Outcomes of *Mycobacterium avium* complex lung disease based on clinical phenotype

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ABSTRACT The effect of the clinical phenotype of *Mycobacterium avium* complex (MAC) lung disease on treatment outcome and redevelopment of nontuberculous mycobacterial (NTM) lung disease after treatment completion has not been studied systematically.

We evaluated 481 treatment-naïve patients with MAC lung disease who underwent antibiotic treatment for ⩾12 months between January 2002 and December 2013.

Out of 481 patients, 278 (58%) had noncavitary nodular bronchiectatic (NB) disease, 80 (17%) had cavitary NB disease and 123 (25%) had fibrocavitary disease. Favourable outcome was higher in patients with noncavitary disease (88%) than in patients with cavitary disease (76% for fibrocavitary and 78% for cavitary NB disease; $p<0.05$). Cavitary disease was independently associated with unfavourable outcomes ($p<0.05$). Out of 402 patients with favourable outcomes, 118 (29%) experienced redevelopment of NTM lung disease, with the same MAC species recurring in 65 (55%) patients. The NB form was an independent risk factor for redevelopment of NTM lung disease ($p<0.05$). In patients with recurrent MAC lung disease due to the same species, bacterial genotyping revealed that 74% of cases were attributable to reinfection and 26% to relapse.

Treatment outcomes and redevelopment of NTM lung disease after treatment completion differed by clinical phenotype of MAC lung disease.

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Introduction

The incidence and prevalence of lung disease caused by nontuberculous mycobacteria (NTM) are increasing worldwide [1, 2]. *Mycobacterium avium* complex (MAC) predominantly consists of *M. avium* and *M. intracellulare* and is the most common aetiology of NTM lung disease worldwide [1, 2]. MAC lung disease usually has two major clinical phenotypes: fibrocavitary and nodular bronchiectatic (NB) [3, 4]. The fibrocavitary form is characterised by cavitary lesions that occur predominantly in the upper lobes and usually develops in older males with underlying lung disease, such as previous pulmonary tuberculosis and/or chronic obstructive pulmonary disease (COPD) [3]. The NB form occurs predominantly in postmenopausal, nonsmoking females [3] and can present as bilateral bronchiectasis with multiple nodules and tree-in-bud opacities on high-resolution computed tomography (HRCT). However, some patients with the NB form also have small cavitary lesions [5–7].

Macrolide-based combination antibiotic therapy is recommended for MAC lung disease, and current guidelines recommend different antibiotic regimens according to clinical phenotype: intermittent, three-times-weekly oral administration of three drugs for noncavitary NB (NC-NB) MAC lung disease; and daily oral drugs with or without parenteral drugs such as streptomycin or amikacin for cavitary MAC lung disease, including cavitary NB (C-NB) and fibrocavitary forms [3]. Treatment outcomes of the C-NB forms may be different from the NC-NB forms of MAC lung disease. However, many published studies that evaluated the clinical efficacy of macrolide-based antibiotic therapy did not differentiate between these clinical phenotypes [8–12], or included mainly NC-NB MAC lung disease and not cavitary disease [13–15].

In addition, recurrence of MAC lung disease or redevelopment of NTM lung disease is not uncommon after treatment completion [13, 16–18]. However, the impact of the clinical phenotype of MAC lung disease on treatment outcomes and on the recurrence of MAC lung disease or redevelopment of NTM lung disease has not yet been studied systematically. The purpose of the present study was to evaluate associations between clinical phenotypes and treatment outcomes, including recurrence of MAC lung disease or redevelopment of NTM lung disease after treatment completion, in patients with MAC lung disease.

Methods

Study population

Consecutive patients with MAC lung disease who received combination antibiotic treatment between January 2002 and December 2013 were identified using the database of the NTM registry of Samsung Medical Center (a 1979-bed referral hospital in Seoul, South Korea). Data from January 2002 to December 2007 were obtained from the retrospective cohort [19, 20], and data since January 2008 were obtained from an ongoing institutional review board-approved prospective observational cohort study to investigate NTM lung disease. Written informed consent was obtained from all participants (ClinicalTrials.gov identifier NCT00970801) [14].

The radiological phenotypes were classified according to the main features on chest radiography and HRCT. The fibrocavitary form was defined by the presence of cavitary opacities and pleural thickening, mainly in the upper lobes on chest radiograph and HRCT (online supplementary figure S1). The NB form was defined by the presence of multifocal bronchiectasis and clusters of small nodules on chest HRCT, regardless of the presence of small cavities in the lungs [6, 14]. The NB form was further classified into cavitary (C-NB) *versus* noncavitary (NC-NB) according to the presence of cavitary lesion(s) (online supplementary figures S2 and S3). When the disease did not belong to either the fibrocavitary form or the NB form, such as for cases with solitary pulmonary nodules, it was deemed unclassifiable.

During a 12-year period, 714 patients with MAC lung disease started antibiotic treatment. All patients met the diagnostic criteria for NTM lung disease [3]. After excluding patients who had a history of previous treatment of NTM lung disease (n=25), patients who had received prior antibiotic therapy for >1 month before transfer to our hospital (n=82), and patients with an unclassifiable form (n=41), 566 patients were started on MAC therapy during the study period. 85 (15%) patients were further excluded from the main analysis, because they received <12 months of antibiotic treatment due to discontinuation of antibiotics, loss to follow-up, transfer-out or death. The remaining 481 patients with newly diagnosed MAC lung disease, either the fibrocavitary or NB form, who received antibiotic therapy for ⩾12 months were included in the final study (figure 1).

Microbiological examinations

During the study period, MAC species were identified using PCR-restriction fragment length polymorphism analysis of the *rpoB* gene or reverse-blot hybridisation of *rpoB* [14, 20]. Drug susceptibility testing was performed using the broth microdilution method [21]. Isolates with a minimum inhibitory concentration of ⩾32 $\mu g \cdot mL^{-1}$ were considered resistant to clarithromycin [21]. For MAC isolates with

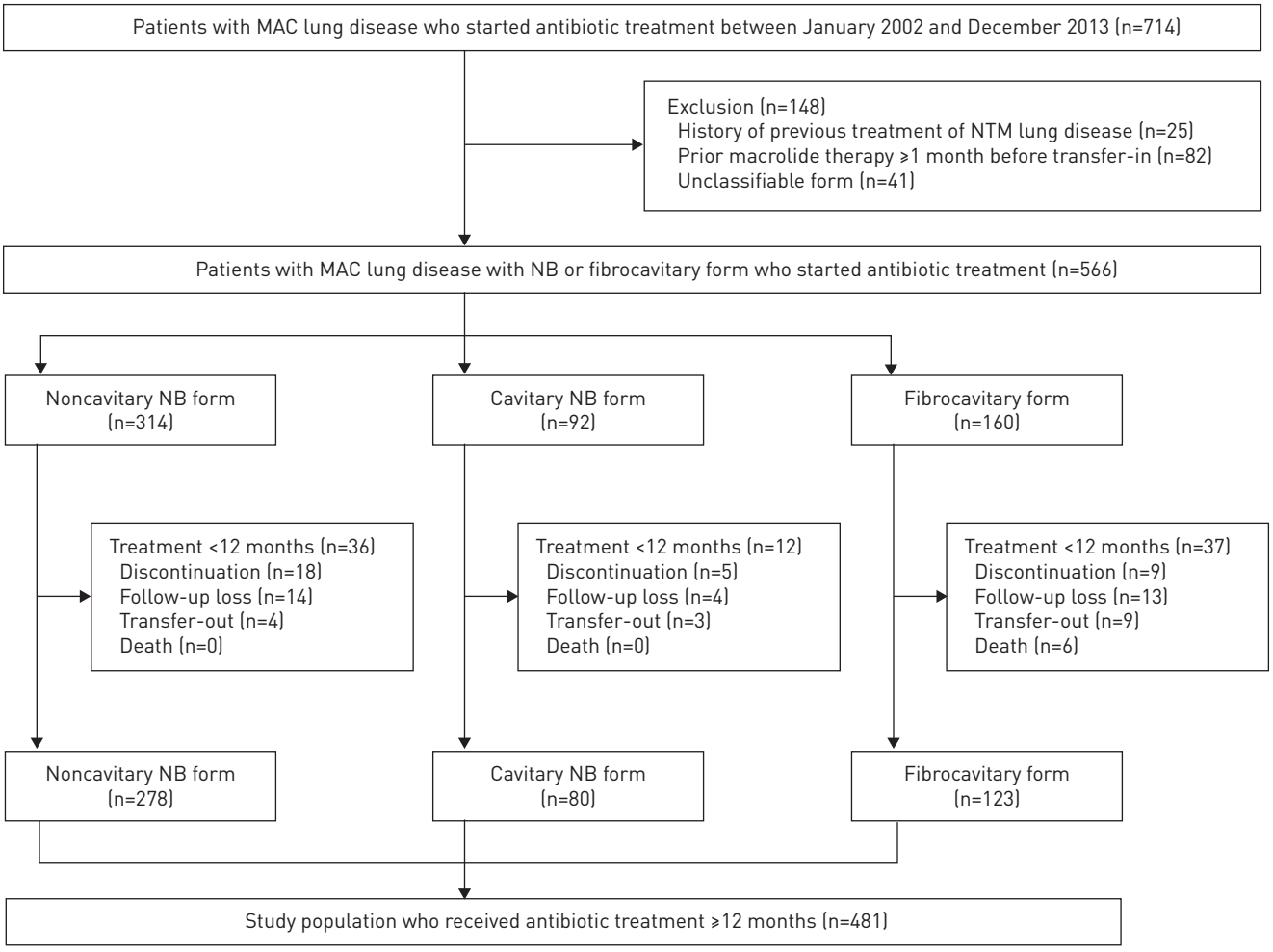

FIGURE 1 Study population. MAC: *Mycobacterium avium* complex; NTM: nontuberculous mycobacterial; NB: nodular bronchiectatic.

clarithromycin resistance, mutations in the 23S rRNA gene were detected using PCR sequencing, as described previously [22].

In this study, "redevelopment" of NTM lung disease was defined as the subsequent diagnosis of NTM lung disease, regardless of causative NTM organism, after treatment completion of MAC lung disease. Cases where MAC lung disease had reappeared due to a different species were classed only as redevelopment. "Recurrence" of MAC lung disease was defined as two or more positive cultures of a MAC species after treatment completion for the same species, *i.e.* a redevelopment of *M. avium* (or *M. intracellulare*) lung disease after treatment completion of lung disease due to the same organism [13]. In cases of recurrent MAC lung disease, "relapse" with the same MAC genotype and "reinfection" with a new MAC genotype were distinguished. Mycobacterial genotyping was performed using repetitive sequence-based PCR (rep-PCR), which was standardised according to the DiversiLab *Mycobacterium* kit protocol [23]. Reports for rep-PCR were generated based on the Kullback–Leibler method, and isolates with identical profiles or >97% similarity were regarded as indistinguishable [24, 25].

Antibiotic therapy and treatment outcomes

All patients who began antibiotic therapy received standardised combination antibiotic therapy, which consisted of an oral macrolide (clarithromycin or azithromycin), rifampicin and ethambutol [3]. Streptomycin was administered intramuscularly three times a week in patients with severe disease for the first several months, at the discretion of the attending physician. In our institution, all patients with MAC lung disease were treated with daily regimens before January 2011. After January 2011, all patients with the NC-NB form were initially treated with intermittent, three-times-weekly therapy regimens [14].

Sputum examinations were performed at 1, 3 and 6 months after initiation of antibiotic treatment and then at 2–3-month intervals during treatment. Sputum culture conversion was defined as three consecutive

negative cultures, and the time to culture conversion was defined as the date of the first negative culture [14]. Favourable outcome was defined as sputum culture conversion after initiation of treatment and maintenance of a negative culture for ⩾12 months on treatment. Unfavourable outcome was defined as no sputum culture conversion or by death. Some clinical data were included in previous studies [14, 19, 20]. After treatment completion, the patients were typically followed-up with sputum examinations every 6 months. Data on final treatment outcomes, follow-up information including redevelopment of NTM lung disease, and analyses of stored MAC isolates were collected in the current study.

Statistical analyses

All data are presented as n (%) for categorical variables and median (interquartile range (IQR)) for continuous variables. Data categorised according to the three clinical phenotypes were compared using the Kruskal–Wallis test for continuous variables and Fisher's exact test for categorical variables. If there was a significant difference among the three groups, then *post hoc* analysis for multiple comparisons was performed with Tukey's test using ranks for continuous variables and Fisher's exact test using the permutation method for categorical variables.

To investigate potential independent factors associated with either unfavourable outcomes or redevelopment of NTM lung disease, multiple logistic regression analysis and multiple Cox regression with backward selection, respectively, were used. Variables including sex, age, body mass index (BMI), aetiological species, clinical phenotypes, sputum smear positivity, combined chronic pulmonary aspergillosis (CPA), COPD, previous lung resection history, combined use of injectable drugs and surgical resection were added to the regression models. p-values and confidence intervals were corrected using Bonferroni's method for multiple testing in multiple regression analysis. When estimating redevelopment of NTM lung disease, death was considered as a competing risk.

The Kaplan–Meier method was used to estimate the cumulative rates of redevelopment of NTM lung disease and the log-rank test was used to compare curves of the rates. A two-sided $p<0.05$ was considered significant. All data sets were analysed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R3.2.3 (R Development Core Team, Vienna, Austria; www.R-project.org).

Results

Baseline characteristics

Out of the 481 patients, 278 (58%) had the NC-NB form, 80 (17%) had the C-NB form, and 123 (25%) had the fibrocavitary form of MAC lung disease (table 1). None of the patients tested positive for HIV. *M. avium* was the more common aetiologic organism in patients with the NC-NB form, whereas *M. intracellulare* was more common in patients with the fibrocavitary form ($p<0.001$). No isolates were resistant to clarithromycin in drug susceptibility testing at the time of diagnosis of MAC lung disease.

Treatment modalities and outcomes

All patients with C-NB and fibrocavitary forms were prescribed three oral drugs daily. About half (51%) of the patients with the NC-NB form received intermittent drug regimens. Streptomycin injection was used more frequently in patients with cavitary (68% (138 out of 203)) than noncavitary disease (26% (72 out of 278), $p<0.001$). Total antibiotic treatment duration was longer in patients with cavitary (24.0 (18.9–26.5) months) than noncavitary disease (19.7 (15.9–24.1) months; $p<0.001$) (table 2).

A favourable outcome was achieved in 84% (402 out of 481) of patients, and was higher for NC-NB disease (88% (246 out of 278)) than for cavitary disease (76% (94 out of 123) with the fibrocavitary form and 78% (62 out of 80) with the C-NB form; $p=0.006$ and $p=0.037$, respectively) (table 2). Unfavourable outcomes occurred in 16% (79 out of 481) patients, and 24 (30%) had died by the end of January 2016.

Risk factors for unfavourable outcomes

Of the 481 patients, the final multiple logistic regression model revealed that male sex (adjusted (a)OR 1.80, 95% CI 1.07–3.02; $p=0.027$) and cavitary disease, including both the C-NB (aOR 2.36, 95% CI 1.24–4.52; $p=0.009$) and fibrocavitary form (aOR 1.99, 95% CI 1.11–3.54; $p=0.020$) were independently associated with unfavourable outcomes (table 3). For 203 patients with cavitary disease, surgical resection was the only independent factor negatively associated with favourable outcome (aOR 0.13, 95% CI 0.02–0.98; $p=0.048$).

Redevelopment of NTM lung disease after treatment completion

Of the 402 patients who completed treatment, 118 (29%) redeveloped NTM lung disease during the median (IQR) follow-up period of 13.6 (4.8–28.3) months, which was the time between treatment completion and the last hospital visit or death. The median (IQR) number of sputum examinations after

TABLE 1 Baseline characteristics of the study population

	Noncavitary NB	Cavitary NB	Fibrocavitary	p-value		
					Non-cavitary NB *versus* fibrocavitary[#]	Cavitary NB *versus* fibrocavitary[#]	Noncavitary NB *versus* cavitary NB[#]
Subjects	278 (58)	80 (17)	123 (25)				
Male	94 (34)	21 (26)	81 (66)	<0.001	<0.001	<0.001	0.392
Age years	58 (50–66)	57 (52–66)	62 (48–70)	0.358			
BMI kg·m^{-2}	20.6 (19.1–22.3)	20.0 (18.3–21.0)	19.4 (17.8–21.2)	<0.001	<0.001	0.914	0.003
Nonsmokers	223 (80)	65 (81)	58 (47)	<0.001	<0.001	<0.001	0.999
Aetiologic organism				<0.001	<0.001	0.423	0.145
Mycobacterium avium	167 (60)	39 (49)	49 (40)				
Mycobacterium intracellulare	111 (40)	41 (51)	74 (60)				
Underlying diseases							
History of TB	88 (32)	33 (41)	78 (63)	<0.001	<0.001	0.006	0.260
COPD	41 (15)	7 (9)	30 (24)	0.009	0.045	0.010	0.357
CPA	1 (0)	1 (1)	18 (15)	<0.001	<0.001	0.001	0.537
Lung cancer	4 (1)	0 (0)	7 (6)	0.019	0.056	0.056	0.687
Previous lung resection	14 (5)	2 (3)	13 (11)	0.048	0.087	0.087	0.747
Diabetes mellitus	21 (8)	6 (8)	14 (11)	0.459			
Sputum smear positivity	104 (37)	61 (76)	105 (85)	<0.001	<0.001	0.264	<0.001
CRP mg·dL^{-1}	0.14 (0.05–0.44)	0.16 (0.07–0.39)	0.50 (0.15–1.64)	<0.001	<0.001	0.002	0.851

Data are presented as n (%) or median (interquartile range), unless otherwise stated. n=481. NB: nodular bronchiectatic form of *Mycobacterium avium* complex lung disease; BMI: body mass index; TB: tuberculosis; COPD: chronic obstructive pulmonary disease; CPA: chronic pulmonary aspergillosis; CRP: C-reactive protein. [#]: *post hoc* analysis using permutation method for multiple comparisons.

treatment completion did not differ between patients with the fibrocavitary (2 (1–4)) and NB (2 (1–4)) forms (p=0.429). In these 118 patients, MAC lung disease from the same species recurred in 65 (55%) cases (31 cases of *M. avium* and 34 cases of *M. intracellulare*) and NTM lung disease from a different NTM species redeveloped in 53 (45%) cases (table 4). Recurrence rates of MAC lung disease (*i.e.* only cases involving the same species) did not differ between patients with *M. avium* (31 (14%) out of 219 patients with favourable outcomes) and *M. intracellulare* (34 (19%) out of 183 patients; p=0.163).

Risk factors for redevelopment of NTM lung disease

NTM lung disease redeveloped in 33% (103 out of 308) of patients with the NB form and 16% (15 out of 94) of patients with the fibrocavitary form (p=0.001). However, rates did not differ between patients with the C-NB (31%, 19 out of 62) and NC-NB forms (34%, 84 out of 246; p=0.602). The cumulative rate of redevelopment of NTM lung disease was higher in patients with the NB form, regardless of the presence of cavities, than in those with the fibrocavitary form (p=0.015; figure 2). These differences remained significant after adjustment using multiple Cox regression (p=0.011; table 5).

Genotyping of paired isolates in recurrent MAC lung disease

In the 65 patients (31 *M. avium* and 34 *M. intracellulare*) with a recurrence of MAC lung disease, paired clinical isolates were available for genotyping in 27 (42%) patients, including 12 (39%) out of 31 patients with *M. avium* and 15 (44%) out of 34 patients with *M. intracellulare*. According to the rep-PCR profiles, 74% (20 out of 27) of the isolates had genotypes different from those of the original isolates, suggesting reinfection, whereas 26% (seven out of 27) had genotypes identical to the initial genotype, suggesting relapse (table 6 and online supplementary figure S4). The proportion of reinfections was higher in patients with the NB form (82%, 18 out of 22) than in those with the fibrocavitary form (40%, two out of five) among patients with a recurrence and available paired isolates, although the difference was not statistically significant (p=0.091). The median (IQR) time interval between treatment completion and recurrence was shorter in patients with relapse (6.0 (4.8–8.5) months) than with reinfection (13.0 (6.0–23.7) months; p=0.040).

Drug susceptibility testing revealed that all reinfection isolates (20 patients) were susceptible to clarithromycin. However, clarithromycin resistance developed in two (29%) out of seven patients with

TABLE 2 Treatment modalities and outcomes of the study population

	Noncavitary NB	Cavitary NB	Fibrocavitary	p-value			
					Noncavitary NB *versus* fibrocavitary[#]	Cavitary NB *versus* fibrocavitary[#]	Noncavitary NB *versus* cavitary NB[#]
Subjects	278 (58)	80 (17)	123 (25)				
Time interval between diagnosis and treatment months	7.0 (2.2–23.2)	5.8 (1.5–16.6)	1.5 (0.5–5.4)	<0.001	<0.001	<0.001	0.242
Treatment regimen[¶]				<0.001	<0.001	0.999	<0.001
Daily	135 (49)	80 (100)	123 (100)				
Intermittent	143 (51)	0 (0)	0 (0)				
Streptomycin	72 (26)	48 (60)	90 (73)	<0.001	<0.001	0.135	<0.001
Duration months	3.0 (2.3–5.1)	3.2 (2.8–5.7)	4.0 (3.0–6.2)	0.004	0.003	0.096	0.677
Surgical resection[+]	11 (4)	5 (6)	20 (16)	0.510			
Time from treatment start to resection months	21.9 (19.6–24.5)	12.7 (11.9–18.3)	12.6 (7.0–18.8)	0.051			
Treatment duration months	19.7 (15.9–24.1)	24.0 (18.2–24.8)	24.1 (19.6–27.5)	<0.001	<0.001	0.435	0.002
Treatment outcomes				0.003	0.006	0.999	0.037
Favourable	246 (88)	62 (78)	94 (76)				
Unfavourable	32 (12)	18 (22)	29 (24)				
Time to culture conversion months	1.2 (0.9–2.8)	2.0 (0.9–4.1)	3.2 (1.4–6.1)	<0.001	<0.001	0.144	0.028
Time from culture conversion to treatment completion months	16.3 (13.5–22.0)	17.2 (13.6–22.5)	18.2 (13.6–22.0)	0.195			

Data are presented as n (%) or median (interquartile range), unless otherwise stated. n=481. NB: nodular bronchiectatic form of *Mycobacterium avium* complex lung disease. [#]: *post hoc* analysis using permutation method for multiple comparisons; [¶]: initial treatment regimen consisted of three oral drugs: a macrolide (clarithromycin or azithromycin), rifampicin and ethambutol; [+]: sputum culture conversion rates after surgical resection: 89% (32/36) in total, 100% (20/20) for fibrocavitary form, 80% (4/5) for cavitary NB and 73% (8/11) for noncavitary NB.

relapsed MAC lung disease. One of the relapse isolates had a point mutation at position 2058 and the other at position 2059 of the 23S rRNA gene.

Discussion

This study evaluated treatment outcomes and redevelopment of NTM lung disease, based on the clinical phenotype of MAC lung disease. Our study included nearly 500 patients with MAC lung disease who had not received prior treatment, and we found that treatment outcomes and redevelopment of NTM lung disease differed according to the clinical phenotype. Favourable outcomes were higher in patients with NC-NB MAC lung disease, compared with patients with the C-NB and fibrocavitary forms. Redevelopment of NTM lung disease was not uncommon in patients with NB MAC lung disease, including those with the C-NB form.

Current guidelines recommend intermittent antibiotic therapy for initial treatment of NC-NB MAC lung disease [3], and recent studies have reported high sputum culture conversion rates (74–86%) in these patients [13–15]. The sputum culture conversion rate in the present study was high (88%) in patients with NC-NB disease, although about half of our patients received daily therapy, because intermittent therapy was not introduced until 2011 in our institution. We previously showed that treatment outcomes did not differ between daily therapy and intermittent therapy in these patients [14]. Therefore, intermittent therapy is a reasonable option for patients with NC-NB MAC lung disease [3].

Daily antibiotic therapy is recommended for patients with cavitary MAC lung disease [3], and parenteral drugs should be considered for the first several months for extensive disease, especially the fibrocavitary form [3]. However, information regarding treatment outcomes in patients with fibrocavitary MAC lung disease is limited [8–12]. Our study included >120 patients with the fibrocavitary form. Although favourable outcomes (76%) for the fibrocavitary form were lower than for the NC-NB form (88%), our

TABLE 3 Risk factors for unfavourable outcomes in the study population

	Favourable	Unfavourable	Univariable analysis		Multivariable analysis	
			OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Subjects	402 (84)	79 (16)				
Male	153 (38)	43 (54)	1.94 (1.20–3.16)	<0.001	1.80 (1.07–3.02)	0.027
Age years	58 (50–67)	61 (52–70)	1.02 (1.00–1.04)	0.055		
BMI kg·m^{-2}	20.2 (18.8–21.9)	19.5 (17.8–21.7)	0.97 (0.89–1.05)	0.440		
Mycobacterium intracellulare	183 (46)	43 (54)	1.43 (0.88–2.32)	0.148		
Sputum smear positivity	215 (54)	55 (70)	1.99 (1.19–3.35)	0.009		
COPD	64 (16)	14 (18)	1.14 (0.60–2.15)	0.691		
Concurrent CPA	14 (4)	6 (8)	2.28 (0.85–6.12)	0.103		
Previous lung resection	23 (6)	6 (8)	1.35 (0.53–3.44)	0.524		
Type of disease						
Noncavitary NB	246 (61)	32 (41)	1.00	Ref.	1.00	Ref.
Cavitary NB	62 (15)	18 (23)	2.23 (1.07–4.65)	0.014	2.36 (1.24–4.52)	0.009
Fibrocavitary	94 (23)	29 (37)	2.37 (1.26–4.48)	0.002	1.99 (1.11–3.54)	0.020
Use of streptomycin	169 (42)	41 (52)	1.49 (0.98–2.41)	0.108		
Surgical resection	32 (8)	4 (5)	0.62 (0.21–1.80)	0.375		

Data are presented as n (%) or as median (interquartile range), unless otherwise stated. n=481. BMI: body mass index; COPD: chronic obstructive pulmonary disease; CPA: chronic pulmonary aspergillosis; NB: nodular bronchiectatic form of *Mycobacterium avium* complex lung disease.

current study showed that active application of injection drugs and combined surgical resection could result in reasonable treatment outcomes in this type of advanced MAC lung disease.

The proportion of patients with and clinical significance of the combination of cavitary lesions with NB MAC lung disease have not been well studied, although the proportion of patients with this combination is reported to range from 12% to 25% [5–7, 14]. In the original report of NB MAC lung disease, 24% (five out of 21) of patients had cavitary lesions at presentation, and an additional 15% (three out of 21) of patients developed cavities during the course of the disease [26]. In the present study, cavitary lesions were detected in 80 (22%) out of 358 patients with NB MAC lung disease. We found that favourable outcomes for C-NB disease were lower (78%) than for NC-NB disease (88%), but similar to that of fibrocavitary disease (76%). These results suggest that careful evaluation of the presence of cavitary lesions using HRCT scans and differentiation between C-NB and NC-NB forms are important before initiating antibiotic treatment in patients with NB MAC lung disease. In addition, further clinical research is needed to evaluate the clinical

TABLE 4 Redevelopment of nontuberculous mycobacterial (NTM) lung disease in 118 patients after successful treatment of *Mycobacterium avium* complex (MAC) lung disease

Initial disease	Subjects	Redevelopment of NTM lung disease	Subjects
M. avium	65	*M. avium*	31 (48)
		M. intracellulare	15 (23)
		M. abscessus complex	14 (22)
		Others[#]	5 (7)
M. intracellulare	53	*M. intracellulare*	34 (64)
		M. avium	9 (17)
		M. abscessus complex	7 (13)
		M. kansasii	1 (2)
		Others[#]	2 (4)

Data are presented as n or n (%). [#]: including mixed infections.

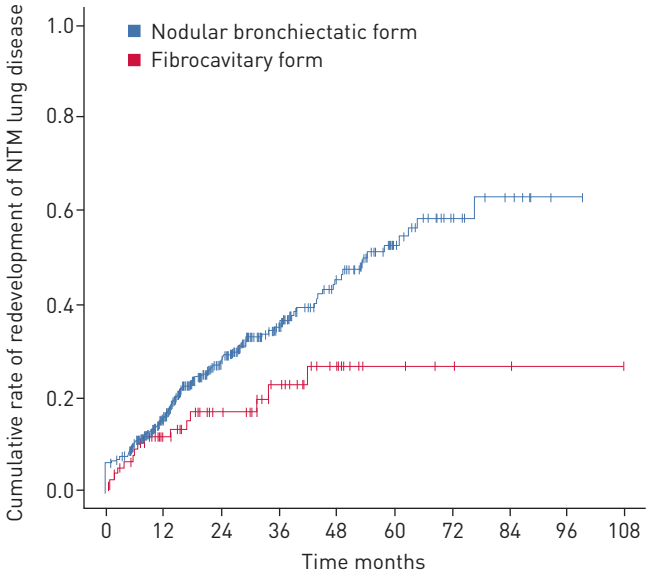

FIGURE 2 Cumulative rate of redevelopment of nontuberculous mycobacterial (NTM) lung disease after treatment completion of *Mycobacterium avium* complex lung disease.

efficacy of optimal doses of macrolides [27–29], clofazimine [12, 30] and inhaled amikacin [31, 32] for cavitary MAC lung disease to improve treatment outcome.

Previous studies found that 22–50% of patients with MAC lung disease experience recurrence of MAC lung disease after successful treatment [13, 16–18]. Additionally, NTM lung disease caused by different species such as *M. abscessus* can develop during or after treatment of NB MAC lung disease [17, 33]. The present study revealed that lung disease due either to the same species of MAC or to a different NTM species could develop after treatment completion of MAC lung disease, and that this occurred more frequently with the C-NB and NC-NB forms than with the fibrocavitary form, consistent with previous reports [16]. Additionally, the majority of recurrences (*i.e.* from the same MAC species) were due to reinfection rather than true relapse. Patients with NB MAC lung disease were typically postmenopausal women who had a unique body morphotype, slender marfanoid body habitus (scoliosis, pectus excavatum and mitral valve prolapse), altered immunophenotype and mucociliary dysfunction [34–36], making them susceptible to environmental NTM exposure. Therefore, patients with the NB form should be followed-up, potentially for the duration of their lifetime, to detect and evaluate the recurrence of MAC or other NTM

TABLE 5 Risk factors for redevelopment of nontuberculous mycobacterial (NTM) lung disease after successful treatment of *Mycobacterium avium* complex (MAC) lung disease

	Redevelopment	No redevelopment	Univariable analysis		Multivariable analysis	
			HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Subjects	118 (29)	284 (71)				
Sex male	44 (37)	109 (38)	1.18 (0.81–1.71)	0.398	1.33 (0.91–1.94)	0.140
Age years	57 (50–66)	59 (50–67)	1.01 (0.99–1.02)	0.549		
BMI kg·m^{-2}	20.2 (18.9–21.5)	20.2 (18.8–22.1)	1.00 (0.94–1.06)	0.976		
Mycobacterium intracellulare	53 (45)	130 (46)	1.01 (0.70–1.45)	0.953		
Sputum smear positivity	64 (54)	151 (53)	1.06 (0.74–1.52)	0.740		
COPD	20 (17)	44 (15)	1.00 (0.61–1.62)	0.984		
CPA	2 (2)	12 (4)	0.64 (0.16–2.56)	0.528		
Previous lung resection	6 (5)	17 (6)	0.88 (0.38–2.02)	0.761		
Type of disease						
Fibrocavitary form	15 (13)	79 (28)	1.00	Reference	1.00	Reference
NB form	103 (87)[#]	205 (72)[¶]	1.93 (1.11–3.35)	0.020	2.08 (1.19–3.65)	0.011
Use of streptomycin	59 (50)	110 (39)	0.88 (0.61–1.26)	0.490		
Surgical resection	4 (3)	28 (10)	0.41 (0.15–1.16)	0.093		

Data are presented as n (%) or as median (interquartile range), unless otherwise stated. n=402. HR: hazard ratio; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CPA: chronic pulmonary aspergillosis; NB: nodular bronchiectatic. [#]: noncavitary NB n=84, cavitary NB n=19; [¶]: noncavitary NB n=162, cavitary NB n=43.

TABLE 6 Genotyping results of paired clinical isolates from patients with recurrent *Mycobacterium avium* complex (MAC) lung disease[#]

	Total	Reinfection[¶]	Relapse[¶]	p-value
Subjects	27 (100)	20 (74)	7 (26)	
Type of disease				0.091
NB	22 (81)	18 (82)	4 (18)	
Noncavitary NB	17	14	3	
Cavitary NB	5	4	1	
Fibrocavitary form	5 (19)	2 (40)	3 (60)	
Aetiology				0.091
M. avium	12 (44)	11 (92)	1 (8)	
M. intracellulare	15 (56)	9 (60)	6 (40)	
Time interval between treatment completion and recurrence months	10.6 (5.5–18.3)	13.0 (6.0–23.7)	6.0 (4.8–8.5)	0.040

Data are presented as n (%), n or median (interquartile range), unless otherwise stated. NB: nodular bronchiectatic form. [#]: "recurrent MAC lung disease" only includes cases where MAC lung disease redeveloped due to the same species; [¶]: repetitive sequence-based PCR profiles indicated that genotypes differed from the original isolates (reinfection) or were identical to the initial genotype (relapse).

lung disease. In contrast, genotyping results indicated that relapse developed more frequently in patients with the fibrocavitary form, suggesting that more effective drugs and longer treatment duration may be warranted with this form. Further studies regarding different treatment strategies against relapse and reinfection in MAC lung disease and methods to reduce environmental exposure in these patients are needed.

The present study has several limitations. First, this study was conducted at a single referral centre with specialised NTM clinics. Therefore, our results might not be generalisable to other centres and geographical areas. Second, patients receiving <12 months of antibiotic treatment (85 (15%) out of 566) were excluded from the main analysis, and therefore favourable outcomes may have been overestimated; such patients were older, more likely to be male and more likely to have fibrocavitary disease (data not shown), and it is possible that older male patients with fibrocavitary disease might be less tolerant of daily antibiotic therapy with injectable drugs than patients with NC-NB disease who received intermittent antibiotic therapy. However, our results demonstrated that treatment outcomes are reasonably acceptable if patients receive treatment for ⩾12 months, which adheres to current guidelines. Third, administration of streptomycin was left to the discretion of the treating physician and not dependent on objective criteria. Fourth, there was no specific measure to monitor patients' compliance with treatment regimens. Fifth, paired clinical isolates were only available in 41% of patients with recurrent MAC lung disease. Sixth, because the follow-up period after successful treatment completion was relatively short, recurrence rates may have been underestimated. Seventh, there is potential overlap between the fibrocavitary and C-NB forms, because patients with the fibrocavitary form can have some nodular and bronchiectatic lesions in lower lung fields. Finally, we only differentiated between *M. avium* and *M. intracellulare* in our study, and several new species closely related to *M. intracellulare*, such as *M. chimaera*, were recently identified. Some studies suggest that recurrence rates differ between *M. intracellulare* and *M. chimaera* [37]. However, *M. chimaera* appears to be relatively rare in South Korea [38–40].

In conclusion, treatment outcome, including redevelopment of NTM lung disease and recurrence of MAC lung disease differed by clinical phenotype in patients with MAC lung disease. Favourable outcomes were lower in patients with cavitary MAC lung disease (both the fibrocavitary and C-NB forms). Redevelopment of NTM lung disease and recurrence of MAC lung disease were not uncommon in patients with NB MAC lung disease, even in those with the C-NB form. Therefore, different treatment regimens and possible interventions to prevent redevelopment or recurrence according to the clinical phenotype of MAC lung disease should be considered.

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