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Incremental Shuttle Walk Distance as an Indicator for Functional Exercise Capacity of Pre-Surgical Patients with Nontuberculous Mycobacterial Lung Disease

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The incidence of nontuberculous mycobacterial lung disease (NTMLD) is increasing worldwide, the number of lung surgeries is increasing accordingly. The disease is progressive and is characterized by exertional intolerance, respiratory dysfunctions, and impaired health-related quality of life (HRQOL). Treatment comprises multidrug antibiotic treatment combined with lung resection. The incremental shuttle walk distance (ISWD) is a standard tool for assessing the patients' tolerance to lung resection. The exertional tolerance, physical functions and HRQOL among pre-surgical patients with NTMLD are clinically important, but not fully studied yet from the viewpoint of physiotherapy. The purpose of this study was to explore the clinical significance of ISWD for assessing the exercise capacity of pre-surgical patients with NTMLD. For peripheral muscle evaluation, the strength of the quadriceps femoris muscle was measured. HRQOL was evaluated using scores of the St. George's Respiratory Questionnaire (SGRQ). Thirty-three patients (mean age 54.9 ± 13 years) were enrolled. The mean ISWD was 505 ± 134 m, shorter than the reference values (ISWD %predicted: 96 ± 27%). Regression analysis showed significant associations between ISWD and percent-predicted vital capacity ($r = 0.38$, $p = 0.03$) and percent quadriceps force/body weight ($r = 0.54$, $p = 0.001$). HRQOL assessed by SGRQ scores was correlated with ISWD ($r < -0.4$, $p < 0.05$). Multiple regression analysis showed that ISWD was significantly associated with leg muscle strength and with HRQOL. In conclusion, ISWD is useful to evaluate the exercise capacity among pre-surgical patients with NTMLD.

Keywords: exertional tolerance; health-related quality of life; incremental shuttle walk distance; nontuberculous mycobacterial lung disease; surgical treatment
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Introduction

Nontuberculous mycobacterial lung disease (NTMLD) is increasing worldwide (van Ingen et al. 2018). In Japan, the most common cause of NTMLD is *Mycobacterium avium* complex lung disease (MACLD) (Namkoong et al. 2016), and at the same time, demonstrate increase in the number of surgical patients (Shiraishi 2016). NTMLD is an indolent but progressive disease that may result in extensive lung destruction and respiratory failure, and it is classified into two types radiologically, the fibrocavitary and nodular bronchiectatic types (Griffith et al. 2007). It is a chronic respiratory condition, characterized by cough and sputum production together with reduced exercise capacity, impaired Health-Related Quality of Life (HRQOL) (Yagi et al. 2018). As the condition progresses there is a decline in exertional tolerance and HRQOL (Asakura et al. 2017). HRQOL is assessed in order to evaluate the effect of NTMLD medical treatment and such evaluations are important along with survival and mortality (Diel et al. 2018;

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Hiramatsu and Shiraishi 2018).

If the disease is limited and localized, in patients with adequate cardiorespiratory reserve the potential benefits of an adjuvant surgical approach should be considered (Mitchell 2019). Annually in Japan, although approximately 80,000 thoracic surgeries are performed, only 500 individuals with NTMLD undergo surgery (Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery et al. 2019). Fukujuji Hospital performs approximately 40 such cases each year and is one of the representative facilities in Japan.

The Japanese guidelines for the indications for surgical treatment of NTMLD (Nontuberculous Mycobacteriosis Control Committee of the Japanese Society for Tuberculosis and International Exchanging Committee of the Japanese Society for Tuberculosis 2011) are when 1) drug therapy is insufficient to eliminate the bacteria, 2) there is enlargement or deterioration of the affected lung regions, such that even if the disease is effectively treated, cavities in the lung and bronchiectasis will remain, and there is a risk of recurrence, and, 3) there is evidence of rapid disease progression, with repeated acute exacerbations from the large-volume lesions. Further, guidelines state that surgery may be performed on individuals in their seventies but only when adequate cardiorespiratory reserve is present.

In the evaluation of exertional tolerance in individuals undergoing surgical resection for lung cancer, the incremental shuttle walk test (ISWT) and 6-min walk test are widely used measures of functional exercise capacity as well as being predictors of post-operative complications (Ha et al. 2016). Reports show an association between a preoperative incremental shuttle walk distance (ISWD) less than 400 m and the development of postoperative complications in this patient population (Ha et al. 2016).

To date, little is known about the physical function and HRQOL of surgical candidates with NTMLD. Furthermore, the relationship between ISWD, peripheral muscle strength, HRQOL and disease severity in this patient population has not been reported. In this study, we aimed to investigate the clinical significance of ISWD for assessing exertional tolerance among pre-surgical patients with NTMLD and to examine the relationship between ISWD and functional measures or HRQOL in these patients.

Methods

Study design and Subjects

This was a cross sectional study, with recruitment and assessments taking place between June 2017 and June 2018. The study was approved by the Human Research Ethics Review Committee of Fukujuji Hospital (approval number 18051), and participants gave written informed consent prior to data collection. All surgical patients were assessed for physical and respiratory function prior to surgery. Eligible patients had a diagnosis with NTMLD, were aged > 18 years, and scheduled for lung resection. Exclusion criteria were comorbid conditions affecting exercise performance (specifically, musculoskeletal or neurological impairment and cardiac disease) and those who underwent two-staged bilateral lung resection. During the recruitment period, 39 individuals underwent surgery however data from six patients were not included; two individuals did not complete all evaluations, one did not complete HRQOL evaluation, one underwent two-staged bilateral surgery, one had cognitive impairment, one had severe spinal stenosis, and one had hemoptysis (Fig. 1). The following measures of physical functions, exertional tolerance and HRQOL were all carried out within two or three days prior to surgery in a rehabilitation center. Sputum smears and sputum cultures were performed upon admission or during an outpatient visit prior to admission. Postoperative complication was defined as any postoperative event, such as bacterial pneumonia, cardiac arrhythmia, prolonged air leak requiring > 7 days of chest tube drainage, atelectasis, bleeding, bronchopleural fistula or respiratory failure.

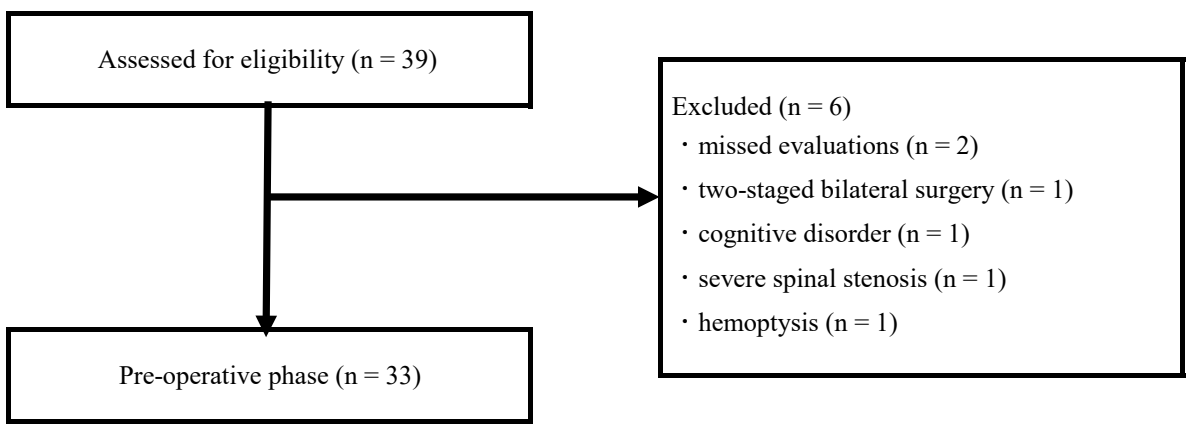

Fig. 1. Number of available participants.
Eligible patients had a diagnosis with NTMLD, were aged > 18 years. Exclusion criteria were comorbid conditions affecting exercise performance and those who underwent two-staged bilateral lung resection. In total, 33 subjects were included in this study.

Physical function measures

Assessment of peripheral muscle strength comprised quadriceps force (QF) evaluated as the peak force developed during a maximal isometric knee extension using a hand-held dynamometer (μ-TusF-1; Anima Corporation Tokyo, Japan). QF of the dominant side was tested in the sitting position with the hip and knee joint flexed at approximately 90°. The highest value of three satisfactory measurements was recorded and expressed in kilograms (kg) as a percentage of body weight (BW). Percent predicted values were calculated using predictive equations for isometric peripheral muscle strength (The National Isometric Muscle Strength (NIMS) Database Consortium 1996).

Functional exercise capacity was assessed using the ISWT and carried out according to a standardized protocol (Singh et al. 1992). This is a threshold symptomatic field test, carried out on a 10-m course with walking speed dictated by an audio signal. The test is continuous and incremental with the speed increasing each minute. The test is terminated by the patient if too breathless to maintain the required speed, or the operator terminates the test when the patient fails to complete a shuttle in the time allowed (Singh et al. 1992). The ISWD was recorded in meters and expressed as a percentage of predicted values obtained in a Japanese sample (Itaki et al. 2018). Functional limitation due to dyspnea was assessed using the modified Medical Research Council (mMRC) Dyspnea Scale (Mahler and Wells 1988).

Spirometric data and evaluation of disease severity using high-resolution computed tomography (HRCT)

A spirometer (CHEST AC-8800: Chest, Tokyo) was used to measure vital capacity (VC) and forced expiratory volume in 1 second (FEV_1), with values expressed as a percentage of predicted normal values (Miller et al. 2005).

The HRCT was used to identify the affected lung segments and the area for resection with discussion of the HRCT findings taking place at a multidisciplinary meeting. The number of affected lung segments was recorded in accordance with published descriptors (Vallilo et al. 2014). The number of segments with irreversible lung damage such as cavitary and bronchiectatic changes was counted. Nodular, infiltrative or atelectatic changes were not counted as these are thought to be reversible changes and are not surgical target.

Health-Related Quality of Life (HRQOL)

HRQOL was assessed using the self-complete version of the Japanese translation of the St George's Respiratory Questionnaire (SGRQ) (Jones et al. 1991). This is a disease-specific tool comprised of 50 items that provides individual scores for the three domains of symptoms, impact and activity as well as a total score. The score for each domain ranges from 0 to 100 with lower scores indicating better HRQOL. The validity of the SGRQ in NTMLD has previously been reported (Maekawa et al. 2013).

Statistical methods

Data were expressed as means with SD or medians with interquartile ranges (IQR) and counts with percentages for categorical variables. The Shapiro-Wilk test was used to examine the distribution of the data. The relationship between variables was examined using Pearson's or Spearman's correlation coefficients according to the distribution of the data. Multiple regression analysis was performed to determine predictors of the ISWD, correcting for risk factors were shown to be significant at $p < 0.05$ on univariate analysis. Multiple regression analysis was undertaken to identify the dependent variables of percent-predicted VC (%VC), percent QF/BW (%QF/BW) and SGRQ all domains. Statistical significance was defined at $p < 0.05$. All analyses were performed using IBM SPSS Statistics 25.0 for Windows (IBM SPSS, Tokyo, Japan).

Results

Participant characteristics

Table 1 shows the preoperative characteristics of the 33 individuals (26 females) with NTMLD. Leg strength was lower than predictive values (The National Isometric Muscle Strength (NIMS) Database Consortium 1996), and exertional tolerance was reduced compared to values for ISWD in a healthy Japanese sample (Itaki et al. 2018). Four patients developed postoperative complications (Table 2). All patients were ambulating with or without a gait aide in the intensive care unit (ICU) as early as the first postoperative day, and were discharged from the ICU on postoperative day two. Finally, all patients had an uneventful postoperative course and were discharged to home.

Relationships between clinical features and ISWD

There was no relationship between age and BMI. There was a weak to moderate relationship between %VC, and %QF/BW with ISWD. All three domains of the SGRQ had a moderate or strong relationship with ISWD (Table 3). There were no associations between clinical symptoms such as sputum or preoperative disease severity assessed by computed tomography and exertional tolerance by ISWD.

Factors determining ISWD in surgical patients with NTMLD

In multiple regression analysis (Table 4), a statistically significant inverse relationship was found between SGRQ symptom scores and ISWD ($p = 0.006$), and there was a relationship with %QF/BW ($p = 0.006$), together explaining 49% of the variance. Thus, ISWD was significantly associated with greater leg muscle strength and with less severe impairment in HRQOL.

Discussion

To our knowledge, this is the first study that has described the relationship between the distance walked on the ISWT and clinical variables including HRQOL in pre-surgical patients with NTMLD. Further, we demonstrated

Table 1. Demographics of the 33 patients who underwent lung resection.

Variables	Values
Age (years)	54.9 ± 13
Sex	
Female	26 (79%)
Male	7 (21%)
BMI (kg/m^2)	20.2 ± 3.2
Smoking status (never/former)	24/9
Disease duration[a)], months	30 (13-82)
Current treatment duration[b)], months	18 (8-42)
Mycobacterium species	
Mycobacterium avium complex	28 (86%)
Mycobacterium abscessus complex	4 (12%)
Mycobacterium lentiflavum	1 (2%)
Sputum status (positive/negative)	13/20
Pre-operative Radiological Features	
Nodular/Bronchiectatic	17 (52%)
Fibrocavity	5 (15%)
Both	11 (33%)
Affected segments[c)]	3 (1-4.5)
Surgical indication	
To control the progression of disease/ To cure disease	16/17
FEV_1 (L)	2.4 ± 0.7
FEV_1 % predicted	94 ± 17
VC (L)	3 ± 0.8
VC % predicted	92 ± 17
mMRC dyspnea score	0 (0)
QF % body weight	52.7 ± 12.3
QF % predicted	97 ± 29
ISWD (m)	505 ± 134
ISWD % predicted	96 ± 27
HR max % predicted[d)]	82 ± 17
Dyspnea - Borg Scale	4 (2-5)
Leg fatigue - Borg Scale	2 (2-4)
SGRQ (n = 32)	
symptom score	25.7 (17.9-33.6)
activity score	18.5 (11.2-29.4)
impact score	12 (7.6-19.5)
total score	14.8 (10.5-20.6)

Data are reported as mean ± SD, n (%) or median (interquartile range).
BMI, body mass index; FEV_1, forced expiratory volume in 1s; VC, vital capacity; mMRC, modified Medical Research Council dyspnea scale; QF, quadriceps force; ISWD, incremental shuttle walk distance; SGRQ, St. George's Respiratory Questionnaire.
[a)]The interval between the diagnosis of the disease and the time of surgery.
[b)]The interval between the start of the current treatment and the time of surgery.
[c)]The number of segments with irreversible lung damage.
[d)]Age-predicted maximal heart rate derived from the formula.

Table 2. Postoperative complications.

	n = 4
Air leak > 7 days	3
Subclavian Artery Injury[a)]	1

There was no operative mortality. All patients were ambulating with or without a gait aide in the intensive care unit as early as the first post-operative day. Finally, all patients had an uneventful postoperative course and were discharged home.
[a)]intraoperative period.

Table 3. Correlations between ISWD and other variables.

	ISWD[a)]	p
Age (years)	−0.25	0.252
BMI (kg/m^2)	−0.05	0.78
FEV_1 % predicted	0.1	0.565
VC % predicted	0.38	0.03
QF % body weight	0.54	0.001
SGRQ		
symptom score	−0.62	< 0.001
activity score	−0.45	0.01
impact score	−0.43	0.014
total score	−0.57	0.001

Statistical significance of $p < 0.05$.
ISWD, incremental shuttle walk distance; BMI, body mass index; FEV_1, forced expiratory volume in 1s; VC, vital capacity; QF, quadriceps force; SGRQ, St. George's Respiratory Questionnaire.
[a)]Data expressed as Pearson's or Spearman's rho.

Table 4. Stepwise regression analysis of ISWD and significantly associated variables.

Predictor	ISWD		
	β	p	R^2
Intercept	379.04	0.001	0.49
SGRQ symptom score	−4.44	0.006	
QF % body weight	4.57	0.006	

Statistical significance of $p < .05$.
ISWD, incremental shuttle walk distance; SGRQ, St. George's Respiratory Questionnaire; QF, quadriceps force.

that in surgical patients the preoperative ISWD was lower than distances achieved in a healthy population, and ISWD had a strong relationship with leg muscle strength and physical symptoms.

Clinical guidelines for resection for lung cancer recommend that the ISWD can be used to estimate maximal oxygen consumption, and if the ISWD is less than 400 m, it is recommended that a cardiopulmonary exercise test be performed as part of the pre-operative evaluation (Ha et al.

2016). Although none of our participants had an ISWD < 400 m, overall the distance achieved was below that of Japanese age-matched standard values (Itaki et al. 2018).

In previous studies in people with bronchiectasis (de Camargo et al. 2018), the ISWD was below the predicted values (55 ± 16%), and determinants of leg strength included age, mMRC, and ISWD. Moreover, the ISWD was an independent predictor of physical activity (step counts per day). Exertional dyspnea predisposes to a sedentary lifestyle in patients with bronchiectasis, with progressive inactivity, and physical deconditioning (Bradley et al. 2015). In our study, the mMRC grade for all patients was zero, therefore we did not consider dyspnea to be a factor influencing levels of physical function or daily physical activity in our sample. The strong relationship between ISWD and all components of the SGRQ was consistent with a previous study demonstrating a similar relationship between the 6-min walk distance (6MWD) and HRQOL, in patients with MACLD (Yagi et al. 2018). In the study with 103 patients (Yagi et al. 2018), 6MWD showed strong correlations with the SGRQ and Short-Form 36 scores. In our analysis we also found a relationship between ISWD and HRQOL. The exertional tolerance assessed by the ISWD, therefore, provides an indication of the HRQOL of pre-surgical patients with NTMLD. Another report showed that the ISWD achieved by individuals with bronchiectasis was strongly associated with measures of spirometry (Yildiz et al. 2018). We also found associations between the ISWD and %VC, but %VC was not related to exertional tolerance in multivariate regression analysis. These findings lead us to hypothesize that exertional tolerance is not related to disease severity in NTMLD (Roberts et al. 2000).

Compared with the study by Yildiz et al. (2018), the respiratory function of our participants was better preserved (%FEV_1 = 94 ± 17% vs. 71 ± 18%). We, therefore, propose that exertional tolerance is strongly related to lower extremity muscle strength and HRQOL when dyspnea is absent and lung function is within the normal range as in our participants. Asakura et al. (2017) assessed 3-dimensional CT, spirometric data and SGRQ in 67 patients with MACLD (mean age 69; range 43-84 years), FEV_1 predicted = 85% (IQR 71-97). Infiltration volume was significantly correlated with SGRQ symptom ($r = 0.42$, $p = 0.003$), activity ($r = 0.41$, $p = 0.003$), impact ($r = 0.52$, $p = 0.0002$), and total score ($r = 0.49$, $p = 0.001$). In our study, participants were younger, their affected lung regions were well confined, and they had better respiratory function than in previous studies, and there was no relationship between the extent of lung damage assessed by HRCT and HRQOL. Thus, factors independent of disease severity may influence exertional tolerance in surgical patients. As a result, exertional tolerance may be strongly related to physical function and HRQOL.

Preoperative exercise training for patients with lung cancer is a promising strategy to optimize physical fitness, which may yield improved outcomes such as reduced length of stay or postoperative complications, however the effects of preoperative rehabilitation in NTMLD have not been examined (Cavalheri and Granger 2017). It is possible in patients such as we studied that exertional tolerance may be improved by strengthening their leg muscles and improving HRQOL.

Studies of patients who have undergone lung resection for cancer have demonstrated that HRQOL remains below pre-operative levels at 3 months post-operation (van der Leeden et al. 2019). However, exercise training in the post-operative phase has been shown to improve HRQOL at 3 months (Kim et al. 2015). In people with bronchiectasis, there was no significant improvement in exertional tolerance when assessed at 9 months following lung resection however HRQOL was remarkably improved (Vallilo et al. 2014). However, in surgical patients with NTMLD the postoperative course remains unknown, therefore it is important that longitudinal studies are performed. Furthermore, in future research of patients with NTMLD undergoing lung resection it is also important to assess the effects of pre-operative exercise training on post-operative recovery of physical function and HRQOL.

We acknowledge there are several limitations to this study. First, relatively few subjects were recruited due to the limited number of surgical procedures for NTMLD that occur annually in our center. However, our hospital is a representative institution for NTMLD surgical treatment in Japan. Second, we lacked comparison of data with a healthy sample or an internal medicine control group. This was because the surgical treatment group is likely to be younger than a general medicine group thus limiting the value of any comparison. Future multicenter studies with recruitment of a larger sample, that includes more severely affected patients, are required to investigate the long-term effects of surgery of NTMLD.

In summary, this is the first study that reports preoperative ISWD in NTMLD surgical patients. Our patients had reduced ISWD compared with healthy age-matched values. The ISWD in pre-surgical patients showed a stronger relationship with peripheral muscle strength and respiratory symptoms as identified by HRQOL, compared with physiological measures of preoperative lung function. These results indicate that even pre-surgical NTMLD patients with progressive decline in lung function should follow an aggressive exercise program to try to maintain muscle strength and HRQOL associated with ISWD.

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Conflict of Interest

The authors declare no conflict of interest.

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