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Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

# Influence of chronic sputum symptoms on quality of life in patients with nontuberculous mycobacterial pulmonary disease: A cross-sectional study

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ARTICLE INFO

*Article history:*
Received 26 April 2021
Received in revised form
19 August 2021
Accepted 29 September 2021
Available online 8 November 2021

*Keywords:*
Sputum
Nontuberculous mycobacteria
HRQOL
Mental health

ABSTRACT

*Background:* The effect of chronic sputum (CS) symptoms on health-related quality of life (HRQOL) in patients with nontuberculous mycobacterial pulmonary disease (NTM-PD) has not been studied. The aim of this study was to clarify the differences in the clinical characteristics of NTM-PD patients with and without CS and to investigate the effect of CS on HRQOL.

*Methods:* This cross-sectional study included patients with NTM-PD who were prescribed pulmonary rehabilitation at the Fukujuji Hospital from March 2016 to June 2019. HRQOL was evaluated using the MOS 36-Item Short-Form Health Survey (SF-36).

*Results:* Of the 99 subjects studied, 71 had CS (CS+) (71.7%), and 28 (28.3%) did not have CS (CS-). Patients in the CS + group had a lower body mass index, forced vital capacity percent predicted, and forced expiratory volume in 1 s percent predicted. Regarding the radiological evaluation, the proportion of patients with the fibrocavitary form and the radiological score were significantly higher in the CS + group. The mental component summary (MCS) score

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https://doi.org/10.1016/j.resinv.2021.09.011
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of the SF-36 were significantly lower in the CS + group. Multiple regression analysis showed that the presence of CS was independently associated with a lower MCS score of the SF-36.

*Conclusions:* NTM-PD patients with CS had more severe disease, with reduced pulmonary function and severe radiological findings. CS was shown to independently affect HRQOL, especially mental status.

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**Abbreviations**

| | |
|---|---|
| AFB | Sputum acid-fast bacilli |
| Alb | Albumin |
| BMI | Body mass index |
| CAM | Clarithromycin |
| COPD | Chronic obstructive pulmonary disease |
| C-NB | Cavitary nodular bronchiectatic |
| CRP | C-reactive protein |
| CS | Chronic sputum |
| FC | Fibrocavitary |
| $FEV_1$% | Forced expiratory volume in one second |
| FVC | Forced vital capacity |
| Hb | Hemoglobin |
| HRCT | High-resolution computed tomography |
| HRQOL | Health-related quality of life |
| MAC | *Mycobacterium avium* complex |
| MCS | Mental component summary |
| NC-NB | Non-cavitary nodular bronchiectatic |
| NTM-PD | Nontuberculous mycobacterial pulmonary disease |
| PCS | Physical component summary |
| PFT | Pulmonary function test |
| SF-36 | the MOS 36-Item Short-Form Health Survey |
| SGRQ | St George's Respiratory Questionnaire |
| TP | Total protein |
| WBC | White blood cell |

## 1. Introduction

The prevalence of nontuberculous mycobacterial pulmonary disease (NTM-PD) has increased in many countries [1,2]. Patients with NTM-PD commonly present with cough, sputum, hemoptysis, and systemic conditions including—fatigue and weight loss. The guidelines recommend long-term multidrug treatment; however, its success rate is not high, and some patients suffer from recurrence due to relapse and reinfection, leading to the need for lifelong follow-up [3–5]. Therefore, the evaluation and improvement of health-related quality of life (HRQOL) are critically important [6].

It has been reported that several clinical parameters correlated with HRQOL in NTM-PD. Maekawa et al. found that high-resolution computed tomography (HRCT) findings such as consolidation, cavity, and lobar volume reduction were associated with HRQOL assessed by St George's Respiratory Questionnaire (SGRQ) [7]. Asakura et al. showed that C-reactive protein (CRP) and age were significant factors affecting HRQOL assessed using the MOS 36-Item Short-Form Health Survey (SF-36) [8]. Six-minute walk test parameters were also reported to be correlated with SGRQ and SF-36 scores [9].

However, no studies have examined the influence of clinical symptoms on HRQOL of the patients. While the most common symptom patients with NTM-PD complain of is chronic cough, associated with or without sputum symptoms, sputum production could have a greater influence on HRQOL status. It has been reported that chronic obstructive pulmonary disease (COPD) persistent sputum producers have more severe clinical characteristics than non-persistent sputum producers; the mean SGRQ and COPD Assessment Test (CAT) scores were higher in persistent sputum producers [10].

Accordingly, this study aimed to compare the clinical characteristics of NTM-PD patients with and without Chronic sputum (CS) symptoms; and determine the influence of CS symptoms on HRQOL in patients with NTM-PD.

## 2. Patients and methods

### 2.1. Study subjects

This study was conducted at the Fukujuji Hospital, Japan Anti-Tuberculosis Association, a 340-bed tertiary hospital for mycobacteriosis in Tokyo, Japan. Among the patients who met the American Thoracic Society/European Respiratory Society/European Society of Clinical Microbiology and Infectious Disease/Infectious Disease Society of America (ATS/ERS/ESCMID/IDSA) criteria, we enrolled patients who underwent HRQOL evaluation at the pulmonary rehabilitation center from March 2016 to June 2019. The exclusion criteria were patients who did not give consent to be included in the evaluation and those with missing test data. Patients with comorbidities—COPD or interstitial pneumonia—were excluded because these diseases have worse effects on HRQOL [11,12]. The present study was approved by the Fukujuji Hospital Institutional Review Board on September 18, 2019 (approval number: 19020).

### 2.2. Clinical variables

Demographic data, including age, body mass index (BMI), smoking history, duration of illness, treatment status, comorbidities, and laboratory data, were collected from the medical chart. Pulmonary function test (PFT) data collected were forced vital capacity percent predicted (FVC% pred) and forced expiratory volume in 1 s percent predicted ($FEV_1$% pred). For laboratory data, CRP and white blood cell (WBC)

were used as indices of inflammation; hemoglobin (Hb), total protein (TP), and albumin (Alb) were analyzed as indices of nutritional status. Imaging findings were classified into four patterns based on chest HRCT findings: non-cavitary nodular bronchiectatic (NC-NB) form, cavitary nodular bronchiectatic (C-NB) form, fibrocavitary (FC) form, and unclassifiable [13]. Two respiratory physicians (KF and KF) independently evaluated the radiological severity score according to a previously reported method [14]. Any discrepancies were resolved by discussion.

Sputum acid-fast bacilli (AFB) smears and mycobacterial cultures were performed according to standard methods. Clarithromycin resistance was defined as a minimum inhibitory concentration ≥32 μg/ml. In the smear test, we recorded the maximum amount of smear result among three tests before the evaluation date. The semiquantitative mycobacterial smear scores were analyzed as ordinal scales corresponding to: -: 0, ±: 1; 1+: 2; 2+: 3; and 3+: 4. Chronic colonization by other bacteria was defined as two or more positive sputum cultures of the same species in the previous year.

### 2.3. CS symptoms and HRQOL assessment

At the start of pulmonary rehabilitation, we evaluated the presence or absence of CS symptoms referring to the reports on the diagnosis of chronic bronchitis based on the SGRQ [10,15,16]. If the patients had sputum symptoms "most days a week" or "several days a week," we defined them as having CS symptoms (CS+). If the patients answered "a few days a month," "only with chest infections," or "not at all," they were categorized as having no CS symptoms (CS-).

All patients completed the SF-36 version2 in Japanese [17,18]. The SF-36 is a questionnaire about the patient's health status and includes eight subscales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). From the subscales, two-component summary scores calculated for are the physical aspect of QOL (physical component summary, PCS) and the mental aspect of QOL (mental component summary, MCS). For PCS and MCS, the two-component summary score results based on the Japanese survey data were used. The national average subscale and summary score were 50 points, and any ratings higher than this indicates higher HRQOL [19].

### 2.4. Statistical analysis

Statistical analyses were conducted using the software program IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). All data are presented as the median (interquartile range (IQR)) for continuous variables and the number (percentage) for categorical variables. The Shapiro-Wilk test tested the assumption of a normal distribution. Differences between parametric data were assessed by two-sample t-tests. The Mann-Whitney *U* test was performed to test the differences between nonparametric data. The chi-square test was performed to compare the categorical variables. The associations between PCS, MCS, and clinical indices (age, BMI, disease duration, FVC% pred, $FEV_1$% pred, CRP, WBC, hemoglobin, TP, albumin, radiographic features, radiological score, and smear score) were analyzed using Spearman's rank correlation coefficient. For the correlation analysis, radiographic features were converted to ordinal scales (NC-NB: 0, C-NB: 1, FC: 2).

Factors affecting HRQOL were analyzed using multiple regression analysis with the dependent variables as PCS and MCS. For the explanatory variables, in addition to age, CRP, FC form, and the radiological severity score, which have been reported to affect HRQOL of NTM-PD patients [8,20,21], the presence or absence of CS symptoms was selected. We considered a P value < 0.05 to be significant.

## 3. Results

### 3.1. Patient characteristics according to the presence or absence of CS

During the study period, 152 NTM patients underwent pulmonary rehabilitation. Two of these patients were excluded as they did not consent to the questionnaire; two patients with COPD, two with interstitial pneumonia, and 47 without sufficient data (one patient with unknown smoking history, 25 missing PFT data, two missing laboratory data, two missing smear test data and 17 with insufficient HRQOL data) were also excluded. The remaining 99 patients were evaluated (Fig. 1).

Table 1 shows the clinical characteristics of the study population. The median age was 67 (IQR; 60.0-72.0) years.

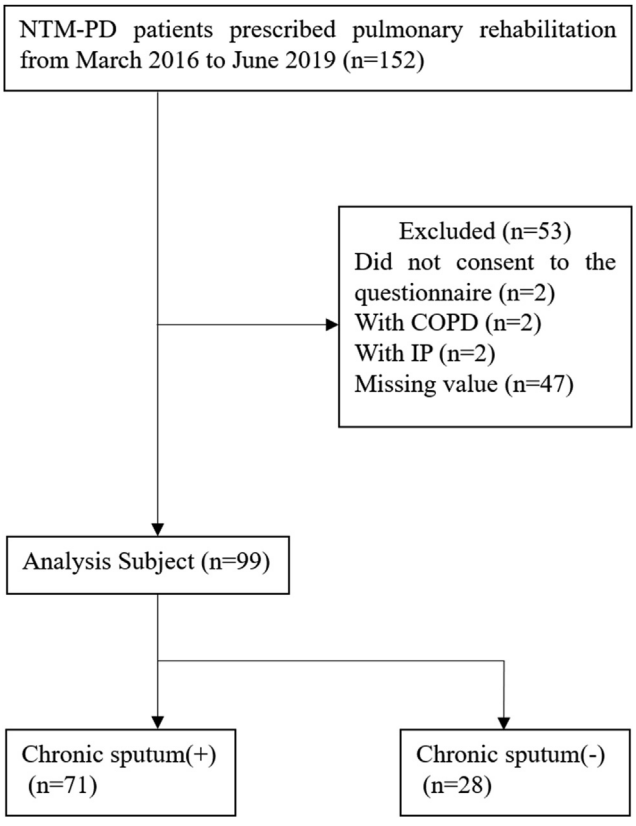


**Fig. 1 – The flowchart for the inclusion and exclusion of the study participants. NTM-PD, nontuberculous mycobacterial pulmonary disease; COPD, chronic obstructive pulmonary disease; IP, interstitial pneumonia.**

Among the 99 patients, 49 (49.5%) were currently on treatment. Seventy-one patients (71.7%) had CS, and 28 patients (28.3%) did not have CS. There were no differences in age, sex, smoking, the duration of illness, treatment status, or comorbidities between the two groups, but BMI ($p = 0.032$), FVC% pred ($p = 0.020$), and $FEV_1$% pred ($p = 0.026$) were significantly lower in the CS + group. Regarding the laboratory data, CRP ($p = 0.027$) and WBC ($p = 0.012$) were higher in the CS + group than in the CS- group. Regarding the radiological evaluation, the proportion of the FC form ($p = 0.002$) and radiological score ($p = 0.027$) were higher in the CS + group. The semiquantitative mycobacterial smear score was significantly higher in the CS + group ($p = 0.025$). *Pseudomonas aeruginosa* and *Staphylococcus aureus* were frequently identified in the CS + group, but these were not statistically significant.

### 3.2. Comparison of the HRQOL scores between patients with and without CS

Table 2 shows the HRQOL scores of the CS+ and CS- groups. In the SF-36 results, the four scores other than physical functioning, role physical, bodily pain, and role emotional were significantly lower

**Table 1 – Clinical characteristics of the study subjects.**

| | All patients (n = 99) | Chronic sputum (+) (n = 71) | Chronic sputum (–) (n = 28) | p-value |
|---|---|---|---|---|
| Age, years | 67 (60.0–72.0) | 67.0 (61.0–72.0) | 66.0 (60.0–72.5) | 0.919 |
| Females | 94 (94.9) | 66 (93.0) | 28 (100) | 0.182 |
| BMI, $kg/m^2$ | 18.0 (16.5–20.1) | 17.9 (16.1–20.1) | 19.0 (17.4–20.4) | 0.032 |
| Smoking history | 16 (16.2) | 13 (18.3) | 3 (10.7) | 0.274 |
| Disease duration, years | 4.0 (2.0–10.0) | 5.0 (1.0–10.0) | 3.0 (3.0–10.8) | 0.693 |
| Treatment status | | | | 0.314 |
| Never treated | 23 (23.2) | 17 (23.9) | 6 (21.4) | |
| Previously treated | 27 (27.3) | 22 (31.0) | 5 (17.9) | |
| Currently treated | 49 (49.5) | 32 (45.1) | 17 (60.7) | |
| Underlying disease | | | | |
| Asthma | 4 (4.1) | 3 (4.2) | 1 (3.6) | 0.683 |
| Old pulmonary TB | 3 (3.0) | 1 (1.4) | 2 (7.1) | 0.192 |
| Pulmonary aspergillosis | 3 (3.0) | 3 (4.2) | 0 (0) | 0.364 |
| Diabetes | 5 (5.1) | 3 (4.2) | 2 (7.1) | 0.620 |
| PFT | | | | |
| FVC % pred, % | 77.7 (59.0–89.5) | 74.6 (57.1–87.8) | 81.7 (75.0–96.1) | 0.020 |
| $FEV_1$% pred, % | 75.9 (58.8–91.0) | 72.0 (56.3–88.8) | 80.8 (73.4–94.0) | 0.026 |
| Laboratory data | | | | |
| CRP, mg/dl | 0.31 (0.09–1.60) | 0.43 (0.10–2.13) | 0.13 (0.07–0.51) | 0.027 |
| WBC, $10^2/\mu l$ | 54.7 (47.0–66.0) | 56.8 (49.0–69.1) | 51.1 (40.8–55.2) | 0.012 |
| Hemoglobin, g/dl | 12.5 (11.6–13.2) | 12.4 (11.5–13.2) | 12.6 (12.2–13.2) | 0.193 |
| Total protein, g/dl | 7.0 (6.7–7.6) | 7.0 (6.7–7.6) | 6.9 (6.4–7.3) | 0.309 |
| Albumin, g/dl | 3.8 (3.4–4.2) | 3.7 (3.3–4.2) | 3.9 (3.6–4.1) | 0.150 |
| Radiographic features | | | | |
| NC-NB | 39 (39.4) | 23 (32.4) | 16 (57.1) | 0.015 |
| C-NB | 41 (41.4) | 30 (42.3) | 11 (39.3) | 0.892 |
| FC | 18 (18.2) | 18 (25.4) | 0 (0) | 0.002 |
| Unclassifiable | 1 (1.0) | 0 (0) | 1 (3.6) | |
| Radiological score | 13 (8.8–16.3) | 14 (9–17) | 11 (7–14) | 0.027 |
| NTM species | | | | |
| MAC | 67 (67.7) | 47 (66.2) | 20 (71.4) | 0.616 |
| *M. abscessus* complex | 26 (26.3) | 20 (28.2) | 6 (21.4) | 0.492 |
| Other | 6 (6.1) | 4 (5.6) | 2 (7.1) | 0.547 |
| CAM resistance | 27 (27.3) | 19 (26.8) | 8 (28.6) | 0.609 |
| Semiquantitative smear score | | | | 0.025 |
| 3+ | 19 (19.2) | 18 (25.4) | 1 (3.6) | |
| 2+ | 25 (25.3) | 20 (28.2) | 5 (17.9) | |
| 1+ | 14 (14.1) | 10 (14.1) | 4 (14.3) | |
| ± | 23 (23.2) | 12 (16.9) | 11 (39.3) | |
| - | 18 (18.2) | 11 (15.5) | 7 (25.0) | |
| Chronic colonization[a] | | | | |
| *Pseudomonas aeruginosa* | 7 (7.1) | 7 (9.9) | 0 (0) | 0.089 |
| *Staphylococcus aureus* | 11 (11.1) | 10 (14.1) | 1 (3.6) | 0.123 |
| Other | 11 (11.1) | 8 (11.3) | 3 (10.7) | 0.623 |

Data are presented as the number (%) of patients, medians (interquartile range, IQR). BMI, body mass index; TB, tuberculosis; PFT, pulmonary function test; FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 s; CRP, C-reactive protein; WBC, white blood cell; NC-NB, non-cavitary nodular bronchiectatic; C-NB, cavitary nodular bronchiectatic; FC, fibrocavitary; NTM, nontuberculous mycobacteria; MAC, *Mycobacterium avium* complex; CAM, Clarithromycin.

[a] Chronic colonization was defined as two or more positive sputum cultures of the same species in the previous year.

**Table 2 – HRQOL scores of the study subjects.**

| | All patients(n = 99) | Chronic sputum(+) (n = 71) | Chronic sputum(–) (n = 28) | p-value |
|---|---|---|---|---|
| SF-36 | | | | |
| PF | 43.4 (32.6–50.6) | 39.8 (32.6–50.6) | 48.8 (32.6–54.2) | 0.133 |
| RP | 42.4 (29.1–55.7) | 35.8 (29.1–52.4) | 47.5 (33.3–55.7) | 0.055 |
| BP | 50.1 (40.3–61.7) | 50.1 (40.3–54.6) | 52.4 (41.4–61.7) | 0.498 |
| GH | 37.8 (32.5–44.2) | 37.8 (32.5–43.1) | 41.5 (35.8–48.9) | 0.003 |
| VT | 46.6 (40.2–49.8) | 43.4 (37.0–49.8) | 49.8 (43.4–58.7) | 0.002 |
| SF | 44.1 (31.2–57.0) | 37.7 (31.2–57.0) | 57.0 (39.3–57.0) | 0.006 |
| RE | 47.7 (31.1–56.1) | 43.6 (31.1–56.1) | 51.9 (39.4–56.1) | 0.084 |
| MH | 49.1 (41.1–54.5) | 46.5 (38.4–54.5) | 54.5 (47.2–59.9) | 0.002 |
| PCS | 42.8 (28.6–52.3) | 37.7 (28.4–51.6) | 46.8 (32.7–52.6) | 0.239 |
| MCS | 47.3 (41.8–53.0) | 45.1 (40.1–50.0) | 52.0 (47.5–56.6) | <0.001 |

Data are presented as medians (interquartile range, IQR). HRQOL, health-related quality of life; SF-36, MOS 36-Item Short-Form Health Survey; PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; PCS, physical component summary; MCS, mental component summary.

**Table 3 – Spearman correlation between HRQOL score and clinical indices.**

| | SF-36 PCS | | SF-36 MCS | |
|---|---|---|---|---|
| | ρ | p-value | ρ | p-value |
| Age | −0.30 | 0.003 | −0.02 | 0.885 |
| BMI | 0.21 | 0.038 | 0.24 | 0.017 |
| Disease duration | −0.07 | 0.488 | −0.19 | 0.056 |
| FVC% pred | 0.31 | 0.002 | 0.19 | 0.058 |
| $FEV_1$% pred | 0.27 | 0.007 | 0.18 | 0.082 |
| CRP | −0.38 | <0.001 | −0.17 | 0.087 |
| WBC | −0.17 | 0.092 | −0.10 | 0.326 |
| Hemoglobin | 0.16 | 0.115 | 0.04 | 0.679 |
| Total protein | −0.02 | 0.868 | −0.09 | 0.365 |
| Albumin | 0.32 | 0.001 | 0.12 | 0.234 |
| Radiographic features | −0.14 | 0.156 | −0.17 | 0.101 |
| Radiological score | −0.27 | 0.006 | −0.22 | 0.029 |
| Smear score | −0.04 | 0.692 | −0.10 | 0.309 |

HRQOL, health-related quality of life; SF-36, MOS 36-Item Short-Form Health Survey; PCS, physical component summary; MCS, mental component summary; BMI, body mass index; FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 s; CRP, C-reactive protein; WBC, white blood cell; ρ, Spearman's rank correlation coefficient.

in the CS + group. In the summary score analyses, MCS was significantly lower in the CS + group ($p < 0.001$), whereas the difference in the PCS score was not significant.

### 3.3. *Correlations between the HRQOL scores and clinical indices*

Table 3 shows the correlation coefficients between PCS, MCS, and clinical indices. Significant correlations of PCS were found with age, BMI, FVC% pred, $FEV_1$% pred, CRP, Alb, and radiological score. Significant correlations with MCS were found for BMI and radiological score.

### 3.4. *Multivariate regression analysis for factors affecting HRQOL*

Multiple regression was performed to analyze the independent factors affecting PCS and MCS (Table 4). For the PCS score, age and CRP were significantly associated. The MCS score was significantly affected by only the presence of CS.

## 4. Discussion

In this study, we analyzed and compared the clinical characteristics of patients with and without CS symptoms in NTM-PD. We also investigated the impact of CS symptoms on HRQOL. The study findings showed that patients with CS symptoms had poor nutrition, low pulmonary function, high amounts of inflammatory markers, severe radiological findings, and higher sputum smear results. HRQOL was decreased

**Table 4 – Multiple regression analysis for factors affecting HRQOL.**

| | SF-36 PCS | | | | SF-36 MCS | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | β | p-value | β | p-value | β | p-value | β | p-value |
| Age | −0.23 | 0.025 | −0.21 | 0.038 | 0.01 | 0.920 | 0.02 | 0.846 |
| CRP | −0.39 | <0.001 | −0.35 | 0.002 | −0.10 | 0.346 | 0.09 | 0.435 |
| FC | −0.13 | 0.203 | 0.04 | 0.726 | −0.20 | 0.047 | −0.07 | 0.530 |
| Radiological score | −0.24 | 0.003 | −0.13 | 0.222 | −0.22 | 0.032 | −0.15 | 0.175 |
| Chronic sputum | −0.12 | 0.231 | −0.04 | 0.709 | −0.38 | <0.001 | −0.37 | <0.001 |

HRQOL, health-related quality of life; SF-36, MOS 36-Item Short-Form Health Survey; PCS, physical component summary; MCS, mental component summary; CRP, C-reactive protein; FC, fibrocavitary; β, standardized partial regression coefficient.

in the NTM-PD patients overall, and it was significantly lower in patients with CS symptoms than in patients without CS symptoms. Importantly, CS symptoms were significantly associated with mental status rather than physical status.

The clinical characteristics of the patients with CS production seemed to be related to the severe condition. A previous study showed the strong correlation between radiological severity and nutritional status in patients with *Mycobacterium avium* complex pulmonary disease (MAC-PD) [22]. The factors associated with sputum discharge included cough, ciliary clearance, and so on [23,24]. Thus, the severity of NTM disease, which indicates malnutrition, decreased respiratory function, severe radiological findings, and the increased bacterial burden will be associated with CS symptoms.

Regarding the HRQOL, the radiological score had significant correlations with PCS and MCS. Previous studies reported that imaging findings are associated with HRQOL in patients with MAC-PD [7,25]; our study findings were consistent with these data. CRP and age were significantly associated with PCS. A previous study also showed that CRP and age affect HRQOL in patients with MAC-PD [8]. The study findings indicated that CRP could be more associated with the physical status of QOL.

We found that CS symptoms significantly influenced MCS. Patients with NTM-PD tended towards having poor health status and more anxiety/depression than healthy controls [26]. Depression and anxiety symptoms have also been reported to be associated with worsening HRQOL in patients with bronchiectasis and COPD [27,28]. Moreover, a previous study that evaluated QOL in patients with bronchiectasis found that daily sputum production was strongly associated with anxiety, and female patients showed a higher risk of depression [29]. Thus, it is essential to note that CS symptoms influence the mental status of NTM-PD patients.

Mental health problems often affect adherence to treatment [30]. Thus, it is necessary to evaluate depression and anxiety for patients with CS symptoms and to provide psychiatric care, such as intervention by a clinical psychologist. For patients with a reduced capacity of sputum discharge, sputum symptoms could be expected to improve by appropriate physical therapy [31,32]. CS symptoms become more apparent with the worsening of NTM-PD; we believe that aggressive chemotherapy before the disease progresses is essential for preventing HRQOL decline. We also consider that patients with CS symptoms need a multidisciplinary approach of care, such as psychological evaluation and respiratory physiotherapy, in addition to drug therapy.

Our study has some important limitations. First, this study was conducted at a single institution and was a cross-sectional retrospective study. The participants were selected from patients who were prescribed pulmonary rehabilitation. Therefore, the study patients frequently had more severe conditions than the general population of NTM-PD patients, with cavitary disease accounting for approximately 60%. Second, the number of subjects analyzed was relatively small and mostly female patients. These limitations might inhibit the generalization of the study findings. Third, the effects of pharmacotherapy were not considered in the assessment of CS symptoms. Finally, the presence of respiratory comorbidities could affect the QOL of study subjects. However, since the number of subjects with respiratory comorbidities is small, the influence of the comorbidities on the study results would be small. Despite these limitations, this study was the first to clearly describe the clinical characteristics of patients with CS symptoms and the association of CS symptoms with mental status in patients with NTM-PD.

## 5. Conclusions

In conclusion, NTM-PD patients with CS symptoms were likely to have undernutrition, low pulmonary function, high inflammatory markers, severe radiological findings, and higher smear findings. The effects of CS on HRQOL, especially for mental status, were also shown. To improve the HRQOL of patients with NTM-PD, multidisciplinary approaches to reducing CS are needed in addition to antimicrobial therapy.

## Conflict of Interest

The authors have no conflicts of interest.

## Acknowledgment

The authors are grateful to all the hospital staff supporting this research. This study was supported by the Japan Agency for Medical Research and Development (JP20fk0108129, 21fk0108129h0802).

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