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Pneumothorax associated with nontuberculous mycobacteria

A retrospective study of 69 patients

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Abstract

The incidence of nontuberculous mycobacterial pulmonary disease (NTMPD) is increasing worldwide. Secondary spontaneous pneumothorax occurs as a complication of underlying lung disease and is associated with higher morbidity, mortality, and recurrence than primary spontaneous pneumothorax. We here investigated the clinical features and long-term outcomes of pneumothorax associated with NTMPD.

We conducted a retrospective study on consecutive adult patients with pneumothorax associated with NTMPD at Fukujuji Hospital and Keio University Hospital from January 1992 to December 2013. We reviewed the medical records of 69 such patients to obtain clinical characteristics, radiological findings, and long-term outcomes, including pneumothorax recurrence and mortality.

The median age of the patients was 68 years; 34 patients were women. The median body mass index was 16.8 kg/m^2. Underlying pulmonary diseases mainly included chronic obstructive pulmonary disease and pulmonary tuberculosis. On computed tomography, nodules and bronchiectasis were observed in 46 (98%) and 45 (96%) patients, respectively. Consolidation, pleural thickening, interlobular septal thickening, and cavities were most common, and observed in 40 (85%), 40 (85%), 37 (79%), and 36 (77%) patients, respectively. Regarding pneumothorax treatment outcomes, complete and incomplete lung expansion were observed in 49 patients (71%) and 15 patients (22%), respectively. The survival rate after pneumothorax was 48% at 5 years. By the end of the follow-up, 33 patients had died, and the median survival was 4.4 years with a median follow-up period of 1.7 years. The rate of absence of recurrence after the first pneumothorax was 59% at 3 years. By the end of the follow-up, 18 patients had experienced pneumothorax recurrence. Furthermore, 12/18 patients (66%) with recurrent pneumothorax died during the study period. Twenty-three patients (70%) died because of NTMPD progression. Low body mass index (BMI) was a negative prognostic factor for pneumothorax associated with NTMPD in multivariate analysis (HR 0.79, 95% CI 0.64−0.96; $P=0.018$)

Patients with pneumothorax associated with NTMPD have advanced disease, a high rate of pneumothorax recurrence, and poor prognosis, regardless of the pneumothorax treatment used. Further improvements in early diagnosis of NTMPD and appropriate management in both NTMPD and NTMPD-associated pneumothorax are needed.

Abbreviations: COPD = chronic obstructive pulmonary disease, CT = computed tomography, MAC = *Mycobacterium avium* complex, NTMPD = nontuberculous mycobacterial pulmonary disease, SSP = secondary spontaneous pneumothorax, TB = tuberculosis.

Keywords: mycobacterium avium complex, nontuberculous mycobacteria, prognosis, recurrent pneumothorax, secondary spontaneous pneumothorax

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MU and TA have contributed equally to this work.

Authors' contributions: MU and TA conceived of the study and wrote the first version of the manuscript. KM, HN, SM, TO, NH, AK, and HG supervised the study and made critical revisions for important intellectual content. All the authors approved the final version as submitted to the journal.

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1. Introduction

The incidence of nontuberculous mycobacterial (NTM) pulmonary disease (NTMPD) has been increasing worldwide.[1,2] In contrast to pulmonary tuberculosis (TB), NTMPD, most commonly caused by the *Mycobacterium avium* complex (MAC), generally causes chronic, indolent, or slowly progressive disease in immunocompetent patients.[3] Therapy involving multiple antimicrobials against NTMPD is not fully effective and is often limited to established NTMPD; moreover, the disease has a high recurrence rate. NTMPD not only affects health-related quality of life,[4] but is also an important cause of morbidity and mortality.[5,6]

Secondary spontaneous pneumothorax (SSP) occurs as a complication of an underlying pulmonary disease, such as chronic obstructive pulmonary disease (COPD), cystic lung diseases, malignancy, pulmonary infections, and interstitial lung diseases.[7] SSP is associated with higher morbidity, mortality, and recurrence than is primary spontaneous pneumothorax.[8,9] Therefore, SSP associated with NTMPD may also be associated with a high recurrence rate and poor prognosis. However, only a few reports have described pneumothorax associated with NTMPD.[10,11] This study aimed to evaluate the clinical features and long-term outcomes of pneumothorax associated with NTMPD and to clarify the impact of pneumothorax on NTMPD.

2. Patients and methods

2.1. Study design and patient selection

This retrospective observational study included all patients with pneumothorax associated with NTMPD treated at Fukujuji Hospital and Keio University Hospital from January 1992 to December 2013. All patients were diagnosed with NTMPD according to the 2007 American Thoracic Society/Infectious Disease Society of America diagnostic criteria.[3] None of the patients had cystic fibrosis or human immunodeficiency virus. Only the first episode of pneumothorax was included for the analysis. We identified 69 cases of pneumothorax associated with NTMPD at the two hospitals between January 1992 and December 2013. The total number of patients diagnosed with NTMPD was available only from January 2004 to December 2013, at both sites; in this period, we identified 1689 patients with NTMPD, of which 49 (2.9%) had pneumothorax associated with NTMPD. Forty-four of 1453 patients (3.0%), 3 of 74 patients (4.1%), and 2 of 162 patients (1.2%) had pneumothorax associated with infection with MAC, *Mycobacterium kansasii*, and other species, respectively. The institutional review boards of Fukujuji Hospital and Keio University Hospital approved this study (#15022 and #20080131).

2.2. Data extraction

Patients' age, sex, body mass index (BMI), smoking status, Charlson comorbidity index (CCI),[12] underlying pulmonary diseases, use of immunosuppressive agents and home oxygen therapy, disease and treatment durations, NTMPD treatment status, bacterial smear and culture results, radiographic features (including computed tomography), and treatment and clinical outcomes for pneumothorax were collected. NTMPD treatment status at the onset of pneumothorax was classified as never treated, previously treated, or presently treated. NTM species was identified by the AccuProbe system (Gen-Probe Inc, San Diego, CA), the COBAS AMPLICOR system (Roche Diagnostic Co., Ltd, Tokyo, Japan), or a DNA−DNA hybridization test (Kyokuto Pharmaceutical Industrial Co., Ltd, Tokyo, Japan), as previously described.[4] For determining clarithromycin susceptibility for MAC, a broth microdilution method (BrothMIC NTM; Kyokuto Pharmaceutical Industrial Co., Ltd, Tokyo, Japan) was used.[13] A minimum inhibitory concentration $\geq 32\,\mu g$ was defined as clarithromycin resistance.[14]

Sputum smear or culture results were defined based on results obtained 3 months before and after pneumothorax. After the onset of pneumothorax, all patients were observed until their date of death, the date of their last visit, or the end of the study (December 31, 2015). The patient's status at the end of the follow-up (deceased or alive, pneumothorax recurrence, and cause of death if applicable) was systematically recorded.

2.3. Radiological findings

Two investigators who were blinded to the clinical data evaluated chest radiography and computed tomography (CT) scans. Discrepancies were resolved through a consensus review. The pattern on chest radiography was classified into the following four forms, according to previous reports: nodular/bronchiectatic (NB), fibrocavitary (FC), NB + FC, or unclassified.[6] Pneumothorax severity was classified as mild (above the clavicle), moderate (between mild and severe), or severe (complete or nearly complete lung collapse). The extent and location of lung involvement were evaluated on CT scans.

2.4. Statistical analysis

Statistical analyses were conducted by using JMP v11.0 (SAS Institute Japan Ltd, Tokyo, Japan). Data are presented as median (interquartile range [IQR] or range), or number (%). Univariate analysis was performed by using Fisher's exact test to compare categorical variables and the Mann−Whitney test (between two groups) or the Kruskal−Wallis test (among three groups) to compare continuous variables. All P values were two-tailed; $P < 0.05$ was considered significant.

We estimated survival rates and the rate of pneumothorax recurrence by using the Kaplan−Meier method. To identify the factors related to survival in pneumothorax associated with NTMPD, we first performed univariate Cox regression analysis. Then, multivariate Cox regression analysis was performed using variables strongly associated with ($P < 0.2$) mortality in univariate analysis, in addition to age, sex, BMI, and CCI. CT findings were not included, as only 47 patients in the study had undergone CT.

3. Results

3.1. Patients and clinical characteristics

The patient characteristics are shown in Table 1. The median (IQR) age of the patients was 68 (61–77) years; 34 patients (49%) were women. The median (IQR) BMI was 17 (15–18) kg/m^2. Thirty-seven (54%), 26 (38%), and 6 (9%) patients had never smoked, were former smokers, and were present smokers, respectively. The underlying pulmonary diseases mainly included COPD (24 patients, 35%) and history of TB (18 patients, 26%). Ten patients (14%) were first diagnosed with NTMPD because of the onset of pneumothorax; 9 patients had underlying pulmonary disease (5 patients with COPD and a history of TB, 3 patients with COPD, and 2 patients with interstitial lung disease). The median (IQR) disease and treatment duration from diagnosis to

Table 1

Clinical characteristics of 69 nontuberculous mycobacteria patients with pneumothorax on admission.

Characteristics	Total	MAC	*M kansasii*	Other	*P* value*
Patients	69 (100)	55 (80)	8 (12)	6 (9)	–
Age, y	68 [61–77]	68 [64–77]	61 [54–74]	67 [47–69]	0.152
Sex, female/male	34/35	29/26	2/6	3/3	0.405
Body mass index, kg/m^2	17 [15−18]	17 [15–18]	18 [15–22]	16 [15–19]	0.499
Smoking status					0.030
Never	37 (54)	33 (60)	2 (25)	2 (33)	
Former	26 (38)	20 (36)	4 (50)	2 (33)	
Present	6 (9)	2 (4)	2 (25)	2 (33)	
Charlson comorbidity index	1 [0–2]	1 [1−2]	1 [0−1]	1 [1–2]	0.637
Underlying pulmonary diseases					
COPD	24 (35)	15 (27)	5 (63)	4 (67)	0.028
History of TB	18 (26)	11 (2)	5 (63)	2 (33)	0.031
Lung surgery	5 (7)	4 (7)	0 (0)	1 (17)	0.448
Interstitial lung disease	3 (4)	3 (5)	0 (0)	0 (0)	1.000
Asthma	1 (1)	1 (2)	0 (0)	0 (0)	1.000
Lung cancer	0 (0)	0 (0)	0 (0)	0 (0)	–
Immunosuppressive agents	6 (9)	4 (7)	1 (13)	1 (17)	0.360
Home oxygen therapy	14 (20)	12 (22)	2 (25)	0 (0)	0.641
Time of NTM diagnosis					0.085
Before pneumothorax	59 (86)	49 (89)	5 (73)	5 (83)	
After pneumothorax onset	10 (14)	6 (11)	3 (38)	1 (17)	
Disease duration†, mo	30 [2−73]	35 [7−83]	2 [0−30]	23 [8−35]	0.032
Treatment duration‡, mo	9 [0−36]	16 [0−41]	2 [0−10]	2 [0−27]	0.250
Treatment status					0.761
Never treated	23 (33)	17 (31)	3 (38)	3 (50)	
Previously treated	19 (28)	17 (31)	1 (13)	1 (17)	
Presently being treated	27 (39)	21 (38)	4 (50)	2 (33)	
CAM-including ≥3 drugs	19 (28)	17 (31)	2 (25)	0 (0)	
CAM-including ≥2 drugs	1 (1)	1 (2)	0 (0)	0 (0)	
Non-CAM including regimen	8 (12)	4 (7)	2 (25)	2 (33)	
Bacterial status§					
Smear-positive	40 (58)	35 (64)	3 (38)	2 (33)	0.171
Culture-positive	56 (81)	45 (82)	5 (63)	6 (100)	0.217

CAM = clarithromycin, COPD = chronic obstructive pulmonary disease, MAC = *Mycobacterium avium* complex, NTM = nontuberculous mycobacteria, TB = tuberculosis.

* Comparison among MAC, *M kansasii*, and other groups.

† From NTM diagnosis to pneumothorax.

‡ Before admission for pneumothorax.

§ 3 months before and after admission. History of tuberculosis indicated old pulmonary tuberculosis diagnosed by radiology and history. Data are shown as the median [interquartile range] or number (%) of patients.

Table 2

The radiological features of 69 patients with PNX-associated NTMPD on admission.

Variables	
Radiographic pattern	
NB form	25 (36)
FC form	12 (17)
NB + FC form	18 (26)
Unclassified form	14 (20)
PNX pattern	
Right only	44 (64)
Left only	23 (33)
Bilateral	2 (3)
PNX severity	
Mild: above the clavicle	12 (17)
Moderate: between mild and severe	42 (61)
Severe: nearly complete collapse	15 (22)
Computed tomography findings*	
Nodule	46 (98)
Bronchiectasis	45 (96)
Consolidation	40 (85)
Subpleural thickening	40 (85)
Interlobular septal thickening	37 (79)
Cavities	36 (77)
Cavities ≤ 3	18 (38)
Cavities ≥ 4	18 (38)
Emphysema	20 (43)
Pleural effusion	9 (19)
Distribution in the lung field	
Right upper lobe	44 (94)
Right middle lobe	40 (85)
Right lower lobe	41 (87)
Left upper lobe	43 (86)
Lingular	42 (89)
Left lower lobe	44 (94)
Total number of lung lobes	6 [5–6]

FC = fibrocavitary, NB = nodular/bronchiectatic, NTMPD = nontuberculous mycobacterial pulmonary disease, PNX = pneumothorax.

* Only the 47 patients who underwent computed tomography within 1 year before admission were included. No patients had scoliosis or pectus excavatum. The data show the number (%) of patients or the median [interquartile range].

pneumothorax were 30 (2–73) and 9 (0–36) months, respectively. Twenty-three patients (33%) had never been treated, 19 (28%) had previously been treated, and 27 (39%) were being treated at the time of the first pneumothorax. Sputum smears and cultures were positive for NTMPD in 40 (58%) and 56 (81%) patients during the 3 months before and after the onset of pneumothorax, respectively. CAM resistance was investigated in 14 patients with MAC-related pulmonary disease, and 5 of the 14 patients had CAM-resistant infections.

In terms of the bacterial species, MAC was the most commonly isolated bacteria and was detected in 55 patients (80%). The "other" group included 6 patients with *Mycobacterium abscessus* (4 patients), *Mycobacterium fortuitum* (1 patient), and *Mycobacterium xenopi* (1 patient). COPD and a history of TB were significantly more prevalent in the *M kansasii* and other groups. Disease duration was significantly longer in the MAC group. The remaining parameters were not significantly different among the 3 bacterial species groups.

3.2. Radiological features

The radiological features are shown in Table 2. The radiological patterns included the NB form in 25 patients (36%), the FC form in 12 patients (17%), the NB + FC form in 18 patients (26%), and the unclassified form in 14 patients (20%). The pneumothorax lesion was predominantly on the right side in 44 patients (64%); in most cases, the pneumothorax severity was moderate (42 patients, 61%). CT findings were available for only 47 patients who had undergone a CT scan within 1 year before the onset of pneumothorax. On CT, nodules and bronchiectasis were observed in 46 (98%) and 45 (96%) patients, respectively. The most common other findings were consolidation, pleural thickening, interlobular septal thickening, and cavities, which were present in 40 (85%), 40 (85%), 37 (79%), and 36 (77%) patients, respectively. Representative figures of CT findings (2-mm-thick slices) before and after the onset of pneumothorax are shown in Figs. 1–3. NTMPD lesions were located in almost all lobes. The clinical characteristics of 69 patients with pneumothorax-associated NTMPD who did or did not undergo a CT scan are shown in Table 3. The only parameter that differed between the groups was the percentage of cases that was culture-positive.

3.3. Pneumothorax treatments and clinical outcomes

The pneumothorax treatments and clinical outcomes are shown in Table 4. Eighteen patients (26%) were only observed and advised to rest. The remaining 51 patients (74%) underwent

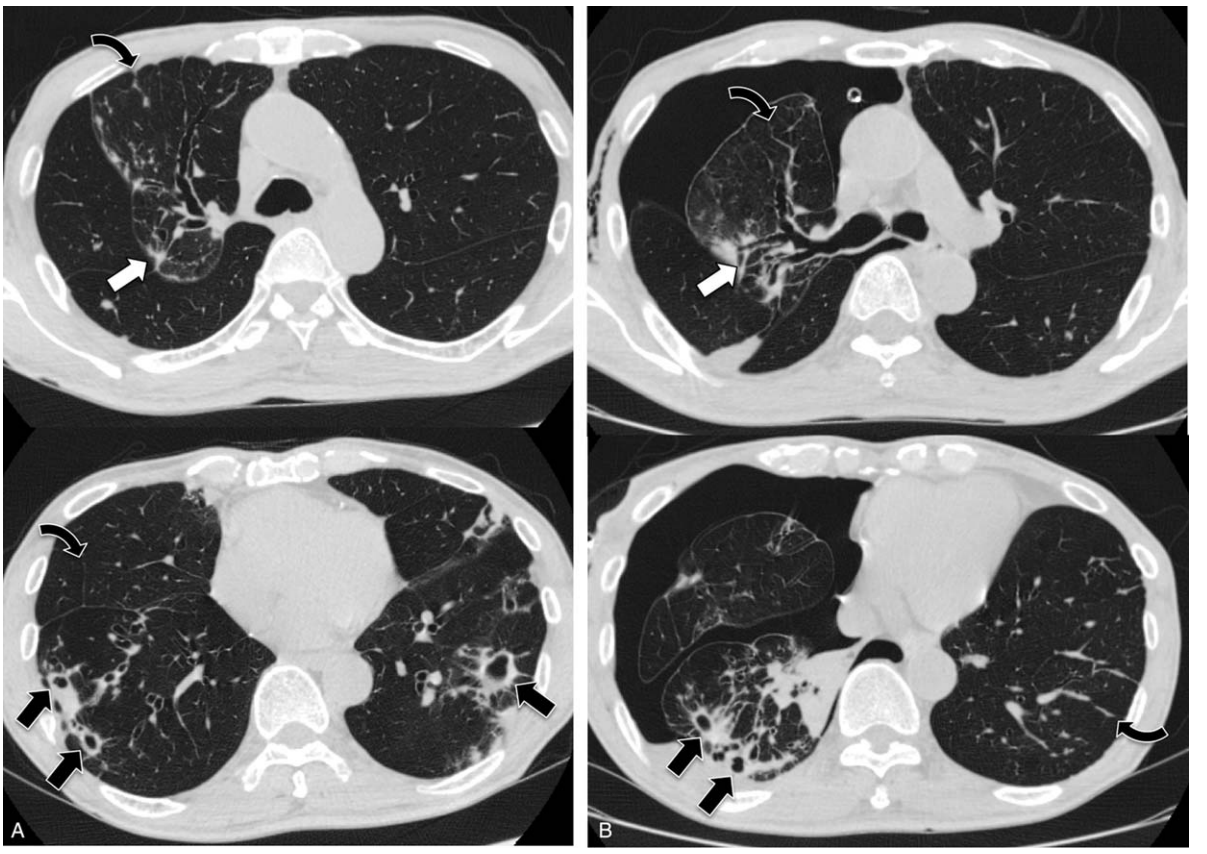

Figure 1. Computed tomography images obtained from a 77-year-old man with *Mycobacterium avium* complex pulmonary disease before (A) and after (B) the onset of pneumothorax, show nodules involving the pleura (white arrows), interlobular septal thickening (curved arrows), and cavities (black arrows).

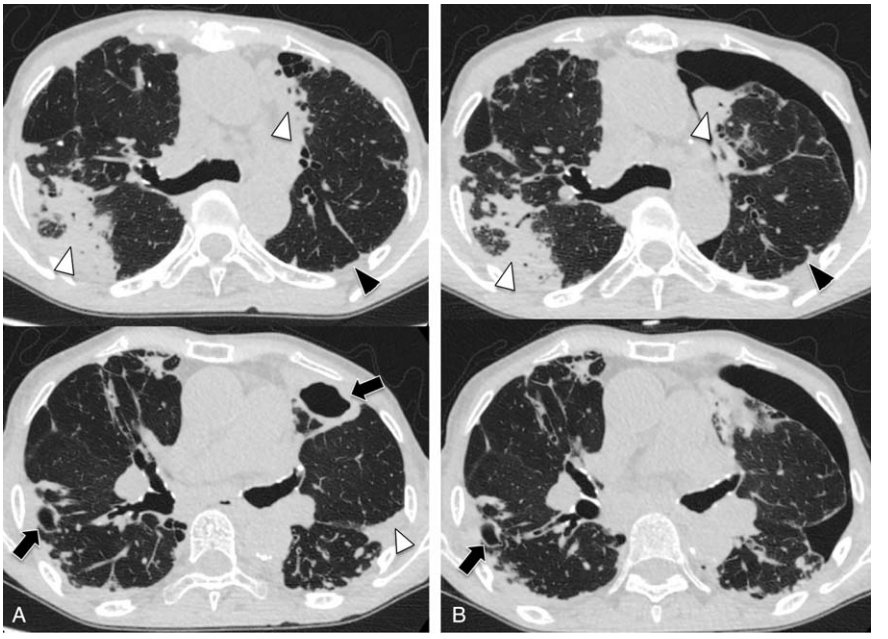

Figure 2. Computed tomography scans obtained from a 76-year-old woman with *Mycobacterium avium* complex pulmonary disease before (A) and after (B) the onset of pneumothorax, show consolidation (white arrowheads), pleural thickening (black arrowheads), and cavities (black arrows).

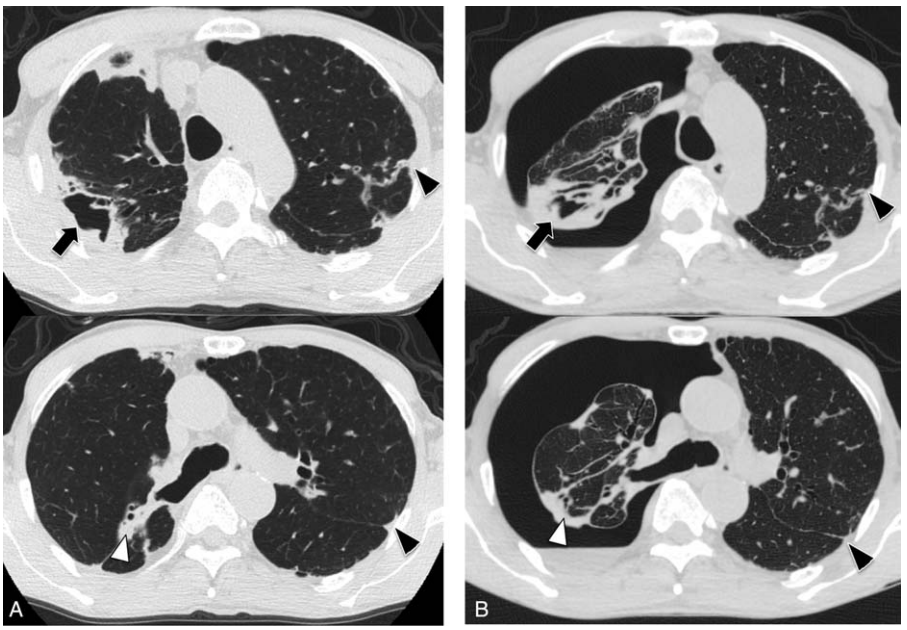

Figure 3. Computed tomography scans obtained from a 68-year-old man with *Mycobacterium avium* complex pulmonary disease before (A) and after (B) the onset of pneumothorax, show consolidation (white arrowheads), pleural thickening (black arrowheads), and cavities (black arrows).

Table 3

Clinical characteristics of 69 patients with pneumothorax-associated nontuberculous mycobacterial pulmonary disease who did or did not undergo computed tomography imaging.

Characteristics	No CT (n = 22)	CT (n = 47)	*P* value
Age, y	65 [56–71]	69 [64–78]	0.064
Sex, female/male	9/13	25/22	0.440
Body mass index, kg/m^2	17 [15–18]	17 [15–18]	0.489
Smoking status			
Never/ former/ present	11 (50)/ 9 (41)/ 2 (9)	26 (55)/ 17 (36)/ 4 (9)	0.926
Charlson comorbidity index	1 [1–2]	1 [1–2]	0.961
Underlying pulmonary diseases			
COPD	9 (41)	15 (32)	0.589
History of TB	7 (32)	11 (23)	0.559
Lung surgery	3 (14)	2 (4)	0.318
Interstitial lung disease	0 (0)	3 (6)	–
Asthma	1 (5)	0 (0)	–
Immunosuppressive agents	1 (5)	5 (11)	0.658
Home oxygen therapy	4 (18)	10 (21)	1.000
Time of NTM diagnosis			0.271
Before pneumothorax	17 (77)	42 (89)	
After the onset of pneumothorax	5 (23)	5 (11)	
Disease duration*, mo	22 [0–39]	34 [6–83]	0.102
Treatment duration†, mo	2 [0–35]	12 [0–37]	0.247
Treatment status			0.336
Never treated	10 (45)	13 (28)	
Previous treatment	5 (23)	14 (30)	
Presently being treated	7 (32)	20 (42)	
Bacterial status‡			
Smear positive	12 (54)	28 (60)	0.795
Culture positive	14 (64)	42 (89)	0.019
Radiographic pattern			0.569
NB form	6 (27)	19 (40)	
FC form	4 (18)	8 (17)	
NB + FC form	8 (36)	10 (21)	
Unclassified form	4 (18)	10 (21)	
Pneumothorax severity			
Mild/ moderate/ severe	4 (18)/ 14 (63)/ 4 (18)	8 (17)/ 28 (60)/ 11 (23)	0.936

COPD = chronic obstructive pulmonary disease, CT = computed tomography, FC = fibrocavitary, MAC = *Mycobacterium avium* complex, NB = nodular/bronchiectatic, NTMPD = nontuberculous mycobacterial pulmonary disease, TB = tuberculosis.

* From NTM diagnosis to pneumothorax.

† Before admission for pneumothorax.

‡ 3 months before and after admission. Data are shown as the median [interquartile range] or number (%) of patients.

chest tube drainage with (7 patients, 10%) or without (44 patients, 63%) pleurodesis and with an endobronchial Watanabe spigot (7 patients, 10%); the median (IQR) duration of drainage was 16 (10–34) days. Only 2 patients underwent surgical intervention. Complete and incomplete expansions were observed in 49 patients (71%) and 15 patients (22%), respectively. Sixty-two patients (93%) were treated with multiple antimicrobial agents after the onset of pneumothorax.

Table 4

Treatment and clinical outcomes of 69 nontuberculous mycobacteria patients with pneumothorax.

Variables	
Treatment	
Rest only	18 (26)
Drainage	38 (55)
Drainage + pleurodesis	6 (9)
Drainage + EWS	6 (9)
Drainage + pleurodesis + EWS	1 (1)
Drainage duration*, d	16 [10–34]
Surgical intervention as the last method	
Thoracotomy	1 (1)
Upper-lobe lobectomy	1 (1)
Treatment outcomes without an operation	
Complete expansion	49 (71)
Incomplete expansion	15 (22)
Unevaluable (because of patient transfer)	3 (4)
Antimicrobial treatment after pneumothorax†	
CAM-including ≥3 drugs	42 (63)
CAM-including ≥2 drugs	5 (7)
CAM only	2 (3)
Non-CAM treatment regimen ≥2 drugs	15 (22)
Nontreatment	3 (4)

CAM = clarithromycin, EWS = endobronchial Watanabe spigot.

* Data included 47 patients; 2 patients who underwent an operation, and 2 patients who were transferred were excluded.

† The data included 67 patients, and excluded 2 who were transferred. The data show the median [interquartile range] or number (%) of patients.

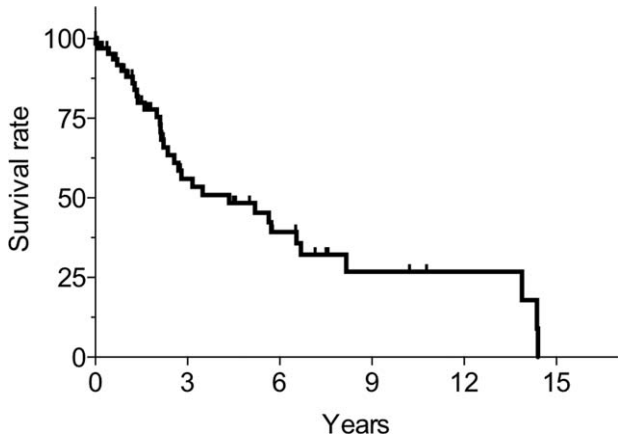

Figure 4. Kaplan–Meier survival curves, from the onset of pneumothorax. The survival rate after pneumothorax was 90% at 1 year, 78% at 2 years, 56% at 3 years, 48% at 5 years, and 32% at 8 years. The median survival was 4.4 years.

3.4. Prognosis and factors related to survival in pneumothorax associated with NTMPD

The median follow-up duration among the 69 patients was 1.7 years (range, 0–14.4 years). The survival rate after pneumothorax was 90% at 1 year, 78% at 2 years, 56% at 3 years, 48% at 5 years, and 32% at 8 years (Fig. 4). At the end of follow-up, 33 patients had died, and the median survival was 4.4 years. Three of 5 patients (60%) with CAM-resistant infections and 3 of 9 patients (33%) with CAM-susceptible infections died during the study period. Overall, 23 patients (70%) died because of NTMPD progression. Other causes of death were complications associated with surgery for NTMPD (bronchial stump fistula, 1 patient), other pulmonary diseases (pneumonia, 3 patients; chronic pulmonary aspergillosis, 2 patients; and lung cancer, 1 patient), and nonpulmonary diseases (cerebral infarction, 1 patient; gastrointestinal bleeding, 1 patient; and liver cirrhosis, 1 patient). The results of univariate Cox regression analysis of the factors related to survival are shown in Table 5. The only predictors of poor prognosis were age (HR 1.05, 95% CI

Table 5

Univariate analysis of factors related to survival in pneumothorax associated with nontuberculous mycobacterial pulmonary disease.

Characteristics	Events (n = 33)	Censored (n = 36)	HR (95% CI)	*P* value
Age, y	68 [62–78]	68 [61–65]	1.05 (1.01–1.09)	0.011
Sex, female (vs male)	17 (52)	17 (47)	1.16 (0.58–2.36)	0.673
Body mass index, kg/m^2	16 [15–18]	17 [16–18]	0.78 (0.65–092)	0.002
Smoking status: never (vs former/present)	19 (58)	18 (50)	1.58 (0.78–3.27)	0.205
Charlson comorbidity index	1 [1–2]	1 [1–2]	0.85 (0.58–1.20)	0.974
Underlying pulmonary diseases				
*COPD (vs none)	12 (36)	12 (33)	0.74 (0.34–1.51)	0.414
*History of TB (vs none)	10 (30)	8 (22)	0.97 (0.43–2.03)	0.931
Home oxygen therapy (vs none)	6 (18)	8 (22)	1.48 (0.55–3.43)	0.410
Time of NTM diagnosis				
*After (vs before PNX)	5 (15)	5 (14)	0.64 (0.19–1.67)	0.388
Disease duration*	30 [5–68]	30 [2–73]	1.00 (1.00–1.01)	0.352
Treatment duration†	12 [0–35]	7 [0–41]	1.01 [0.99–1.02]	0.307
Treatment status				
Never (vs previous/present)	12 (36)	11 (31)	0.98 (0.44–2.05)	0.956
Bacterial status‡				
Smear-positive (vs negative)	23 (70)	17 (47)	1.49 (0.72–3.32)	0.286
Culture-positive (vs negative)	29 (88)	27 (75)	2.26 (0.85–7.70)	0.110
Mycobacterium species				
MAC (vs other)	27 (82)	28 (78)	1.27 (0.55–3.45)	0.593
Radiographic pattern				
NB (vs other)	12 (36)	13 (36)	1.12 (0.53–2.23)	0.763
Pneumothorax severity				
Moderate/severe (vs mild)	23 (38)	34 (94)	0.50 (0.24–1.12)	0.091
CT findings§ (vs none)				
Cavity ≥4	12 (55)	6 (24)	1.73 (0.74–4.10)	0.203
Consolidation	21 (95)	19 (76)	5.81 (1.20–105)	0.025
Emphysema	7 (32)	13 (52)	0.62 (0.24–1.50)	0.302
Interlobular septal thickening	17 (77)	20 (80)	1.00 (0.40–3.07)	0.993
Subpleural thickening	21 (95)	19 (76)	4.36 (0.90–78.6)	0.072
Treatment for PNX				
Rest only (vs others)	12 (36)	7 (19)	1.82 (0.85–3.73)	0.118
Complete expansion (vs others)‖	25 (76)	24 (73)	0.61 (0.28–1.46)	0.250
Onset of CPA during follow-up (vs none)	5 (15)	1 (3)	0.54 (0.16–1.42)	0.231
Recurrent PNX (vs none)	12 (36)	6 (17)	0.63 (0.27–1.35)	0.242

CI = confidence interval, COPD = chronic obstructive pulmonary disease, CPA = chronic pulmonary aspergillosis, CT = computed tomography, HR = hazard ratio, MAC = *Mycobacterium avium* complex, NB = nodular/bronchiectatic, NTM = nontuberculous mycobacterial, PNX = pneumothorax, TB = tuberculosis.

* From NTM diagnosis to pneumothorax.

† Before admission for pneumothorax.

‡ 3 months before and after admission.

§ Only the 47 patients who underwent computed tomography within 1 year before admission were included. Twenty-two patients had died by the end of follow-up.

‖ n = 66, as 3 patients were transferred during the follow-up period. Data are shown as the median [interquartile range] or number (%) of patients.

Table 6

Multivariate analysis of factors related to survival in pneumothorax associated with nontuberculous mycobacterial pulmonary disease.

Variables	Adjusted HR	95% CI	*P* value
Age	1.04	0.999–1.08	0.059
Sex, female (vs male)	0.78	0.32–1.87	0.587
Body mass index, kg/m^2	0.79	0.64–0.96	0.018
Charlson comorbidity index	1.00	0.58–1.62	0.990
Culture-positive (vs negative)	2.25	0.68–9.68	0.197
PNX severity: moderate/severe (vs mild)	1.45	0.37–5.64	0.595
Treatment: rest only (vs other)	2.87	0.63–11.6	0.166

CI = confidence interval, HR = hazard ratio, PNX = pneumothorax.

1.01–1.09; $P = 0.011$) and BMI (HR 0.78, 95% CI 0.65–0.92; $P = 0.002$). The results of multivariate Cox regression analysis incorporating variables strongly associated ($P < 0.2$) with mortality in univariate analysis in addition to age, sex, BMI, and CCI are shown in Table 6. A low BMI was the only factor associated with a negative prognostic for pneumothorax associated with NTMPD (HR 0.79, 95% CI 0.64–0.96; $P = 0.018$).

The rate of pneumothorax recurrence after the first pneumothorax was 20% at 1 year, 32% at 2 years, and 41% at 3 years (Fig. 5). No further pneumothorax recurrence was noted after 3 years. By the end of the follow-up, 18 patients had experienced pneumothorax recurrence. Moreover, 6 patients and 2 patients had experienced recurrence of pneumothorax 2 and 3 times, respectively. Furthermore, 12/18 patients (66%) with recurrent pneumothorax died during the follow-up period.

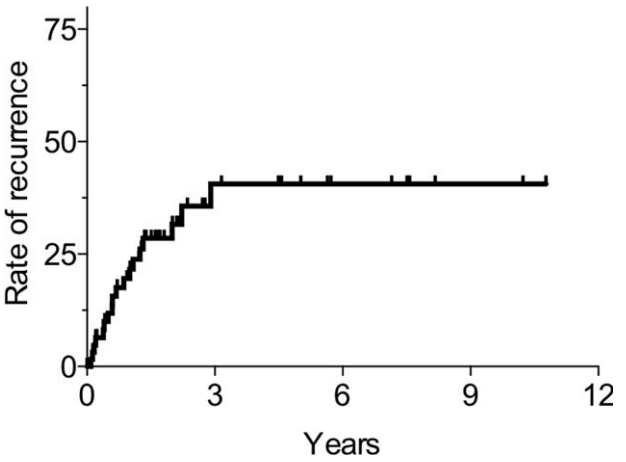

Figure 5. The rate of pneumothorax recurrence in patients, from the diagnosis of pneumothorax, according to the Kaplan–Meier method. The rate of pneumothorax recurrence after the first pneumothorax was 20% at 1 year, 32% at 2 years, and 41% at 3 years.

4. Discussion

To our knowledge, the present study of 69 cases is the largest clinical study of pneumothorax associated with NTMPD to date. This study revealed important findings in patients with NTMPD-associated pneumothorax, including the clinical characteristics and radiological features that indicated an advanced stage of NTMPD with various lesions, a poor prognosis, and a high pneumothorax recurrence rate within 3 years. One recent study of Japanese patients with MAC pulmonary disease, not identified as pneumothorax, showed that the survival rate at 5 years was 76.1%.[6] Another study in Denmark also indicated that the 5-year survival rate of MAC pulmonary disease was 60.3%.[15] Moreover, a study in Finland showed that the median survival in MAC-related and other NTM-related pulmonary disease was 13.0 years and 4.6 years, respectively.[16] In comparison to previous studies, our study showed a high mortality rate, despite mainly including patients with MAC-related pulmonary disease. Therefore, pneumothorax has a high impact on prognosis in patients with NTMPD.

NTMPD, which were mostly because of MAC infection in this study, was classified into 4 main forms.[6,17] The present study showed a higher proportion of the FC and unclassified form, which are associated with a higher mortality than the NB form.[6] Moreover, the proportion of men, former and present smokers, and percentages of patients with COPD and a history of TB were higher in this study than in previous studies.[4,18,19] Smoking is not only a risk factor for primary spontaneous pneumothorax and pneumothorax recurrence,[7] but also affects the development of COPD, especially in patients with NTMPD.[20] Therefore, smoking may also increase pneumothorax in patients with NTMPD. Although the disease and treatment duration and treatment status varied in our study, 9 of 10 patients who were diagnosed with NTMPD with the onset of pneumothorax had underlying pulmonary disease, particularly COPD. Kobashi et al[10] also reported that 3 patients with a history of COPD were diagnosed at the onset of pneumothorax. Underlying pulmonary disease may lead to a delay in the diagnosis of NTMPD and may thereby result in the onset of pneumothorax.

We found several CT findings that correlate with the onset of pneumothorax. The radiological features of NTMPD generally included nodules, consolidation, bronchiectasis, and cavities. In the present study, patients with pneumothorax associated with NTMPD had extended lesions, indicating a more advanced stage of the disease, compared with those reported in previous studies.[17,21,22] Notably, cavities, consolidation, pleural thickening, and interlobular septal thickening were more common in our study, in addition to nodules and bronchiectasis. Cavities and consolidation were reported as important predictors of progression requiring treatment, as well as of a poor prognosis.[21,23] In pneumothorax associated with pulmonary TB, the organism invades the pleura and causes liquefactive necrosis, followed by pleural rupture.[24] In NTMPD, Wittram and Weisbrod[25] reported that 15 of 26 patients demonstrated pleural involvement upon CT. Moreover, Hagiwara et al[11] described pathological evidence of air leakage from MAC lesions. Taken together, these findings suggest that pleural involvement may be strongly associated with the onset of pneumothorax and with a poor prognosis.

We revealed that patients with pneumothorax associated with NTMPD had poor prognoses and high rates of pneumothorax recurrence within 3 years. A poor prognosis and high recurrence were also reported in SSP associated with other respiratory diseases;[26] specifically, pneumothorax with COPD, the main cause of SSP, is reported to have a higher mortality and morbidity, a lower healing rate, and a higher recurrence rate after chest tube drainage.[27,28] Pneumothorax with cystic fibrosis, especially in the elderly, also has a high recurrence rate with a poor prognosis, with a median survival of only 30 months.[29] Pneumothorax with pulmonary fibrosis also has a poor

prognosis, with high postoperative mortality, despite surgical intervention.[30,31] However, little is known about the prognostic factors related to long-term survival in specific pulmonary diseases. In patients with NTMPD in general, the FC form of the disease, a low BMI, presence of cavities, advanced age, and male sex are poor prognostic factors.[6,15,17] Our cases had these clinical features associated with a poorer prognosis. Moreover, we revealed that a low BMI is the only prognostic factor in patients with pneumothorax associated with NTMPD. A low BMI is known to be a risk factor not only for NTMPD progression, but also for recurrent spontaneous pneumothorax,[32] and may be associated with a poor prognosis and recurrent pneumothorax. CAM resistance has also been reported to be a poor prognostic factor for MAC pulmonary disease.[33] Although recent studies revealed various mechanisms of resistance in NTM, the relationship between in vitro antibiotic susceptibility testing and treatment outcome in a clinical setting has not been established.[34] Since CAM resistance may have been associated with mortality rate in the present study, further investigations, including microbiological studies, are required.

There are several limitations to our study. First, the study design was retrospective; there may be some confounding factors, and our microbiological data were limited. Second, the timing of the diagnosis or antimicrobial treatment could modify the clinical course of NTMPD. Finally, the choice of pneumothorax treatment was affected by the decision of the pulmonary physician. Prospective enrollment and data collection from a large cohort of patients with NTMPD in a multicenter clinical trial would be ideal, but it would be considerably difficult because of the low rate of pneumothorax complications.

In conclusion, we have here described the clinical characteristics of patients with pneumothorax associated with NTMPD and have shown an advanced disease stage, a high rate of pneumothorax recurrence, and a poor prognosis, regardless of the pneumothorax treatment. Further improvements in early diagnosis of NTMPD and appropriate management in both NTMPD and NTMPD-associated pneumothorax are needed.

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