampin during the treatment period	n = 13
Adverse event-related discontinuation of ethambutol and rifampin during the treatment period	n = 5

*Macrolide, ethambutol, and rifampin.

†Treatment regimen comprising macrolide, ethambutol, rifampin, and injectable aminoglycoside.

TABLE 2 Clinical characteristics, treatment modality, and mortality rate of 351 patients with cavitary *Mycobacterium avium* complex pulmonary disease based on culture conversion status at treatment completion

Characteristics	Total (n = 351)	Culture conversion at treatment completion (n= 245)	No culture conversion at treatment completion (n = 106)	*P*-value
Age (years)	62.9 ± 10.5	62.0 ± 10.6	65.0 ± 10.0	0.012
Age ≥65 years	167 (47.6%)	104 (42.4%)	63 (59.4%)	0.003
Male sex	147 (41.9%)	81 (33.1%)	66 (62.3%)	<0.001
Body mass index (kg/m^2)	20.1 ± 2.7	20.2 ± 2.7	19.9 ± 2.7	0.257
Body mass index <18.5 kg/m^2	100 (28.5%)	62 (25.3%)	38 (35.8%)	0.045
Current or past smoker	112 (31.9%)	57 (23.3%)	55 (51.9%)	<0.001
History of tuberculosis	176 (50.1%)	107 (43.7%)	69 (65.1%)	<0.001
History of NTM treatment	41 (11.7%)	20 (8.2%)	21 (19.8%)	0.002
Charlson Comorbidity Index	3.0 (1.0–4.0)	3.0 (1.0–4.0)	4.0 (3.0–5.0)	0.007
Etiology				0.049
Mycobaterium avium	157 (44.7%)	118 (48.2%)	39 (36.8%)	
Mycobaterium intracellulare	194 (55.3%)	127 (51.8%)	67 (63.2%)	
Positive AFB smear at treatment initiation	195 (55.6%)	122 (49.8%)	73 (68.9%)	0.001
Radiologic type				<0.001
Cavitary nodular bronchiectatic type	246 (70.1%)	191 (78.0%)	55 (51.9%)	
Fibrocavitary type	105 (29.9%)	54 (22.0%)	51 (48.1%)	
Number of involved lobes*	4.0 (3.0–4.0)	4.0 (3.0–5.0)	3.0 (3.0–4.0)	0.902
Number of involved lobes ≥3*	311 (88.6%)	216 (88.2%)	95 (89.6%)	0.693
Total number of cavities	1.0 (1.0-2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	0.025
Number of cavities ≥2	150 (42.7%)	98 (40.0%)	52 (49.1%)	0.115
Maximum size of cavity (cm)	2.3 (1.6–3.9)	2.2 (1.5–3.1)	3.6 (2.1–5.6)	<0.001
Maximum size of cavity >2cm	174 (49.6%)	107 (43.7%)	67 (63.2%)	0.001
Baseline pulmonary function test				
FVC (%, predicted, n = 86)	73.0 ± 16.6	75.6 ± 16.1	68.5 ± 16.8	0.054
FEV1 (%, predicted n = 86)	69.1 ± 21.3	71.6 ± 19.1	64.8 ± 24.3	0.155
DLco (%, predicted n = 39)	65.7 ± 19.2	70.4 ± 20.7	59.6 ± 15.6	0.083
Total treatment duration (months)	14.7 (13.4–16.8)	14.4 (13.4–15.7)	16.5 (12.4–17.7)	0.390
Treatment regimen				0.058
Standard regimen	166 (47.3%)	124 (50.6%)	42 (39.6%)	
Non-standard regimen	185 (52.7%)	121 (49.4%)	64 (60.4%)	
BACES score (n = 63)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	4.0 (2.0–5.0)	0.033
Follow-up duration after treatment initiation (years)	4.0 (2.3–7.6)	4.4 (2.3–8.3)	3.1 (2.1–4.8)	0.001
Death	51 (14.5%)	13 (5.3%)	38 (35.8%)	<0.001
MAC specific mortality	13 (3.7%)	3 (1.2%)	10 (9.4%)	0.001

Data are presented as the mean ± standard deviation, median (interquartile range), or frequency (proportion).

Abbreviation: NTM, nontuberculous mycobacteria; AFB, acid-fast bacillus; FVC, forced vital capacity; FEV1,

forced expiratory volume in one second; DLco, diffusing capacity for carbon monoxide; BACES, body mass index, age, cavity, erythrocyte sedimentation rate, and sex

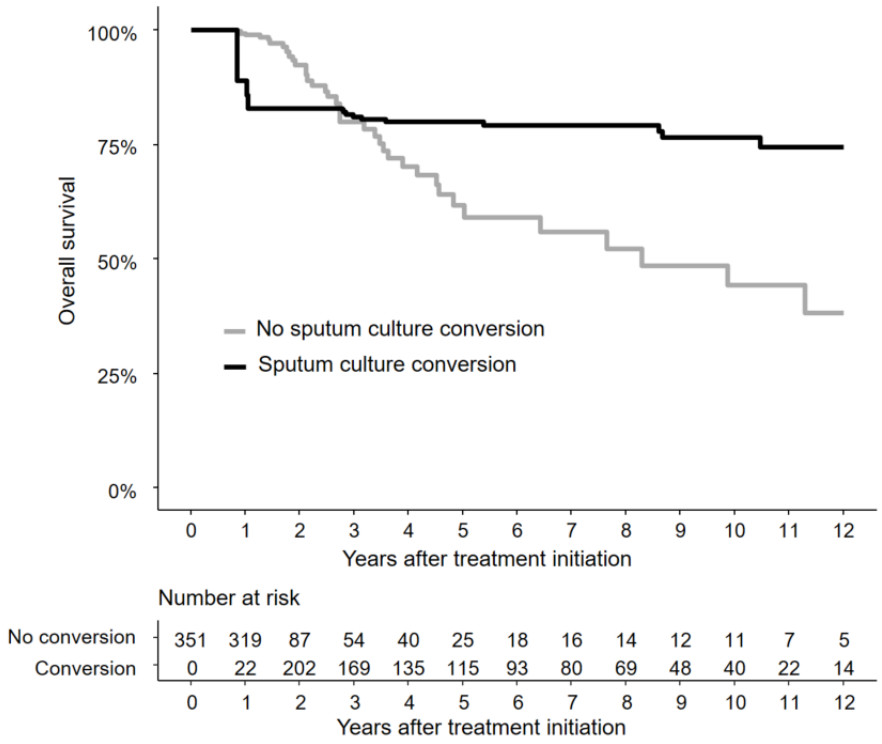
*The lingular segment was considered a separate lobe, which resulted in the inclusion of a total of six lung lobes for analysis

Mortality rate according to the achievement of culture conversion

Out of the 245 patients who achieved culture conversion at the end of their treatment, 13 individuals (5.3%) experienced all-cause mortality over a median follow-up period of 4.4 years (IQR 2.3–8.3). Conversely, patients who did not achieve culture conversion had a significantly higher rate of all-cause mortality, with 38 individuals (35.8%) experiencing mortality during a median follow-up duration of 3.1 years (IQR 2.1–4.8) ($P < 0.001$, Table 2). The overall cumulative mortality rates at 5 and 10 years for the 245 patients who achieved culture conversion were 20.0% and 23.5%, respectively. In comparison, patients who failed to achieve culture conversion had higher mortality rates during the follow-up period, with overall cumulative mortality rates at 5 and 10 years of 38.4% and 55.7%, respectively. Figure 4 displays the estimated mortality curve using the Simon-Makuch method for the entire group of 351 patients based on the achievement of culture conversion.

The MAC-specific mortality rate was 1.2% (3/245) in patients who achieved culture conversion and 9.4% (10/106) in patients who did not achieve culture conversion, showing a significant difference between the two groups ($P = 0.001$, Table 2). The overall 5- and 10-year cumulative MAC-specific mortality rates were 1.2% and 2.9%, respectively, in patients who achieved culture conversion, while in patients who did not achieve culture conversion, the rates were 13.3% and 20.5%, respectively.

Figure 4. Simon–Makuch estimate of the cumulative mortality rate of *Mycobacterium avium* complex pulmonary disease according to the achievement of culture conversion at treatment completion in 351 patients with cavitary *Mycobacterium avium* complex pulmonary disease



Multivariate analysis of all-cause mortality

Risk factors associated with all-cause mortality of 351 patients with cavitary MAC-PD were ascertained and the results are present in Table 3. In univariate analysis, nonachievement of culture conversion at treatment completion was one of the factors associated with an increased mortality risk in cavitary MAC-PD.

Cox regression analysis with time-dependent covariates was performed to identify prognostic factors for mortality. Along with male sex, Charlson Comorbidity Index, and size of cavity, the nonachievement of culture conversion at treatment completion was significantly associated with higher mortality (adjusted HR 5.73, 95% CI 2.86–11.50; $P < 0.001$; Table 3).

TABLE 3. Extended Cox model of of mortality-associated risk factors in 351 patients with cavitary *Mycobacterium avium* complex pulmonary disease

Characteristics	Total (n = 351)	Died (n = 51)	Mortality rate†	Univariate analysis		Multivariate analysis‡	
				HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Age	351	51	27.8	1.07 (1.04–1.10)	<0.001	1.01(0.98–1.05)	0.569
Age ≥65 years	167	37	39.7	4.32 (2.32–8.05)	<0.001		
Male sex	147	40	53.0	7.74 (3.92–15.30)	<0.001	2.78 (1.29–5.97)	0.009
Body mass index				0.88 (0.79–0.98)	0.019	0.89 (0.80–1.00)	0.052
Body mass index <18.5 kg/m^2	100	19	44.9	1.78 (1.01–3.14)	0.048		
Current or past smoker	112	33	51.6	5.20 (2.91–9.29)	<0.001		
History of tuberculosis	176	35	37.6	2.25 (1.24–4.06)	0.007		
History of NTM treatment	41	6	20.7	1.22 (0.52–2.87)	0.651		
Charlson Comorbidity Index				1.42 (1.28–1.57)	<0.001		
0–1	98	3	10.4	1.00	<0.001	1.00	0.001
2–3	141	17	22.1	5.72 (1.67–19.60)	0.006	4.74 (1.23–18.20)	0.024
≥4	112	31	57.5	15.78 (4.78–52.12)	<0.001	8.28 (2.06–33.24)	0.003
Mycobacterium intracellulare	194	34	41.5	2.34 (1.29–4.23)	0.005		
Positive acid-fast bacilli smear at treatment initiation	195	38	38.4	3.08 (1.64–5.80)	<0.001		
Number of involved lobes ≥3	311	40	19.5	0.46 (0.24–0.90)	0.022		
Number of cavities ≥2	150	30	40.4	2.53 (1.44–4.45)	0.001		
Maximum size of cavity > 2cm	174	43	47.0	6.60 (3.10–14.05)	<0.001	3.32 (1.48–7.48)	0.004
Non-standard regimen	185	30	32.2	1.60 (0.91–2.80)	0.101		
No culture conversion at treatment completion*	106	38	62.0	7.38 (3.85–14.16)	<0.001	5.73 (2.86–11.50)	<0.001

Data are presented as the frequency

Abbreviations: HR, hazard ratio; CI, confidence interval; NTM, nontuberculous mycobacteria.

*Time-dependent covariate analysis

†Kaplan–Meier estimates at 12 years

Subgroup analysis according to the radiologic type

Table 4 presents the clinical characteristics, treatment regimen, and mortality of patients with FC type according to the treatment outcome. Among 105 patients with FC type, the achievement of culture conversion was noted 54 (51.4%) patients. Of these 54 patients, 14.8% (8/54) died during the median duration of 3.7 years (IQR 1.6–5.9) after treatment initiation. In 51 patients who did not achieve culture conversion at the end of treatment, the rate of all-cause mortality reached 52.9% (27/51) during the follow-up duration of median 2.9 years (IQR 2.0–4.3), which had statistical significance compared with mortality rate of those with culture conversion (*P* value <0.001, Table 4). The overall 5- and 10-year cumulative mortality rates for 105 patients with FC type was 35.3%, and 58.2%, respectively. The cumulative mortality rate of those with FC type who achieved culture conversion and did not in 5-, 10-year was 11.6%, and 28.4%, and 59.6%, and 82.3%, respectively.

In addition, the clinical characteristics of 246 patients with C-NB type are shown in Table 5 Overall, 77.6% (191/246) achieved culture conversion at the end of treatment. The overall mortality rate were lower compared with those with FC type: the number of patients with death was 16 (6.5%) during the median 4.1 years (2.3–7.4) of follow-up period after treatment initiation. However, statistical significant difference of mortality was still noted between the patients who achieved culture conversion and did not. That is, the all-cause mortality rate was 2.6% (5/192) and 20.0% (11/55), respectively, over the follow-up period of median 4.1 (2.3–7.6) and 4.2 (2.1–12.8) years (*P* value < 0.001, Table 5). Overall, the 5- and 10-year cumulative mortality rates for the patients with C-NB type was 7.4% and 10.4% The cumulative mortality rate of those with culture conversion and without in 5- and 10-year was 2.9%, 4.9%, and 23.5%, 31.2%, respectively.

The cumulative mortality rate of FC and C-NB type according to treatment outcome at the end of treatment based on the Kaplan–Meier method are shown in Figure 5-A and 5-B, respectively. Subgroup analysis of patients with fibrocavitary and C-NB types revealed that the distinct association of sputum culture-conversion and the mortality rate did not differ in each radiologic type; adjusted HR: 5.08 (95% CI 2.18–11.82) and 6.48 (95% CI 2.13–19.65), respectively (*P* for interaction = 0.724, Table 6).

TABLE 4 Clinical characteristics, treatment modality, and the mortality rate 105 patients of fibrocavitary type *Mycobacterium avium* complex pulmonary disease according to culture conversion at the end of treatment at treatment completion

Characteristics	Total (n = 105)	Culture conversion at treatment completion (n= 54)	No culture conversion at treatment completion (n = 51)	*P*-value
Age (years)	65.0 ± 9.7	65.3 ± 10.2	64.7 ± 9.1	0.764
Age ≥65 years	65 (61.9%)	35 (64.8%)	30 (58.8%)	0.527
Male sex	84 (80.0%)	41 (75.9%)	43 (84.3%)	0.283
Body mass index (kg/m^2)	19.4 ± 3.0	19.7 ± 3.2	19.1 ± 2.8	0.302
Body mass index <18.5 kg/m^2	44 (41.9%)	18 (33.3%)	26 (51.0%)	0.067
Current or past smoker	68 (64.8%)	33 (61.1%)	35 (68.6%)	0.420
History of tuberculosis	79 (75.2%)	38 (70.4%)	41 (80.4%)	0.234
History of NTM treatment	8 (7.6%)	2 (3.7%)	6 (11.8%)	0.153
Charlson Comorbidity Index	4.0 (3.0–5.0)	4.0 (3.0–6.0)	4.0 (4.0–5.0)	0.581
Etiology				0.042
Mycobaterium avium	28 (26.7%)	19 (35.2%)	9 (17.6%)	
Mycobaterium intracellulare	77 (73.3%)	35 (64.8%)	42 (82.4%)	
Positive AFB smear at treatment initiation	82 (78.1%)	42 (77.8%)	40 (78.4%)	0.935
Number of involved lobes*	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (3.0–4.0)	0.013
Number of involved lobes ≥3*	78 (74.3%)	35 (64.8%)	43 (84.3%)	0.022
Total number of cavities	1.0 (1.0–3.0)	1.0 (1.0–2.0)	2.0 (1.0–3.0)	0.088
Number of cavities ≥2	52 (49.5%)	23 (42.6%)	29 (56.9%)	0.114
Maximum size of cavity (cm)	4.9 (3.9–6.1)	4.4 (3.4–5.2)	5.4 (4.4–6.5)	0.001
Maximum size of cavity >2cm	97 (92.4%)	48 (88.9%)	49 (96.1%)	0.271
Baseline pulmonary function test				
FVC (%, predicted, n = 35)	67.7 ± 18.3	69.7 ± 19.2	65.9 ± 17.7	0.545
FEV1 (%, predicted n = 35)	63.5 ± 24.7	67.2 ± 20.9	60.1 ± 28.0	0.406
DLco (%, predicted n = 13)	50.7 ± 12.2	46.7 ± 12.7	55.3 ± 10.9	0.220
Total treatment duration (months)	15.1 (11.8–17.7)	15.1 (12.0–17.7)	15.0 (11.7–17.7)	0.677
Treatment regimen				0.735
Standard regimen	45 (42.9%)	24 (44.4%)	21 (41.2%)	
Non-standard regimen	60 (57.1%)	30 (55.6%)	30 (58.8%)	
BACES score (n = 18)	4.0 (4.0–5.0)	4.0 (4.0–5.0)	4.0 (4.0–5.0)	0.961
Follow-up duration after treatment initiation (years)	3.1 (1.9–5.3)	3.7 (1.6–5.9)	2.9 (2.0–4.3)	0.272
Death	35 (33.3%)	8 (14.8%)	27 (52.9%)	<0.001
MAC specific mortality	7 (6.7%)	2 (3.7%)	5 (9.8%)	0.261

Data are presented as the mean ± standard deviation, median (interquartile range), or frequency (proportion). Abbreviation: NTM, nontuberculous mycobacteria; AFB, acid-fast bacillus; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLco, diffusing capacity for carbon monoxide; BACES, body mass index, age, cavity, erythrocyte sedimentation rate, and sex

*The lingular segment was considered a separate lobe, which resulted in the inclusion of a total of six lung lobes for analysis

TABLE 5 Clinical characteristics, treatment modality, and the mortality rate of 246 patients of cavitary nodular bronchiectatic type *Mycobacterium avium* complex pulmonary disease according to culture conversion at the end of treatment

Characteristics	Total (n = 246)	Culture conversion at treatment completion (n= 191)	No culture conversion at treatment completion (n = 55)	*P*-value
Age (years)	62.0 ± 10.8	61.0 ± 10.6	65.3 ± 10.8	0.008
Age ≥65 years	102 (41.5%)	69 (36.1%)	33 (60.0%)	0.002
Male sex	63 (25.6%)	40 (20.9%)	23 (41.8%)	0.002
Body mass index (kg/m^2)	20.4 ± 2.5	20.4 ± 2.5	20.6 ± 2.5	0.589
Body mass index <18.5 kg/m^2	56 (22.8%)	44 (23.0%)	12 (21.8%)	0.849
Current or past smoker	44 (17.9%)	24 (12.6%)	20 (36.4%)	<0.001
History of tuberculosis	97 (39.4%)	69 (36.1%)	28 (50.9%)	0.048
History of NTM treatment	33 (13.4%)	18 (9.4%)	15 (27.3%)	0.001
Charlson Comorbidity Index	3.0 (1.0–4.0)	2.0 (1.0–4.0)	5.0 (3.0–5.0)	0.019
Etiology				0.723
Mycobaterium avium	129 (52.4%)	99 (51.8%)	30 (54.5%)	
Mycobaterium intracellulare	117 (47.6%)	92 (48.2%)	25 (45.5%)	
Positive AFB smear at treatment initiation	113 (45.9%)	80 (41.9%)	33 (60.0%)	0.018
Number of involved lobes*	4.0 (3.0–5.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	0.615
Number of involved lobes ≥3*	233 (94.7%)	181 (94.8%)	52 (94.5%)	1.000
Total number of cavities	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–3.0)	0.416
Number of cavities ≥2	98 (39.8%)	75 (39.3%)	23 (41.8%)	0.733
Maximum size of cavity (cm)	1.6 (1.1–2.4)	1.6 (1.1–2.3)	1.6 (1.2–2.7)	0.769
Maximum size of cavity >2cm	77 (31.3%)	59 (30.9%)	18 (32.7%)	0.796
Baseline pulmonary function test				
FVC (%, predicted, n = 51)	76.5 ± 14.5	78.3 ± 13.9	71.8 ± 15.6	0.154
FEV1 (%, predicted n = 51)	72.9 ± 18.0	73.6 ± 18.2	70.9 ± 17.9	0.629
DLco (%, predicted n = 26)	73.2 ± 17.7	81.5 ± 12.8	62.0 ± 17.7	0.003
Total treatment duration (months)	14.5 (13.8–16.6)	14.4 (13.7–15.7)	15.7 (13.2–17.9)	0.250
Treatment regimen				0.064
Standard regimen	121 (49.2%)	100 (52.4%)	21 (38.2%)	
Non-standard regimen	125 (50.8%)	91 (47.6%)	34 (61.8%)	
BACES score (n = 45)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	3.0 (2.0–4.0)	0.352
Follow-up duration after treatment initiation (years)	4.1 (2.3–7.4)	4.1 (2.3–7.6)	4.2 (2.1–12.8)	0.052
Death	16 (6.5%)	5 (2.6%)	11 (20.0%)	<0.001
MAC specific mortality	6 (2.4%)	1 (0.5%)	5 (9.1%)	0.002

Data are presented as the mean ± standard deviation, median (interquartile range), or frequency (proportion). Abbreviation: NTM, nontuberculous mycobacteria; AFB, acid-fast bacillus; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLco, diffusing capacity for carbon monoxide; BACES, body mass index, age, cavity, erythrocyte sedimentation rate, and sex

*The lingular segment was considered a separate lobe, which resulted in the inclusion of a total of six lung lobes for analysis

TABLE 6. Effect of nonachievement of culture conversion at treatment completion on mortality according to the radiologic classification

CT type	N	Died	Mortality rate*	Univariate analysis			Multivariate analysis†		
				HR (95% CI)	*P*-value	*P* for interaction	HR (95% CI)	*P*-value	*P* for interaction
FC	51	27	90.7	3.77 (1.69–8.43)	0.001	0.334	5.08 (2.18–11.82)	<0.001	0.724
C-NB	55	11	30.8	7.23 (2.47–21.20)	<0.001		6.48 (2.13–19.65)	0.001	

Abbreviations: FC, fibrocavitary; C-NB, cavitary nodular bronchiectatic; HR, hazard ratio; CI, confidence interval

*Kaplan–Meier estimates at 12 years

†Using backward elimination

Figure 5-A Kaplan–Meier plot of the cumulative mortality rate of Mycobacterium avium complex pulmonary disease according to the achievement of culture conversion at treatment completion in patients with fibrocavitary type

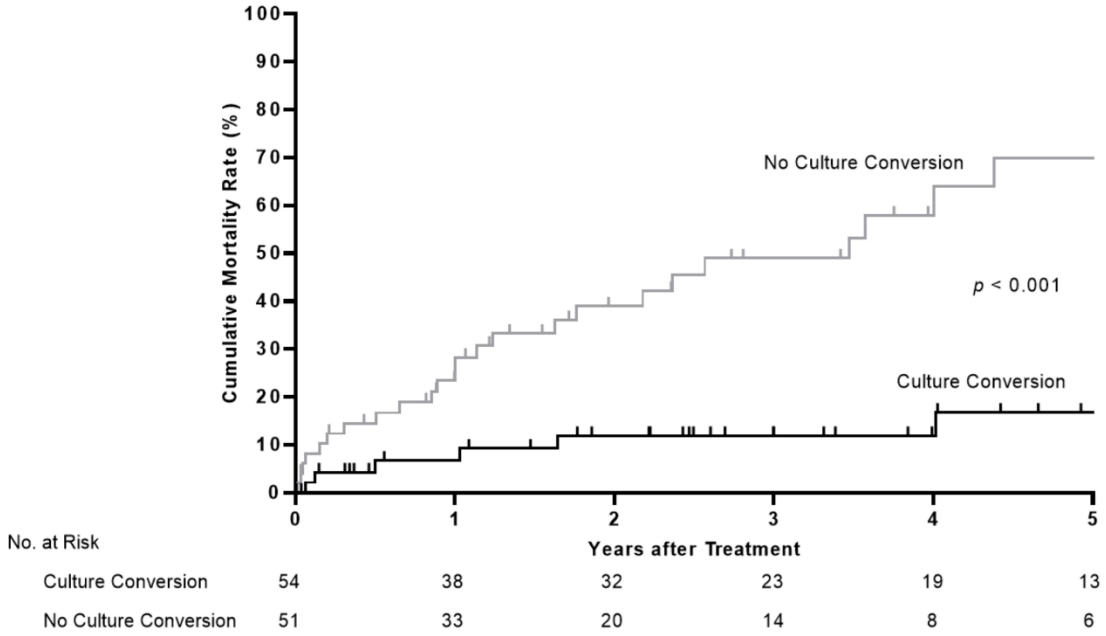
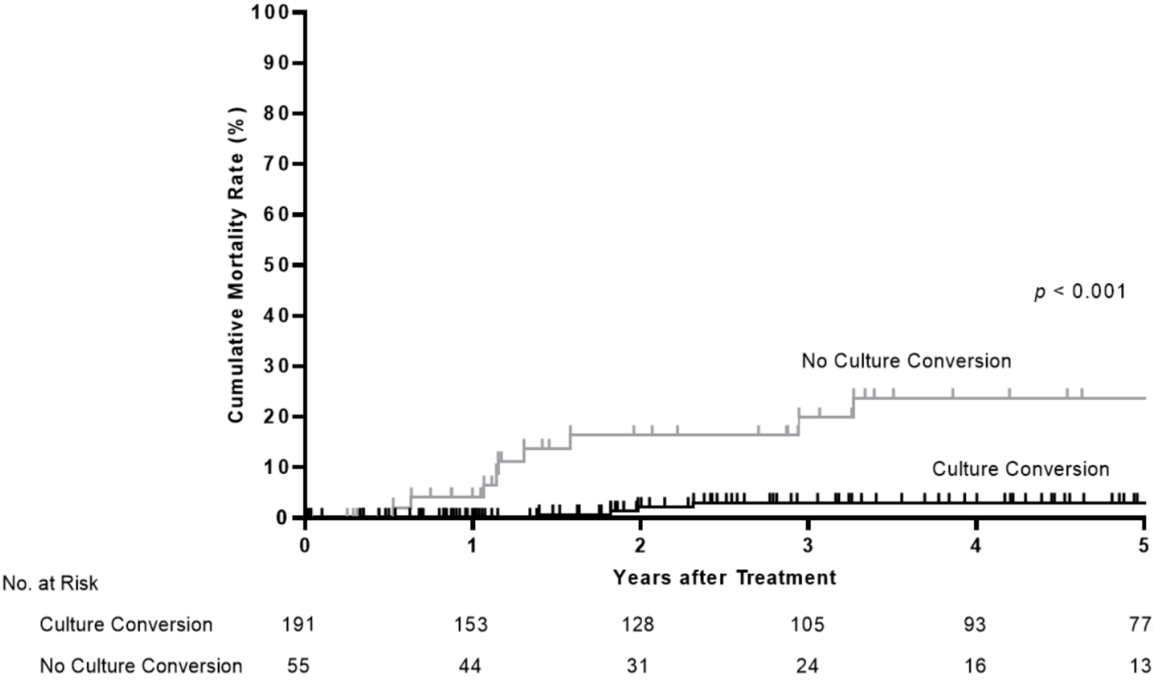


Figure 5-B Kaplan–Meier plot of the cumulative mortality rate of Mycobacterium avium complex pulmonary disease according to the achievement of culture conversion at treatment completion in patients with cavitary nodular bronchiectatic type.



Landmark analysis

Figure 6 presents the 2-year landmark analysis of the effects of culture conversion at the treatment completion on mortality rate for the 289 patients who survived at least 2 year after treatment initiation. In the 2-year landmark analysis, achievement of sputum culture conversion was significantly associated with decreased mortality in patients with cavitary MAC-PD ($P < 0.001$, log-rank test). Among 289 patients, 202 patients had culture conversion, and their cumulative 5- and 10-year cumulative mortality rates were 3.6% and 7.9%, respectively. In contrast, the overall 5- and 10-year cumulative mortality rates of 87 patients without culture conversion were 32.2% and 49.7%, respectively. Cox regression analysis revealed a significant association between non-achievement of culture conversion and the mortality rate (adjusted HR: 7.01, 95% CI 3.24–15.16, $P < 0.001$, Table 7)

Figure 6. Kaplan–Meier curves according to achievement of culture conversion from the 2-year landmark analysis of 289 patients who survived for 2 years after treatment initiation

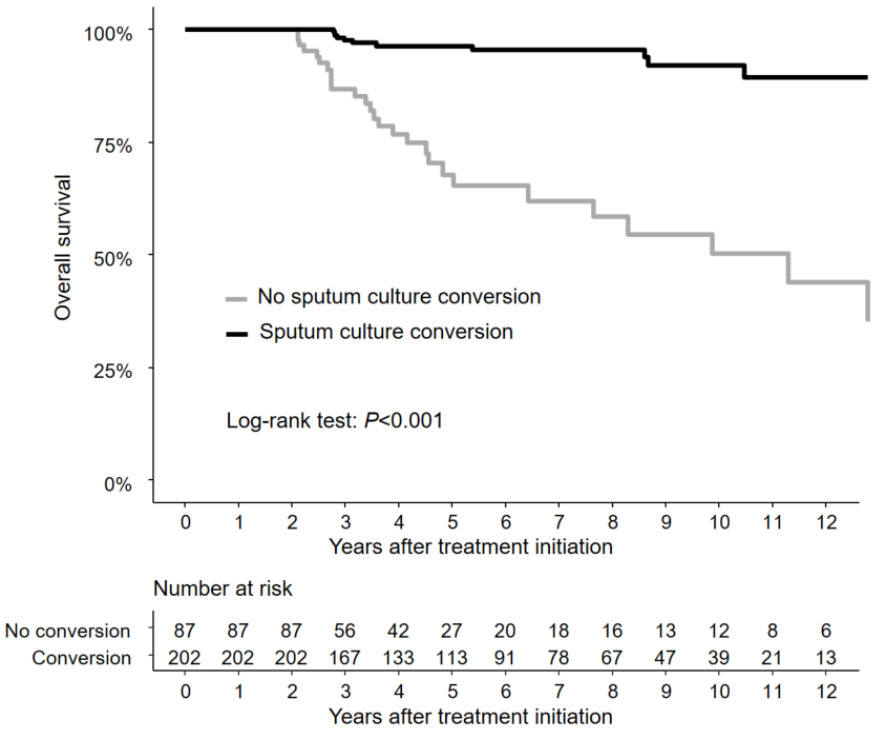


TABLE 7. Landmark analysis at 2 years of mortality-associated risk factors in 289 patients with cavitary *Mycobacterium avium* complex pulmonary disease

Characteristics	N	Died	Mortality	Univariate analysis		Multivariate analysis[†]	
	(n = 289)	(n = 37)	rate[*]	HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Age	289	37	24.6	1.08 (1.04–1.12)	<0.001	1.07 (1.04–1.11)	<0.001
Age ≥ 65 years	124	26	35.0	4.28 (2.10–8.74)	<0.001		
Male sex	109	27	47.9	6.38 (3.04–13.41)	<0.001	2.34 (1.04–5.28)	0.040
Body mass index				0.93 (0.82–1.06)	0.288		
Body mass index < 18.5 kg/m^2	80	13	41.0	1.73 (0.88–3.40)	0.114		
Current or past smoker	87	23	46.5	5.02 (2.56–9.85)	<0.001		
History of tuberculosis	145	26	34.0	2.44 (1.21–4.94)	0.013		
History of NTM treatment	37	4	16.6	1.23 (0.43–3.50)	0.694		
Charlson Comorbidity Index				1.41 (1.25–1.59)	<0.001		
0–1	89	3	10.4	1.00	<0.001		
2–3	119	13	19.8	4.78 (1.35–16.86)	0.015		
≥4	81	21	52.8	12.24 (3.61–41.53)	<0.001		
Mycobacterium intracellulare	152	23	37.5	2.12 (1.08–4.18)	0.030	2.05 (1.00–4.19)	0.050
Positive AFB smear at treatment initiation	149	25	33.6	2.37 (1.19–4.73)	0.015		
Number of involved lobes ≥3	258	28	21.7	0.40 (0.19–0.84)	0.016		
Number of cavities ≥2	117	21	36.1	2.55 (1.33–4.92)	0.005		
Maximum size of cavity >2 cm	135	29	41.9	4.63 (2.11–10.13)	<0.001	2.71 (1.20–6.10)	0.016
Non-standard regimen	148	20	28.0	1.41 (0.74–2.69)	0.303		
No culture conversion at treatment completion within 2 years	87	27	56.0	8.33 (4.02–17.26)	<0.001	7.01 (3.24–15.16)	<0.001

Data are presented as the frequency (proportion); age was included regardless of statistical significance.

Abbreviations: HR, hazard ratio; CI, confidence interval; NTM, nontuberculous mycobacteria; AFB, acid-fast bacillus.

[*]Kaplan–Meier estimates at 12 years

[†]Backward elimination was used

Subgroup analysis: severe BACES score

Furthermore, we evaluated the difference in the mortality rate based on the BACES [body mass index (BMI), age, cavity, erythrocyte sedimentation rate (ESR), and sex] score. As ESR was not routinely measured at our center, the result of BACES score was available in only 17.9% (63/351) of participants. Among these patients, 42.9% (27/63) were classified as having severe disease according to BACES score (4–5) points. Among them, 59.3% (16/27) patients achieved culture conversion. The 5-year cumulative mortality rates for the 27 patients with severe BACES score was 56.5%. The nonachievement of culture conversion at treatment completion was significantly related to higher mortality (crude HR: 11.18, 95% CI 1.32–94.83, $P = 0.027$)

Discussion

In this retrospective study conducted at a tertiary referral center in South Korea, the relationship between sputum culture conversion and mortality rate was investigated in 351 patients with cavitary MAC-PD who received macrolide-containing regimens for at least 6 months. This study is the first of its kind to examine the association between culture conversion and mortality in cavitary MAC-PD patients. The findings revealed that patients who did not achieve culture conversion had a significantly higher mortality rate compared to those who did.

Figure 4 illustrates that within approximately 3 years of starting treatment, patients who achieved culture conversion had a higher mortality rate. However, after 3 years, when a certain proportion of patients achieved culture conversion, significant differences in all-cause mortality became evident based on treatment outcome. Patients without culture conversion experienced significantly higher mortality compared to those who achieved culture conversion. Taking into account the time it took for culture conversion to occur (median 1.2 years, range 0.5–2.6), a landmark time of 2 years after treatment initiation was selected. Landmark analysis conducted on 289 patients who survived for at least 2 years after treatment initiation clearly demonstrated the impact of sputum culture conversion on the mortality rate during the follow-up period in cavitary MAC-PD patients (Figure 6).

Previous studies have consistently shown that the presence of cavitary lesions is associated with increased mortality in patients with NTM-PD. For instance, a study conducted in Japan in 2012 found that the FC type was a negative prognostic factor for MAC-specific mortality (16). Another study conducted in South Korea analyzed data from 1445 patients diagnosed between 1997 and 2013 in a tertiary referral center in South Korea by Jhun et al. and demonstrated that patients with FC and C-NB types had significantly higher mortality rates compared to those with the NC-NB type throughout the

entire follow-up period (15). Recently, along with low body mass index/old age/elevated ESR/male sex, the radiological evidence of lung cavitation was suggested as one of the 5 factors (BACES score) for predicting mortality of patients with NTM-PD (17). The association between the presence of lung cavitation on radiological imaging and elevated mortality rates appears reasonable, as cavitation is a well-established indicator of a substantial mycobacterial burden (32). Consequently, it is possible that this high mycobacterial burden is connected to suboptimal treatment response and the potential emergence of drug resistance (33).

However, previous studies that examined the connection between the presence of cavitary lesions and mortality in MAC-PD did not adequately explore the potential impact of treatment outcomes on the mortality rate. For example, in a study involving patients with the BACES score, treatment was only initiated in approximately 59% of the enrolled patients (17). Thus, it is likely that the anticipated mortality rate initially determined by the BACES score would vary between patients who did not receive treatment due to other medical factors (such as extremely poor overall health) and those who achieved culture conversion after following guideline-based therapy, even if these patients had the same risk score at the beginning. Similarly, a study conducted by Jhun et al. solely examined whether the mortality rates differed based on the initiation of treatment for cavitary MAC-PD, without considering the treatment outcome upon completion (15).

Given the findings of a recent study, which discovered a negative correlation between receiving macrolide treatment for one year or more and mortality associated with NTM (10), and another study that indicated a decreased mortality risk in cavitary NTM-PD patients who achieved culture conversion at one year after starting treatment (27), it is probable that the treatment outcome at the completion of therapy is linked to the mortality of MAC-PD. In contrast to previous studies that simply discussed the connection between culture conversion and mortality in NTM-PD patients regardless of the presence of cavities (10, 27), our analysis specifically focused on cavitary MAC-PD cases. Moreover, in our study, we employed the Simon–Makuch estimate and conducted Cox regression analysis, using culture conversion as a time-dependent covariate, to minimize the potential bias that patients with more severe disease were more prone to mortality. Our findings indicate that, even among the same disease classified into the cavitary-type MAC-PD category, the mortality rate significantly differs based on whether they achieve culture conversion after treatment. This observation applies to both the FC type and the C-NB type of cavitary MAC-PD.

Additionally, we demonstrated the correlation between sputum culture conversion and the mortality rate among patients who had the same prognostic score, known as the BACES score. In a study conducted by Kim et al., the estimated 5-year mortality rate based on the BACES score was 47.8% for a score of

4 and 82.9% for a score of 5 (17). Our study's patient population had comparable mortality rates, with a 5-year cumulative death rate of 56.5% among 27 patients who scored 4–5 on the BACES score. However, it is worth noting that the mortality rate differed significantly depending on the culture conversion status (crude HR: 11.18, 95% CI: 1.32–94.83). These findings suggest that the predicted mortality rate based on the initial BACES score can be individually applied to each patient based on their treatment response, specifically their achievement of culture conversion after treatment. This indicates that culture conversion can serve as an additional prognostic factor, referred to as an "on-treatment factor."

Patients with NTM-PD who did not exhibit a positive response to treatment experienced a considerably faster deterioration in lung function compared to those who achieved successful treatment outcomes; the rates of decline in FEV1 and FVC were –52.2 mL/year, –28.2 mL/year, and –50.4 mL/year, –26.0 mL/year, respectively (34). It is reasonable to infer that patients whose lung function declines rapidly due to failure to achieve culture conversion are at higher risk of mortality due to progressive respiratory failure and various complications associated with the deterioration of lung function. Additionally, the presence of persistent cavitary lesions and structural damage to the lung parenchyma resulting from treatment failure may create an environment that increases susceptibility to secondary infections, further contributing to the elevated mortality rate (10, 35).

There were several limitations in this study. The first and most significant limitation was that it was a retrospective analysis conducted at a single tertiary referral center. Additionally, while recent studies on the prognosis and outcomes of NTM-PD have utilized the BACES score (17, 27, 36), we only assessed the impact of treatment outcomes on mortality in a limited number of patients using this scoring system. This was due to the lack of routine ESR measurements during the study period at our center. Furthermore, unlike previous studies that evaluated outcomes in cavitary MAC-PD and included patients who received a standard treatment regimen for at least one year (12, 28, 29, 36, 37), we included patients treated with a macrolide-containing regimen for a minimum duration of six months. This decision was based on the belief that a treatment duration of at least six months was necessary to assess the impact of treatment outcomes on mortality, and we did not specifically evaluate the treatment effect of the standard regimen. Therefore, our study results may not be directly applicable to individuals treated with a standard regimen for one year or longer.

Conclusion

In conclusion, our study demonstrated that among patients diagnosed with cavitary MAC-PD who were treated with a macrolide-containing regimen for a minimum of six months, those who did not achieve culture conversion had a significantly higher mortality rate compared to those who did achieve culture conversion. These findings underscore the importance of assessing sputum culture conversion as a primary microbiological endpoint in this patient population. Moreover, our study suggests that the failure to achieve culture conversion could be considered an additional prognostic factor during treatment. This is noteworthy because the initially predicted mortality, determined by prognostic scoring systems or radiologic classification in MAC-PD patients, can be notably influenced by the achievement of sputum culture conversion.

References

1. Falkinham JO. Nontuberculous mycobacteria in the environment. Tuberculosis. 2022;137:102267.
2. Holland SM. Nontuberculous Mycobacterial Infections. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson JL, editors. Harrison's Principles of Internal Medicine, 21e. New York, NY: McGraw-Hill Education; 2022.
3. Floto RA, Olivier KN, Saiman L, Daley CL, Herrmann JL, Nick JA, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis: executive summary. Thorax. 2016;71(1):88-90.
4. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367-416.
5. Honda JR, Alper S, Bai X, Chan ED. Acquired and genetic host susceptibility factors and microbial pathogenic factors that predispose to nontuberculous mycobacterial infections. Curr Opin Immunol. 2018;54:66-73.
6. Ko R-E, Moon SM, Ahn S, Jhun BW, Jeon K, Kwon OJ, et al. Changing Epidemiology of Nontuberculous Mycobacterial Lung Diseases in a Tertiary Referral Hospital in Korea between 2001 and 2015. J Korean Med Sci. 2018;33(8).
7. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. Am J Respir Crit Care Med. 2012;185(8):881-6.
8. Prevots DR, Shaw PA, Strickland D, Jackson LA, Raebel MA, Blosky MA, et al. Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. Am J Respir Crit Care Med. 2010;182(7):970-6.
9. Adjemian J, Olivier KN, Prevots DR. Epidemiology of Pulmonary Nontuberculous Mycobacterial Sputum Positivity in Patients with Cystic Fibrosis in the United States, 2010-2014. Ann Am Thorac Soc. 2018;15(7):817-26.
10. Lee H, Myung W, Lee EM, Kim H, Jhun BW. Mortality and Prognostic Factors of Nontuberculous Mycobacterial Infection in Korea: A Population-based Comparative Study. Clin Infect Dis. 2021;72(10):e610-e9.
11. Harada K, Hagiya H, Funahashi T, Koyama T, Kano MR, Otsuka F. Trends in the Nontuberculous Mycobacterial Disease Mortality Rate in Japan: A Nationwide Observational Study, 1997-2016. Clin Infect Dis. 2021;73(2):e321-e6.
12. Koh W-J, Moon SM, Kim S-Y, Woo M-A, Kim S, Jhun BW, et al. Outcomes of Mycobacterium avium complex lung disease based on clinical phenotype. European Respiratory Journal. 2017;50(3):1602503.
13. Kwon Y-S, Koh W-J, Daley CL. Treatment of Mycobacterium avium Complex Pulmonary Disease. Tuberc Respir Dis. 2019;82(1):15-26.
14. Pan SW, Shu CC, Feng JY, Su WJ. Treatment for Mycobacterium avium complex lung disease. J Formos Med Assoc. 2020;119 Suppl 1:S67-s75.
15. Jhun BW, Moon SM, Jeon K, Kwon OJ, Yoo H, Carriere KC, et al. Prognostic factors associated with long-term mortality in 1445 patients with nontuberculous mycobacterial pulmonary disease: a 15-year follow-up study. European Respiratory Journal. 2020;55(1):1900798.
16. Hayashi M, Takayanagi N, Kanauchi T, Miyahara Y, Yanagisawa T, Sugita Y. Prognostic factors of 634 HIV-negative patients with Mycobacterium avium complex lung disease. Am J Respir Crit Care Med. 2012;185(5):575-83.

17. Kim HJ, Kwak N, Hong H, Kang N, Im Y, Jhun BW, et al. BACES Score for Predicting Mortality in Nontuberculous Mycobacterial Pulmonary Disease. Am J Respir Crit Care Med. 2021;203(2):230-6.
18. Fleshner M, Olivier KN, Shaw PA, Adjemian J, Strollo S, Claypool RJ, et al. Mortality among patients with pulmonary non-tuberculous mycobacteria disease. Int J Tuberc Lung Dis. 2016;20(5):582-7.
19. Stout JE, Koh WJ, Yew WW. Update on pulmonary disease due to non-tuberculous mycobacteria. Int J Infect Dis. 2016;45:123-34.
20. Lee G, Lee KS, Moon JW, Koh WJ, Jeong BH, Jeong YJ, et al. Nodular bronchiectatic Mycobacterium avium complex pulmonary disease. Natural course on serial computed tomographic scans. Ann Am Thorac Soc. 2013;10(4):299-306.
21. Kim SJ, Park J, Lee H, Lee YJ, Park JS, Cho YJ, et al. Risk factors for deterioration of nodular bronchiectatic Mycobacterium avium complex lung disease. Int J Tuberc Lung Dis. 2014;18(6):730-6.
22. Hwang JA, Kim S, Jo KW, Shim TS. Natural history of Mycobacterium avium complex lung disease in untreated patients with stable course. Eur Respir J. 2017;49(3).
23. Mitnick CD, Franke MF, Rich ML, Alcantara Viru FA, Appleton SC, Atwood SS, et al. Aggressive regimens for multidrug-resistant tuberculosis decrease all-cause mortality. PLoS One. 2013;8(3):e58664.
24. Velásquez GE, Becerra MC, Gelmanova IY, Pasechnikov AD, Yedilbayev A, Shin SS, et al. Improving outcomes for multidrug-resistant tuberculosis: aggressive regimens prevent treatment failure and death. Clin Infect Dis. 2014;59(1):9-15.
25. Wang M-G, Wu S-Q, He J-Q. Efficacy of bedaquiline in the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis. BMC Infectious Diseases. 2021;21(1):970.
26. Schnippel K, Ndjeka N, Maartens G, Meintjes G, Master I, Ismail N, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med. 2018;6(9):699-706.
27. Im Y, Hwang NY, Kim K, Kim H, Kwon OJ, Jhun BW. Impact of Time Between Diagnosis and Treatment for Nontuberculous Mycobacterial Pulmonary Disease on Culture Conversion and All-Cause Mortality. Chest. 2022;161(5):1192-200.
28. Lee JH, Park YE, Chong YP, Shim TS, Jo KW. Efficacy of Fluoroquinolones as Substitutes for Ethambutol or Rifampin in the Treatment of Mycobacterium avium Complex Pulmonary Disease According to Radiologic Types. Antimicrob Agents Chemother. 2022;66(2):e0152221.
29. Chae G, Park YE, Chong YP, Lee HJ, Shim TS, Jo KW. Treatment Outcomes of Cavitary Nodular Bronchiectatic-Type Mycobacterium avium Complex Pulmonary Disease. Antimicrob Agents Chemother. 2022;66(9):e0226121.
30. Togo T, Atsumi J, Hiramatsu M, Shimoda K, Morimoto K, Uchimura K, et al. Residual Destructive Lesions and Surgical Outcome in Mycobacterium avium Complex Pulmonary Disease. Ann Thorac Surg. 2020;110(5):1698-705.
31. van Ingen J, Aksamit T, Andrejak C, Böttger EC, Cambau E, Daley CL, et al. Treatment outcome definitions in nontuberculous mycobacterial pulmonary disease: an NTM-NET consensus statement. European Respiratory Journal. 2018;51(3):1800170.
32. Ong CW, Elkington PT, Friedland JS. Tuberculosis, pulmonary cavitation, and matrix metalloproteinases. Am J Respir Crit Care Med. 2014;190(1):9-18.
33. Urbanowski ME, Ordonez AA, Ruiz-Bedoya CA, Jain SK, Bishai WR. Cavitary tuberculosis: the gateway of disease transmission. Lancet Infect Dis. 2020;20(6):e117-e28.
34. Park HY, Jeong BH, Chon HR, Jeon K, Daley CL, Koh WJ. Lung Function Decline According to Clinical Course in Nontuberculous Mycobacterial Lung Disease. Chest.

2016;150(6):1222-32.
35. Meghji J, Lesosky M, Joekes E, Banda P, Rylance J, Gordon S, et al. Patient outcomes associated with post-tuberculosis lung damage in Malawi: a prospective cohort study. Thorax. 2020;75(3):269-78.
36. Kim BG, Jhun BW, Kim H, Kwon OJ. Treatment outcomes of Mycobacterium avium complex pulmonary disease according to disease severity. Sci Rep. 2022;12(1):1970.
37. Kwon YS, Han M, Kwon BS, Kim OH, Lee HY, Shim TS, et al. Discontinuation rates attributed to adverse events and treatment outcomes between clarithromycin and azithromycin in Mycobacterium avium complex lung disease: A propensity score analysis. J Glob Antimicrob Resist. 2020;22:106-12.