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Original Research

Clinical phenotypes of nontuberculous mycobacterial disease by cluster analysis based on pulmonary function

Nobuyoshi Hamao [a], Isao Ito [a,*], Issei Oi [a], Masahiro Shirata [a], Kensuke Nishioka [a], Yasuyuki Hayashi [a], Seiichiro Imai [b], Toyohiro Hirai [a]

[a] Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin-kawaracho, Sakyo, Kyoto, 606-8507, Japan
[b] Kyoto University Hospital Preemptive Medicine and Lifestyle-Related Disease Research Center, 53 Shogoin-kawaracho, Sakyo, Kyoto, 606-8507, Japan

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ABSTRACT

Background: Nontuberculous mycobacterial pulmonary disease (NTM-PD) often exhibits pulmonary function impairment, such as obstructive or restrictive pattern, with variation among patients according to the damaged lesions in the lung.
Methods: Patients with NTM-PD were consecutively enrolled between September 2019 and December 2020 at the Respiratory Infection Clinic of our hospital. Patients' data were comprehensively collected through laboratory examinations, PFT, chest computed tomography, and questionnaires for the assessment of subjective symptoms and health-related quality of life (HRQOL). Hierarchical cluster analysis was performed using PFT parameters to compare the clinical findings among clusters.
Results: Data of 104 patients were analyzed and classified into four clusters. The restrictive pattern with decreased forced expiratory volume in 1 s (FEV_1) group showed high serum C-reactive protein and low albumin levels, severe radiological findings, and low HRQOL. In the restrictive pattern with preserved FEV_1 group, HRQOL was as low as that in the restrictive pattern with decreased FEV_1 group, and bacterial exacerbation was observed relatively frequently. HRQOL in the obstructive impairment group was maintained in comparison with that in the normal group.
Conclusion: NTM-PD phenotypes were identified using cluster analysis based on PFT. Two different severe phenotypes were also observed. In the early stages of NTM-PD, PFT may be useful in recognizing disease progression.

1. Introduction

Nontuberculous mycobacterial pulmonary disease (NTM-PD) is an emerging problem worldwide due to its increasing incidence and mortality [1–4]. NTM-PD is thought to initiate in the terminal bronchiole and spreads transbronchially to produce cavities, consolidations, and bronchiectasis in radiological and pathological observations [5–7]. Subjective symptoms and deterioration of pulmonary function test (PFT) were related to progression of radiological findings [8–10]. Due to variations in the extent of disease progression among patients, NTM-PD exhibits a broad spectrum of clinical presentations, ranging from localized pneumonic infiltrate to progressive lung destruction [5,11,12]. Therefore, the phenotype of NTM-PD is variable in terms of subjective symptoms, pulmonary function, radiological findings, and disease progression.

PFT is useful in assessing the severity of pulmonary disease due to its relative simplicity, and quantitative nature of its results. Deterioration in pulmonary function is associated with poor physical function and

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography; CRP, C-reactive protein; D_{LCO}, diffusing capacity of lung for carbon monoxide; D_{LCO}/VA, D_{LCO} per unit of alveolar volume; ERV, expiratory reserve volume; $FEF_{25–75\%}$, forced expiratory flow between 25% and 75% of vital capacity; FRC, functional residual capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRQOL, health-related quality of life; IC, inspiratory capacity; IQR, interquartile range; mMRC, modified Medical Research Council; NTM, nontuberculous mycobacterium; NTM-PD, nontuberculous mycobacterial pulmonary disease; PEF, peak expiratory flow; PFT, pulmonary function test; RV, residual volume; SD, standard deviation; SF-36, short form-36; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity; VAS, visual analogue scale; VC, vital capacity.

* Corresponding author. Department of Respiratory Medicine, Kyoto University Hospital 54 Shogoin-kawaracho, Sakyo, Kyoto, 606, Japan.
E-mail address: isaoito@kuhp.kyoto-u.ac.jp (I. Ito).

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Table 1
CT scoring system for the assessment of nontuberculous mycobacterial disease.

CT findings	0	1	2	3
Bronchiectasis (9 points)				
Severity (Bronchus diameter/adjacent vessel diameter)	Absent	Mild (1–2)	Moderate (2–3)	Severe (3-)
Extent	Absent	1-5 segments	6-9 segments	>9 segments
Mucus plugging	Absent	1-5 segments	6-9 segments	>9 segments
Bronchiolitis (6 points)				
Severity	Absent	Mild (<1 cm from pleura)	Moderate (1–3 cm from pleura)	Severe (extending to central lung)
Extent	Absent	1-5 segments	6-9 segments	>9 segments
Cavity (9 points)				
Severity (diameter)	Absent	<3 cm	3–5 cm	>5 cm
Wall thickness	Absent	<1 mm	1–5 mm	>5 mm
Extent (number)	Absent	1–3	4–5	>5
Nodule (3 points)	Absent	1-5 segments	6-9 segments	>9 segments
Consolidation (3 points)	Absent	1-2 segments	3-5 segments	>5 segments

This table is cited from reference 23. CT, computed tomography.

Table 2
Patients' characteristics.

	N = 104
Age (years), average ± SD	69.6 ± 8.8
Female, n (%)	87 (83.7)
Smoking history, n (%)	23 (22.3)
Respiratory comorbidity, n (%)	17 (16.3)
Bronchial asthma, n (%)	7 (6.7)
COPD, n (%)	5 (4.8)
Interstitial pneumonia, n (%)	4 (3.8)
Old tuberculosis, n (%)	2 (1.9)
Cancer history, n (%)	24 (23.3)
Autoimmune disease, n (%)	11 (10.7)
Species*	
M. avium, n (%)	75 (72.1)
M. intracellulare, n (%)	31 (29.8)
M. abscessus, n (%)	5 (4.8)
Others†, n (%)	4 (3.8)
Unidentified, n (%)	2 (1.9)
Disease duration (months), median (interquartile range)	77 (33, 131.5)
Positive in sputum smear within one year, n (%)	9 (8.7)
Positive in sputum culture within one year, n (%)	13 (12.5)
Anti-NTM treatment, n(%)	71 (68.3)
Current treatment, n (%)	47 (45.2)
Former treatment (completed treatment), n (%)	14 (13.5)
Former treatment (discontinued treatment), n (%)	10 (9.6)
Radiological pattern	
NB, n (%)	75 (72.1)
NB + FC, n (%)	24 (23.1)
FC, (%)	5 (4.8)
Presence of cavities, n (%)	29 (27.9)

SD, standard deviation; COPD, chronic obstructive pulmonary disease; NTM, nontuberculous mycobacterium; NB, Nodular bronchiectasis type; FC, Fibrocavitary type. *Co-infection was included. †There was one case each infected with *M. gordonae*, *M. lentiflavum*, *M. paragordonae* and *M. shimoidei*.

survival rate in the general population [13–17]. NTM-PD shows several features on PFT according to the impairment of the lung, such as restrictive or obstructive impairment, small airway obstruction, and pulmonary diffusion capacity [10,18,19]. The correlation between pulmonary function and other findings such as radiological features and health-related quality of life (HRQOL) in NTM-PD has been reported previously [9,10]. PFT reflects disease progression and physical function in NTM-PD patients, and clinical phenotypes based on PFT would help in easily and properly evaluating the severity of NTM-PD patients.

This study aimed to propose a phenotype classification system for patients with NTM-PD using cluster analysis. Cluster analysis is a statistical method in which patients are classified into groups based on their similarities. Cluster analysis was used to classify patients, including those with bronchial asthma and chronic obstructive pulmonary disease (COPD) [20,21], and this method helped identify disease phenotypes. We performed cluster analysis according to pulmonary function and investigated the relationship between the pattern of pulmonary function and other clinical findings, such as subjective symptoms, laboratory tests, radiological findings, and HRQOL.

2. Materials and methods

2.1. Patients

Patients aged ≥16 years with NTM-PD were consecutively recruited from the pulmonary infection clinic at our hospital, which covered patients who were 16 years or older and suspected or diagnosed with any respiratory infection. NTM-PD was diagnosed according to the American Thoracic Society or Infectious Disease Society of America statements [22]. The exclusion criteria were active malignancy (newly diagnosed malignancies, progression of known malignancies, or treatment for malignancies within three months), pregnancy, cognitive impairment, exacerbation of lower respiratory tract infection within three months, and missing data.

2.2. Setting and design

The patients were enrolled between September 2019 and December 2020. This study was approved by the relevant ethics committee, and the approval number was R2067. Written informed consent was obtained from all study subjects. We prospectively collected comprehensive data on the patients' clinical characteristics, subjective symptoms, laboratory findings, PFT, chest computed tomography (CT) results, and HRQOL within three months of inclusion. A visual analog scale (VAS) was used to assess the degree of subjective symptoms. Dyspnea was assessed using the modified Medical Research Council (mMRC) dyspnea scores. The severity of the radiological findings was evaluated using the scoring system developed by Kim et al. (Table 1. [23]). CTs scans were scored by two pulmonologists with 10 and 12 years of experience, and the final decision was made by consensus. HRQOL was measured using the St George's Respiratory Questionnaire (SGRQ) and the Short Form (SF)-36 questionnaire. The primary outcome was SGRQ total score, and the secondary outcome was SGRQ component score, SF-36, and the frequency of bacterial colonization and bacterial exacerbation requiring antibiotic treatment in the past one year.

2.3. Pulmonary function test

Patients underwent pulmonary function tests using the CHESTAC-8900 and DISCOM-51 (Chest MI Corp., Tokyo, Japan) according to the American Thoracic Society/European Respiratory Society recommendations [24]. Carbon monoxide diffusing capacity was measured using the single-breath method. The predicted values of each parameter were calculated according to the guidelines of the Japanese Respiratory Society [25,26].

2.4. Statistical analysis

Categorical variables are expressed by frequency and percent, and continuous variables are expressed as the mean ± standard deviation or median with interquartile range according to the normality of the distribution of the variables. Cluster analysis was performed using the Ward's minimum-variance hierarchical clustering method [27]. Variables for cluster analysis were vital capacity (VC; % predicted), forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio, forced

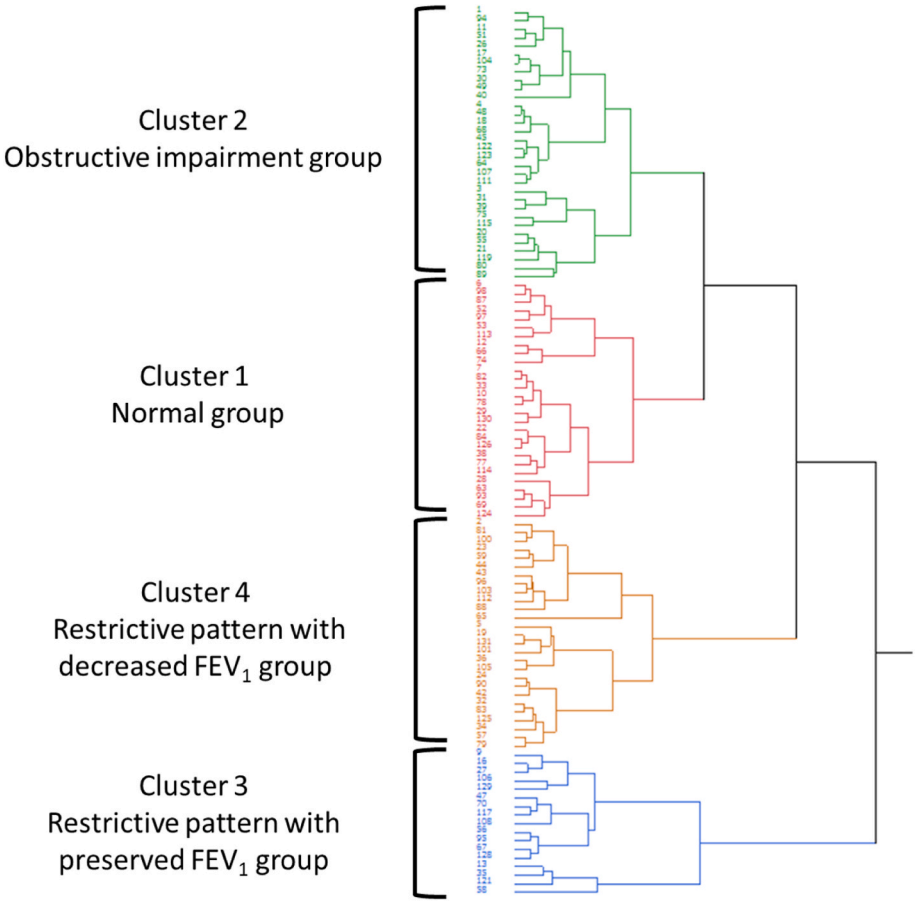
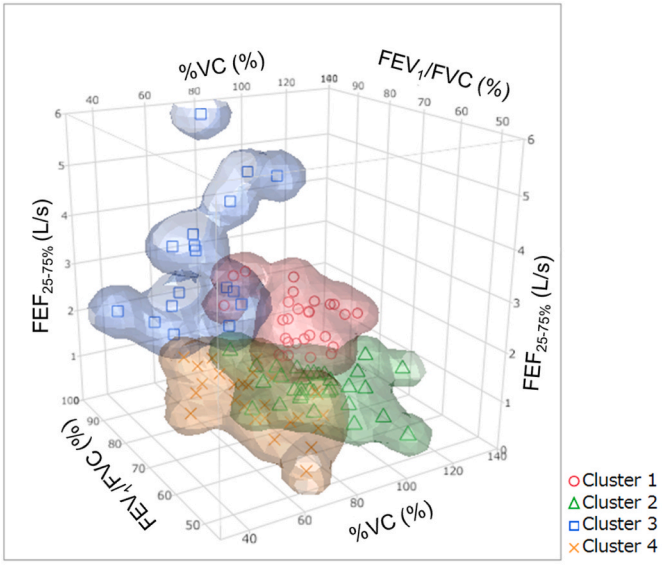
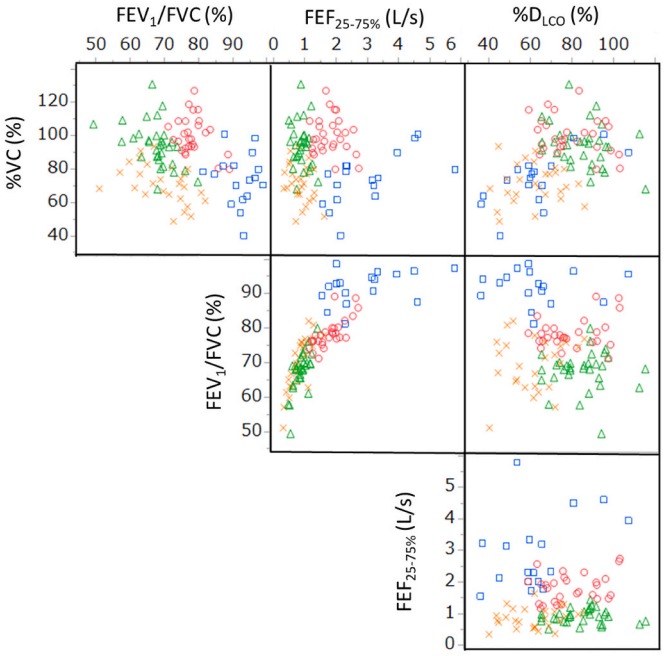


Fig. 1. Tree diagram for cluster analysis. Overall, 28 (26.9%) patients were classified into Cluster 1; 32 (30.8%) into Cluster 2; 17 (16.3%) into Cluster 3; and 27 (26.0%) into Cluster 4.



(a)



(b)

Fig. 2. (a) The distribution of patients according to pulmonary function test. Circle, triangle, square and cross represent patients in Clusters 1, 2, 3 and 4, respectively. (b) The distribution of patients in 2-dimensional data plot. Circle, triangle, square and cross represent patients in Clusters 1, 2, 3 and 4, respectively.

expiratory flow between 25% and 75% of vital capacity ($FEF_{25–75\%}$), and diffusing capacity of lung for carbon monoxide (D_{LCO}; % predicted), which were selected as measures of restrictive and obstructive impairment, small airway obstruction and lung diffusing capacity in PFT. We determined the number of clusters by comparing the clinical features in three-to five-group models. To compare differences among clusters, analysis of variance with post hoc Tukey's tests, Kruskal-Wallis test with post hoc Steel-Dwass test or chi-square test were used for normally distributed continuous and non-normally distributed continuous or categorical variables, respectively. Spearman's rank correlation test was performed to assess the correlation between CT score and BMI, VAS scale for subjective symptoms, mMRC, laboratory data, and pulmonary function parameters. A value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP version 14.0.0 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

A total of 110 patients were enrolled between September 2019 and December 2020. One patient without laboratory findings, one without

Table 3
Comparison of pulmonary function test findings among four clusters.

	Cluster 1 Normal group	Cluster 2 Obstructive impairment group	Cluster 3 Restrictive pattern with preserved FEV_1 group	Cluster 4 Restrictive pattern with decreased FEV_1 group	*P*-value
N	28	32	17	27	
VC (L), average ± SD†,‡,§, ||	2.8 ± 0.4	2.6 ± 0.5	2.2 ± 0.7	2.0 ± 0.4	**<0.001**
%VC (%), average ± SD*,†,‡,§, ||,¶	99.8 ± 11.1	94.0 ± 13.3	73.8 ± 15.5	71.1 ± 11.5	**<0.001**
FVC (L), average ± SD†,‡, ||	2.8 ± 0.5	2.5 ± 0.5	2.2 ± 0.6	2.0 ± 0.5	**<0.001**
%FVC (%), average ± SD†,‡,§, ||,¶	100.7 ± 12.5	95.2 ± 13.8	75.8 ± 14.6	72.8 ± 12.2	**<0.001**
FEV_1 (L), average ± SD*,‡,§, ||,¶	2.2 ± 0.4	1.7 ± 0.3	2.0 ± 0.6	1.4 ± 0.3	**<0.001**
%FEV_1 (%), average ± SD*,†,‡,§, ||,¶	101.9 ± 14.3	82.3 ± 11.2	90.3 ± 17.6	65.0 ± 11.0	**<0.001**
FEV_1/FVC (%), median (IQR) *,†,§, ||,¶	77.5 (76.1, 79.9)	68.3 (65.4, 69.8)	92.9 (88.5, 96.1)	71.4 (63.0, 75.8)	**<0.001**
$FEF_{25–75\%}$ (L/sec), median (IQR) *,†,‡,§,¶	1.9 (1.5, 2.1)	0.9 (0.7, 1.0)	2.3 (2.0, 3.6)	0.8, (0.6, 1.1)	**<0.001**
FRC (L), average ± SD‡,¶	2.8 ± 0.7	2.7 ± 0.4	3.0 ± 0.5	2.4 ± 0.4	**<0.001**
%FRC (%), average ± SD‡,§, ||	113.0 ± 18.3	108.5 ± 11.4	110.0 ± 17.9	93.6 ± 12.0	**<0.001**
RV (L), median (IQR)†,§,¶	1.7 (1.5, 1.9)	1.7 (1.6, 1.9)	2.1 (1.8, 2.4)	1.6 (1.4, 1.8)	**<0.001**
%RV (%), median (IQR) ||,¶	112.2 (103.2, 128.7)	113.4 (103.0, 120.0)	123.3 (105.1, 140.9)	100.7 (92.6, 110.9)	**0.002**
TLC (L), average ± SD‡, ||,¶	4.6 ± 0.7	4.4 ± 0.7	4.3 ± 0.8	3.6 ± 0.6	**<0.001**
%TLC (%), average ± SD†,‡,§, ||	114.9 ± 9.3	111.1 ± 12.5	98.7 ± 16.2	89.0 ± 12.0	**<0.001**
RV/TLC (%), median (IQR)†,‡,§, ||	39.1 (34.7, 42.5)	41.4 (35.6, 43.0)	50.4 (42.8, 54.0)	44.9 (42.3, 48.2)	**<0.001**
D_{LCO} (ml/min/Torr), average ± SD†,‡,§, ||	17.0 ± 3.4	17.6 ± 2.8	13.6 ± 4.2	13.2 ± 2.9	**<0.001**
%D_{LCO} (%), average ± SD†,‡,§, ||	79.7 ± 13.1	85.3 ± 12.1	63.0 ± 18.3	62.2 ± 12.6	**<0.001**
D_{LCO}/VA (ml/min/Torr/L), average ± SD§	4.68 ± 0.77	5.16 ± 0.86	4.07 ± 1.15	4.74 ± 0.91	**0.006**
%D_{LCO}/VA (%), average ± SD§	94.0 ± 14.7	104.5 ± 16.8	87.4 ± 20.9	96.6 ± 16.7	**0.023**

FEV_1, forced expiratory volume in 1 s; SD, standard deviation; IQR, interquartile range; VC, vital capacity; FVC, forced vital capacity; $FEF_{25–75\%}$, forced expiratory flow between 25% and 75% of vital capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; D_{LCO}, diffusing capacity of lung for carbon monoxide; D_{LCO}/VA, D_{LCO} per unit of alveolar volume. *The difference between clusters 1 and 2, †clusters 1 and 3, ‡clusters 1 and 4, § clusters 2 and 3, || clusters 2 and 4, ¶ clusters 3 and 4 were statistically significant.

SGRQ, and four without diffusing capacity of the lungs were excluded. Finally, data from 104 patients were analyzed in the present study. The patient characteristics are shown in Table 2. The average age was 69.6 years, and 87 patients (83.7%) were female. Overall, 23 (22.3%) patients had smoking history, and 17 (16.3%) had respiratory comorbidity: 7 (6.7%) bronchial asthma, 5 (4.8%) COPD, 4 (3.8%) interstitial pneumonia, and 2 (1.9%) old tuberculosis. None of the patients received home-based oxygen therapy. Seventy-one (68.3%) patients had a history of treatment with anti-nontuberculous mycobacterium (NTM) drugs.

3.2. Classification by cluster analysis

The patients were divided into four groups by cluster analysis using respiratory function parameters (Figs. 1 and 2(a)). The relationship between these parameters is shown in Fig. 2(b). Each cluster exhibited a distinct respiratory function pattern (Table 3). Cluster 1 mainly included patients with %VC ≥ 80% and 70% ≤ FEV_1/FVC <85% (Fig. 2(b)), and Cluster 1 was named as the normal group. Most patients in Cluster 2 showed %VC ≥ 80% and FEV_1/FVC <70%, and was named Cluster 2 as obstructive impairment group. Most patients in Clusters 3 and 4 had % VC <80%. Cluster 3 was characterized by FEV_1/FVC ≥85%. High FEV_1/FVC was observed because FVC was impaired; however, FEV_1 was preserved within the normal range, namely %FEV_1 ≥80%, in Cluster 3. Therefore, Cluster 3 was named as restrictive pattern with preserved FEV_1 group. Cluster 3 comprised of patients with high $FEF_{25–75\%}$ or low %D_{LCO} among those with high FEV_1/FVC (Fig. 2(b)). Cluster 4 tended to exhibit %VC <80% and FEV_1/FVC <85%, which are typical restrictive patterns. We named Cluster 4 as restrictive pattern with a decreased FEV_1 group to express the difference between Clusters 3 and 4.

We determined the number of groups by comparing models with three to five clusters (e-Tables 1 and 2). The normal group (Cluster 1) and the obstructive impairment group (Cluster 2) were not distinguished in the three-cluster model. In the five-cluster model, the restrictive pattern with preserved FEV_1 group (Cluster 3) was divided into two groups according to the degree of reduction in %VC. Five patients, divided from the restrictive pattern with preserved FEV_1 group (Cluster 3) in the five-cluster model, had similar PFT features to those in the normal group (Cluster 1). Therefore, we adopted a four-cluster model.

3.3. Features of each cluster

Restrictive pattern in the decreased FEV_1 group was the most severe phenotype among the four clusters. Patients in the restrictive pattern with decreased FEV_1 group complained of dyspnea more frequently than those in the other clusters (Table 4). The VAS scores for dyspnea of restrictive pattern in the decreased FEV_1 group were higher than those in the normal group ($P = 0.001$), and the mMRC of restrictive pattern with decreased FEV_1 group was higher than that in the normal and obstructive impairment groups ($P < 0.001$). High serum C-reactive protein (CRP) and low serum albumin levels were also observed in restrictive pattern with decreased FEV_1 group ($P < 0.001$, <0.001, respectively; Table 4). Total lung capacity (TLC) in the restrictive pattern with decreased FEV_1 group was the lowest among the clusters (Fig. 3). Restrictive pattern in the decreased FEV_1 group had the highest CT score ($P = 0.004$, Fig. 4(a)). Bronchiolitis and cavity scores in the restrictive pattern with decreased FEV_1 group were higher than in the normal group ($P = 0.039$, 0.034, respectively; Fig. 4(b) and (c)). The HRQOL of patients in the restrictive pattern with decreased FEV_1 group tended to be impaired in terms of activity, impact, and total SGRQ scores ($P = 0.017$, 0.030, and 0.010, respectively; Table 5).

Patients in the restrictive pattern with preserved FEV_1 group complained of severe symptoms as restrictive pattern with decreased FEV_1 group (Table 4). Among the radiological findings, consolidation was observed most frequently (Table 4), and the consolidation score was highest in the restrictive pattern with preserved FEV_1 group ($P < 0.001$, Fig. 4(d)). The HRQOL impairment in the restrictive pattern with preserved FEV_1 group was comparable to that in the restrictive pattern with decreased FEV_1 group (Table 5). Bacterial exacerbation requiring

Table 4
Comparison of characteristics, subjective symptoms, laboratory data, and radiological findings among four clusters.

	Cluster 1 Normal group	Cluster 2 Obstructive impairment group	Cluster 3 Restrictive pattern with preserved FEV_1 group	Cluster 4 Restrictive pattern with decreased FEV_1 group	*P*-value
N	28	32	17	27	
Age (years), median (IQR)	69.5 (60.3, 73.8)	70.0 (65.3, 74.0)	74.0 (67.0, 78.0)	70.0 (64.0, 77.0)	0.26
Female, n (%)	25 (89.3)	29 (90.6)	11 (64.7)	22 (81.5)	0.096
Smoking history, n (%)	7 (25.9)	4 (12.5)	6 (35.3)	6 (22.2)	0.30
Height (cm), average ± SD	157.3 ± 7.0	156.1 ± 6.7	159.6 ± 9.6	156.4 ± 9.2	0.517
Body weight (kg), average ± SD	49.7 ± 6.3	50.3 ± 9.1	45.0 ± 10.5	45.2 ± 9.1	0.051
BMI, average ± SD[†,§, ‖]	20.1 ± 2.2	20.5 ± 2.9	17.4 ± 2.4	18.4 ± 2.6	**<0.001**
BMI <18.5, n (%)[†,§,¶]	8 (28.6)	9 (28.1)	14 (82.4)	16 (59.3)	**<0.001**
Respiratory comorbidity, n (%)	3 (10.7)	4 (12.5)	5 (29.4)	5 (18.5)	0.36
Bronchial asthma, n (%)	3 (10.7)	0 (0.0)	0 (0.0)	4 (14.8)	0.070
COPD, n (%)	0 (0.0)	3 (9.4)	2 (11.8)	0 (0.0)	0.11
Interstitial pneumonia, n (%)	1 (3.6)	0 (0.0)	2 (11.8)	1 (3.7)	0.24
Old tuberculosis, n (%)	0 (0.0)	1 (3.1)	1 (5.9)	0 (0.0)	0.43
Cancer history, n (%)	9 (33.3)	7 (21.9)	3 (17.7)	5 (18.5)	0.53
Autoimmune disease, n (%)	1 (3.7)	4 (12.5)	1 (5.9)	5 (18.5)	0.30
Disease duration (months), median (interquartile range)	91.5 (43.8, 130.5)	61 (26.3, 109.3)	74 (33.5, 112)	102 (55, 173)	0.19
Positive in sputum smear within one year, n (%)	1 (3.6)	4 (12.5)	1 (5.9)	3 (11.1)	0.60
Positive in sputum culture within one year, n (%)	4 (14.3)	3 (9.4)	1 (5.9)	5 (18.5)	0.58
Anti-NTM treatment					0.63
Current treatment, n (%)	12 (42.9)	14 (43.8)	8 (47.1)	13 (48.2)	
Former treatment (completed treatment), n (%)	1 (3.6)	4 (12.5)	3 (17.7)	6 (22.2)	
Former treatment (discontinued treatment), n (%)	3 (10.7)	4 (12.5)	2 (11.8)	1 (3.7)	
Subjective symptoms					
VAS cough, median (IQR)	13 (4, 30)	13 (5.3, 31)	28 (5.5, 60)	28 (6, 51)	0.25
VAS sputum, median (IQR)	8 (4, 51)	13 (4.3, 25.8)	32 (13.5, 66)	25 (6, 51)	0.097
VAS difficulty of expectoration, median (IQR)	9 (4, 33)	10.5 (3.3, 43.8)	18 (8.5, 56.5)	21 (3, 51)	0.61
VAS hemosputum, median (IQR)	0 (0, 2)	1 (0, 2.8)	2 (0, 11)	2 (0, 14)	**0.021**
VAS fatigue, median (IQR)	13 (4, 32)	16 (6, 36.8)	40 (10.5, 54.5)	27 (7, 48)	0.093
VAS fever, median (IQR)	0 (0, 2)	2 (0, 4)	4 (1, 23)	3 (0, 18)	**0.034**
VAS dyspnea, median (IQR)[†,‡]	2 (0, 5)	2 (0, 16.3)	20 (5.5, 54)	13 (2, 27)	**0.001**
VAS anorexia, median (IQR)	1 (0, 5)	2 (1, 9.8)	10 (3.5, 29)	3 (0,0.20)	0.055
mMRC, median (IQR)[‡, ‖]	0 (0, 1)	0 (0, 1)	1 (0, 1.5)	1 (0, 1)	**<0.001**
Laboratory findings					
Hb (g/dl), average ± SD	13.3 ± 0.8	13.6 ± 1.4	13.1 ± 1.6	12.8 ± 1.2	0.093
WBC (10 [3]/μl), median (IQR)	5.7 (4.7, 7.0)	5.5 (4.2, 6.3)	5.4 (4.5, 6.5)	5.7 (4.3, 7.4)	0.83
CRP (mg/dl), median (IQR)[‡, ‖]	0.0 (0.0, 0.1)	0.0 (0.0, 0.2)	0.4 (0.1, 0.9)	0.2 (0.0, 0.9)	**<0.001**
Total protein (g/dl), median (IQR)	7.2 (6.8, 7.5)	7.2 (7.0, 7.5)	7.3 (6.9, 7.7)	7.3 (6.9, 7.7)	0.50
Albumin (g/dl), average ± SD[‡]	4.2 ± 0.3	4.3 ± 0.3	4.0 ± 0.5	4.0 ± 0.3	**0.002**
Radiological findings					
NB/NB + FC/FC, n (%)	25 (89.3)/2 (7.1)/1 (3.6)	24 (75.0)/6 (18.8)/2 (6.3)	10 (58.8)/7 (41.2)/0 (0.0)	16 (59.3)/9 (33.3)/2 (7.4)	0.10
Presence of cavities, n (%) [*,†,‡]	3 (10.7)	8 (25.0)	7 (41.2)	11 (40.7)	**0.047**
Presence of consolidation, n (%) [*,†,§, ‖,¶]	5 (17.9)	3 (9.4)	10 (58.8)	10 (7.3)	**0.001**

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; IQR, interquartile range; SD, standard deviation; COPD, chronic obstructive pulmonary disease; NTM, nontuberculous mycobacterium; VAS, visual analog scale; mMRC, modified British Medical Research Council; Hb, hemoglobin; WBC, white blood cell; CRP, C-reactive protein; NB, Nodular bronchiectasis type; FC, Fibrocavitary type. *The difference between clusters 1 and 2, †clusters 1 and 3, ‡clusters 1 and 4, § clusters 2 and 3, ‖ clusters 2 and 4, ¶ clusters 3 and 4 were statistically significant.

antibiotic treatment other than antimycobacterial agents occurred marginally more frequently in the restrictive pattern with preserved FEV_1 group ($P = 0.061$, Table 5).

The obstructive impairment group was similar to the normal group in terms of subjective symptoms, laboratory data, and radiological findings. The HRQOL scores of the obstructive impairment group were not impaired compared to those of the normal group. Bronchiectasis and nodule scores on CT did not differ among the four groups (Fig. 4(e) and (f)).

We then determined the cutoff values of PFT between each group for the clinical application of the classification. Cluster 1, 2, 3 and 4 were reclassified: Group 1 as patients with %VC ≥ 80 and 70 ≤ FEV_1/FVC <85, Group 2 as %VC ≥ 80 and FEV_1/FVC <70, Group 3 as FEV_1/FVC ≥85, and Group 4 as %VC < 80 and FEV_1/FVC <85 (e-Figure 1). The characteristics of each group by reclassification were similar to the results of cluster classification (e-Table 3 and e-Figure 2).

3.4. Correlation between CT score and other parameters

The result of Spearman's rank correlation test is shown in e-Table 4. High CT total score was correlated with low pulmonary function. Bronchiolitis score was associated with $FEF_{25–75\%}$ which indicated the degree of small airway obstruction. $\%D_{LCO}$ was correlated with CT total score, but $\%D_{LCO}$/VA was not. Consolidation score was inversely correlated with %VC and BMI but it was not correlated with $\%FEV_1$ and FEV_1/FVC.

4. Discussion

To the best of our knowledge, this is the first study to perform a

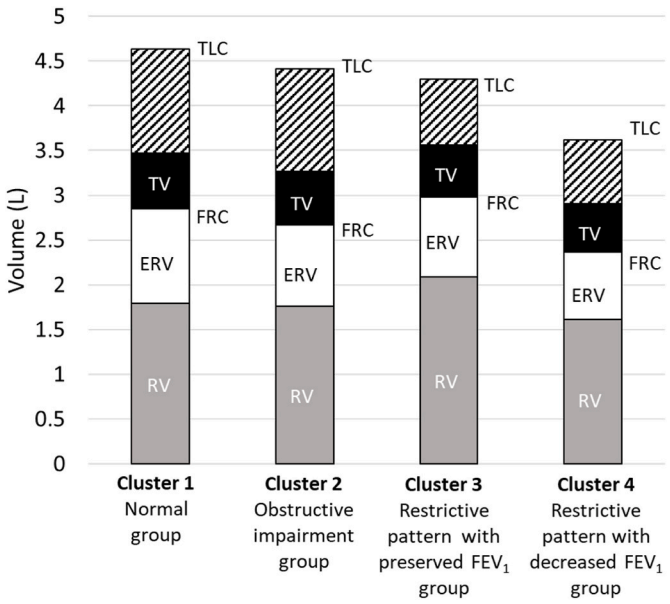


Fig. 3. Average lung volumes and capacities in each cluster. ERV, expiratory reserve volume; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; TV, tidal volume.

cluster analysis based on PFT findings in patients with NTM. Clinical data were collected comprehensively, and subjective symptoms, laboratory and radiological findings, and HRQOL were compared among the clusters. Using cluster analysis, patients were divided into four clusters with distinctive features. Two severe phenotypes with different patterns of pulmonary function impairment have been identified.

In this study, $FEF_{25–75\%}$ was selected as a variable for cluster analysis. Kubo et al. showed that air trapping in CT findings was correlated not with FEV_1/FVC but with $FEF_{25–75\%}$ [18]. Asakura et al. showed the correlation between $FEF_{25–75\%}$ and total lung volume or infiltration volume in CT findings, and the negative correlation between $FEF_{25–75\%}$ and SGRQ score [28]. Because of these findings, $FEF_{25–75\%}$ was selected as a variable for cluster analysis. In the classification without $FEF_{25–75\%}$, obstructive impairment pattern was not classified (e-Table 5). $\%D_{LCO}/VA$ was a candidate variable for cluster analysis. However, we were concerned that $\%D_{LCO}/VA$ was not an appropriate parameter describing lung diffusion capacity of NTM-PD. NTM infection is not diffuse but a focal or multifocal lung disease, and the diffusion capacity of lung regions without abnormalities remains normal. In addition, $\%D_{LCO}$ is more appropriate to predict pulmonary oxygenation than $\%D_{LCO}/VA$ in interstitial pneumonia [29]. Indeed, in our study, $\%D_{LCO}$ was correlated with VAS dyspnea, mMRC and SGRQ total score, but $\%D_{LCO}/VA$ was not correlated with them (e-Table 6). For these reasons, $\%D_{LCO}/VA$ was not selected as a variable for cluster analysis. In cluster classification with $\%D_{LCO}/VA$, obstructive impairment group was not classified, and patients with restrictive pattern were divided into two clusters based on the degree of $\%D_{LCO}/VA$ (e-Table 7). NTM-PD is thought to initiate in the terminal bronchiole and spreads transbronchially and gradual decline of FEV1 was observed in natural course of NTM-PD patients [30]. Obstructive impairment is an important factor in the assessment of NTM-PD. The classification without $\%D_{LCO}/VA$ was more clinically useful than that with $\%D_{LCO}/VA$ because the obstructive impairment group was classified.

In Cluster 4, which is the restrictive pattern with decreased FEV_1 group, the HRQOL were the worst among clusters. It was previously reported that impaired HRQOL in patients with pulmonary NTM was related to a decline in FVC [31]. In our study, this relationship was evident in Cluster 4. Moreover, patients in Cluster 4 showed high serum CRP levels based on laboratory findings. It was reported that the SGRQ and SF-36 were inversely correlated with CRP in patients with NTM [32]. The worst HRQOL of patients in Cluster 4 could be attributed not only to respiratory dysfunction, but also to inflammation.

In Cluster 3, which comprise the restrictive pattern with preserved FEV_1 group, low VC, and high FRC and RV were observed. TLC was preserved in Cluster 3 compared to Cluster 4, although VC was equivalently low in both groups. This PFT pattern is commonly observed in restrictive disorders such as neuromuscular disease and underweight populations [33–36], and the BMI of this group was the lowest among the four groups. Respiratory muscle weakness and chest immobility due to low physical activity are associated with a decline in pulmonary function in patients with low BMI patients [36]. Respiratory muscle weakness and impaired chest mobility cause a decline in cough peak flow [37,38]. Respiratory muscle weakness, physical inactivity, and impaired chest wall mobility are associated with weak cough and impaired secretion clearance [37–39]. In Cluster 3, a high consolidation score in CT findings and a high frequency of bacterial exacerbation were observed. A possible explanation for these results is the impairment of secretion clearance caused by expiratory muscle weakness. In addition, exacerbation of bronchiectasis was associated with high mortality [40] and a decline in lung function [41]. Low BMI was related to disease progression and poor prognosis in patients with NTM [42,43]. Therefore, there was concern about disease progression and poor prognosis of patients in this cluster.

In Cluster 2, which is the obstructive impairment group, the HRQOL was not impaired compared to Cluster 1, the normal group. It was reported that FEV_1 and $FEF_{25–75\%}$ were inversely correlated with HRQOL score [28]. Clusters 1 and 2 included radiologically early stage patients with NTM-PD. There were no significant differences in laboratory data and CT findings between Clusters 1 and 2; however, the FEV_1/FVC and $FEF_{25–75\%}$ in Cluster 2 were lower than those in Cluster 1. Assessment of disease progression using PFT may enable the selection of patients with early stage NTM-PD for treatment initiation to maintain HRQOL.

Using the Spearman's rank correlation test between CT score and other parameters, we found that there was a correlation between $FEF_{25–75\%}$ and bronchiolitis. This result supported $FEF_{25–75\%}$ as the parameter for identifying small airway obstruction. Consolidation score was correlated with low BMI and %VC, and not correlated with $\%FEV_1$ and FEV_1/FVC. This result was compatible with the characteristics of the restrictive pattern with preserved FEV_1 group: low BMI, low VC, preserved FEV_1 and high consolidation score.

The results of the comparison of clinical data in the re-classification according to the cutoff values of PFT were similar to those of the cluster classification. Cluster classification is difficult to apply directly to clinical practice because there are no criteria for the four phenotypes. Thus, we re-classified the groups by clarifying the cutoff values of PFT to distinguish among the groups and found that the clarified definition of the groups is sufficient to categorize patients with NTM-PD into four phenotypes.

This study has several limitations. First, this was a cross-sectional study, in which follow-up data were not obtained. Radiological severity was most severe in Clusters 3 and 4, moderate in Cluster 2, and mild in Cluster 1. Two severe disease phenotypes were identified by cluster analysis; however, it was unclear how NTM-PD progressed over time. A longitudinal study is required to determine the clinical course of each cluster. Second, this was a single-center cohort study. Patient characteristics differed among hospitals. This study showed a relatively low rate of underlying bronchial asthma (6.7%) and COPD (4.8%), in contrast to two previous cohorts with higher rates of underlying bronchial asthma (13.7% [44], 33.2% [45]) and COPD (37.3% [44], 25.6% [45]). To generalize the findings of our study, it is necessary to confirm whether the same results can be obtained from other populations. However, this difference in underlying diseases made it possible to compare patient groups with minimal effects of chronic airway disease.

In conclusion, patients with NTM-PD were divided into four phenotypes using cluster analysis based on PFT. Restrictive pattern with

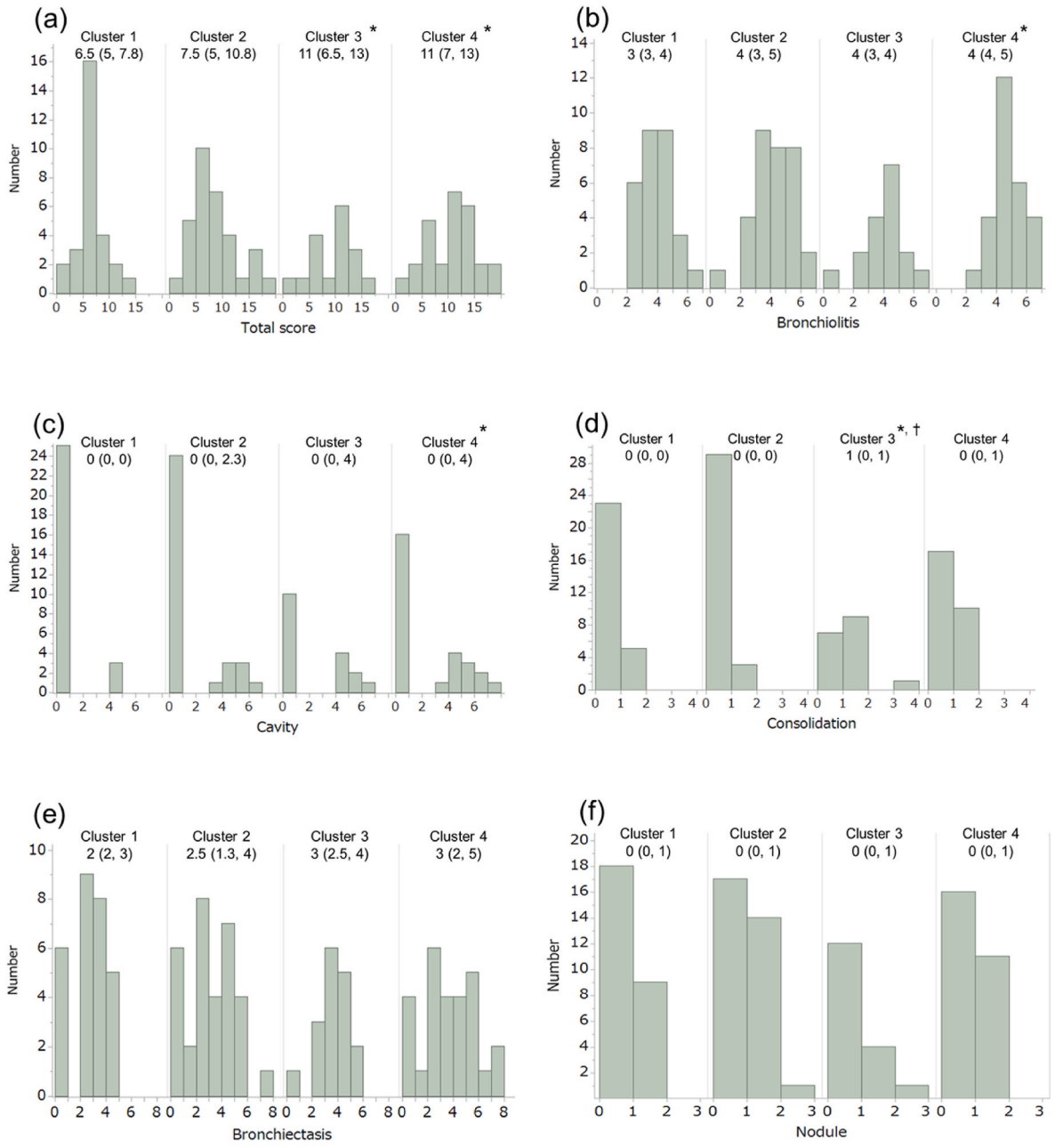


Fig. 4. Histogram of CT scores in each cluster. The x-axis in the histogram is the total or each component of CT score. Radiological findings were assessed according to the CT scoring method reported by Kim et al. (Table 1). The median and interquartile range of the score were shown beneath each cluster. *The score was higher than that of Cluster 1, and †Cluster 2.

Table 5
Comparison of health-related quality of life and other outcomes among four clusters.

	Cluster 1 Normal group	Cluster 2 Obstructive impairment group	Cluster 3 Restrictive pattern with preserved FEV_1 group	Cluster 4 Restrictive pattern with decreased FEV_1 group	*P*-value
N	28	32	17	27	
SGRQ					
Symptom, median (IQR)	29.7 (14.6, 44.6)	33.8 (19.0, 46.0)	42.1 (19.7, 67.9)	35.6 (26.8, 63.1)	0.13
Activity, median (IQR)	12.0 (0.0, 40.0)	21.1 (5.4, 41.7)	41.7 (20.8, 54.1)	30.4 (18.5, 48.3)	**0.017**
Impacts, median (IQR)	12.5 (2.7, 19.9)	9.4 (0.4, 21.7)	23.4 (11.5, 47.7)	22.4 (4.1, 32.3)	**0.030**
Total, median (IQR)	14.1 (6.1, 27.5)	14.6 (8.7, 29.5)	30.2 (18.2, 52.7)	29.5 (16.3, 42.3)	**0.010**
SF-36					
Physical functioning, median (IQR)	50.3 (42.1, 53.7)	51.7 (43.5, 54.4)	46.2 (31.2, 51.7)	46.2 (35.3, 51.7)	0.064
Role physical, median (IQR)	49.5 (34.3, 56.7)	52.4 (39.4, 56.7)	48.1 (35.1, 50.9)	45.2 (39.4, 53.8)	0.54
Bodily pain, median (IQR)	48.9 (39.3, 53.8)	48.4 (39.3, 53.8)	43.8 (36.6, 55.2)	49.3 (39.3, 61.1)	0.40
General health, average ± SD	45.0 ± 8.2	47.8 ± 8.7	40.9 ± 5.1	43.9 ± 10.7	0.059
Vitality, median (IQR)	52.9 (47.8, 59.0)	51.4 (43.8, 55.9)	49.8 (39.2, 57.5)	49.8 (40.7, 59.0)	0.74
Social functioning, median (IQR)	57.7 (46.4, 57.7)	52.1 (40.8, 57.7)	46.4 (35.2, 57.7)	46.4 (40.8, 57.7)	0.18
Role emotional, median (IQR)	45.6 (34.5, 56.8)	47.5 (42.8, 56.8)	45.6 (41.9, 53.1)	49.4 (34.5, 56.8)	0.89
Mental health, median (IQR)	52.0 (49.5, 59.6)	49.5 (44.4, 61.5)	54.5 (45.7, 59.6)	52.0 (47.0, 59.6)	0.73
Bacterial colonization, n (%)	1 (3.6)	4 (12.5)	2 (11.8)	6 (22.2)	0.23
Bacterial exacerbation requiring antibiotic treatment in the past one year, n (%)	0 (0.0)	1 (3.1)	3 (17.7)	1 (3.7)	0.061

FEV_1, forced expiratory volume in 1 s; SGRQ, St. George's Respiratory Questionnaire; IQR, interquartile range; SF-36, short form 36. SD, standard deviation. There was no significant difference in HRQOL score between clusters in post hoc Steel-Dwass test.

decreased FEV_1 group showed the most severe phenotype in terms of subjective symptoms, laboratory test, radiological findings, and HRQOL. Restrictive pattern in the preserved FEV_1 group was another severe phenotype with distinct features, such as a high consolidation score on chest CT and a high frequency of bacterial exacerbation. HRQOL was maintained in the obstructive impairment group, and PFT may be useful for detecting disease progression in the early phase of NTM-PD.

5. Summary conflict of interest statements

None.

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CRediT authorship contribution statement

Nobuyoshi Hamao: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Isao Ito:** Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Issei Oi:** Methodology, Investigation, Data curation, Conceptualization. **Masahiro Shirata:** Methodology, Investigation, Data curation, Conceptualization. **Kensuke Nishioka:** Investigation, Data curation. **Yasuyuki Hayashi:** Investigation, Data curation. **Seiichiro Imai:** Methodology, Conceptualization. **Toyohiro Hirai:** Supervision, Conceptualization.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2024.107600.

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