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The therapeutic impact of maximum chemotherapy possession days during three consecutive months in non-tuberculous mycobacterial lung disease: A real-world experience

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ABSTRACT

Purpose: Adherence to guideline recommendations in the treatment of non-tuberculous mycobacterial lung disease (NTM-LD) is often difficult. Thus, this study aimed to investigate the impact of the integrity of NTM-LD treatment on treatment outcomes.

Materials and methods: The participants were screened from the National Taiwan University Hospital-Integrative Medical Database (NTUH-iMD) and the Taiwan National Health Insurance Research Database (NHIRD). The longest treatment duration during 3 consecutive months was defined as maximum chemotherapy possession days (MCPDs) and was categorized as low (28–55 days), medium (56–90 days), and maximum (≥91 days). We analyzed microbiological cure and 3-year mortality using MCPDs.

Results: Low, medium, and maximum MCPD groups had 83 (19.2 %), 94 (21.8 %), and 255 (59.0 %) participants in the NTUH-iMD cohort (N = 432) and 1203 (26.5 %), 1251 (27.6 %), and 2084 (45.9 %) participants in the NHIRD cohort (N = 4538), respectively. In the NTUH-iMD cohort, multivariable analysis showed that adjusted hazard ratios (aHRs) of 3-year mortality were 0.51 (95 % CI: 0.29–0.90) and 0.29 (0.18–0.49) in medium and maximum MCPD groups compared with the low MCPD group. The trends of survival benefit by maximum MCPDs were also found in the NHIRD cohort. The maximum MCPD group had 45.9 % participants with microbiologic cure, which was significantly higher than in medium and low MCPD groups (27.7 % and 4.0 %, respectively; $p < 0.001$).

Conclusion: Maximum MCPD for NTM-LD increased microbiological cure and reduced 3-year mortality by 71 % compared with low MCPD group. Maintaining NTM-LD treatment integrity as possible might positively impact disease outcomes.

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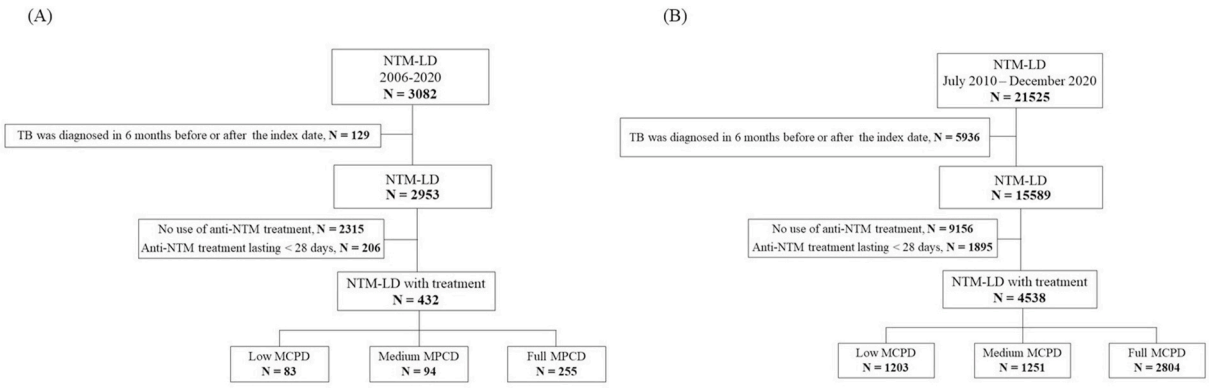

Fig. 1. Flow chart of participants' enrollment in (A) NTUH-iMD and (B) NHIRD
Abbreviations: NTM-LD: non-tuberculous mycobacteria lung disease; NTUH-iMD: National Taiwan University Hospital integrative medical database; NHIRD: National Health Insurance Research database *Microbiologic diagnostic criteria of NTM-LD: the criteria were (1) $\geq$ 2 sputum tests isolating the same species of NTM, (2) $<$ 3 sets of negative cultures, and (3) no other NTM species identified between the 2 positive cultures of a certain NTM species.

1. Introduction

Non-tuberculous mycobacteria (NTM) are environmental pathogens that are widely distributed and have the potential to colonize the respiratory tract, subsequently leading to pulmonary infections, particularly in individuals who are at risk. Recent trends indicate a rise in the incidence of lung disease associated with NTM (NTM-LD). This condition has a considerable negative impact on health status, quality of life, and survival rates, particularly among older adults and those with multiple comorbidities.[1,2] Lee et al. reported that the outcome of NTM-LD might be worse compared to pulmonary tuberculosis.[3]

In contrast to pulmonary tuberculosis, the treatment of NTM-LD is characterized by increased complexity and duration.[4] Although the established guidelines uniformly advocate for standard treatment regimens, referred to as guideline-based therapy (GBT), which should be maintained for a minimum of 12 months following sputum conversion,[4,5] adherence to long-term treatment remains a significant challenge. The reasons of non-compliance of GBT might be multi-factorial. It might include prolonged treatment duration, adverse drug effects and drug interaction of GBT.[6] In addition, the possible complications of GBT might further compromise the compliance and confidence of GBT treatment in both physicians and patients.[7,8] Various studies have indicated that the continuation of GBT at the six-month treatment is observed in only 17 %–41 % of patients with *Mycobacterium avium* complex lung disease (MAC-LD).[9,10] Consequently, a common challenge in the management of NTM therapy is the need to address adverse effects and to modify treatment regimens.

In addition to adjustments in treatment protocols, instances of treatment interruption are occasionally observed.[11] However, the majority of previous research has primarily focused on the consequences of non-compliance with GBT, comparison among various treatment regimens, and differing durations of treatment.[12,13] A study conducted in the Netherlands investigated the medication possession rate for NTM-LD treatment during the initial month; however, it did not explore the relationship between this rate and treatment outcomes.[11] There is a paucity of information regarding the significance of uninterrupted NTM-LD treatment. Consequently, we undertook a retrospective study to analyze the maximum number of treatment days over a consecutive three-month period, with the aim to investigate the therapeutic implications of treatment duration integrity on three-year mortality and microbiological cure rates.

2. Materials and methods

2.1. Study design and participant recruitment

This retrospective study was undertaken to examine cohorts from the National Taiwan University Hospital-Integrative Medical Database (NTUH-iMD) spanning the years 2006–2020, as well as data from the Taiwan National Health Insurance Research Database (NHIRD) maintained by the Health and Welfare Data Science Center (HWDC) from June 2010 to December 2020. The study received approval from the Institutional Review Board of the hospital's Research Ethics Committee (Approval No: 201704001RINB). Given the retrospective nature of the research, the requirement for written informed consent was waived.

We conducted a screening of patients from the NTUH-iMD who met the microbiological diagnostic criteria for NTM-LD as outlined in the 2020 guidelines established by the American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA).[4] Conversely, within the medical database of the National Health Insurance Research Database (NHIRD), we identified patients during the study period based on diagnostic codes. Candidates were included if they had received a diagnosis of NTM-LD on two separate occasions using any of the three primary diagnostic codes associated with outpatient or emergency care, or on one occasion using any of the five primary diagnostic codes for hospital admissions. The index date for NTM-LD was defined as the date on which the microbiological diagnostic criteria were met in the NTUH-iMD cohort, or the first instance of diagnostic coding for NTM-LD in the NHIRD cohort.

Following the screening process, we excluded individuals diagnosed with pulmonary tuberculosis within a six-month period preceding or following the index date of NTM-LD, as well as those co-infected with the human immunodeficiency virus. Patients were eligible for enrollment if they received *anti*-NTM treatment for a minimum duration of 28 days within any consecutive three-month interval during the three years of the index date. *Anti*-NTM treatment was operationally defined as the administration of at least two active species-specific *anti*-NTM medications, in accordance with the guidelines established by the British Thoracic Society in 2017 and the joint recommendations of ATS/ERS/ESCMID/IDSA in 2020 (Supplement Table S1).[4,5]

2.2. Demographics, clinical data, and outcomes

The identification of comorbidities was conducted as detailed in Supplement Table S2. In the NTUH-iMD, cavitation was defined based on reports from chest computed tomography (CT) conducted within six months prior to or three years following the index date. The grade of

Table 1
The clinical characteristics of subjects in NTUH-iMD.

	All (n = 432)	Low MCPD (n = 83)	Medium MCPD (n = 94)	Maximum MCPD (n = 255)	p
Age (years)	61.0 ± 14.2	65.9 ± 14.8	61.1 ± 14.8	59.3 ± 13.5	0.001
Age >65	173 (40.1)	46 (55.4)	41 (43.6)	86 (33.7)	0.002
Sex (Male)	201 (46.5)	44 (53.0)	46 (48.9)	111 (43.5)	0.28
BMI (n = 310)	103 (33.2)	17 (32.7)	25 (34.77)	61 (32.87 %)	0.95
AFS (n = 424)					
negative	46 (10.9)	7 (8.6)	11 (12.0)	28 (11.2)	0.65
Weakly positive	112 (26.4)	20 (24.7)	29 (31.5)	63 (25.1)	
Strongly positive	266 (62.7)	54 (66.7)	52 (56.5)	160 (63.8)	
Species					
MABC	92 (21.3)	24 (28.9)	18 (19.2)	50 (19.6)	0.69
MAC	233 (53.9)	40 (48.2)	50 (53.2)	143 (56.1)	
MK	57 (13.2)	8 (9.6)	13 (13.8)	36 (14.1)	
RGM	35 (8.1)	8 (9.6)	9 (9.6)	18 (7.1)	
SGM	15 (3.5)	3 (3.6)	4 (4.3)	8 (3.1)	
Smoking (active or former)	80 (19.5)	12 (15.8)	17 (19.8)	51 (20.6)	0.65
CKD	22 (5.1)	7 (8.4)	6 (6.4)	9 (3.5)	0.17
ESRD	2 (0.5)	0 (0.0)	1 (1.1)	1 (0.4)	0.65
Chronic respiratory failure	12 (2.8)	4 (4.8)	6 (6.4)	2 (0.8)	0.004
Asthma	22 (5.1)	6 (7.2)	6 (6.4)	10 (3.9)	0.38
COPD	83 (19.2)	19 (22.9)	18 (19.2)	46 (18.0)	0.62
Bronchiectasis	147 (34.0)	29 (34.9)	28 (29.8)	90 (35.3)	0.62
IPF	18 (4.2)	4 (4.8)	3 (3.2)	11 (4.3)	0.84
Cancer	65 (15.1)	12 (14.5)	19 (20.2)	34 (13.3)	0.28
GERD	42 (9.7)	9 (10.8)	8 (8.5)	25 (9.8)	0.87
HF	25 (5.8)	9 (10.8)	5 (5.3)	11 (4.3)	0.084
DM	45 (10.4)	10 (12.1)	12 (12.8)	23 (9.0)	0.52
Sinusitis	14 (3.2)	2 (2.4)	3 (3.2)	9 (3.5)	1.00
Autoimmune					
RA	5 (1.2)	0 (0.0)	1 (1.1)	4 (1.6)	0.83
SLE	4 (0.9)	0 (0.0)	0 (0.0)	4 (1.6)	0.49
Sicca syndrome	11 (2.6)	2 (2.4)	1 (1.1)	8 (3.1)	0.64
Dermatomyositis	1 (0.2)	0 (0.0)	1 (1.1)	0 (0.0)	0.41
Transplantation	8 (1.9)	1 (1.2)	2 (2.1)	5 (2.0)	1.00
Cavity	70 (16.2)	10 (12.1)	16 (17.0)	44 (17.3)	0.52
Treatment duration (days)	253.2 ± 207.3	38.7 ± 10.7	122.8 ± 73.7	371.1 ± 188.8	<0.001
Intermittent therapy	19 (4.4)	5 (6.0)	5 (5.3)	9 (3.5)	0.56
The duration from diagnosis to treatment (days)	128.0 ± 212.5	184.5 ± 274.0	118.4 ± 225.5	113.1 ± 180.1	0.03
Days of Follow-up	800.5 ± 365.7	680.7 ± 420.9	684.6 ± 419.3	882.3 ± 298.4	<0.001
Mortality	97 (22.5)	29 (34.9)	29 (30.9)	39 (15.3)	<0.001

Data represented with mean ± standard deviation or number (%).
Abbreviations: AFS: acid fast staining; BMI: body mass index; CKD: chronic renal disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ESRD: end-stage renal disease; GERD: gastroesophageal reflux disease; HF: heart failure; IPF: idiopathic pulmonary fibrosis; MABC: *Mycobacterium abscessus complex*; MAC: *Mycobacterium avium complex*; MK: *Mycobacterium kansasii*; NTUH-iMD: National Taiwan University Hospital integrative medical database; RA: rheumatoid arthritis; RGM: rapid-growing mycobacteria; SGM: slow-growing mycobacteria; SLE: systemic lupus erythema.
The case numbers of cirrhosis, polymyositis and pneumoconiosis were zero.

acid-fast staining (AFS) and the identification of NTM species were exclusively available in the NTUH-iMD, but not in NHIRD. The classification of NTM species was performed in accordance with our previous research as outlined in Supplement Table S3[14]. The AFS grades of trace to 2+ were classified as weak positive, while grades of 3+ or 4+ were classified as strong positive.

The primary outcome of this study was three-year mortality. Data regarding mortality within three years from the index date were acquired through the integration of the medical databases from NTUH-iMD and NHIRD with the Death Registry System maintained by the Ministry of Health and Welfare in Taiwan.[14] In NTUH-iMD, microbiologic cure was assumed as a secondary outcome, defined in accordance with the criteria established by NTM-NET.[15]

2.3. Group classification by anti-NTM treatment

The most days in three consecutive months of *anti*-NTM treatment were indicated as maximum chemotherapy possession days (MCPDs). We classified them into three distinct groups: 28–55 days (low), 56–90 days (medium), and ≥91 days (maximum) MCPD groups. A single course of anti- NTM therapy was defined as a continuous treatment period that was not interrupted for more than three consecutive months.

2.4. Statistical analysis

All statistical analyses were conducted using SAS 9.4 (Cary, NC, USA). Categorical and continuous variables were compared using the chi-square (or Fisher exact) and Student t tests, respectively. ANOVA was used for the comparison of multiple groups. Multivariable hazard ratios (HRs) were calculated by Cox proportional hazard regression. Factors with $p < 0.05$ in univariable analysis were included in the multivariable analysis while keeping the significant factors in the final multivariable model. Additionally, the study covered an extended timeframe. Variations in NTM-LD treatment, and supportive care for comorbidities over the years of NTM-LD diagnosis could potentially confound the study findings. As a result, the year of NTM-LD diagnosis was incorporated into multivariable analysis. Kaplan-Meier (KM) survival and log-rank tests were used to analyze 3-year survival curves. Consistence between NTUH-iMD and NHIRD was verified by Cohen's Kappa coefficient or McNemar's test. Statistical significance was set as $p < 0.05$.

3. Results

3.1. The NTUH-iMD cohort

3.1.1. Participants' selection and demographic and clinical characteristics

Fig. 1A illustrates the recruitment of participants (n = 432) in the NTUH-iMD cohort. The distribution of participants across the low, medium, and maximum MCPD groups was 83 (19.2 %), 94 (21.8 %), and 255 (59.0 %), respectively (Table 1). The maximum MCPD group was significantly younger than the other two groups ($p = 0.001$). There were no significant differences in sex, body mass index (BMI), smoking status, or comorbidities among the groups, with the exception of chronic respiratory failure (CRF) related to ventilator dependence. The maximum

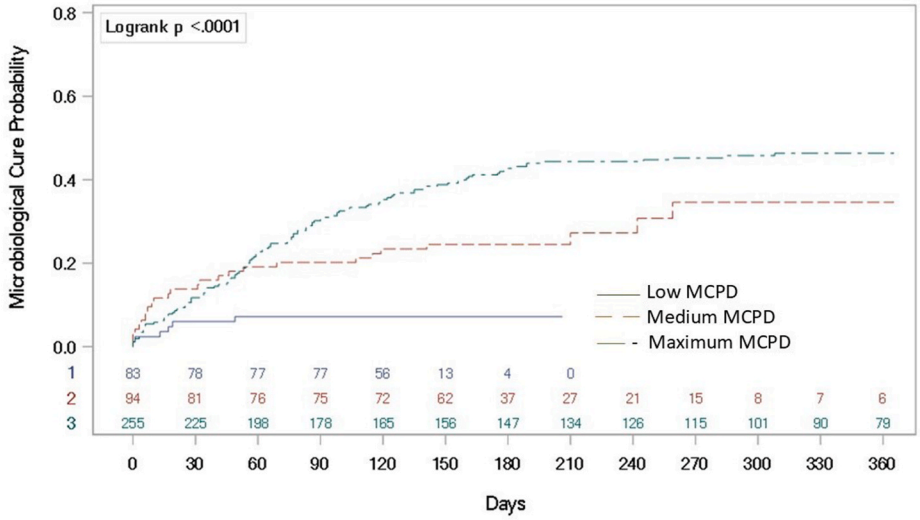

Fig. 2. The Kaplan-Meier curves of the probability of microbiologic cure in three MCPD groups in NTUH-iMD
Abbreviations: MCPD: maximum chemotherapy possession days; NTUH-iMD: National Taiwan University Hospital integrative medical database; NHIRD: National Health Insurance Research database.

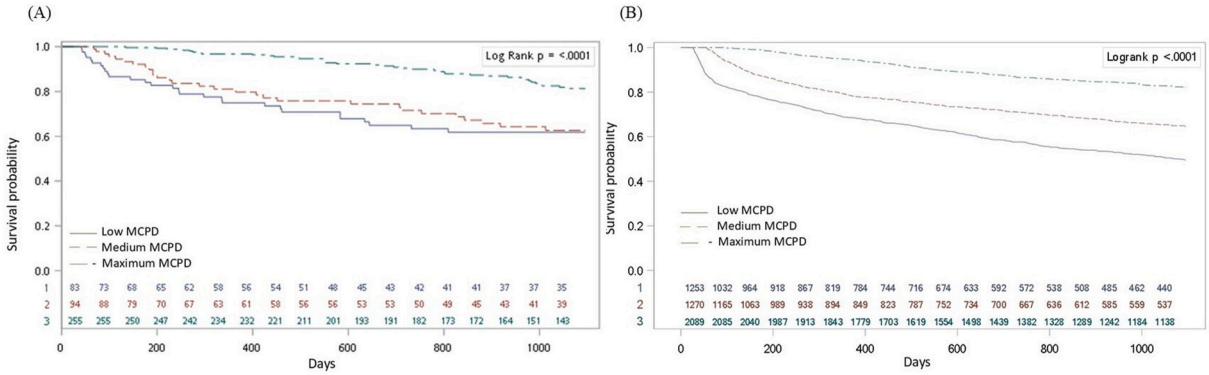

Fig. 3. The Kaplan-Meier survival curve of three MCPD groups in (A) NTUH-iMD and (B) NHIRD
Abbreviations: MCPD: maximum chemotherapy possession days; NTUH-iMD: National Taiwan University Hospital integrative medical database; NHIRD: National Health Insurance Research database.

MCPD group exhibited the lowest prevalence of CRF at 0.8 % ($p = 0.004$). Furthermore, there were no significant differences in the presence of mycobacterial species, AFS grades, or cavitation among the three groups. Only 4.4 % of participants reported ever utilizing intermittent treatment three times a week, with no significant differences observed across the MCPD groups.

3.1.2. *The temporal components of anti-NTM treatment*

The interval between diagnosis and the commencement of treatment was significantly prolonged in the low MCPD group when compared to the medium and maximum MCPD groups ($p = 0.03$). A majority of participants (91.0 %) underwent only a single course of treatment. Additionally, the duration of treatment was notably greater in the maximum MCPD group (371.1 ± 188.8 days) relative to the other groups ($p < 0.001$).

3.1.3. *MCPD associated with microbiologic cure*

A total of 149 participants, representing 34.5 % of the cohort population, met the criteria for microbiologic cure. Among these individuals, 6 (4.0 %) were classified in the low MCPD group, 26 (27.7 %) in the medium MCPD group, and 117 (45.9 %) in the maximum MCPD group. Fig. 2 illustrates the KM curves for the probability of microbiologic cures, revealing that the rate of microbiologic cure was significantly greater in the maximum MCPD group ($p < 0.001$).

3.1.4. *Three-year mortality and its associated factors*

The three-year mortality rates for the low, medium, and maximum MCPD groups were recorded at 34.9 %, 30.9 %, and 15.3 %, respectively ($p < 0.001$) (Table 1). Kaplan-Meier survival curves for the three MCPD groups indicated that the maximum MCPD group exhibited the highest survival rates, whereas the low MCPD group demonstrated the lowest survival rates ($p < 0.001$, Fig. 3A). The univariable analysis of factors influencing three-year mortality revealed that age ≥65 years, male, and active or former smoking status were significant demographic risk factors for mortality (Table 2). In terms of NTM species, *Mycobacterium avium complex* (MAC) and *Mycobacterium kansasii* (MK) were associated with a reduced risk of three-year mortality. Comorbidities such as chronic kidney disease (CKD), CRF, cancer, diabetes mellitus (DM), heart failure (HF), gastroesophageal reflux disease (GERD), and chronic airway diseases, including chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), were identified as risk factors for mortality, while bronchiectasis appeared to confer a protective effect against mortality. The maximum MCPD group was found to be a protective factor against mortality when compared to the low MCPD group. However, the year of diagnosis was not a significant factor associated with mortality ($p = 0.90$).

Table 2
Risk factors of 3-year mortality in NTUH-iMD by multivariate analysis.

	Crude HR	p	Adjusted HR	p
MCPD Groups				
Low (28–55 days)	reference		reference	
Medium (56–90 days)	0.88 (0.52–1.47)	0.61	0.51 (0.29–0.90)	0.02
Maximum (≧ 91 days)	0.34 (0.21–0.55)	<0.001	0.29 (0.18–0.49)	<0.001
The year of diagnosis	1.00 (0.95–1.06)	0.90		
AFS				
Negative	reference			
Weakly positive	1.09 (0.56–2.13)	0.80		
Strongly positive	1.25 (0.79–1.96)	0.34		
Culture				
SGM	reference			
MABC	0.77 (0.32–1.85)	0.56		
MAC	0.36 (0.15–0.86)	0.021		
MK	0.32 (0.11–0.93)	0.037		
RGM	0.59 (0.22–1.63)	0.31		
Age>65	2.10 (1.4–3.13)	<0.001		
Male	2.40 (1.58–3.64)	<0.001	1.87 (1.22–2.86)	0.004
BMI <18.5	1.00 (0.64–1.58)	0.98		
Smoking (active or former)	2.00 (1.27–3.13)	0.003		
CKD	2.47 (1.28–4.75)	0.007		
ESRD	3.93 (0.97–15.96)	0.056		
Chronic respiratory failure	15.55 (8.24–29.34)	<0.001	9.56 (4.83–18.91)	<0.001
Asthma	1.47 (0.68–3.17)	0.33		
COPD	2.06 (1.34–3.17)	0.001		
Bronchiectasis	0.40 (0.24–0.67)	<0.001		
IPF	3.17 (1.65–6.10)	<0.001		
Cancer	6.04 (4.01–9.09)	<0.001	5.81 (3.76–8.99)	<0.001
GERD	2.03 (1.17–3.52)	0.012		
HF	4.74 (2.80–8.00)	<0.001	5.26 (3.02–9.15)	<0.001
DM	2.69 (1.64–4.40)	<0.001	2.90 (1.75–4.81)	<0.001
Sinusitis	1.74 (0.71–4.29)	0.23		
Autoimmune				
RA	0.96 (0.13–6.90)	0.97		
SLE	2.56 (0.63–10.40)	0.19		
Sicca syndrome	NA[a]	NA[a]		
Dermatomyositis	NA[a]	NA[a]		
Transplantation	1.30 (0.32–5.27)	0.71		
Cavity	0.92 (0.53–1.60)	0.77		
Treatment duration	0.997 (0.996–0.998)	<0.001		
The duration from diagnosis to treatment	0.997 (0.996–0.999)	0.002	0.998 (0.996–1.000)	0.015

Abbreviations: AFS: acid fast staining; BMI: body mass index; CKD: chronic renal disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ESRD: end-stage renal disease; GERD: gastroesophageal reflux disease; HF: heart failure; IPF: idiopathic pulmonary fibrosis; MABC: *Mycobacterium abscessus complex*; MAC: *Mycobacterium avium complex*; MK: *Mycobacterium kansasii*; NTUH-iMD: National Taiwan University Hospital integrative medical database; RA: rheumatoid arthritis; RGM: rapid-growing mycobacteria; SGM: slow-growing mycobacteria; SLE: systemic lupus erythema.

[a] No mortality cases in the co-morbidities.

In the multivariable analysis, several factors were identified as significant risk factors for mortality. Specifically, male sex, CRF, cancer, HF, and DM were associated with increased mortality risk. Furthermore, both medium and maximum MCPD groups were associated with a reduced risk of mortality when compared to low MCPD group, with adjusted hazard ratios (aHRs) of 0.51 (95 % CI: 0.29–0.90, $p < 0.001$) for medium MCPD and 0.29 (95 % CI: 0.18–0.49, $p < 0.001$) for maximum MCPD. Subgroup analyses examining the impact of MCPDs on mortality, which included participants aged 65 years and older, as well as various comorbidities such as CRF, ESRD, cancer, HF, COPD, asthma, bronchiectasis, idiopathic pulmonary fibrosis (IPF), and treatment durations exceeding 360 days, demonstrated that medium and maximum MCPD groups positively influenced survival outcomes in comparison to low MCPD group (see Fig. 4A).

3.2. Validation of MCPD impact using the NHIRD

3.2.1. Participants' enrollment, clinical characteristics, and treatment

Fig. 1B presents a flowchart detailing the selection process of participants, encompassing a total of 4538 participants. Among these, 1203 (26.5 %) were classified into the low MCPD group, 1251 (27.6 %) into the medium MCPD group, and 2084 (45.9 %) into the maximum MCPD group. Notably, participants in the maximum MCPD group were significantly younger than those in the other two groups ($p < 0.001$) (Table 3). Additionally, this group exhibited a lower prevalence of comorbidities, such as ESRD, CRF, cancer, cirrhosis, COPD, HF, DM, GERD, and systemic lupus erythematosus (SLE), in comparison to the other groups. Conversely, the maximum MCPD group reported the highest incidence of bronchiectasis among the three categories ($p < 0.001$). Furthermore, the maximum MCPD group demonstrated more use of intermittent therapy (4.7 %, $p = 0.003$), the shortest interval from diagnosis to the commencement of treatment (49.7 ± 147.1 days, $p < 0.001$), the longest duration of treatment (324.5 ± 187.9 days, $p < 0.001$), and the lowest three-year mortality rate (14.9 %, $p < 0.001$) when compared to the other MCPD groups.

3.2.2. Factors associated with mortality

The univariable analysis revealed that various comorbidities, such as CRF, ESRD, asthma, COPD, IPF, cancer, HF, and DM, were identified as risk factors for mortality (Table 4). Conversely, bronchiectasis emerged as a protective factor against mortality. Furthermore, individuals in the medium and maximum MCPD groups exhibited a reduced risk of mortality when compared to those in the low MCPD group, with HR of 0.58 and 0.24, respectively, both statistically significant ($p < 0.001$). The KM survival curves indicated significant differences in 3-year mortality rates among the three groups (Fig. 3B). However, intermittent therapy was not significantly associated with mortality ($p = 0.81$). The multivariable analysis indicated that low MCPD, along with the aforementioned comorbidities—excluding asthma and DM—were associated with increased mortality. The aHRs for three-year mortality in the medium and maximum MCPD groups were 0.72 and 0.51, respectively, in comparison to the low MCPD group ($p < 0.001$). Additionally, bronchiectasis and prolonged treatment duration were identified as protective factors against mortality. Consistent with findings from the NTUH-iMD study, subgroup analyses regarding the impact of MCPD on mortality also indicated that the medium and maximum MCPD groups conferred a protective effect against mortality when compared to the low MCPD group (Fig. 4B).

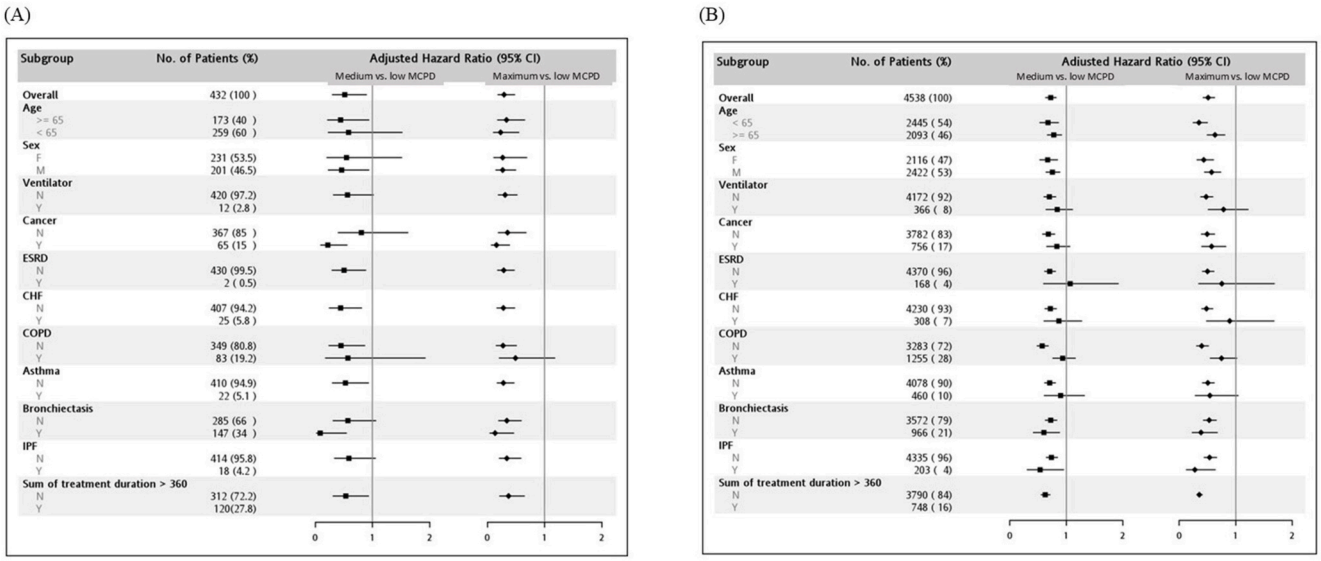

Fig. 4. Subgroup analyses of the effects of MCPD in 3 months on mortality in (A) NTUH-iMD and (B) NHIRD
Abbreviations: MCPD: maximum chemotherapy possession days; NTUH-iMD: National Taiwan University Hospital integrative medical database; NHIRD: National Health Insurance Research database.

3.3. Consistency of comorbidities derived from NTUH-iMD and NHIRD

The comorbidity data obtained from the NTUH-iMD were cross-referenced with the NHIRD database to ensure consistency. Conditions such as pneumoconiosis, cirrhosis, and dermatomyositis were excluded from the analysis due to having zero or one recorded case. Within the NTUH-iMD cohort, the reclassification of comorbidities and the categorization of MCPD groups by the NHIRD demonstrated consistency. (Table S4 and Fig. S1).

4. Discussion

The guidelines for the management of NTM-LD emphasize the importance of treatment protocols that are contingent upon the NTM species involved and the appropriate duration of therapy.[4] Nevertheless, clinical practice is often hindered by issues such as drug resistance, extended treatment periods, and adverse events related to the therapy. Previous studies in differential areas indicate that modifications and interruptions to the NTM-LD treatment regimen are common during the treatment process, the issue of treatment integrity might be complicated with the outcome.[9,10] The results of the current study highlight that the integrity of NTM-LD treatment is significantly associated with both microbiological cure and mortality outcomes.

Various factors, such as the prolonged duration of treatment, adverse effects associated with the treatment, and the fragility of patients, can hinder adherence to and continuation of therapy. A multitude of studies have documented instances of suboptimal adherence and discontinuation of GBT in real-world settings.[9,10,16] It is not uncommon for temporary interruptions or modifications in antibiotic therapy during the treatment of NTM-LD. The current study highlights the therapeutic importance of sustaining NTM-LD treatment and minimizing interruptions. Some research indicates that dual-drug regimens tend to result in fewer adverse effects that necessitate pauses or modifications compared to three-drug regimens, particularly during the initial phases of treatment.[6,17,18] Consequently, certain experts have advocated for a gradual and stepwise introduction of antibiotics when commencing treatment for NTM-LD.[19,20] Prior research has indicated that intermittent therapy, as opposed to daily therapy, may be suitable for certain patients, as it can result in fewer adverse effects without compromising treatment efficacy.[21] In addition to choose adequate drug regimens, engaging in shared decision-making with patients with NTM-LD prior to the commencement of treatment, well education and support by healthcare teams might also enhance adherence and integrity of the treatment.[22]

As previously indicated, there are additional factors that affect the outcomes of NTM-LD beyond the established treatment protocols and their duration. Research conducted by Mourad et al. demonstrated that patients with NTM-LD who also have comorbid conditions experience poorer outcomes compared to those without such comorbidities.[23] Moreover, several studies have emphasized the significant influence of specific comorbidities on mortality associated with NTM-LD, which may be comparable to the mortality directly attributable to NTM-LD itself.[2,14] The current study further corroborates the detrimental effects of comorbidities, including the need for ventilator support, the presence of cancer, HF, and DM on mortality rates. This finding highlights the critical importance of addressing comorbid conditions concurrently with the treatment of NTM-LD. Maintaining a heightened awareness of potential co-morbidities for early diagnosis, along with the implementation of multidisciplinary treatment teams, may be beneficial in the management of NTM-LD.

In contrast, the adjusted HR of three-year mortality in bronchiectasis was reported in NHIRD group was significantly less than 1, suggesting that bronchiectasis is linked to a reduced risk of three-year mortality, while comparing with others including those with fibrocavitary pattern. The relationship between bronchiectasis and mortality associated with NTM-LD is complex. It is well established that NTM-LD presents primarily in two radiological patterns: fibrocavitary and nodular bronchiectasis. The severity of the disease and associated mortality are generally greater in the fibrocavitary pattern compared to the nodular bronchiectasis pattern.[24] Numerous studies have also indicated that bronchiectasis is less frequently associated with mortality among co-morbidities of NTM-LD.[1,3,14] Despite that radiological patterns were lacked in the databases, bronchiectasis itself may not serve as a direct protective factor, it may, in certain instances, correlate with less severe NTM-LD with a diminished risk of death.[24,25]

Several studies have indicated that specific NTM species may be associated with increased mortality rates. A study conducted in Canada found that MK exhibited the highest odds ratio for 5-year mortality when compared to the control population.[1] Our prior research corroborated these findings, revealing an eight-year mortality rate of up to 60 % for MK.[14] The pathogenic virulence of MK among NTM species has been documented in various studies.[26,27] However, the current study

Table 3
The clinical characteristics of subjects in NHIRD.

	All (n = 4538)	Low MCPD (n = 1203)	Medium MCPD (n = 1251)	Maximum MCPD (n = 2084)	p
Age	61.8 ± 15.6	64.7 ± 16.0	61.8 ± 16.4	60.2 ± 14.7	<0.001
Age> 65	2093 (46.1)	657 (54.6)	575 (46.0)	861 (41.3)	<0.001
Sex (Male)	2422 (53.4)	722 (60.0)	672 (53.7)	1028 (49.3)	<0.001
ESRD	168 (3.7)	56 (4.7)	57 (4.6)	55 (2.6)	0.002
Chronic respiratory failure	366 (8.1)	151 (12.6)	124 (9.9)	91 (4.4)	<0.001
Pneumoconiosis	-[a]	-[a]	-[a]	-[a]	0.61
Asthma	460 (10.1)	139 (11.6)	120 (9.6)	201 (9.6)	0.16
COPD	1255 (27.7)	395 (32.8)	330 (26.4)	530 (25.4)	<0.001
Bronchiectasis	966 (21.3)	200 (16.6)	239 (19.1)	527 (25.3)	<0.001
IPF	203 (4.5)	59 (4.9)	44 (3.5)	100 (4.8)	0.16
Cancer	756 (16.7)	229 (19.0)	225 (18.0)	302 (14.5)	0.001
Cirrhosis	14 (0.3)	7 (0.6)	4 (0.3)	3 (0.1)	0.092
GERD	615 (13.6)	140 (11.6)	161 (12.9)	314 (15.1)	0.015
HF	308 (6.8)	116 (9.6)	104 (8.3)	88 (4.2)	<0.001
DM	902 (19.9)	303 (25.2)	261 (20.9)	338 (16.2)	<0.001
Sinusitis	94 (2.1)	22 (1.8)	29 (2.3)	43 (2.1)	0.70
Autoimmune					
RA	89 (2.0)	25 (2.1)	18 (1.4)	46 (2.2)	0.28
SLE	71 (1.6)	19 (1.6)	11 (0.9)	41 (2.0)	0.049
Sicca syndrome	165 (3.6)	34 (2.8)	45 (3.6)	86 (4.1)	0.16
Dermatomyositis	-[a]	-[a]	-[a]	-[a]	0.82
Polymyositis	-[a]	-[a]	-[a]	-[a]	0.91
Transplantation	61 (1.3)	19 (1.6)	13 (1.0)	29 (1.4)	0.49
Treatment duration (days)	192 ± 183.1	41.5 ± 15.5	116.1 ± 76.2	324.5 ± 187.9	<0.001
Intermittent therapy	162 (3.6)	25 (2.1)	39 (3.1)	98 (4.7)	0.003
The duration from diagnosis to treatment (days)	70.4 ± 181.1	104.8 ± 225.5	71.6 ± 179.6	49.7 ± 147.1	<0.001
Days of Follow-up (days)	736.9 ± 394.5	595.7 ± 430.5	693.3 ± 410.8	844.5 ± 326.5	<0.001
Mortality	1237 (27.3)	547 (45.5)	379 (30.3)	311 (14.9)	<0.001

Data represented with mean ± standard deviation or number (%).
Abbreviations: AFS: acid fast staining; BMI: body mass index; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ESRD: end-stage renal disease; GERD: gastroesophageal reflux disease; HF: heart failure; IPF: idiopathic pulmonary fibrosis; MCPD: maximum chemotherapy possession days; NHIRD: National Health Insurance Research Database; RA: rheumatoid arthritis; SLE: systemic lupus erythema.
[a] In accordance with privacy regulations in Taiwan, the exact number of patients is not specified if it is less than 3.

Table 4
Risk factors of 3-year mortality in NHIRD by multivariate analysis.

	Crude HR	p	Adjusted HR	p
MCPD Groups				
Low (28–55 days)	Reference		Reference	
Medium (56–90 days)	0.58 (0.51–0.66)	<0.001	0.74 (0.64–0.85)	<0.001
Maximum (≧ 91 days)	0.24 (0.21–0.28)	<0.001	0.51 (0.42–0.63)	<0.001
The diagnosis of year	1.00 (0.97–1.02)	0.77		
Age>65	3.02 (2.68–3.41)	<0.001	2.27 (2.00–2.57)	<0.001
Male	1.85 (1.64–2.08)	<0.001	1.35 (1.20–1.53)	<0.001
ESRD	2.00 (1.58–2.53)	<0.001	1.86 (1.47–2.36)	<0.001
Chronic respiratory failure	5.17 (4.52–5.91)	<0.001	3.45 (3.00–3.97)	<0.001
Pneumoconiosis	1.61 (0.23–11.35)	0.64		
Asthma	1.26 (1.07–1.49)	0.007		
COPD	2.03 (1.81–2.27)	<0.001	1.27 (1.12–1.44)	<0.001
Bronchiectasis	0.57 (0.48–0.67)	<0.001	0.74 (0.63–0.87)	<0.001
IPF	2.03 (1.64–2.51)	<0.001	2.62 (2.11–3.26)	<0.001
Cancer	2.97 (2.63–3.35)	<0.001	3.12 (2.76–3.53)	<0.001
Cirrhosis	1.98 (0.94–4.15)	0.072		
GERD	1.00 (0.85–1.17)	0.96		
HF	2.75 (2.34–3.23)	<0.001	1.52 (1.29–1.80)	<0.001
DM	1.71 (1.51–1.93)	<0.001		
Sinusitis	0.97 (0.65–1.44)	0.88		
Autoimmune				
RA	1.23 (0.85–1.78)	0.26		
SLE	1.03 (0.65–1.62)	0.90		
Sicca syndrome	0.69 (0.49–0.98)	0.038		
Dermatomyositis	0 (0–2.96E87)	0.93		
Polymyositis	1.51 (0.21–10.68)	0.68		
Transplantation	1.41 (0.93–2.15)	0.11		
The duration from diagnosis to treatment (days)	1.0001 (0.9999–1.0004)	0.35		
Treatment duration	0.996 (0.995–0.996)	<0.001	0.998 (0.997–0.999)	<0.001
Intermittent therapy	1.04 (0.77–1.41)	0.81		

Abbreviations: AFS: acid fast staining; BMI: body mass index; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ESRD: end-stage renal disease; GERD: gastroesophageal reflux disease; HF: heart failure; IPF: idiopathic pulmonary fibrosis; MCPD: maximum chemotherapy possession days; NHIRD: National Health Insurance Research Database; RA: rheumatoid arthritis; SLE: systemic lupus erythema.

revealed a negative association between MK and three-year mortality in the univariate analysis. This inconsistency with previous research may be attributed to the fact that the study population consisted of individuals undergoing treatment. The treatment response for MK lung disease (MK-LD) was notably favorable, with success rates reaching up to 90 %,[28,29] which is significantly higher than the 60 %–70 % response rates observed for MAC and the 30 %–40 % rates for MABC.[28] It is important to note that nearly 20 % of MK-LD patients in our earlier study were receiving treatment.[14] Therefore, timely and appropriate therapeutic interventions may enhance patient outcomes.

A component of our research involved a retrospective analysis of data sourced from a single medical center. However, the robustness of the study is underscored by the validation of its findings through nationwide data from NHIRD. Nonetheless, the current study had some limitations. First of all, the specifics regarding treatment regimens and their durations were derived from prescription records, and there was a lack of direct monitoring of drug utilization. Secondly, the datasets utilized in this study did not include information on NTM subspecies or drug sensitivity testing. Consequently, the distribution of subspecies within MAC and MABC may have an impact on the results.[2] Although data on drug sensitivity were not available, it is noteworthy that over half of the cases of NTM-LD were attributed to MAC, with macrolide

resistance in MAC in Taiwan being approximately 5 %.[30] Thirdly, there was a major concern about immortal bias that survival status might affect the sampling of the longest treatment duration during three consecutive months of the entire treatment course. If focusing on the first 3 months of treatment, the impact of the treatment integrity on treatment outcome also yielded comparable results to those in main text (Please see Supplement data, Tables S5 and S6, Figs. S2 and S3). Finally, making alternative diagnosis other than NTM-LD shortly after initiating treatment might lead the bias on classification of MCPDs. To avoid the concern, one inclusion criteria of the present study was that participants must have received NTM-LD treatment for at least 28 days.

In conclusion, the current research indicates that maximum MCPD was responsible for approximately 50 % of the treatment cases for NTM-LD, potentially leading to improved microbiological cure rates and a reduction in three-year mortality compared to medium and low MCPDs. Consequently, maintaining the integrity of NTM-LD treatment is important. Certain comorbidities were identified as contributors to increased mortality. The effective management of comorbid conditions might also play an important role in NTM-LD treatment, independent of treating NTM-LD itself.

CRediT authorship contribution statement

Ping-Huai Wang: Writing – original draft. **Yu-Feng Wei:** Writing – review & editing. **Chia-Jung Liu:** Writing – review & editing. **Chung-Yu Chen:** Writing – review & editing. **Shu-Wen Lin:** Writing – review & editing. **Sheng-Wei Pan:** Writing – review & editing. **Su-Mei Wang:** Formal analysis, Data curation. **Chin-Chung Shu:** Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Chin-Hao Chang:** Formal analysis, Data curation, Conceptualization. **Chong-Jen Yu:** Writing – review & editing.

Ethics approval and consent to participate

Approval for the study was granted by the respective Research Ethics Committees (201704001RINB). Informed consent was waived because it was a retrospective study, and the data were delinked from personal information.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of competing interest

All of the authors declare no conflict of interest.

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Appendix A. Supplementary data

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References

1. Marras TK, Campitelli MA, Lu H, et al. Pulmonary nontuberculous mycobacteria–associated deaths, ontario, Canada, 2001–2013. *Emerg Infect Dis*. 2017;23:468–476. https://doi.org/10.3201/eid2303.161927.
2. Jhun BW, Moon SM, Jeon K, et al. Prognostic factors associated with long-term mortality in 1445 patients with nontuberculous mycobacterial pulmonary disease: a 15-year follow-up study. *Eur Respir J*. 2020;55, 1900798. https://doi.org/10.1183/13993003.00798-2019.
3. 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:e610–e619. https://doi.org/10.1093/cid/ciaa1381.
4. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Clin Infect Dis*. 2020;71:e1–e36. https://doi.org/10.1093/cid/ciaa241.
5. Haworth CS, Banks J, Capstick T, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). *Thorax*. 2017;72:ii1–ii64. https://doi.org/10.1136/thoraxjnl-2017-210927.
6. Miwa S, Shirai M, Toyoshima M, et al. Efficacy of clarithromycin and ethambutol for Mycobacterium avium complex pulmonary disease. A preliminary study. *Ann Am Thorac Soc*. 2014;11:23–29. https://doi.org/10.1513/AnnalsATS.201308-266OC.
7. Ushiki A, Tanaka S, Yamanaka M, et al. Effect of multidrug therapy on the prognosis of Mycobacterium avium complex pulmonary disease. *Sci Rep*. 2024;14:4438. https://doi.org/10.1038/s41598-024-55135-0.
8. Adjemian J, Prevots DR, Gallagher J, Heap K, Gupta R, Griffith D. Lack of adherence to evidence-based treatment guidelines for nontuberculous mycobacterial lung disease. *Ann Am Thorac Soc*. 2014;11:9–16. https://doi.org/10.1513/AnnalsATS.201304-085OC.
9. van Ingen J, Wagner D, Gallagher J, et al. Poor adherence to management guidelines in nontuberculous mycobacterial pulmonary diseases. *Eur Respir J*. 2017;49. https://doi.org/10.1183/13993003.01855-2016.
10. Ku JH, Henkle E, Carlson KF, et al. Evaluation of Mycobacterium avium complex pulmonary disease treatment completion and adherence to ATS/IDSA guidelines. *Clin Infect Dis*. 2023;76:e1408–e1415. https://doi.org/10.1093/cid/ciac394.
11. Hoefsloot W, Dacheva E, van der Laan R, et al. Real-world treatment patterns in patients with nontuberculous mycobacterial lung disease in The Netherlands based on medication dispensing data. *BMC Pulm Med*. 2023;23:218. https://doi.org/10.1186/s12890-023-02460-1.
12. Diel R, Nienhaus A, Ringshausen FC, et al. Microbiologic outcome of interventions against Mycobacterium avium complex pulmonary disease: a systematic review. *Chest*. 2018;153:888–921. https://doi.org/10.1016/j.chest.2018.01.024.
13. Pasipanodya JG, Ogbonna D, Deshpande D, Srivastava S, Gumbo T. Meta-analyses and the evidence base for microbial outcomes in the treatment of pulmonary Mycobacterium avium-intracellulare complex disease. *J Antimicrob Chemother*. 2017;72:i3–i19. https://doi.org/10.1093/jac/dkx311.
14. Wang PH, Pan SW, Wang SM, Shu CC, Chang CH. The impact of nontuberculous mycobacteria species on mortality in patients with nontuberculous mycobacterial lung disease. *Front Microbiol*. 2022;13, 909274. https://doi.org/10.3389/fmicb.2022.909274.
15. van Ingen J, Aksamit T, Andrejak C, et al. Treatment outcome definitions in nontuberculous mycobacterial pulmonary disease: an NTM-NET consensus statement. *Eur Respir J*. 2018;51. https://doi.org/10.1183/13993003.00170-2018.
16. Kwak N, Park J, Kim E, Lee CH, Han SK, Yim JJ. Treatment outcomes of Mycobacterium avium complex lung disease: a systematic review and meta-analysis. *Clin Infect Dis*. 2017;65:1077–1084. https://doi.org/10.1093/cid/cix517.
17. Abate G, Stapleton JT, Rouphael N, et al. Variability in the management of adults with pulmonary nontuberculous mycobacterial disease. *Clin Infect Dis*. 2021;72:1127–1137. https://doi.org/10.1093/cid/ciaa252.
18. Ito Y, Miwa S, Shirai M, et al. Macrolide resistant Mycobacterium avium complex pulmonary disease following clarithromycin and ethambutol combination therapy. *Respir Med*. 2020;169, 106025. https://doi.org/10.1016/j.rmed.2020.106025.
19. Griffith DE, Aksamit TR. Managing Mycobacterium avium complex lung disease with a little help from my friend. *Chest*. 2021;159:1372–1381. https://doi.org/10.1016/j.chest.2020.10.031.
20. Ali J. A multidisciplinary approach to the management of nontuberculous mycobacterial lung disease: a clinical perspective. *Expet Rev Respir Med*. 2021;15:663–673. https://doi.org/10.1080/17476348.2021.1887734.
21. Jeong BH, Jeon K, Park HY, et al. Intermittent antibiotic therapy for nodular bronchiectatic Mycobacterium avium complex lung disease. *Am J Respir Crit Care Med*. 2015;191:96–103. https://doi.org/10.1164/rccm.201408-1545OC.
22. Nasiri MJ, Ebrahimi G, Arefzadeh S, Zamani S, Nikpor Z, Mirsaeidi M. Antibiotic therapy success rate in pulmonary Mycobacterium avium complex: a systematic review and meta-analysis. *Expert Rev Anti Infect Ther*. 2020;18:263–273. https://doi.org/10.1080/14787210.2020.1720650.
23. Mourad A, Baker AW, Stout JE. Reduction in expected survival associated with nontuberculous mycobacterial pulmonary disease. *Clin Infect Dis*. 2021;72:e552–e557. https://doi.org/10.1093/cid/ciaa1267.

24. Kim H-J, Kwak N, Hong H, et al. BACES score for predicting mortality in nontuberculous mycobacterial pulmonary disease. *Am J Respir Crit Care Med*. 2021; 203:230–236. https://doi.org/10.1164/rccm.202004-1418oc.
25. 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. https://doi.org/10.1164/rccm.200604-571ST.
26. Stout JE, Koh WJ, Yew WW. Update on pulmonary disease due to non-tuberculous mycobacteria. *Int J Infect Dis*. 2016;45:123–134. https://doi.org/10.1016/j.ijid.2016.03.006.
27. Huang HL, Cheng MH, Lu PL, Liu CJ, Chong IW, Wang JY. Predictors of developing Mycobacterium kansasii pulmonary disease within 1 year among patients with single isolation in multiple sputum samples: a retrospective, longitudinal, multicentre study. *Sci Rep*. 2018;8, 17826. https://doi.org/10.1038/s41598-018-36255-w.
28. Cheng L-P, Chen S-H, Lou H, et al. Factors associated with treatment outcome in patients with nontuberculous mycobacterial pulmonary disease: a large population-based retrospective cohort study in shanghai. *Tropical Medicine and Infectious Disease*. 2022;7:27. https://doi.org/10.3390/tropicalmed7020027.
29. Huang HL, Lu PL, Lee CH, Chong IW. Treatment of pulmonary disease caused by Mycobacterium kansasii. *J Formos Med Assoc*. 2020;119(Suppl 1):S51–s57. https://doi.org/10.1016/j.jfma.2020.05.018.
30. Pan SW, Shu CC, Feng JY, et al. Impact of different subspecies on disease progression in initially untreated patients with Mycobacterium avium complex lung disease. *Clin Microbiol Infect*. 2021;27. https://doi.org/10.1016/j.cmi.2020.04.020, 467.e469-467.e414.