Decreased incremental shuttle walk test distance characterized by fibrocavitary lesions in non-tuberculous mycobacterial pulmonary disease

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Abstract

Background: Patients with non-tuberculous mycobacterial pulmonary disease (NTM-PD) have impaired exercise capacity, but the underlying factors are unknown. We investigated the characteristics of patients with NTM-PD and impaired exercise capacity.

Methods: In total, 149 patients with NTM-PD participated in this study. Patients completed the incremental shuttle walk test (ISWT) to assess exercise capacity. Peripheral muscle strength and pulmonary function were also assessed. Radiological findings were classified into three phenotypes: non-cavitary nodular bronchiectatic (NC-NB) form, cavitary nodular bronchiectatic form, and fibrocavitary (FC) form.

Results: The median ISWT distance (ISWD) and %ISWD were 450 meters and 88%. Participants were classified into three groups according to %ISWD, with %ISWD <60% as the severely decreased group, 60%-80% as the moderately decreased group, and >80% as the normal or mildly decreased group. In a comparison of %ISWD among phenotypes, FC form had significantly lower %ISWD than those with NC-NB form. In the severely decreased group, peripheral muscle strength and pulmonary function were significantly lower than the other two groups. From a radiological standpoint, significantly more patients had FC form in the group with severely decreased %ISWD.

Conclusions: Decreased ISWD is characterized by a deterioration in physical function and the presence of FC lesions in NTM-PD.

Keywords

non-tuberculous mycobacteria; *Mycobacterium avium* complex; incremental shuttle walk test; exercise capacity; pulmonary rehabilitation.

1. Introduction

Pulmonary infections caused by non-tuberculous mycobacteria (NTM) have increased worldwide in recent years, especially among middle-aged women [1]. *Mycobacterium avium* complex (MAC) is the most common NTM infection in Japan, followed by infection caused by *M. kansasii* and *M. abscessus* [2]. The main symptoms of NTM pulmonary disease (NTM-PD) are cough, sputum, and dyspnea. Systemic symptoms such as fatigue, weight loss, and psychological disorders are also recognized [3, 4].

Patients with NTM-PD are classified into three patterns based on chest high-resolution computed tomography (HRCT) findings: non-cavitary nodular bronchiectatic (NC-NB) form, cavitary nodular bronchiectatic (C-NB) form, and fibrocavitary (FC) form [5]. Furthermore, larger cavities and bronchiectasis can be seen as the disease progresses [6]. It has been elucidated that the presence of cavitary lesions is associated with an unfavorable outcome and can be a prognostic factor [5, 7, 8]. The FC form in NTM-PD is characterized by development in older men with a smoking history and underlying pulmonary diseases such as previous pulmonary tuberculosis, chronic obstructive pulmonary disease (COPD), and chronic pulmonary aspergillosis [5].

Although the mainstay of treatment for NTM-PD is long-term multidrug therapy, recurrence after treatment is common and the cure is difficult [3]. Therefore, alternative treatment goals, such as the improvement of symptoms, radiological lesions, and health-related quality of life (HRQOL) are suggested [9]. To achieve these goals, pulmonary rehabilitation and airway clearance techniques (ACTs) could be an important approach because pulmonary rehabilitation and ACTs performed in chronic respiratory diseases such as COPD and interstitial lung disease (ILD) has been shown to result in substantial improvement in exercise capacity, HRQOL, and dyspnea [10, 11]. Therefore, it is suggested that early intervention with pulmonary rehabilitation, in addition to

appropriate antibiotic therapy, may play an important role in the treatment of patients with NTM-PD [12]. To date, however, few studies have examined pulmonary rehabilitation and ACTs for NTM-PD [13].

Exercise capacity is commonly used to evaluate disease status in chronic respiratory diseases [14]. Moreover, exercise capacity is associated with prognosis, exacerbation, and HRQOL and is recognized as an important clinical variable [15]. In NTM-PD, exercise capacity is also an important evaluation item and is used to evaluate the efficacy of treatment [16]. In our previous study, we reported that exercise capacity was significantly associated with decreased HRQOL in NTM-PD [17, 18]. However, the characteristics of patients with NTM-PD and reduced exercise capacity remain uncertain. The purpose of the present study was to identify the characteristics of patients with NTM-PD who have reduced exercise capacity.

2. Patients and Methods

2.1. Patients and study design

This was a cross-sectional study. Patients were recruited from the Respiratory Care and Rehabilitation Center, Fukujuji Hospital, Japan Anti-Tuberculosis Association in Tokyo, Japan from April 2016 to September 2020. All patients met the clinical practice guideline diagnostic criteria for NTM-PD [19]. We excluded 92 patients who did not complete all evaluations, three patients over 80 years of age, and one patient with an unclassifiable radiological pattern. Finally, 149 patients were included in the analysis (Figure 1). The present study was approved by the Fukujuji Hospital Institutional Review Board (number: 19011, 19020).

2.2. Clinical variables

Demographic data, including age, body mass index (BMI), smoking history, disease duration, employment status, serum C-reactive protein (CRP), albumin, total protein, hemoglobin, sputum acid-fast bacillus smears and comorbidities were collected from patients' medical charts. Mycobacterial cultures were performed in accordance with previous study methods [20]. In the smear test, we investigated the maximum amount of smear confirmed by the past three sputum tests immediately before the evaluation date. Chronic colonization of other bacteria was defined as two or more positive sputum cultures of the same species in the previous year. Radiological phenotypes were classified into three patterns according to the main features on chest HRCT: NC-NB form, C-NB form, and FC form [5].

2.3. Exercise capacity

Functional exercise capacity was assessed using the incremental shuttle walk test (ISWT) and carried out in accordance following a standardized protocol [21]. This is a threshold symptomatic field test conducted on a 10-meter course with the walking speed dictated by an audio signal. The test is continuous and incremental, with the speed increasing each minute. The ISWT distance (ISWD) was recorded in meters and expressed as a percentage of the predicted Japanese values [22].

2.4. Pulmonary function

Pulmonary function was measured using an electronic spirometer (CHEST AC-8800; CHEST M.I., INC., Tokyo, Japan) while the patient was in a stable condition. Pulmonary function was measured using a spirometer in accordance with published guidelines [23]. Pulmonary function test data were examined for forced expiratory volume in 1 second (FEV_1), percentage predicted FEV_1 (%FEV_1), vital capacity (VC),

76 percentage predicted VC (%VC), and FEV_1/forced vital capacity (FVC).

77

78 **2.5. Dyspnea**

79 The modified Medical Research Council Dyspnea Scale (mMRC) was used to evaluate
80 dyspnea perception [24]. This scale ranges from 0 to 4 with higher scores representing
81 greater functional limitations owing to dyspnea.

82

83 **2.6. HRQOL**

84 HRQOL was assessed using the Japanese version of the COPD assessment test (CAT)
85 [25]. The CAT comprises eight items: cough, phlegm, chest tightness, breathlessness,
86 ability to perform activities of daily living, confidence in leaving the home, sleep, and
87 energy. Each question is scored on a six-point scale (0–5) yielding a total possible score
88 ranging from 0 (best possible health) to 40 (worst possible health). The CAT has been
89 validated in patients with NTM-PD [26].

90

91 **2.7. Peripheral muscle strength**

92 Quadriceps force (QF) was evaluated as the peak force developed during a maximal
93 isometric knee extension maneuver using a hand-held dynamometer with a fixing belt
94 (μ-Tas F-1; Anima Corporation, Tokyo, Japan), according to a standard protocol [27].
95 The QF of the dominant side was tested in the sitting position with the hip and knee
96 joint flexed at approximately 90°. The highest value among at least three maneuvers
97 was recorded and expressed in kilogram force (kgf). The handgrip force (HF) of the
98 dominant hand was assessed using a dynamometer (Smedley's hand dynamometer; MIS
99 TOKYO, Tokyo, Japan). The HF was tested with participants in a standing position with
100 the elbow extended. The highest value of two attempts was recorded in kilograms (kg).

Percent predicted QF (%QF) and HF (%HF) values were calculated using predictive equations for isometric peripheral muscle strength [28].

2.8. Statistical analyses

Statistical analyses were performed using IBM SPSS software version 25 (IBM Corp., Armonk, NY, USA). Data are expressed as median (interquartile range) or number (percentage). The distribution of the data was assessed using the Shapiro–Wilk test. Study participants were classified into three groups according to percent predicted ISWD (%ISWD), with %ISWD <60% as the severely decreased group, 60%-80% as the moderately decreased group, and >80% as the normal or mildly decreased group. Data categorized according to the three groups were compared using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test for continuous variables and Pearson's chi-square test with adjusted residuals for categorical variables. If there was a significant difference among the three groups, then we performed post-hoc analysis for multiple comparisons with Tukey's test for ANOVA and Dunn's test with Bonferroni correction in the Kruskal-Wallis test. A p value of <0.05 was considered statistically significant. Adjusted residuals in the chi-square test were considered significant if they were greater than or equal to 1.96 and less than or equal to -1.96.

3. Results

Among the 149 included patients with NTM-PD, median age was 66 years, and 141 (94.6%) were women. Of the NTM species, 81 (54.4%) were *M. avium*, 17 (11.4%) were *M. intracellulare*, 17 (11.4%) were *M. abscessus*, 27 (18.1%) were *M. massiliense*, and 7 (4.7%) were other species, including mixed infections. As for the radiological pattern, 67 (45.0%) patients had NC-NB form, 55 (36.9%) had C-NB form, and 27

(18.1%) had FC form. The median ISWD and %ISWD were 450 meters and 88%, respectively (Table 1). Of the %ISWD, <60% as the severely decreased group were 16 (10.7%) patients, 60%-80% as the moderately decreased group were 36 (24.2%) patients, and >80% as the normal or mildly decreased group were 97 (65.1%) patients.

The %ISWD in the severe group (%ISWD <60%, n=16) was associated with significantly higher age ($p<0.001$), a lower % FEV_1 ($p<0.001$), %VC ($p<0.001$), albumin ($p<0.001$), and hemoglobin ($p<0.001$) than the other two groups. %QF and %HF were significantly lower in the severe group, and mMRC, CAT, and serum CRP were significantly higher, in comparison with the other two groups (Table 2).

In a comparison of %ISWD among the three phenotype groups (NC-NB form, C-NB form and FC form), patients with FC form had significantly lower %ISWD than those with NC-NB form (ANOVA: $p=0.038$, NC-NB form vs. FC form; $p=0.029$) (Figure 2). As for %ISWD, there were significantly more patients with FC form and significantly fewer with NC-NB form ($p=0.046$) in the severe group (Table 2 and Figure 2).

4. Discussion

In the present study, the patients with severely decreased %ISWD had significantly more FC form and less NC-NB form. Moreover, the notable findings in the present study were that patients with NTM-PD in association with FC form showed greater impairment in ISWD than those with NC-NB form. Cavitary lesions in FC form occur predominantly in the upper lobes and are accompanied by extensive pleural thickening in the lungs, as compared with NC-NB form [5]. Furthermore, the volume of the cavitary lesions has been shown to influence the decrease in %FEV_1 and diffusing capacity of the lung for carbon monoxide [29]. This characteristic finding of FC form may be related to the decrease in ISWD.

151 The %ISWD in the severely decreased group was significantly associated with higher
152 age, CRP, and scores on the mMRC and CAT as well as lower values of %FEV_1, %VC,
153 albumin, hemoglobin, %QF, and %HF in comparison with the normal or mildly
154 decreased group. The association between exercise capacity and parameters such as
155 pulmonary function, serum CRP, albumin, hemoglobin, peripheral muscle strength, and
156 dyspnea has been widely reported in patients with COPD [30, 31, 32, 33]. This is also
157 the case in patients with ILD and bronchiectasis [34, 35]. It is likely that patients with
158 NTM-PD exhibit the same parallel relationship between exercise performance and
159 various exercise-related parameters as patients with other chronic respiratory diseases.
160 In the present study, there were few men (5.4%) and only 14% were former or current
161 smokers; thus, no significant differences were noted in sex or smoking history. Despite
162 the participants in our study comprising some patients with co-existing other lung
163 diseases, the number of patients with co-existing other lung diseases was small and their
164 causes were uncertain.
165 It has been that decreased exercise capacity can be improved with pulmonary
166 rehabilitation [36]. There are also some data showing that pulmonary rehabilitation is
167 more effective in patients with severely reduced exercise capacity and FEV_1 [37, 38].
168 The benefits are well described in patients with COPD but are also demonstrated in
169 ILD, asthma, bronchiectasis, and tuberculosis[39, 40, 41, 42]. It is considered that
170 NTM-PD occurs in the presence of these pre-existing structural lung diseases [43].
171 Although few reports demonstrate the efficacy of pulmonary rehabilitation or ACTs in
172 NTM-PD [13], evidence has been accumulating in other diseases with similarities to
173 NTM-PD such as bronchiectasis and tuberculosis. Therefore, pulmonary rehabilitation
174 and ACTs should be provided as non-pharmacological treatments for NTM-PD.
175 Furthermore, the results of the present study suggest the importance in providing

pulmonary rehabilitation for patients with FC phenotype as early as possible to avoid a decrease in exercise capacity.

Our study had some limitations. First, this was a single-center study. We enrolled patients with an age comparable to participants in previous studies [26, 44]. However, pulmonary function, BMI, and HRQOL were worse in sample in comparison with previous studies. Therefore, the present study may have included patients with more severe disease than those in past studies. Second, there were few male participants included. It is possible that smoking and comorbidities in men have a greater impact on exercise capacity.

5. Conclusion

In conclusion, in patients with NTM-PD, we identified that impaired ISWD is characterized by decrements in peripheral muscle strength, pulmonary function, dyspnea, and HRQOL, and also the presence of FC lesions.

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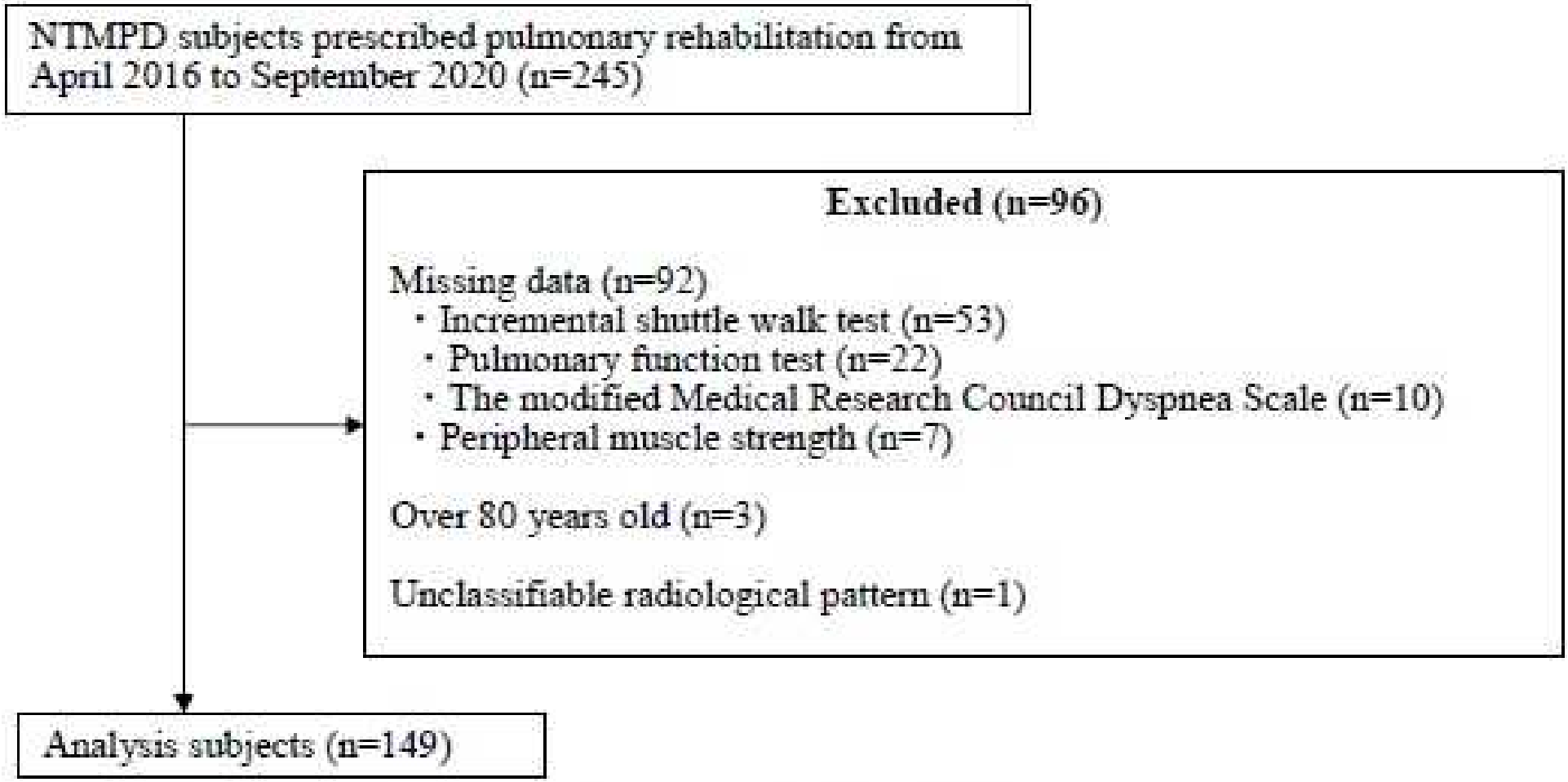

Figure1. Flow chart from subject recruitment to study completion.

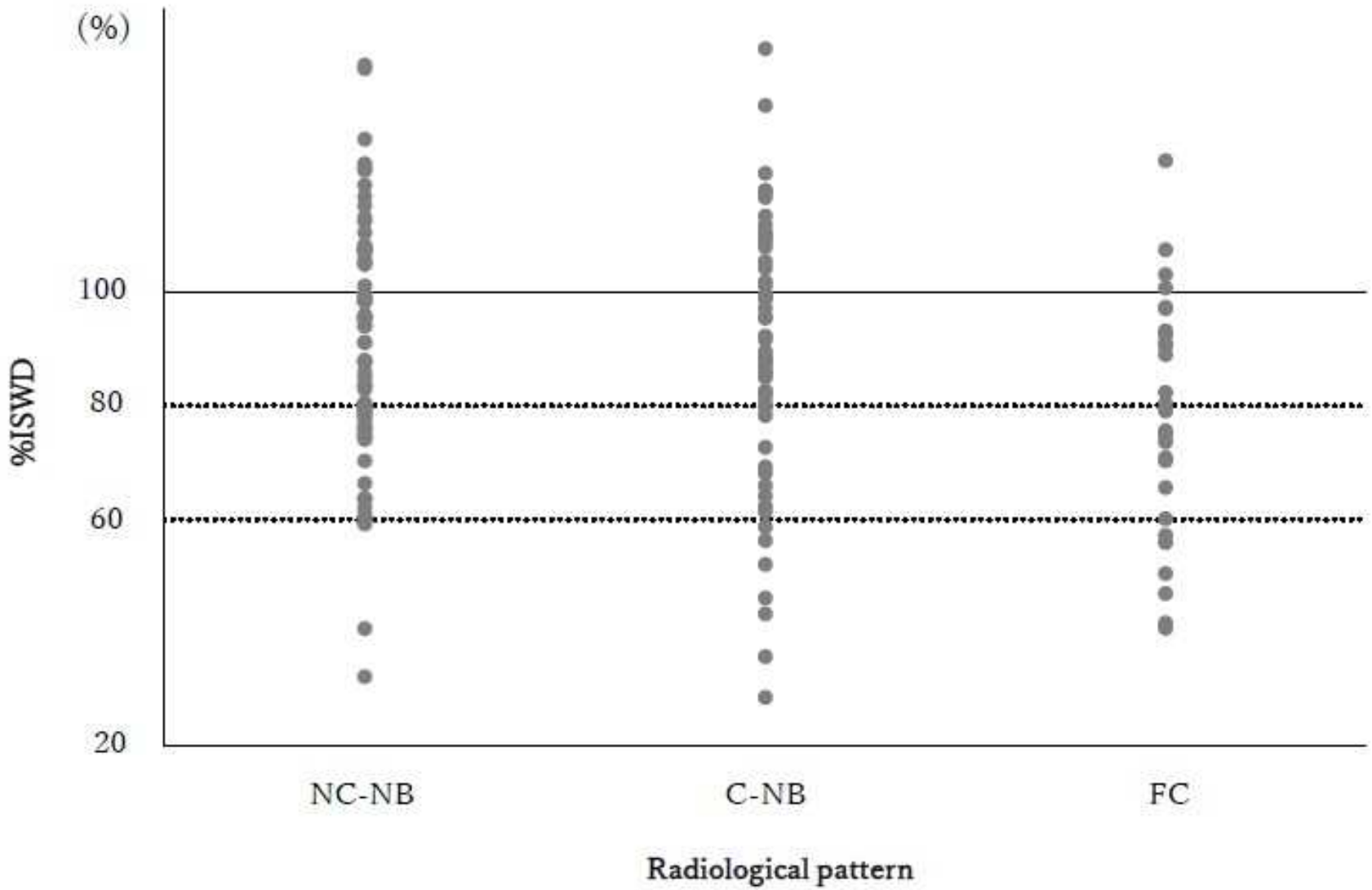

Figure 2. Comparison of the %ISWD of three radiological patterns.
FC type had significantly lower %ISWD than NC-NB type (ANOVA; p=0.038, NC-NB type vs FC type; p=0.029).

Table 1

Clinical characteristics of the 149 patients with non-tuberculous mycobacteria pulmonary disease

Variable	
Age, y	66.0 (59.5–71.0)
Male/Female, n (%)	8.0 (5.4)/141 (94.6)
Height, cm	156.0 (152.7–160.4)
Weight, kg	44.5 (40.0–51.1)
BMI, kg/m^2	18.2 (16.6–20.5)
Disease duration, y	5 (2–11)
Smoking history	
Never/Former/Current	128(86)/21(14)/0(0)
Brinkman Index, (n=21)	80 (24–495)
Employment status, n (%)	
Office work	14 (9.4)
Health	9 (6.0)
Other	23 (15.4)
Homemaker or retired	103 (69.1)
VC %predicted, %	78.4 (62.8–89.2)
FEV_1 %predicted, %	79.3 (63.3–92.7)
FEV_1/FVC＜70%, n (%)	21 (14.1)
Quadriceps force, kgf	23.3 (18.2–26.8)
Quadriceps force %predicted	106.7 (87.9–128.4)
Handgrip force, kg	21.2 (18.0–24.5)
Handgrip force %predicted	89.9 (79.1–102.7)
mMRC , grade0/1/2/3/4, n(%)	76(51.0)/ 52(34.9)/19(12.8)/2(1.3)/0(0)
Radiological pattern	
NC-NB/C-NB/FC	67(45.0)/55(36.9)/27(18.1)
NTM species	
M. avium	81 (54.4)
M. intracellulare	17 (11.4)
M. abscessus	17 (11.4)
M. massiliense	27 (18.1)
M. avium + *M.abscessus*	4 (2.7)
M. lentiflavum	2 (1.3)
M. avium + *M. lentiflavum*	1 (0.7)
Semiquantitative smear score	
-/±/+1/+2/+3	45(30.2)/34(22.8)/31(20.8)/24(16.1)/15(10.1)
Underlying pulmonary disease	
History of tuberculosis	8 (5.4)

Bronchial Asthma	4 (2.7)
Interstitial lung disease	2 (1.3)
COPD	1 (0.7)
Previous lung resection	14 (9.4)
Chronic colonization	
Aspergillus	4 (2.7)
Pseudomonas aeruginosa	8 (5.4)
Staphylococcus aureus	12 (8.1)
Other	11 (7.4)
CAT	13 (7–21)
CRP, mg/dL	0.14 (0.06–0.7)
Albumin, g/dL	3.9 (3.5–4.2)
Total protein, g/dL	7.0 (6.7–7.3)
Hemoglobin, g/dL	12.6 (11.6–13.2)
ISWD, m	450 (350–540)
ISWD %predicted	88 (75–105)

Data expressed as median (interquartile range) or number (%).

BMI, body mass index; VC, vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea scale; NC-NB, non-cavitary nodular bronchiectatic type; C-NB, cavitary nodular bronchiectatic type; FC, fibrocavitary type; NTM, Nontuberculous mycobacteria; MAC, *Mycobacterium avium* complex; COPD, chronic obstructive pulmonary disease; CAT, COPD assessment test; CRP, C-reactive protein; ISWD, incremental shuttle walk test distance; %ISWD, percentage predicted ISWD.

Table2

Comparison of the clinical characteristics of three groups of %ISWD.

Variables	<60% (n=16)	60-80% (n=36)	>80% (n=97)	p-value			
					<60% vs 60-80%	60-80% vs >80%	<60% vs >80%
Age	69.5 (68.0–74.8)	69.0 (64.3–74.0)	63.0 (58.0–69.5)	<0.001	1.000	0.003	0.006
Female	16 (100)	33 (92)	92 (95)	0.463			
BMI	17.2 (15.6–19.7)	17.8 (16.6–20.4)	18.6 (16.8–20.9)	0.090			
Disease duration	5.0 (2.0–12.0)	6.0 (2.0–12.5)	5.0 (1.0–9.5)	0.473			
Smokers (Former)	1 (6)	4 (11)	16 (17)	0.467			
Brinkman Index	550 (550–550)	60 (12.5–362.5)	78 (24.8–531.3)	0.407			
VC %predicted	57.6 (47–77)	65.8 (53–86)	82.2 (71–91)	<0.001	0.015	0.005	<0.001
FEV_1 %predicted	59.2 (48–74)	71.8 (52–95)	82.0 (69–94)	<0.001	0.093	0.072	<0.001
mMRC	2 (2–2)	1 (0–1)	0 (0–1)	<0.001	0.022	0.032	<0.001
Radiological pattern				0.046			
NC-NB	3 (18.8)	19 (52.8)	45 (46.4)				
Adjusted residuals	-4.2	2.8	1.4				
C-NB	7 (43.8)	9 (25.0)	39 (40.2)				
Adjusted residuals	1.1	-4.3	3.2				
FC	6 (37.5)	8 (22.2)	13 (13.4)				
Adjusted residuals	3.1	1.5	-4.6				
Semiquantitative smear score*	2 (1–4)	1.5 (1–2)	1 (0–2.5)	0.132			
History of tuberculosis	2 (12.5)	2 (5.6)	4 (4.1)	0.387			
Previous lung resection	2 (12.5)	5 (13.9)	7 (7.2)	0.455			

Aspergillus	0 (0)	2 (5.6)	2 (2.1)	0.423			
Pseudomonas aeruginosa	1 (6.3)	0 (0)	7 (7.2)	0.257			
CAT	20.5 (16.3–14.8)	13.5 (7.3–22.8)	11.0 (6.3–19.0)	0.001	0.047	0.672	0.001
CRP	3.82 (0.68–5.76)	0.12 (0.63–1.50)	0.12 (0.05–0.45)	<0.001	0.003	0.275	<0.001
Albumin	3.4 (3.0–3.9)	3.8 (3.4–4.1)	4.0 (3.7–4.2)	<0.001	0.140	0.114	0.001
Total protein	7.2 (6.5–7.6)	7.0 (6.6–7.2)	7.0 (6.7–7.3)	0.721			
Hemoglobin	11.1 (10.5–11.9)	12.9 (11.7–13.5)	12.7 (12.0–13.3)	<0.001	<0.001	1.000	<0.001
QF %predicted	88.5 (72–107)	103.5 (87–130)	111.1 (91–129)	0.014	0.191	0.815	0.013
HF %predicted	82.2 (56–92)	88.6 (79–92)	95.5 (82–107)	0.002	0.673	0.050	0.006

Data expressed as median (interquartile range) or number (%).

%ISWD, percent predicted incremental shuttle walk test distance; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; VC, vital capacity; mMRC, modified Medical Research Council dyspnea scale; NC-NB, non-cavitary nodular bronchiectatic type; C-NB, cavitary nodular bronchiectatic type FC, fibrocavitary type; CAT, chronic obstructive pulmonary disease assessment test; QF, quadriceps force; HF, handgrip force.

*The semiquantitative smear scores were analyzed as ordinal scales corresponding to: -:0, ±: 1; 1+: 2; 2+: 3; and 3+: 4.

Adjusted residuals in the chi-square test were considered significant if they were greater than or equal to 1.96 and less than or equal to -1.96.