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Health-related quality of life associates with clinical parameters in patients with NTM pulmonary disease

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Running Head : Influence factors of HRQoL in NTM-PD patients

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SUMMARY

BACKGROUND: Previous studies have shown a reduction in health-related quality of life (HRQoL) in patients with non-tuberculous mycobacterial pulmonary disease (NTM-PD). However, the causes of this decline and the factors that contribute to it are unknown. This study was conducted to analyse the association between the St George's Respiratory Questionnaire (SGRQ) and clinical parameters, including age, disease duration, body composition, pulmonary function, chest X-ray findings, blood data and physical function.

METHODS: We performed a single-centre, cross-sectional, retrospective study of 101 patients with NTM-PD from December 2016 to October 2019. The relationship between the SGRQ scores and clinical parameters was evaluated.

RESULTS: The median patient age was 67.0 years. Pulmonary function, radiological score, albumin levels, C-reactive protein levels and incremental shuttle walk test distance (ISWD) were significantly correlated with the total and component scores on the SGRQ. Multiple regression analysis showed that the SGRQ score was significantly associated with radiological score, pulmonary function and ISWD.

CONCLUSION: This study was the first to assess the effect of clinical parameters on the SGRQ in patients with NTM-PD. HRQoL as determined using the SGRQ was associated with the radiological score, pulmonary function and ISWD in patients with NTM-PD.

KEY WORDS: non-tuberculous mycobacterial pulmonary disease; HRQoL; St George's Respiratory Questionnaire; exercise tolerance; radiological score; pulmonary function

The incidence of non-tuberculous mycobacterial pulmonary disease (NTM-PD) is increasing globally, with a high incidence in middle-aged women.¹ In Japan, the incidence is much higher in females than in males,² and the number of female patients is increasing in Korea as well.³ Differences in clinical parameters by sex⁴ and a poorer prognosis in men have been reported.⁵

NTM-PD is mainly treated with long-term chemotherapy. Although NTM-PD incidence has steadily increased, treatment of NTM-PD is complex, and its outcome is unsatisfactory.¹ Moreover, NTM-PD has a high recurrence rate, either due to relapse or reinfection.⁶

The goals for NTM-PD treatment are to achieve a negative bacterial conversion, terminate drug therapy and avoid recurrence. NTM-PD is a refractory disease, and in addition to a negative bacterial conversion, alternative treatment goals include improvement in symptoms, radiographic findings and health-related quality of life (HRQoL).^{1,7}

The St George's Respiratory Questionnaire (SGRQ) is a commonly used HRQoL assessment instrument for respiratory disease that is also effective in patients with NTM-PD.^{8,9} Patients with NTM-PD have an impaired HRQoL, and the SGRQ score has been associated with radiographic findings.^{8,10} In previous HRQoL studies, Mehta et al. showed that the SGRQ score was lower in patients with impaired pulmonary function, as well as in patients with NTM-PD, than in a healthy Canadian population.¹⁰ Maekawa et al. showed an association between SGRQ score and exercise tolerance using the 6-min walk test (6MWT) and high-resolution computed tomography (CT) scores.⁸ Asakura et al. reported that radiological findings, especially infiltration, are important parameters for HRQoL, and HRQoL is associated with C-reactive protein (CRP).^{11,12}

However, the cause of impaired HRQoL in patients with NTM-PD when the associated factors described in previous are included studies remains unclear, as do the factors that most influence the clinical parameters on the SGRQ score. We therefore analysed the association between SGRQ scores and clinical parameters, including age, disease duration, body composition, pulmonary function, chest X-ray (CXR) findings, blood data and physical function. The purpose of this study was to determine the factors that contribute to HRQoL in patients with NTM-PD.

STUDY POPULATION AND METHODS

Study populations

This study was conducted retrospectively at Fukujuji Hospital, Japan Anti-Tuberculosis Association, Tokyo, Japan. We evaluated 151 patients with NTM-PD who fulfilled the American Thoracic Society guidelines for diagnosing of NTM infection,¹ and who were evaluated by the Department of Pulmonary Rehabilitation at the hospital from December 2016 to October 2019. Patient data from before the physical therapy intervention were used.

We excluded 13 patients who did not complete the SGRQ questionnaire, and 37 patients who failed to complete all evaluations (19 were missing incremental shuttle walk test distance [ISWD] data, 3 were missing quadriceps force [QF] data, and 15 were missing pulmonary function test [PFT] data). Finally, 101 patients were included in the analysis (Figure). The Fukujuji Hospital Institutional Review Board, Tokyo, Japan, approved this study (number: 19020).

Clinical data

Clinical characteristics, including age, sex, disease duration, smoking history, body mass index (BMI) and percentage of ideal body weight, were collected from patients' medical records. Activity limitations due to dyspnoea were assessed using the modified Medical Research Council (mMRC) dyspnoea scale.¹³

Evaluation of spirometry data, radiological severity score and laboratory data

PFT data were examined for vital capacity percent predicted (VC% predicted) and forced expiratory volume in 1 sec percent predicted (FEV₁% predicted). Imaging findings were classified into three patterns based on chest computed tomography (CT) findings: non-cavitary nodular bronchiectatic (NC-NB) type, cavitary nodular bronchiectatic (C-NB) type or fibrocavitary (FC) type.⁶

Two respiratory physicians scored the radiological severity from chest CT scans and CXR using a previously reported method.¹⁴ The radiological severity score was defined as the sum of these scores according to the calculations described above, with total scores ranging from 0–96.¹⁴

We collected the most recent laboratory data from patients' medical records, including serum albumin levels as indices of nutritional status, CRP levels as indices of inflammation, and sputum culture results for *M. avium* complex, *M. abscessus* complex, and other species.

Physical function measures

Peripheral muscle strength compressed QF was assessed as the peak force developed during a maximal isometric knee extension using a hand-held dynamometer (μ -TusF-1; Anima Corporation, Tokyo, Japan) as per standard protocols.¹⁵ The highest value of three satisfactory measurements was recorded and expressed in kilograms of force (kgf) as percentage of body weight.

Functional exercise tolerance was assessed using the ISWD and evaluated as per a standardised protocol.¹⁶ ISWD was recorded in meters and expressed as a percentage of predicted values obtained from a Japanese sample.¹⁷

Health-related quality of life

Patients completed the Japanese version of the SGRQ,¹⁸ comprising three components (symptom, activity and impact) and a total score. The symptom component measures respiratory symptoms; the activity component evaluates the impairment of mobility or physical activities; the impact component assesses social, psychological and other effects of pulmonary dysfunction. The score for each component and the total score ranged from 0 (best) to 100 (worst).

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows v25.0 (IBM Corp, Armonk, NY, USA). $P < 0.05$ was considered significant. All data are presented as the number (percentage) for categorical variables and the median (interquartile range [IQR]) for continuous variables. The Shapiro-Wilk test was used to test the assumption of a normal distribution. The association between SGRQ scores and each clinical measure was determined using Pearson's or Spearman's correlation coefficients. The correlation coefficients were defined as follows: correlation coefficients of <0.20 as being interpreted as "slight, almost negligible relationships", correlations of 0.20 to 0.40 as "low

correlation", correlations of 0.40 to 0.70 as "moderate correlation", correlations of 0.70 to 0.90 as "high correlation, marked relationship" and correlation >0.90 as "very high correlation".¹⁹

Stepwise multiple regression analysis was performed to identify which clinical parameters were significantly related to the SGRQ total and component scores as dependent variables. Age, disease duration, FEV₁% predicted, radiological score, albumin, CRP, QF and ISWD were included in the multivariate analysis. FEV₁% predicted was included as an independent variable because patients with mycobacterial *avium* complex pulmonary disease (MAC-PD) exhibit a significantly increased residual volume, small airway dominance and air trapping than healthy individuals.²⁰

RESULTS

Patient characteristics

One hundred and one patients were evaluated in this study (Figure 1). Their median total SGRQ score was 34.4 (IQR 19.9–46.7), and all SGRQ scores were comparable to or higher than those of previous studies.^{7,10,11,21}

Table 1 gives the patient characteristics. The median age was 67.0 years (IQR 60.5–71.8). Most had low BMI 18.0 kg/m² (IQR 16.6–20.2). The median radiological score was 12 (8–15), and the radiological patterns were classified as NC-NB type (44 patients, 43.6%), C-NB type (15 patients, 14.9%) and FC type (42 patients, 41.6%). The proportion of *M. avium* complex and *M. abscessus* complex were respectively 68.3% and 29.7%. The ISWD <AQ>Author: do you mean "mean ISWD"? Ed</AQ> was 430 m (340–540).

Correlations between the SGRQ score and clinical parameters

Table 2 shows the correlation coefficients between the SGRQ score and clinical parameters. All SGRQ scores had low to moderate correlation with pulmonary function; FEV₁% predicted (total score: $r = -0.454$, $P < 0.001$; symptom score: $r = -0.406$, $P < 0.001$; activity score: $r = -0.428$, $P < 0.001$; impact score: $r = -0.387$, $P < 0.001$) and radiological score (total score: $r = 0.426$, $P < 0.001$; symptom score: $r = 0.411$, $P < 0.001$; activity score: $r = 0.401$, $P < 0.001$; impact score: $r = 0.380$, $P < 0.001$) and ISWD (total score: $r = -0.429$, $P < 0.001$; symptom score: $r = -0.286$, $P = 0.004$; activity score: $r = -$

0.466, $P < 0.001$; impact score: $r = -0.355$, $P < 0.001$). Neither age nor BMI was significantly associated with SGRQ scores.

Factors determining HRQoL in patients with NTM-PD

Multiple regression analysis was performed to analyse the independent factors affecting the SGRQ score (Table 3). When we performed stepwise multiple regression analysis using clinical parameters, radiological score, FEV₁% predicted and ISWD were identified as independent variables for the SGRQ total score. For the SGRQ symptom score, radiological score and FEV₁% predicted were independent variables. For the SGRQ activity score and impact scores, radiological score, ISWD and FEV₁% predicted were independent variables.

DISCUSSION

We analysed the clinical parameters affecting SGRQ scores in patients with NTM-PD. Worsening SGRQ scores were significantly associated with worse radiological findings, poor lung function and poor exercise tolerance among other clinical parameters. To our knowledge, this study was the first to assess the effect of radiological score and ISWD on HRQoL using the SGRQ in patients with NTM-PD.

NTM-PD-associated mortality and morbidity are increasing in Japan,² and NTM-PD-associated mortality is reported worldwide.²² Furthermore, the HRQoL of patients with NTM-PD is reportedly reduced.^{10,23} In our study, the patients were characterised as thin body types who still had NTM-PD even several years after the original diagnosis. In addition, radiological scores were higher than those reported in previous studies,^{24,25} suggesting that the patients presented moderately to severely advanced disease (Table 1).

As previously reported for MAC-PD,¹¹ CRP levels were also correlated with SGRQ scores in our population. Similar to previous study results, our results support that CRP levels are associated with HRQoL. Albumin levels were also correlated with SGRQ scores (Table 2). Nutritional status, including albumin levels, are reported to be indicators of disease progression, but we found no association between albumin levels and SGRQ scores. Furthermore, the abdominal fat ratio, albumin levels and presence of cavities were associated with NTM-PD progression.²⁶ Albumin levels were correlated with SGRQ scores, but this was not reflected in the independent factors affecting the SGRQ score in

multivariate regression analysis. Nutritional status must be assessed to understand and predict the NTM-PD pathogenesis and prognosis.

Independent factors for SGRQ were radiological score, pulmonary function and exercise tolerance (Table 3). SGRQ-based HRQoL has been suggested to correlate with radiological findings and pulmonary function.^{10,12} NTM infection is also reported to destroy lung structure, predominantly in the small airways, resulting in lung dysfunction.²⁰ In the present study, FEV₁% predicted was an influential factor on the SGRQ score; NTM-PD with obstructive airway impairment, as well as chronic obstructive pulmonary disease, could reduce the HRQoL.²⁷ Previous studies have shown that higher radiological scores and delayed chemotherapeutic intervention are associated with increased mortality rates,^{24,25} suggesting that therapeutic intervention should be initiated at the earliest stage of disease.

Patients with NTM-PD exhibit a reduced ISWD compared with that of age-matched healthy controls. The ISWD% predicted decreased to 86.2% in patients in the present study (Table 1). The SGRQ score has been associated with exercise tolerance (6MWT and ISWD) in patients with NTM-PD.^{21,28} This study also suggested that ISWD may be an important predictor of HRQoL in patients with NTM-PD. Moreover, reduced exercise tolerance is strongly associated with the prognosis in respiratory disease.^{29,30} Although chemotherapy and surgical treatment are the mainstay of patients with NTM-PD,^{1,31} one study reported the effectiveness of respiratory physiotherapy for patients with NTM-PD.³² Furthermore, a review article suggested the need for non-pharmacological therapies, including pulmonary rehabilitation,³³ which should prevent the progression of disease in patients with NTM-PD by improving respiratory symptoms, HRQoL and physical functioning. In future studies, we plan to demonstrate the effectiveness of our system of respiratory physiotherapy as a treatment option for patients with NTM-PD.

Our study had several limitations. First, it was a single-centre, cross-sectional, retrospective study. Participants were selected from among patients who underwent pulmonary rehabilitation. The number of male patients in our study was small, and it is necessary to examine the difference in HRQoL by sex in the future. Second, radiological scores in the present study were higher than those in previous studies;^{24,25} therefore, our patients were considered to have relatively severe NTM-PD. Finally, because this study was cross-sectional in design, we could not clearly demonstrate whether SGRQ scores

were sensitive to disease progression or improvement after patients with NTM-PD were treated.

CONCLUSION

This study was the first to assess the effect of clinical parameters on HRQoL in patients with NTM-PD. SGRQ-based HRQoL was associated with radiological score, pulmonary function and ISWD in patients with NTM-PD.

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Conflicts of interest: none declared.

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Table 1 Clinical characteristics of the patients with NTM-PD ($n = 101$)

| Variables | Median | [IQR] |
|--|--------|--------------|
| Age, years | 67.0 | [60.5–71.8] |
| Female sex, n (%) | 96 | (95.0) |
| Duration of disease* | 5.0 | [2.0–11.0] |
| History of smoking, n (%) | | |
| Never | 84 | (83.2) |
| Former | 17 | (16.8) |
| Body mass index, kg/m^2 | 18.0 | [16.6–20.2] |
| % ideal body weight, % | 82.0 | [75.6–92.7] |
| mMRC Grade | 1 | [0–1] |
| Pulmonary function test | | |
| Vital capacity % predicted, % | 75.5 | [61.3–85.3] |
| FEV ₁ % predicted, % | 78.4 | [63.5–90.2] |
| Radiological score | 12 | [8–15] |
| Radiological pattern, n (%) | | |
| Non-cavitary nodular bronchiectatic type | 44 | (43.6) |
| Cavitary nodular bronchiectatic type | 15 | (14.9) |
| Fibrocavitary type | 42 | (41.6) |
| Laboratory data | | |
| Albumin, g/dl | 3.9 | [3.4–4.2] |
| CRP, mg/dl | 0.2 | [0.6–1.1] |
| <i>Mycobacterium</i> species, n (%) | | |
| <i>M. avium</i> complex | 69 | (68.3) |
| <i>M. abscessus</i> complex | 30 | (29.7) |
| <i>M. lentiflavum</i> | 2 | (2.0) |
| QF, kgf | 23.6 | [18.0–26.6] |
| QF% body weight, % | 51.8 | [43.3–58.7] |
| ISWD, m | 430 | [340–540] |
| ISWD % predicted, % | 85.9 | [71.3–102.5] |
| SGRQ | | |
| Total score | 34.4 | [19.9–46.7] |
| Symptom score | 51.9 | [30.2–64.5] |
| Activity score | 41.5 | [18.4–55.0] |
| Impact score | 25.4 | [15.3–38.3] |

* Interval between disease diagnosis and time of pulmonary rehabilitation evaluation.

NTM-PD = non-tuberculous mycobacterial pulmonary disease; IQR = interquartile range; mMRC = modified Medical Research Council; FEV₁ = forced expiratory volume in 1 sec; CRP = C-reactive protein; QF = quadriceps force; ISWD = incremental shuttle walk test distance; SGRQ = St George's Respiratory Questionnaire.

Table 2 Correlations between SGRQ component or total score and clinical parameters*

| | Total score | | Symptom score | | Activity score | | Impact score | |
|------------------------------|-------------|----------------|---------------|----------------|----------------|----------------|--------------|----------------|
| | <i>r</i> | <i>P</i> value | <i>r</i> | <i>P</i> value | <i>r</i> | <i>P</i> value | <i>r</i> | <i>P</i> value |
| Age | † | 0.781 | † | 0.965 | † | 0.907 | † | 0.361 |
| Duration of disease | 0.261 | 0.008 | † | 0.213 | 0.223 | 0.025 | 0.295 | 0.003 |
| BMI | † | 0.276 | † | 0.569 | † | 0.106 | † | 0.532 |
| Vital capacity % predicted | -0.469 | <0.001 | -0.389 | <0.001 | -0.498 | <0.001 | -0.369 | <0.001 |
| FEV ₁ % predicted | -0.454 | <0.001 | -0.406 | <0.001 | -0.428 | <0.001 | -0.387 | <0.001 |
| Radiological score | 0.426 | <0.001 | 0.411 | <0.001 | 0.401 | <0.001 | 0.380 | <0.001 |
| Albumin | -0.351 | <0.001 | -0.336 | 0.001 | -0.347 | 0.001 | -0.277 | 0.005 |
| CRP | 0.430 | <0.001 | 0.447 | <0.001 | 0.438 | <0.001 | 0.338 | 0.001 |
| Quadriceps force | -0.265 | 0.007 | † | 0.159 | -0.295 | 0.003 | -0.227 | 0.022 |
| ISWD | -0.429 | <0.001 | -0.286 | 0.004 | -0.466 | <0.001 | -0.355 | <0.001 |

*Correlations are expressed as Pearson's or Spearman's coefficients.

† Not statistically significant in the regression analysis.

SGRQ = St. George's Respiratory Questionnaire; *r* = correlation coefficient; BMI = body mass index; FEV₁ = forced expiratory volume in 1 sec; CRP = C-reactive protein; ISWD = incremental shuttle walk test distance.

Table 3 Clinical parameters influencing SGRQ score in multivariate regression analysis*

| | Total score | | | Symptom score | | | Activity score | | | Impact score | | |
|----------------------------------|-------------|---------|----------------|---------------|---------|----------------|----------------|---------|----------------|--------------|---------|----------------|
| | <i>t</i> | β | <i>P</i> value | <i>t</i> | β | <i>P</i> value | <i>t</i> | β | <i>P</i> value | <i>t</i> | β | <i>P</i> value |
| FEV ₁ % predicted | -2.90 | -0.26 | 0.005 | -3.04 | -0.30 | 0.003 | -2.64 | -0.24 | 0.010 | -2.23 | -0.22 | 0.028 |
| Radiological score | 3.03 | 0.28 | 0.003 | 2.74 | 0.27 | 0.007 | 2.43 | 0.22 | 0.017 | 2.76 | 0.27 | 0.007 |
| ISWD | -3.18 | -0.27 | 0.002 | † | † | † | -3.82 | -0.33 | <0.001 | -2.35 | -0.22 | 0.021 |
| Cumulative <i>R</i> ² | 0.36 | † | † | 0.23 | † | † | 0.35 | † | † | 0.25 | † | † |

* Results calculated using stepwise multiple regression analysis.

† Not statistically significant in the multivariate regression analysis.

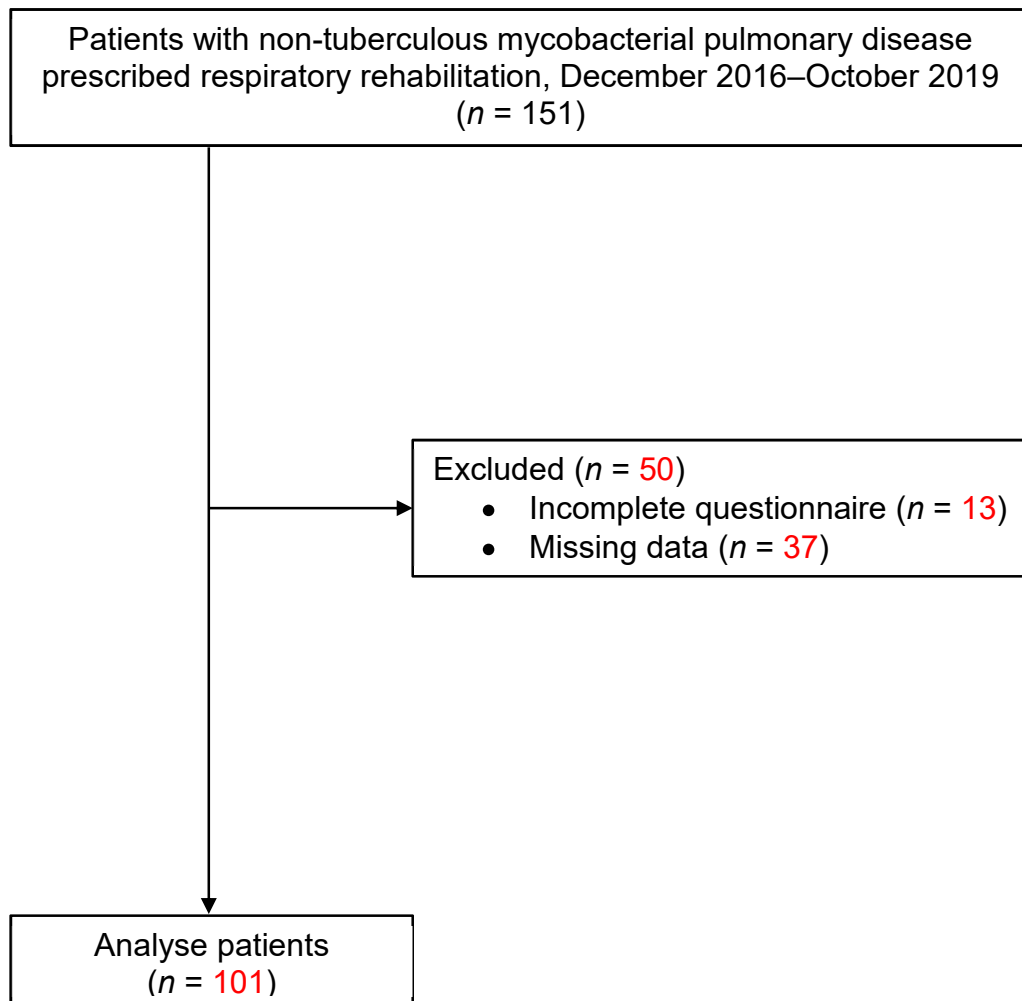
t = test-statistic; β = standardised coefficient; SGRQ = St George's Respiratory Questionnaire; FEV₁ = forced expiratory volume in 1 sec;

ISWD = incremental shuttle walk test distance.

FIGURE LEGEND

Figure Flowchart for patient selection.

Figure



RÉSUMÉ