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Predictors of radiographic progression for NTM–pulmonary disease diagnosed by bronchoscopy

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ABSTRACT

Objectives: A single isolate of nontuberculous mycobacterium (NTM) from bronchoscopic samples satisfies the microbiological criterion for diagnosing NTM-pulmonary disease (PD). Studies investigating patients with NTM-PD and multiple culture-negative sputum samples but culture-positive bronchoscopic samples are lacking. We investigated the clinical characteristics, outcome, and predictors of radiographic progression in this special population.

Methods: Patients with negative NTM culture from ≥2 expectorated sputum samples within the 3 months prior to bronchoscopy diagnosis of NTM-PD between 2009 and 2017 were included. Patient characteristics and clinical course were described. Predictors for radiographic progression of NTM-PD within 2 years were analysed by using multivariate logistic regression.

Results: Among 66 patients with bronchoscopy-diagnosed NTM-PD, radiographic progression occurred within 2 years in 17 (26%). Of the 60 patients not initially treated, radiographic progression occurred in 17 (28%). Among them, 10 never received treatment, with 6 deteriorating and 3 dying. Of the 6 and 7 patients who received treatment immediately after NTM-PD diagnosis and after radiographic progression, respectively, none had further radiographic progression. The independent predictors of radiographic progression were male sex, body mass index <18.5 kg/m^2, use of inhaled corticosteroids, and acid-fast smear grade ≥2 of index bronchoscopic samples.

Conclusions: Among patients with bronchoscopy-diagnosed NTM-PD, one fourth experienced radiographic progression within 2 years. The risk was even higher in those with the aforementioned predictors, immediate treatment or close monitoring is recommended. For others, conservative management by regular microbiological monitoring for sputum samples and image follow-up may be the optimal choice.

1. Introduction

The prevalence of pulmonary disease (PD) caused by nontuberculous mycobacteria (NTM) is increasing worldwide, and prompt diagnosis and timely intervention of NTM-PD should be considered when patients encounter clinical deterioration. According to the current statements of the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) published in 2007 [1] and the British Thoracic Society (BTS) guidelines published in 2017 [2], diagnosis of NTM-PD should be made on the basis of microbiological evidence from respiratory

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specimens in conjunction with appropriate clinical and radiographic findings. For patients with little or even no sputum and those with persistent culture-negative sputum, bronchoscopy can facilitate the diagnosis of NTM-PD [3–5], and a single NTM isolate from bronchoscopic samples can satisfy the microbiological criterion required for a diagnosis.

Data are limited regarding the prognosis of patients with culture-negative sputum samples and with NTM-PD that is diagnosed only after culture of bronchoscopic samples. A prospective study conducted by Kim et al. in South Korea demonstrated variations in the outcomes of patients with NTM-PD that was diagnosed through bronchoscopy [6]. Those with little sputum (n = 47) tended to have a poorer outcome in terms of culture conversion and disease progression than did those with no sputum (n = 21). However, the size of each group was too small to clearly illustrate the clinical characteristics of the groups. Furthermore, the optimal time at which to initiate antimicrobial treatment for these patients remains uncertain. The decision to begin the lengthy and potentially toxic treatment for NTM-PD should be carefully made [3].

We therefore conducted this multicentre, retrospective cohort study of patients with negative mycobacterial culture in at least 2 sputum samples and with NTM-PD diagnosed through bronchoscopic culture. The objectives of this study are to investigate the risk and predictors of radiographic progression.

2. Material and methods

2.1. Study design

The present retrospective cohort study was conducted in 2 tertiary referral medical centres, namely National Taiwan University Hospital (NTUH) and Kaohsiung Medical University Hospital (KMUH), and their 4 branch hospitals. The study was approved by the medical centres' institutional review boards (NTUH REC 201508017RIND and KMUH IRB-E −20150063), which waived the informed consent requirement because data used in this retrospective study had been deidentified.

2.2. Patient selection

For the period from June 2009 to June 2017, patients meeting the following criteria were identified from the mycobacteriology database: 1) ≥2 sputum samples provided within a 3-month period; 2) all sputum samples culture negative for NTM; 3) bronchoscopy within the 12 months following collection of the first sputum sample; and 4) NTM isolated from bronchoscopic samples. Among the patients, those with the following conditions were excluded: 1) any clinical samples yielding *M. tuberculosis* complex; 2) duration of follow-up being less than 2 years after bronchoscopy; and 3) clinical and radiographic findings incompatible with a diagnosis of NTM-PD [1,2].

Acid-fast smear (AFS), mycobacterial cultures, and NTM species identification were performed as described in a previous study [7]. The patients were followed until radiographic progression of NTM-PD, death, or the censor date, which was 1 July 2019.

2.3. Study outcome

The primary outcome was radiographic progression of NTM-PD within 2 years, defined as an increase in the radiographic score and assessed through chest radiography and computed tomography (CT; preferred). The secondary outcome was treatment response and mortality due to NTM-PD within 2 years.

2.4. Data collection and measurements

Medical records, images, and mycobacteriology results were reviewed. We recorded clinical characteristics from medical records, including age, sex, body mass index (BMI), smoking status, pulmonary and systemic comorbidities, structural lung disease, image findings, results of AFS and mycobacterial culture, clinical course, and treatment. Structural lung disease included previous history of pulmonary tuberculosis, chronic obstructive pulmonary disease (COPD), and bronchiectasis.

Two pulmonologists interpreted chest radiographs and CT scans. The patterns were categorised as fibrocavitary (FC), nodular bronchiectatic (NB), or other [8]. The extent of pulmonary lesions was noted as either focal or multifocal. In addition, the radiographic score was used to assess the severity of pulmonary lesions [9]. Briefly, each lung was divided into 3 areas. Each area was noted on a four-point scale of 0–3 for the extent of infiltration, with a maximum score of 18 for the most extensive involvement.

2.5. Statistical analysis

Numerical variables are presented as the mean ± standard deviation and were compared using independent-samples *t* tests. Categorical variables are expressed as number (percentage) and were compared using the chi-squared test or Fisher's exact test, as appropriate.

Multivariate logistic regression was used to identify independent factors associated with radiographic progression of NTM-PD. Variables with a *p* value of less than 0.1 in the univariate analysis were entered into the multivariate analysis with forward stepwise regression. Adjusted odds ratios (aORs) with 95% confidence intervals and *p* values were calculated. Statistical significance was set at $p < 0.05$ (two-sided). All statistical analyses were performed using IBM SPSS version 20.0 (IBM, Armonk, NY, USA).

3. Results

3.1. Study population

Fig. 1 presents a flowchart of patient selection and enrolment. From June 2009 to June 2017, there were 97,865 cases in the microbiological databases of 6 hospitals in which patients provided ≥2 expectorated sputum samples within a 3-month interval. After selection, a total of 66 cases of NTM-PD diagnosed through bronchoscopy were included for further analysis.

3.2. Clinical characteristics

The mean age of the enrolled patients was 63.4 ± 17.9 years, and 47% of the patients were men. The most common pulmonary and systemic comorbidity was bronchiectasis (47%) and diabetic mellitus (21%), respectively; 68% had structural lung disease. NB was the most common radiographic pattern (72%). The most common NTM species was MAC (55%), followed by *M. kansasii* (MK; 18%) and *M. abscessus* complex (17%). The FC radiographic pattern was more common in the male patients than in the female patients (23% [7 in 31] vs. 6% [2 in 35]; $p = 0.046$). Structural lung disease (77% [24 in 31] vs. 60% [21 in 35]; $p = 0.133$) and MK-PD (26% [8 in 31] vs. 11% [4 in 35]; $p = 0.131$) were more common, yet insignificantly, in the male patients. During the follow-up, radiographic progression occurred in 17 (26%) cases (Fig. 1 and Table 1). Compared with the patients without radiographic progression, those with radiographic progression were more likely to be male (71% vs. 39%; $p = 0.024$); to be malnourished (41% vs. 16%; $p = 0.035$); to have structural lung disease (88% vs. 61%; $p = 0.035$); and to be inhaled corticosteroid (ICS) users (29% vs. 4%; $p = 0.010$). Radiographically, multifocal involvement was more likely in the cases with radiographic progression (100% vs. 80%; $p = 0.043$; Table 2). The AFS grade of bronchoscopic samples was more likely to be ≥ 2 in cases with radiographic progression (29% vs. 8%; $p = 0.025$).

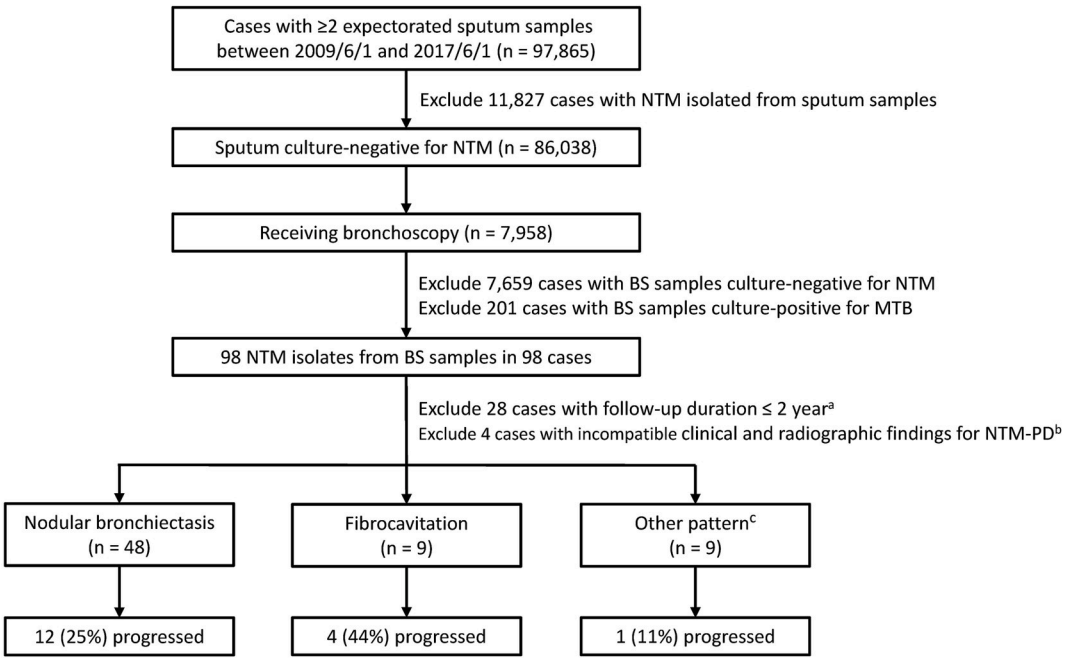

Fig. 1. Flowchart of case selection.
Abbreviation: BS, bronchoscopic; MTB, *Mycobacterium tuberculosis*; NTM, nontuberculous mycobacteria.[a] 20 died within 6 months. The cause of death was bacterial sepsis complicated with acute respiratory failure in 9 (*Pseudomonas aeruginosa*: 4; *Klebsiella pneumoniae*: 2; *Escherichia coli*: 2; methicillin-resistant *Staphylococcus aureus*: 1), pneumonia in 7 (*Acinetobacter baumannii*: 4; *Pseudomonas aeruginosa*: 1; *Enterobacteriaceae*: 1; *Streptococcus pneumoniae*: 1), and 1 each for intra-abdominal infection without positive culture, neutropenic fever after chemotherapy for lung cancer, lung cancer progression, and acute myocardial infarction. Another 8 cases were excluded due to no microbiology or imaging follow-up.[b] In these 4 cases, bronchoscopy was performed under the suspicion of lung cancer.[c] Other patterns included consolidations in 8 cases and RLL atelectasis with pleural effusion in 1.

3.3. Risk factors for radiographic progression

The results of univariate logistical regression for predictors of radiographic progression are displayed in Table 3 (left panel). Multivariate analysis revealed 4 independent predictors of radiographic progression: male sex (aOR 4.60 [1.01–20.90]), BMI < 18.5 kg/m^2 (aOR 6.15 [1.38–27.35]), ICS use (aOR 9.84 [1.47–65.98]), and initial bronchoscopic sample AFS grade ≥ 2 (aOR 6.86 [1.16–40.71]; Table 3, right panel).

3.4. Clinical course, treatment, and outcome

Of the 17 (26% of 66) patients who experienced radiographic progression within the 2 years from the index date, the median time to progression was 10.9 months (Table 4); 11 (65%) cases of radiographic progression occurred within the first year. The radiographic progression rate was 29% (17 in 59) if excluding the seven patients with pulmonary disease caused by the two and unidentified NTM species.

Over the 2-year follow-up, the number of sputum samples obtained was significantly higher in cases with radiographic progression than those without (5.6 ± 4.9 vs 2.9 ± 2.5, $p = 0.007$; Table 3). NTM was isolated in follow-up sputum samples from 17 patients, with the same NTM species being discovered as that isolated from bronchoscopic samples in 13 cases and different NTM species being identified in 4 cases. Compare to those without same NTM species isolated from follow-up sputum, those with the same NTM species were more likely to have a BMI <18.5 (46% vs 17%, $p = 0.024$), more structural lung disease (92% vs. 62%, $p = 0.037$) and chronic kidney disease, stage 3–5 (23% vs 6%, $p = 0.050$). Fibrocavitory pattern (39% vs. 8%, $p = 0.004$) with more extensive involvement (77% vs. 45%, $p = 0.041$) at initial radiographic examination, AFS grade ≥2 (39% vs. 8%, $p = 0.004$) and isolation of *M. kansassi* (39% vs. 13%, $p = 0.034$) from initial bronchoscopic sample were also associated with isolation of same NTM species in follow-up sputum (Supplementary Table 1). In addition, isolation of the same NTM species from follow-up sputum was more common in the radiographic progression group than in the other group (47% vs. 10%, $p < 0.001$).

Six patients received treatment for NTM-PD immediately after bronchoscopic samples indicated NTM (Fig. 2). Among them, 4 had improvement in pulmonary lesions and none experienced radiographic progression. Among the 60 cases in which treatment was not begun immediately after bronchoscopic samples yielded NTM, radiographic progression occurred in 17 (28%).

The mortality rate within 2 years was higher in the patients with radiographic progression than in those without (3 [18%] vs. 1 [2%], $p = 0.050$), and none received anti-NTM therapy (Table 4).

4. Discussion

This multicentre cohort study had 2 major findings. First, radiographic progression occurred within 2 years in one quarter of the patients with NTM-PD diagnosed through bronchoscopy. Second, risk factors for radiographic progression were male sex, BMI <18.5 kg/m^2, initial bronchoscopic sample AFS grade ≥2, and ICS use.

Because of the indolent clinical course of NTM-PD, not every patient who meets the diagnostic criteria of NTM-PD requires immediate antimicrobial therapy [1,2]. The current study demonstrated that the 2-year radiographic progression rate of untreated NTM-PD diagnosed through bronchoscopy (28%) was lower than that of either in MAC-PD [10–12] or *M. abscessus*-PD [13–15] diagnosed using expectorated sputum samples, with 35%–50% and 40%–60% deterioration if untreated within 3 years, respectively. The low progression rate in the current study was probably due to the culture negativity of the initial expectorated sputum samples, implying a lower mycobacterial burden [16]. Therefore, regular monitoring rather than immediate anti-NTM treatment may be an appropriate option.

To date, several studies have explored the predictors of clinical and radiological deterioration in patients with NTM-PD diagnosed using

Table 1
Clinical characteristics of the 66 patients with bronchoscopy-diagnosed nontuberculous mycobacterial pulmonary disease, stratified by radiological progression.

	Progression (n = 17)	No progression (n = 49)	*p*-value
Age (year)	64.4 ± 16.3	63.1 ± 16.3	0.937
Male sex	12 (71%)	19 (39%)	0.024
Body-mass index (kg/m^2)	18.9 ± 6.0	18.4 ± 6.9	0.424
< 18.5	7 (41%)	8 (16%)	0.035
Smoking status			0.264
Never smoker	7 (41%)	32 (65%)	–
Ex-smoker	7 (41%)	10 (21%)	–
Current smoker	3 (18%)	7 (14%)	–
Pulmonary comorbidity	16 (94%)	36 (74%)	0.073
Structural lung disease[a]	15 (88%)	30 (61%)	0.035
Bronchiectasis	10 (59%)	21 (43%)	0.256
History of pulmonary tuberculosis	4 (24%)	8 (16%)	0.507
COPD	3 (18%)	6 (12%)	0.576
Asthma	3 (18%)	5 (10%)	0.418
Lung cancer	4 (24%)	5 (10%)	0.168
Systemic Comorbidity			
Diabetes mellitus	5 (29%)	9 (18%)	0.337
Extra-pulmonary cancer	3[b] (18%)	7[c] (14%)	0.739
Chronic kidney disease, stage 3–5	2 (12%)	4 (8%)	0.656
Liver cirrhosis	2 (12%)	1 (2%)	0.097
Autoimmune disease	0	3[d] (6%)	0.563
Old cerebrovascular accidence	1 (6%)	3 (6%)	0.971
Steroid user[e]	3 (18%)	8 (16%)	>0.999
ICS user[f]	5 (29%)	2 (4%)	0.010
Ventilator dependent	1 (6%)	2 (4%)	>0.999
Initial symptom			
Sputum	12 (71%)	39 (80%)	0.445
Cough	13 (76%)	35 (71%)	0.688
Hemoptysis	8 (47%)	14 (29%)	0.164
Dyspnea	7 (41%)	12 (25%)	0.190
Weight loss	3 (18%)	4 (8%)	0.362

Abbreviation: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid.
Data are the number (percentage) or mean ± standard deviation.
[a] Structural lung disease includes old pulmonary tuberculosis, bronchiectasis, and COPD.
[b] 1 had hepatocellular carcinoma, 1 lymphoma, and 1 gastric cancer.
[c] 3 had breast cancer, 2 nasopharyngeal carcinoma, 1 colon cancer, and 1 endometrial carcinoma.
[d] 2 had Sicca syndrome, and 1 had rheumatic arthritis.
[e] Steroid use was defined as consumption of steroids with an equivalent dose of prednisolone equal to or greater than 100 mg within the 6 months prior to index bronchoscopy.
[f] ICS use was defined as continuous use of ICSs for at least 1 year prior to index bronchoscopy. In the radiographic progression group, 3 received ICS due to COPD and 2 due to asthma. In the nonprogression group, 1 received ICS due to COPD-asthma overlap syndrome and 1 due to asthma.

expectorated sputum samples. In a study including 57 patients with MAC-PD, risk factors for radiographic progression were old age, slenderness, positive sputum smear for acid-fast bacilli, and cavitation [17]. The results of 2 studies of NB MAC-PD conducted in South Korea and Japan suggest that radiographic progression tends to occur in patients with malnutrition, old age, and extensive lung involvement [14,18]. Regarding *M. abscessus*-PD, some genetic determinants of its virulence have been widely studied [19]. In addition to subspecies, patients with cavitation, multiple lung involvement, and old age have been reported as predictors for *M. abscessus*-PD progression [19–21]. In agreement with other reports, the current study demonstrated that malnutrition is associated with radiographic deterioration. Poor leptin–adiponectin regulation in lean patients has been demonstrated to alter the immune modulation of T-cell response and increase the susceptibility of the patient to inflammation that causes lung injury [22,23].

Table 2
Initial radiographic findings and microbiological results of the 66 patients with bronchoscopy-diagnosed nontuberculous mycobacterial pulmonary disease, stratified by radiological progression.

	Progression (n = 17)	No progression (n = 49)	*p*-value
Initial radiographic finding			
Predominant pattern			
Fibrocavitory	4 (24%)	5 (10%)	0.220
Nodular bronchiectasis	12 (71%)	36 (74%)	0.818
Others[a]	1 (6%)	8 (16%)	0.301
Multifocal involvement	17 (100%)	39 (80%)	0.043
Radiographic score	6.4 ± 2.5	5.5 ± 2.2	0.212
Microbiology			
No. of sputum samples before bronchoscopy	4.0 ± 1.4	3.0 ± 1.0	0.001
Bronchoscopic sample AFS grade ≥2	5 (29%)	4 (8%)	0.025
NTM species			
M. avium intracellular complex	9 (53%)	27 (55%)	0.877
M. kansasii	5 (29%)	7 (14%)	0.164
M. abscessus	3 (18%)	8 (16%)	>0.999
M. gordonae	0	4 (8%)	0.565
M. fortuitum	0	2 (4%)	>0.999
Unidentified species	0	1 (2%)	>0.999

Abbreviation: AFS, acid-fast smear; NTM, nontuberculous mycobacteria.
Data are number (percentage) or mean ± standard deviation.
[a] Other patterns included consolidations in 8 cases and atelectasis with pleural effusion at the right lung in 1.

As noted in patients with tuberculosis, AFS positivity implies a high mycobacterial load and is associated with severe disease [24,25]. In addition, high-grade sputum AFS positivity (≥3) was associated with radiographic progression within 1 year in a study enrolling 221 patients with MK-PD in Taiwan [26]. In agreement with these reports, the current study demonstrated that an AFS grade ≥2 of index bronchoscopic samples was significantly associated with subsequent disease progression.

The finding of this study that male sex is an independent predictor of radiographic progression is interesting. A nationwide population-based study conducted in Denmark revealed that male sex was associated with poorer long-term prognosis of NTM-PD [27]. In another study conducted in Japan, male patients with MAC-PD had a higher 5-year mortality rate than their female counterparts [10]. In addition, male patients were more likely than female patients to have FC lesions and a history of cigarette smoking with more pulmonary comorbidities [16]. The presence of FC lesions has been demonstrated to be a poor prognostic factor for MK-PD [26] and MAC-PD [14]. In the current study, a significantly higher prevalence of FC disease and nonsignificantly higher prevalence of structural lung disease and MK-PD were noted in the male patients. MK is considered one of the most virulent NTM species and has a radiographic progression rate and mortality rate within 1 year of 64% and 28%, respectively [26].

The present study revealed that ICS use within the 1 year prior to diagnosis of NTM-PD was associated with subsequent radiographic progression. Many concerns have been raised that ICS can alter pulmonary immunity by suppressing multiple cytokine mediators of the host response to intracellular pathogens [28,29] and attenuate the adaptive cellular immune response through the interferon-gamma-mediated pathway [30]. Clinical studies conducted in Taiwan, Japan, and Denmark have shown that patients with COPD using an ICS had a dose-dependent increase in the risk of subsequent NTM-PD than those not using an ICS [31–33]. In a case–control study in which data retrieved from a healthcare delivery system in northern California were analysed, the risk of NTM disease was discovered to be 1.8- to 2.7-fold higher among ICS users than nonusers, regardless of age [34]. Although ICS-containing treatment of COPD can reduce the number of exacerbations and improve symptoms [35], carefully

Table 3
Univariate and multivariate logistical regression analysis for potential predictors of radiographic progression of bronchoscopy-diagnosed nontuberculous mycobacterial pulmonary disease.

Variables	Univariate analysis		Multivariate analysis[a]	
	Crude OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Age (years)	1.05 (0.97–1.04)	0.783		
Male sex	3.79 (1.15–12.47)	0.028	4.60 (1.01–20.90)	0.048
BMI < 18.5 (kg/m2)	3.59 (1.05–12.24)	0.041	6.15 (1.38–27.35)	0.017
Cough	1.30 (0.36–4.68)	0.688		
Sputum	0.62 (0.18–2.15)	0.448		
Dyspnea	2.16 (0.67–6.92)	0.195		
Hemoptysis	2.22 (0.71–6.92)	0.168		
Structural lung disease	4.75 (0.98–23.14)	0.054		
COPD	1.54 (0.34–6.96)	0.578		
History of pulmonary TB	1.58 (0.41–6.10)	0.509		
Bronchiectasis	1.91 (0.62–5.83)	0.259		
Lung cancer	2.71 (0.63–11.58)	0.179		
Diabetes mellitus	1.85 (0.52–6.59)	0.341		
CKD, stage 3–5	1.50 (0.25–9.03)	0.658		
Inhaled corticosteroid user	9.79 (1.69–56.81)	0.011	9.84 (1.47–65.98)	0.019
Systemic corticosteroid use	1.00 (0.23–4.28)	>0.999		
Initial radiographic score	1.16 (0.92–1.48)	0.213		
Nodular bronchiectatic pattern	0.87 (0.26–2.94)	0.818		
Fibrocavitary pattern	2.71 (0.63–11.58)	0.179		
Radiographic score	1.16 (0.92–1.48)	0.213		
Bronchoscopic sample AFS ≥2	4.69 (1.09–20.20)	0.038	6.86 (1.16–40.71)	0.034
MAC	0.92 (0.30–2.77)	0.877		
M. abscessus	1.10 (0.26–4.72)	0.900		
M. kansasii	2.50 (0.67–9.31)	0.172		

Abbreviation: AFS, acid-fast smear; BMI, body-mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacterium; TB, tuberculosis.

[a] Variables with a *p* value of less than 0.1 in the univariate analysis were then entered into the multivariate logistic regression analysis with forward stepwise regression.

assessing the phenotypes and using inhaled long-acting bronchodilators as an alternative are essential if potential risks are to be minimised [36], especially in patients with concomitant NTM-PD.

This retrospective study has two limitations. The first is lacking of a standardised follow-up and treatment protocol. The time point at which treatment was initiated was dependent on clinicians' decisions. Therefore, we are unable to make any conclusions regarding to treatment and outcome. The second is that in this cohort study, only small proportion of patients harbouring negative culture for NTM from expectorated sputum samples received bronchoscopy, and the indication for bronchoscopy was difficult to analyse retrospectively.

Table 4
Clinical course and outcome of the 66 patients with bronchoscopy-diagnosed nontuberculous mycobacterial pulmonary disease, stratified by radiological progression.

	Progression (n = 17)	No progression (n = 49)	*p*-value
Time to radiologic progression (months)	10.8 [6.1–13.5]	–	<0.001
Final Radiographic score	9.3 ± 4.3	5.1 ± 2.0	<0.001
Follow-up sputum study within 2 years			
Number of samples	5.6 ± 4.9	2.9 ± 2.5	0.007
Positive for same NTM species	8 (47%)	5 (10%)	<0.001
Presence of other NTM species	2[a] (12%)	2[b] (4%)	0.273
Mortality within 2 years	3[c] (18%)	1[d] (2%)	0.050

Abbreviation: NTM-PD, nontuberculous mycobacterial pulmonary disease.
Data are the number (percentage) or median [Q1-Q3].

[a] *M. abscessus* was obtained from 1 patient whose initial bronchoscopic sample was culture positive for *M. kansasii*. In the other patient whose initial bronchoscopic sample was culture positive for *M. avium* complex (MAC), a photochromogen was isolated during follow-up.

[b] *M. fortuitum* was obtained from 1 patient whose initial bronchoscopic sample was culture positive for MAC. In the other patient whose initial bronchoscopic sample contained *M. abscessus*, MAC was isolated during follow-up.

[c] One patient died of MAC-PD at 11 months after the index date. He did not receive anti-MAC treatment due to old age (78 years). Another patient received anti-*M. kansasii* treatment but this was discontinued 10 days later due to intolerance. She died of *M. kansasii*-PD at 13 months after the index date. The remaining patient died of lung cancer at 1 year after the index date.

[d] This patient died of lung cancer at 17 months after the index date.

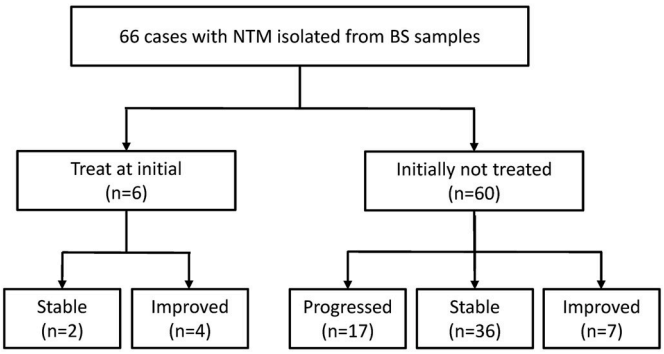

Fig. 2. Clinical course of the 66 patients with bronchoscopy-diagnosed nontuberculous mycobacterial pulmonary disease.
Abbreviation: BS, bronchoscopic; NTM, nontuberculous mycobacteria.

5. Conclusions

In conclusion, radiographic progression occurred within 2 years was noted in one quarter of patients with NTM-PD diagnosed through bronchoscopy. The predictors of progression include male sex, BMI <18.5 kg/m^2, ICS use, and bronchoscopic sample AFS grade ≥2. For patients with these risk factors, immediate treatment or close monitoring is recommended. For others, conservative management by regular microbiological monitoring for sputum samples and image follow-up may be the optimal choice.

Data sharing statement

All data were deposited in the Information Technology Office of NTUH and the Statistical Analysis Laboratory, Department of Medical Research, KMUH. The data are not available for sharing without permission.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2019.105847.

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Author contributions

HLH, JYW, and IWC designed the study. MHC, MRL, CJL, and PLL performed the database analysis. HLH and CJL contributed to the statistical analysis. HLH, JYW, and IWC contributed to data interpretation and prepared the first draft of the manuscript. MHC, MRL, and PLL critically revised the draft manuscript. JYW and IWC were responsible for coordination. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

[1] D.E. Griffith, T. Aksamit, B.A. Brown-Elliott, A. Catanzaro, C. Daley, F. Gordin, S. M. Holland, R. Horsburgh, G. Huitt, M.F. Iademarco, M. Iseman, K. Olivier, S. Ruoss, C.F. von Reyn, R.J. Wallace Jr., K. Winthrop, An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases, Am. J. Respir. Crit. Care Med. 175 (4) (2007) 367–416.

[2] C.S. Haworth, J. Banks, T. Capstick, A.J. Fisher, T. Gorsuch, I.F. Laurenson, A. Leitch, M.R. Loebinger, H.J. Milburn, M. Nightingale, P. Ormerod, D. Shingadia, D. Smith, N. Whitehead, R. Wilson, R.A. Floto, British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD), Thorax 72 (Suppl 2) (2017) ii1–ii64.

[3] J.H. Huang, P.N. Kao, V. Adi, S.J. Ruoss, Mycobacterium avium-intracellulare pulmonary infection in HIV-negative patients without preexisting lung disease: diagnostic and management limitations, Chest 115 (4) (1999) 1033–1040.

[4] E. Tanaka, R. Amitani, A. Niimi, K. Suzuki, T. Murayama, F. Kuze, Yield of computed tomography and bronchoscopy for the diagnosis of Mycobacterium avium complex pulmonary disease, Am. J. Respir. Crit. Care Med. 155 (6) (1997) 2041–2046.

[5] E. Sugihara, N. Hirota, T. Niizeki, R. Tanaka, M. Nagafuchi, T. Koyanagi, N. Ono, T. Rikimaru, H. Aizawa, Usefulness of bronchial lavage for the diagnosis of pulmonary disease caused by Mycobacterium avium-intracellulare complex (MAC) infection, J. Infect. Chemother. 9 (4) (2003) 328–332.

[6] H.J. Kim, J.H. Lee, S.H. Yoon, S.A. Kim, M.S. Kim, S.M. Choi, J. Lee, C.H. Lee, S. K. Han, J.J. Yim, Nontuberculous mycobacterial pulmonary disease diagnosed by two methods: a prospective cohort study, BMC Infect. Dis. 19 (1) (2019) 468.

[7] H.L. Huang, M.H. Cheng, P.L. Lu, C.C. Shu, J.Y. Wang, J.T. Wang, I.W. Chong, L. N. Lee, Epidemiology and predictors of NTM pulmonary infection in Taiwan - a retrospective, Five-year multicenter study, Sci. Rep. 7 (1) (2017) 16300.

[8] S.J. Hong, T.J. Kim, J.H. Lee, J.S. Park, Nontuberculous mycobacterial pulmonary disease mimicking lung cancer: clinicoradiologic features and diagnostic implications, Medicine (Baltim.) 95 (26) (2016), e3978.

[9] G.L. Snider, L. Doctor, T.A. Demas, A.R. Shaw, Obstructive airway disease in patients with treated pulmonary tuberculosis, Am. Rev. Respir. Dis. 103 (5) (1971) 625–640.

[10] M. Hayashi, N. Takayanagi, T. Kanauchi, Y. Miyahara, T. Yanagisawa, Y. Sugita, Prognostic factors of 634 HIV-negative patients with Mycobacterium avium complex lung disease, Am. J. Respir. Crit. Care Med. 185 (5) (2012) 575–583.

[11] J.A. Hwang, S. Kim, K.W. Jo, T.S. Shim, Natural history of Mycobacterium avium complex lung disease in untreated patients with stable course, Eur. Respir. J. 49 (3) (2017).

[12] S.W. Pan, C.C. Shu, J.Y. Feng, J.Y. Wang, Y.J. Chan, C.J. Yu, W.J. Su, Microbiological persistence in patients with Mycobacterium avium complex lung disease: the predictors and the impact on radiographic progression, Clin. Infect. Dis. 65 (6) (2017) 927–934.

[13] M.R. Lee, L.T. Keng, C.C. Shu, S.W. Lee, C.H. Lee, J.Y. Wang, L.N. Lee, C.J. Yu, P. C. Yang, Risk factors for Mycobacterium chelonae-abscessus pulmonary disease persistence and deterioration, J. Infect. 64 (2) (2012) 228–230.

[14] S.J. Kim, J. Park, H. Lee, Y.J. Lee, J.S. Park, Y.J. Cho, H.I. Yoon, C.T. Lee, J.H. Lee, Risk factors for deterioration of nodular bronchiectatic Mycobacterium avium complex lung disease, Int. J. Tuberc. Lung Dis. 18 (6) (2014) 730–736.

[15] K. Jeon, O.J. Kwon, N.Y. Lee, B.J. Kim, Y.H. Kook, S.H. Lee, Y.K. Park, C.K. Kim, W. J. Koh, Antibiotic treatment of Mycobacterium abscessus lung disease: a retrospective analysis of 65 patients, Am. J. Respir. Crit. Care Med. 180 (9) (2009) 896–902.

[16] D.E. Griffith, Nontuberculous Mycobacterial Disease: A Comprehensive Approach to Diagnosis and Management, Springer, 2018.

[17] Y. Yamazaki, K. Kubo, A. Takamizawa, H. Yamamoto, T. Honda, S. Sone, Markers indicating deterioration of pulmonary Mycobacterium avium-intracellulare infection, Am. J. Respir. Crit. Care Med. 160 (6) (1999) 1851–1855.

[18] S. Kitada, T. Uenami, K. Yoshimura, Y. Tateishi, K. Miki, M. Miki, H. Hashimoto, T. Fujikawa, M. Mori, K. Matsuura, M. Kuroyama, R. Maekura, Long-term radiographic outcome of nodular bronchiectatic Mycobacterium avium complex pulmonary disease, Int. J. Tuberc. Lung Dis. 16 (5) (2012) 660–664.

[19] J. Park, J. Cho, C.H. Lee, S.K. Han, J.J. Yim, Progression and treatment outcomes of lung disease caused by Mycobacterium abscessus and Mycobacterium massiliense, Clin. Infect. Dis. 64 (3) (2017) 301–308.

[20] H. Nagano, R. Amitani, N. Okamoto, M. Yoshida, M. Taki, K. Hanaoka, Y. Nakamura, C. Yoshimura, Y. Nishizaka, [A clinical study of pulmonary Mycobacterium abscessus infection], Kansenshogaku Zasshi Journal of the Japanese Association for Infectious Diseases 87 (6) (2013) 726–731.

[21] S.J. Shin, G.E. Choi, S.N. Cho, S.Y. Woo, B.H. Jeong, K. Jeon, W.J. Koh, Mycobacterial genotypes are associated with clinical manifestation and progression of lung disease caused by Mycobacterium abscessus and Mycobacterium massiliense, Clin. Infect. Dis. 57 (1) (2013) 32–39.

[22] M. Kartalija, A.R. Ovrutsky, C.L. Bryan, G.B. Pott, G. Fantuzzi, J. Thomas, M. J. Strand, X. Bai, P. Ramamoorthy, M.S. Rothman, V. Nagabhushanam, M. McDermott, A.R. Levin, A. Frazer-Abel, P.C. Giclas, J. Korner, M.D. Iseman, L. Shapiro, E.D. Chan, Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes, Am. J. Respir. Crit. Care Med. 187 (2) (2013) 197–205.

[23] G. Fantuzzi, Adipose tissue, adipokines, and inflammation, J. Allergy Clin. Immunol. 115 (5) (2005) 911–919, quiz 920.

[24] H.K. Kang, B.H. Jeong, H. Lee, H.Y. Park, K. Jeon, H.J. Huh, C.S. Ki, N.Y. Lee, W. J. Koh, Clinical significance of smear positivity for acid-fast bacilli after >/=5 months of treatment in patients with drug-susceptible pulmonary tuberculosis, Medicine (Baltim.) 95 (31) (2016), e4540.

[25] F.M. Perrin, N. Woodward, P.P. Phillips, T.D. McHugh, A.J. Nunn, M.C. Lipman, S. H. Gillespie, Radiological cavitation, sputum mycobacterial load and treatment response in pulmonary tuberculosis, Int. J. Tuberc. Lung Dis. 14 (12) (2010) 1596–1602.

[26] C.J. Liu, H.L. Huang, M.H. Cheng, P.L. Lu, C.C. Shu, J.Y. Wang, I.W. Chong, Outcome of patients with and poor prognostic factors for Mycobacterium kansasii-pulmonary disease, Respir. Med. 151 (2019) 19–26.

[27] C. Andrejak, V.O. Thomsen, I.S. Johansen, A. Riis, T.L. Benfield, P. Duhaut, H. T. Sorensen, F.X. Lescure, R.W. Thomsen, Nontuberculous pulmonary mycobacteriosis in Denmark: incidence and prognostic factors, Am. J. Respir. Crit. Care Med. 181 (5) (2010) 514–521.

[28] C.M. Patterson, R.L. Morrison, A. D'Souza, X.S. Teng, K.I. Happel, Inhaled fluticasone propionate impairs pulmonary clearance of Klebsiella pneumoniae in mice, Respir. Res. 13 (1) (2012) 40.

[29] C. Janson, G. Stratelis, A. Miller-Larsson, T.W. Harrison, K. Larsson, Scientific rationale for the possible inhaled corticosteroid intraclass difference in the risk of pneumonia in COPD, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 3055–3064.

[30] S.A. Cowman, J. Jacob, D.M. Hansell, P. Kelleher, R. Wilson, W.O.C. Cookson, M. F. Moffatt, M.R. Loebinger, Whole-blood gene expression in pulmonary nontuberculous mycobacterial infection, Am. J. Respir. Cell Mol. Biol. 58 (4) (2018) 510–518.

[31] S. Ni, Z. Fu, J. Zhao, H. Liu, Inhaled corticosteroids (ICS) and risk of mycobacterium in patients with chronic respiratory diseases: a meta-analysis, J. Thorac. Dis. 6 (7) (2014) 971–978.

[32] C. Andrejak, R. Nielsen, V.O. Thomsen, P. Duhaut, H.T. Sorensen, R.W. Thomsen, Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis, Thorax 68 (3) (2013) 256–262.

[33] M. Hojo, M. Iikura, S. Hirano, H. Sugiyama, N. Kobayashi, K. Kudo, Increased risk of nontuberculous mycobacterial infection in asthmatic patients using long-term inhaled corticosteroid therapy, Respirology 17 (1) (2012) 185–190.

[34] V.X. Liu, K.L. Winthrop, Y. Lu, H. Sharifi, H.U. Nasiri, S.J. Ruoss, Association between inhaled corticosteroid use and pulmonary nontuberculous mycobacterial infection, Ann Am Thorac Soc 15 (10) (2018) 1169–1176.
[35] E. Festic, P.D. Scanlon, Incident pneumonia and mortality in patients with chronic obstructive pulmonary disease. A double effect of inhaled corticosteroids? Am. J. Respir. Crit. Care Med. 191 (2) (2015) 141–148.
[36] D. Singh, A. Agusti, A. Anzueto, P.J. Barnes, J. Bourbeau, B.R. Celli, G.J. Criner, P. Frith, D.M.G. Halpin, M. Han, M.V. Lopez Varela, F. Martinez, M. Montes de Oca, A. Papi, I.D. Pavord, N. Roche, D.D. Sin, R. Stockley, J. Vestbo, J.A. Wedzicha, C. Vogelmeier, Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019, Eur. Respir. J. 53 (5) (2019).