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Impact of chronic *Pseudomonas aeruginosa* infection on health-related quality of life in *Mycobacterium avium* complex lung disease

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Abstract

Background: In bronchiectasis patients, chronic *Pseudomonas aeruginosa* (PA) infection has been associated with worse health-related quality of life (HRQL), but little is known about *Mycobacterium avium* complex lung disease (MACLD) patients in this context. This study aimed to evaluate HRQL and investigate the impact of chronic PA infection in MACLD patients.

Methods: This cross-sectional study was conducted using the Registry of Prospective Cohort Study including MACLD patients. The 36-item Short-Form health survey (SF-36) and St. George's Respiratory Questionnaire (SGRQ) were administered to assess clinical outcomes. Clinical variables included treatment and sputum culture status, pulmonary function tests, cavitory lesions, and modified Reiff scores on high-resolution computed tomography.

Results: The study included 244 MACLD patients (median age, 68 years; 196 women), 19 of whom had chronic PA infection. Modified Reiff score was higher in patients with chronic infection than in those without ($P = 0.028$). Regarding SF-36 scores, physical functioning subscale scores were significantly lower in patients with chronic infection ($P = 0.029$). Additionally, SGRQ symptoms, impact, and total scores were significantly higher in patients with chronic infection. During analysis of covariance comparisons, SGRQ symptoms and impact scores were significantly higher for patients with chronic infection ($P = 0.043$ and 0.021 , respectively).

Conclusions: MACLD patients with chronic PA infection exhibited significantly higher SGRQ scores, indicating impaired HRQL. Chronic PA infection was significantly associated with the severity of bronchiectasis.

Keywords: Colonisation, Nontuberculous mycobacteria (NTM), *Pseudomonas aeruginosa*, St. George's Respiratory Questionnaire (SGRQ), 36-item short-form health survey (SF-36)

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Background

The incidence of lung disease caused by nontuberculous mycobacteria (NTM) has increased worldwide [1, 2]. *Mycobacterium avium* complex (MAC), the most common cause of NTM in Japan, generally causes chronic, slowly progressive lung disease in middle-aged men with risk factors such as smoking and structural lung diseases or in nonsmoking women without any of these risk factors [3]. Antimicrobial therapy for MAC lung disease (MACLD) for >12 months yields a success rate of approximately 75% [4], but high rates of recurrence have been reported after discontinuation of treatment [5]. Further studies have shown that the use of multiple antimicrobials is associated with multiple potential adverse effects, including ethambutol-induced ocular toxicity [3]. Because of the increasing prevalence and chronicity of MACLD, as well as the limited data regarding antimicrobial therapies associated with potential adverse effects, to monitor the patient's overall health status, patient-reported outcome measures that represent health-related quality of life (HRQL) have become increasingly important for MACLD [6].

Bronchiectasis is a respiratory disease characterised by permanent dilation of the bronchus and chronic respiratory symptoms such as daily sputum, coughing, shortness of breath, and recurrent respiratory infections [7]. The severity of bronchiectasis has been associated with worse HRQL, as evaluated by St. George's Respiratory Questionnaire (SGRQ) and Leicester Cough Questionnaire, and with a poor prognosis [8]. In addition to idiopathic causes, the aetiology of bronchiectasis can include factors such as previous severe respiratory infection, primary or secondary immunodeficiency, allergic bronchopulmonary aspergillosis, rheumatic or connective tissue disease, chronic obstructive pulmonary disease (COPD), or an impairment of ciliary clearance such as primary ciliary dyskinesia [9]. NTM has been described as both a cause of bronchiectasis and a secondary feature of established bronchiectasis that results from another aetiology [10]. Notably, most MACLD patients had bronchiectasis in high-resolution computed tomography (HRCT) studies [11, 12].

Previous studies have reported that in bronchiectasis patients, chronic *Pseudomonas aeruginosa* (PA) infection was associated with worse HRQL and with significant increases in disease exacerbation, hospital admission, and patient mortality [13]. Additionally, few studies have investigated the frequencies of or risk factors for chronic PA infection in MACLD patients [14]. Accordingly, little is known about the impact of chronic PA infection on HRQL in MACLD patients. The current study aimed to evaluate HRQL via the 36-item Short-Form health survey (SF-36) and SGRQ to investigate the impact of chronic PA infection on MACLD patients.

Methods

Study population

This single-centre cross-sectional study was conducted using the prospective, observational cohort registry at Keio University Hospital with patients aged 20 years or older who had been diagnosed with MACLD (UMIN000007546). MACLD was diagnosed in accordance with the 2007 American Thoracic Society/ Infectious Disease Society of America guidelines [3]. Patients with MACLD who completed the HRQL questionnaire between May 2012 and July 2014 were included in the study. The Keio University Hospital ethics review board approved the study protocol (#20110267). All patients provided written informed consent. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (<http://www.strobe-statement.org/>).

HRQL assessment

For the HRQL assessment, all patients completed the SF-36 version 2 [15] and the SGRQ in Japanese [16]. Both questionnaires have been validated for MACLD [17]. The internal consistencies of the SF-36 and SGRQ were assessed using Cronbach's α .

The SF-36 included eight subscales: physical functioning, role-physical, bodily pain, general health perception, vitality, social functioning, role-emotional, and mental health. Three summary scores were derived from the eight subscales, which were adjusted for Japanese patients: physical, mental, and role/social component summary scores [18]. The eight subscales ranged from 0 to 100, and the three summary scores were transformed to fit a norm-based score for the general Japanese population, with a mean score of 50 and a standard deviation of 10. Higher scores indicated better HRQL.

The SGRQ included symptoms, activity, and impact components that corresponded with measures of respiratory symptoms, impairment of physical activity, and social and psychological disturbances, respectively. The total score was calculated with the inclusion of each component. Possible scores were derived from the SGRQ range of 0–100, with higher scores indicating worse respiratory HRQL.

Assessment of clinical parameters

Assessed patient characteristics included age, sex, body mass index (BMI), disease duration, smoking status, underlying pulmonary diseases, Charlson Comorbidity Index (CCI) [19], treatment status, bacterial smear and culture results for MAC, and laboratory data. Treatment status was classified as never treated, previously treated, or currently treated. MAC isolates were identified as previously described [20]. Sputum smear or culture data were defined based on results obtained between 6 months

before and 6 months after registration. If patients did not expectorate sputum, then they were recorded as negative. Chronic PA infection was deemed present when PA was isolated from sputum culture on two or more occasions ≥ 3 months apart during the period of 6 months prior to registration through 6 months after registration [21].

Assessment of pulmonary function tests and high-resolution computed tomography

Pulmonary function tests (PFTs) and HRCT images were evaluated within 1 week of HRQL assessment. Patients who were in stable condition performed PFTs with an electronic spirometer (Chestac-9800 or HI-801; Chest M.I., Tokyo, Japan) in accordance with American Thoracic Society/European Respiratory Society recommendations.

HRCT images were assessed for the presence of cavitory lesions and severity of bronchiectasis. Two pulmonologists who were blinded to the clinical data performed the evaluations, and consensus review with an additional investigator was utilised to resolve any discrepancies. Bronchiectasis was assessed using a modified Reiff score, as in previous bronchiectasis studies [21]. The number of lobes involved (of a total of six; the lingula was considered separate) and the degree of dilatation (tubular = 1, varicose = 2, and cystic = 3) were calculated (range, 0–18).

Statistical analyses

All statistical analyses were performed using JMP version 12.0 (SAS Institute Japan Ltd., Tokyo, Japan). Continuous variables were analysed as median and interquartile range (IQR) or number and percentage (%). Fisher's exact test and the Mann-Whitney test were used for comparisons between two groups, and the Kruskal-Wallis test was used for comparisons between three groups during the analysis of categorical and continuous variables, respectively. To investigate the impact of chronic PA infection on HRQL, we first performed univariate analysis on each of the HRQL scores. An analysis of covariance (ANCOVA), adjusted for age, sex, BMI, CCI, and underlying pulmonary disease, was then performed to test the statistical significance of group differences. All P -values < 0.05 were considered statistically significant.

Results

Patient characteristics and clinical features

A total of 244 patients with MACLD were included in the study. Table 1 shows clinical characteristics of the 244 MACLD patients with and without chronic PA infection. The median age of the patients was 68 years and the IQR was 62–75 years. A total of 196 patients (80%) were women, and the median duration of disease was 5.7 years. The median BMI was 19.5 kg/m², and 220

patients (90%) reported that they had never smoked. A history of pulmonary tuberculosis was the most common underlying pulmonary disease ($n = 23$, 9.4%), followed by asthma ($n = 8$, 3.2%), lung cancer ($n = 3$, 1.2%), COPD ($n = 2$, 0.8%), and interstitial lung disease ($n = 1$, 0.4%). With regard to treatment status of MACLD, 116 (48%) had never been treated, 40 (16%) had been treated previously but were not currently being treated, and 88 (36%) were currently undergoing treatment. Sputum smear test results or cultures obtained 6 months before and 6 months after registration were positive for MAC in 83 (34%) and 138 (57%) patients, respectively. CCI was significantly higher in patients with chronic PA infection than in those without ($P = 0.048$). Patients with chronic infection tended to be older than those without, and they were less likely to yield a positive sputum smear or culture; however, these tendencies were not statistically significant.

PFT results, HRCT findings, and laboratory data

Table 2 shows the results of PFTs, HRCT findings, and laboratory data in our cohort of MACLD patients. The median values of PFT results were within normal ranges, and there were no significant differences between patients with and without chronic PA infection. There was weak evidence that forced expiratory volume in the first second was lower in patients with chronic infection ($P = 0.079$). During the HRCT analyses, the incidence of cavitory lesions did not differ significantly between the two groups. Almost all patients exhibited bronchiectasis, and the modified Reiff score was higher for patients with chronic infection than for those without (Fig. 1). During laboratory analyses, white blood cell counts, haemoglobin, and C-reactive protein (CRP) were within normal ranges. However, haemoglobin was significantly lower ($P = 0.049$) in patients with chronic PA infection compared with those without; in contrast, CRP was significantly higher ($P = 0.005$) in patients with chronic PA infection.

SF-36 and SGRQ

Table 3 shows the results of SF-36 and SGRQ in our cohort of MACLD patients. The internal consistency of these scores was good (Cronbach's α coefficients: SF-36, 0.89–0.91; SGRQ 0.91–0.95). With regard to SF-36 subscales, the physical functioning scores were significantly lower in patients exhibiting chronic PA infection compared with those patients without chronic PA infection ($P = 0.029$). Nearly all of the SGRQ scores were significantly higher in patients exhibiting chronic infection compared with those without (P -values: symptom, 0.008; impact, 0.006; total, 0.012); notably, the activity scores were not significantly different between groups.

Table 1 Clinical characteristics of 244 *Mycobacterium avium* complex lung disease patients with and without chronic *Pseudomonas aeruginosa* infection

Characteristic	All patients (n = 244)	With chronic infection (n = 19)	Without chronic infection (n = 225)	P value
Age, years	68 (62–75)	74 (67–76)	67 (61–75)	0.055
Sex, female	196 (80)	14 (74)	182 (81)	0.546
Disease duration, years	5.7 (2.3–9.7)	5.3 (2.3–10.3)	5.8 (2.3–9.6)	0.622
Body mass index, kg/m ²	19.5 (17.5–21.3)	18.8 (17.3–21.2)	19.6 (17.5–21.3)	0.515
Smoking status				1.000
Never	220 (90)	17 (89)	202 (90)	
Former	25 (10)	2 (11)	23 (10)	
Current	0 (0)	0 (0)	0 (0)	
Charlson Comorbidity Index	0 (0–1)	1 (1–1)	0 (0–1)	0.048
Underlying pulmonary disease				
History of pulmonary TB	23 (9)	4 (21)	19 (8)	0.089
Asthma	8 (3)	1 (1)	7 (3)	0.482
COPD	2 (1)	0 (0)	2 (1)	1.000
Lung cancer	3 (1)	1 (1)	2 (1)	1.000
Interstitial lung disease	1 (0.4)	0 (0)	1 (0.4)	1.000
Treatment status				0.452
Never	116 (48)	10 (53)	106 (47)	
Previous	40 (16)	1 (5)	39 (17)	
Current	88 (36)	8 (42)	80 (36)	
Bacterial status ^a				
Positive smear	83 (34)	3 (15)	80 (36)	0.083
Positive culture	138 (57)	7 (37)	131 (59)	0.090

Data show the median (interquartile range) or number (%) of patients

TB, tuberculosis; COPD, chronic obstructive pulmonary disease

^aBacterial status for mycobacterium

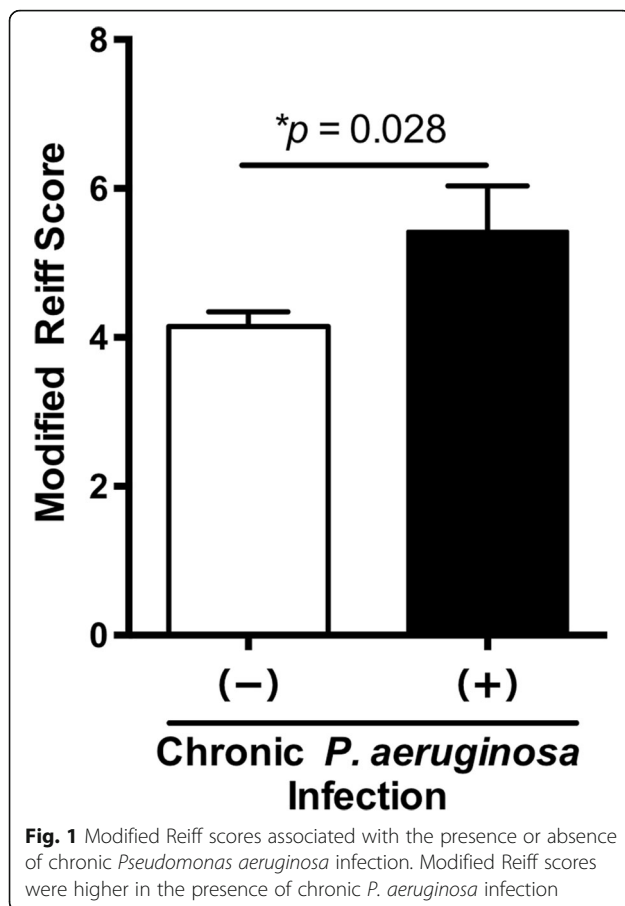
Table 2 Pulmonary function test results, high-resolution computed tomography findings and laboratory data in 244 *Mycobacterium avium* complex lung disease patients with and without chronic *Pseudomonas aeruginosa* infection

	All patients (n = 244)	With chronic infection (n = 19)	Without chronic infection (n = 225)	P value
PFT	(n = 243)	(n = 19)	(n = 224)	
%FVC	95 (81–108)	94 (75–102)	96 (82–109)	0.234
%FEV ₁	87 (73–99)	81 (66–98)	88 (74–100)	0.079
HRCT findings				
Cavitary lesion	59 (24)	4 (21)	55 (24)	1.000
Presence of bronchiectasis	233 (95)	19 (100)	214 (95)	0.609
Modified Reiff score	4 (2–6)	5 (3–7)	3 (2–6)	0.028
Laboratory data				
WBC/ μ L	5250 (4500–6375)	5700 (4700–7400)	5200 (4500–6200)	0.209
Haemoglobin, g/dL	13 (12–14)	12 (11–13)	13 (12–14)	0.049
CRP, mg/dL	0.1 (0.0–0.3)	0.3 (0.1–1.9)	0.1 (0.0–0.3)	0.005

Data show the median (interquartile range) or number (%) of patients

PFT, pulmonary function test; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; HRCT, high-resolution computed tomography;

WBC, white blood cell; CRP, C-reactive protein



Comparisons of physical component subscale score and SGRQ based on nominal variables using ANCOVA

There was no significant difference in physical component subscale score between patients with and without chronic infection ($P = 0.303$). However, SGRQ symptoms and impact scores were significantly higher in patients exhibiting chronic infection (symptoms, $P = 0.043$; impact, $P = 0.021$). There was weak evidence indicating that total SGRQ scores were higher for patients with chronic infection ($P = 0.069$) (Fig. 2).

Clinical characteristics associated with chronic PA infection in MACLD patients

Table 4 shows the clinical characteristics associated with chronic PA infection in the subset of 19 MACLD patients who exhibited signs of this illness. Other underlying diseases included rheumatoid arthritis ($n = 2$), mixed connective tissue disease ($n = 1$), gastroesophageal reflux disease ($n = 1$), liver cirrhosis ($n = 1$), and chronic sinusitis ($n = 1$). During PFTs, six patients exhibited restrictive dysfunction and six exhibited obstructive dysfunction. Ten patients (53%) provided sputum cultures and smears that were negative for NTM. With regard to treatment status for MACLD, 10 (53%) patients had

never been treated, one (5%) had been treated in the past but was not currently being treated, and eight (42%) were currently undergoing treatment. Four patients provided sputum cultures and smears that were negative for NTM, despite never having been treated for MACLD. For patients who had previously received or were currently receiving multiple antimicrobial therapy, the median treatment duration was 4.3 years (IQR, 2.9–10.1 years).

Discussion

To our knowledge, this is the first study to evaluate the effects of chronic PA infection on HRQL, as determined by the SF-36 and SGRQ, using only MACLD patients; many of these MACLD patients exhibited bronchiectasis. Our results showed that chronic PA infection reduced HRQL as determined by the SGRQ. The severity of bronchiectasis in HRCT, but not the presence of cavitory lesions, was associated with chronic PA infection in MACLD patients. We also determined clinical characteristics associated with treatment and bacterial infection status in these patients.

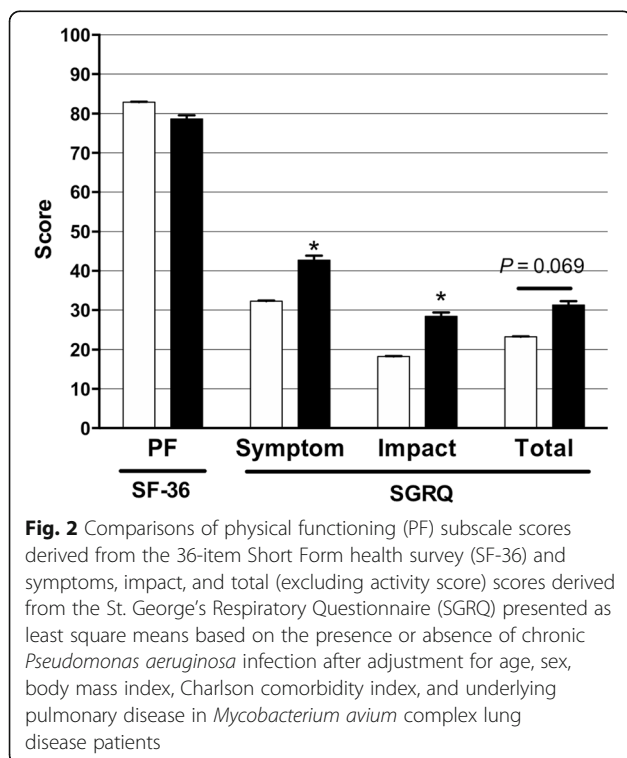
In the present study, chronic PA infection worsened SGRQ scores of MACLD patients, which is consistent with previous studies wherein bacterial infection affected HRQL in COPD and bronchiectasis patients [22–25]. In COPD patients, bacterial colonisation (particularly *Haemophilus influenzae*) and total bacterial load were the primary factors associated with increased daily symptoms and poorer SGRQ scores [22–24]. In studies of bronchiectasis, SGRQ-determined HRQL was significantly worse in patients with chronic PA infection compared to other patient groups [21, 25]. Although there was a small number of patients with chronic PA infection in the current study, our results suggest that chronic infection may affect the physical functioning and role-physical subscales of the SF-36, as well as the physical component summary. The mechanisms by which chronic PA infection influences HRQL are unclear; however, bronchiectasis patients with chronic PA infection exhibit higher cytokine production [26, 27], which may have contributed to the higher CRP values observed in the current study.

Severity of bronchiectasis, rather than the presence of cavitory lesions, was significantly associated with the presence of chronic PA infection in MACLD patients during this study. This association is consistent with previous reports regarding chronic PA infection in bronchiectasis patients [28]. An Italian study of a cohort of bronchiectasis patients indicated that NTM lung disease produced cylindrical bronchiectasis, a disease of lesser severity, and fewer pulmonary exacerbations than chronic PA infection [29]. In addition to bronchiectasis, MACLD may manifest as various types of lesions, including infiltrates, nodules, and cavitory lesions. Notably,

Table 3 Health-related quality of life in the 244 *Mycobacterium avium* complex lung disease patients with and without chronic *Pseudomonas aeruginosa* infection

	All patients (n = 244)	With chronic infection (n = 19)	Without chronic infection (n = 225)	P value
SF-36				
Physical functioning	90 (75–95)	85 (69–90)	90 (78–95)	0.029
Role-physical	88 (63–100)	75 (56–88)	88 (63–100)	0.057
Bodily pain	74 (52–100)	74 (41–100)	74 (52–100)	0.269
General health	52 (40–62)	47 (40–52)	52 (40–65)	0.292
Vitality	63 (44–75)	56 (50–75)	63 (44–75)	0.654
Social functioning	88 (63–100)	75 (38–100)	88 (63–100)	0.135
Role-emotional	92 (58–100)	92 (58–100)	92 (58–100)	0.926
Mental health	75 (60–85)	70 (55–80)	75 (60–85)	0.461
PCS	48 (40–54)	40 (36–48)	48 (40–54)	0.071
MCS	50 (44–56)	49 (43–55)	51 (44–46)	0.702
RCS	51 (39–56)	50 (34–55)	51 (40–57)	0.451
SGRQ				
Symptom	30 (16–48)	48 (30–52)	30 (14–46)	0.008
Activity	24 (6–46)	35 (19–48)	23 (6–46)	0.141
Impact	12 (4–31)	27 (17–42)	11 (3–30)	0.006
Total	20 (8–36)	30 (23–49)	18 (8–36)	0.012

Data show the median (interquartile range) or number (%) of patients SF-36, 36-item Short-Form health survey; PCS, physical component summary; MCS, mental component summary; RCS, role/social component summary; SGRQ, St. George’s Respiratory Questionnaire



cavitary lesions have been associated with reduced pulmonary function and lower HRQL, and they are predictive of disease progression requiring treatment and an ultimately poor prognosis [12, 30, 31]. Moreover, cavitary lesions have been revealed as an independent risk factor for MACLD that may develop into chronic pulmonary aspergillosis [32], because *Aspergillus* colonises both the airway and cavitary lesions. It has also been reported that bronchiectasis is associated with lower pulmonary function and is predictive of disease progression requiring treatment, despite its unknown impact on prognosis [12, 33]. Although it remains unclear whether chronic PA infection is the cause or result of advanced disease, our current study indicates that chronic PA infection is associated with bronchiectasis, in contrast to the *Aspergillus* colonisation that is associated with both bronchiectasis and cavitary lesions.

The nine patients who were either undergoing treatment for MACLD or had previously undergone treatment for MACLD received long-term antimicrobial therapy during this study; however, 10 patients exhibited chronic PA infection despite no history of treatment for MACLD. Moreover, four out of 10 patients exhibited negative results during analysis of both sputum smears and cultures. Previous studies indicated that NTM-infected bronchiectasis patients,

Table 4 Clinical characteristics of the 19 *Mycobacterium avium* complex lung disease patients with chronic *Pseudomonas aeruginosa* infection

No.	Age	Sex	BMI	CCI	Underlying disease	MACLD duration years	Hb	CRP	%FVC	%FEV ₁	Sputum smear/culture ^a	Cavity	Modified Reiff score	Treatment status for MACLD	Treatment regimen ^b	Treatment duration, years
1	74	F	17.3	0		10.3	13.1	1.1	99	86	-/-	+	7	Current	CAM + RFP	8.8
2	76	F	16.2	1	Old pTB, GERD	2.3	12.1	0.0	95	86	-/+	-	3	Never		
3	75	M	20.2	1	LC post-lobectomy	3.2	13.8	0.5	71	55	+/+	-	4	Current	CAM + EB + RFP	3.4
4	76	F	17.3	1	MCTD	2.1	11.0	0.2	94	114	-/+	-	5	Never		
5	57	F	18.8	1	RA	5.3	11.7	4.2	68	54	-/-	-	4	Current	CAM + EB + RFP	5.2
6	69	F	26.1	0		15.9	13.1	0.3	78	68	-/-	+	7	Previous	CAM + RFP + EB + KM	4.3
7	77	M	21.4	1	Old pTB, ABPM	6.5	9.8	0.2	116	105	-/-	-	3	Never		
8	77	F	14.9	1		1.9	12.2	0.0	98	102	+/+	-	7	Never		
9	67	M	18.5	0	Old pTB	2.3	14.6	0.1	112	83	-/-	-	1	Current	CAM + EB + RFP	2.3
10	74	F	19.5	0		13.0	13.5	1.2	87	75	-/-	-	10	Current	CAM + EB + RFP	11.4
11	81	F	18.4	0		14.8	11.0	0.3	103	102	+/+	-	7	Never		
12	67	F	21.2	1	RA	3.3	13.0	2.4	98	71	-/-	-	6	Never		
13	73	F	18.5	0		9.7	10.5	5.4	80	82	-/-	+	11	Never		
14	71	M	21.9	2	Liver cirrhosis	5.1	15.0	0.1	102	82	-/+	-	6	Never		
15	69	M	16.9	0	Old pTB	6.5	12.7	1.9	58	65	-/+	+	8	Current	CAM + EB + RFP	1.7
16	77	F	20.9	1		9.5	12.0	5.0	92	70	-/-	-	2	Never		
17	63	F	16.8	1		4.3	11.7	0.2	69	64	-/+	-	5	Current	CAM + RFP	4.1
18	74	F	21.4	1		0.6	13.4	0.0	106	98	-/+	-	2	Never		
19	35	F	18.9	0	Chronic sinusitis	14.5	10.7	0.0	75	66	-/-	-	5	Current	AZM + RFP + EB	13.4

BMI, body mass index; CCI, Charlson comorbidity index; MACLD, *Mycobacterium avium* complex lung disease; Hb, haemoglobin; CRP, C-reactive protein; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; CAM, clarithromycin; RFP, rifampicin; pTB, pulmonary tuberculosis; GERD, gastroesophageal reflux disease; LC, lung cancer; EB, ethambutol; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis; KM, kanamycin; ABPM, allergic bronchopulmonary mycosis; AZM, azithromycin;

^aSputum smear or culture for *Mycobacterium*. ^bTreatment regimen included multiple antimicrobial therapy for MACLD

including those with cystic fibrosis, had a lower rate of chronic PA infection compared with NTM-uninfected patients [34–36]. In the present study, MACLD patients with chronic PA infection exhibited a lower rate of NTM-positive sputum cultures, regardless of similar treatment status. Although the parameters involved in the interaction between PA and NTM in the lung are unknown, these results may reflect a dominant pathogenic species, as has been suggested in previous studies [34–36]. Furthermore, it was recently reported that almost half of untreated patients with stable MACLD exhibited spontaneous conversion [37]. Therefore, bronchiectasis patients with chronic PA infection (that is predictive of a poor prognosis) may include post-MACLD patients.

The current study had several potential limitations. First, the study design was cross-sectional; therefore, it was difficult to determine causal associations, particularly with regard to the influence of treatment or the presence of MAC on bronchiectasis. Moreover, we could not identify a risk factor for or assess the impact of chronic PA infection on prognosis. Second, the method and frequency of sputum smear/culture testing for PA were dependent on each attending physician rather than an established protocol. Furthermore, in our study, we used the most stringent definition of chronic infection that was used in previous studies [13], resulting in a very small number of patients who were classified as having chronic PA infection. Although these biases may have underestimated chronic PA infection, we identified impaired HRQL associated with chronic PA infection. Third, we did not include patients who exhibited chronic PA infection without NTM infection. Although these patients are an important control group, their exact classification might be difficult due to the spontaneous conversion of MACLD [37]. Finally, we did not identify any factors associated with pulmonary physicians' decisions regarding the initiation, continuation, or discontinuation of antimicrobial therapy for MACLD or chronic PA infection. However, the indications for treatment, optimal durations of treatment for patients with MACLD, and management approaches for chronic PA infection were unclear in this study. Further studies that include MACLD patients with chronic PA infection are needed to investigate the relationships between antimicrobial treatment and patient outcomes. Additionally, to clarify risk factors and the influence of chronic PA infection on prognosis, prospective observational multicentre studies are needed that incorporate microbiological data and imaging, especially those involving newly diagnosed MACLD and bronchiectasis patients.

Conclusions

MACLD patients with chronic PA infection exhibited a significantly lower HRQL than those without, as indicated by higher SGRQ scores. Chronic PA infection was significantly associated with the severity of bronchiectasis.

Abbreviations

ANCOVA: Analyses of covariance; BMI: Body mass index; CCI: Charlson comorbidity index; CF: Cystic fibrosis; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; HRCT: High-resolution computed tomography; HRQL: Health-related quality of life; IQR: Interquartile range; MAC: *Mycobacterium avium* complex; MACLD: *Mycobacterium avium* complex lung disease; NTM: Nontuberculous mycobacteria; PA: *Pseudomonas aeruginosa*; PFTs: Pulmonary function tests; SF-36: 36-item Short-Form health survey; SGRQ: St. George's Respiratory Questionnaire; TB: Tuberculosis

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Availability of data and materials

The data will not be shared because of participant confidentiality.

Authors' contributions

HK, TA, and NH designed the study, acquired and interpreted data, and wrote, revised, and approved the final manuscript. SS, HN, KY, YF, SO SU, YU, and HF acquired and interpreted data and revised and approved the final manuscript. TN, MI, and TB interpreted data and revised and approved the final manuscript. All authors have read and approved the final version of this manuscript.

Ethics approval and consent to participate

The Keio University Hospital ethics review board approved the study protocol (#20110267). All patients provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

- Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. *Clin Chest Med*. 2015;36(1):13–34.
- Namkoong H, Kurashima A, Morimoto K, Hoshino Y, Hasegawa N, Ato M, et al. Epidemiology of pulmonary nontuberculous mycobacterial disease, Japan. *Emerg Infect Dis*. 2016;22(6):1116–7.
- Griffith DE, Akshamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of

- nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175(4):367–416.
4. Kwak N, Park J, Kim E, Lee CH, Han SK, Yim JJ. Treatment outcomes of *Mycobacterium avium* Complex lung disease: a systematic review and meta-analysis. *Clin Infect Dis*. 2017; <https://doi.org/10.1093/cid/cix517>.
 5. Lee BY, Kim S, Hong Y, Lee SD, Kim WS, Kim DS, et al. Risk factors for recurrence after successful treatment of *Mycobacterium avium* Complex lung disease. *Antimicrob Agents Chemother*. 2015;59(6):2972–7.
 6. Satta G, McHugh TD, Mountford J, Abubakar I, Lipman M. Managing pulmonary nontuberculous mycobacterial infection. Time for a patient-centered approach. *Ann Am Thorac Soc*. 2014;11(1):117–21.
 7. McShane PJ, Naureckas ET, Tino G, Streck ME. Non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med*. 2013;188(6):647–56.
 8. McDonnell MJ, Aliberti S, Goeminne PC, Dimakou K, Zucchetti SC, Davidson J, et al. Multidimensional severity assessment in bronchiectasis: an analysis of seven European cohorts. *Thorax*. 2016;71(12):1110–8.
 9. Lonni S, Chalmers JD, Goeminne PC, McDonnell MJ, Dimakou K, De Soya A, et al. Etiology of non-cystic fibrosis bronchiectasis in adults and its correlation to disease severity. *Ann Am Thorac Soc*. 2015;12(12):1764–70.
 10. Mirsaedi M, Hadid W, Ericoussi B, Rodgers D, Sadikot RT. Non-tuberculous mycobacterial disease is common in patients with non-cystic fibrosis bronchiectasis. *Int J Infect Dis*. 2013;17(11):e1000–4.
 11. Wallace RJ Jr, Brown-Elliott BA, McNulty S, Philley JV, Killingley J, Wilson RW, et al. Macrolide/Azalide therapy for nodular/bronchiectatic *Mycobacterium avium* Complex lung disease. *Chest*. 2014;146(2):276–82.
 12. Lee G, Lee KS, Moon JW, Koh WJ, Jeong BH, Jeong YJ, et al. Nodular bronchiectatic *Mycobacterium avium* Complex pulmonary disease. Natural course on serial computed tomographic scans. *Ann Am Thorac Soc*. 2013;10(4):299–306.
 13. Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. Comprehensive analysis of the impact of *Pseudomonas aeruginosa* colonization on prognosis in adult bronchiectasis. *Ann Am Thorac Soc*. 2015;12(11):1602–11.
 14. Fujita K, Ito Y, Hirai T, Kubo T, Togashi K, Ichiyama S, et al. Prevalence and risk factors for chronic co-infection in pulmonary *Mycobacterium avium* Complex disease. *BMJ Open Respir Res*. 2014;1(1):e000050.
 15. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 health survey for use in Japan. *J Clin Epidemiol*. 1998;51(11):1037–44.
 16. Jones PW, Quirk FH, Baveystock CM, Littlejohns PA. Self-complete measure of health status for chronic airflow limitation. The St. George's respiratory questionnaire. *Am Rev Respir Dis*. 1992;145(6):1321–7.
 17. Asakura T, Funatsu Y, Ishii M, Namkoong H, Yagi K, Suzuki S, et al. Health-related quality of life is inversely correlated with C-reactive protein and age in *Mycobacterium avium* Complex lung disease: a cross-sectional analysis of 235 patients. *Respir Res*. 2015;16:145.
 18. Suzukamo Y, Fukuhara S, Green J, Kosinski M, Gandek B, Ware JE. Validation testing of a three-component model of short Form-36 scores. *J Clin Epidemiol*. 2011;64(3):301–8.
 19. Charlson ME, Pompei P, Ales KL, MacKenzie CRA. New method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–83.
 20. Ueyama M, Asakura T, Morimoto K, Namkoong H, Matsuda S, Osawa T, et al. Pneumothorax associated with nontuberculous mycobacteria: a retrospective study of 69 patients. *Medicine (Baltimore)*. 2016;95(29):e4246.
 21. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med*. 2014;189(5):576–85.
 22. Khurana S, Ravi A, Sutula J, Milone R, Williamson R, Plumb J, et al. Clinical characteristics and airway inflammation profile of COPD persistent sputum producers. *Respir Med*. 2014;108(12):1761–70.
 23. Desai H, Eschberger K, Wrona C, Grove L, Agrawal A, Grant B, et al. Bacterial colonization increases daily symptoms in patients with chronic obstructive pulmonary disease. *Ann Am Thorac Soc*. 2014;11(3):303–9.
 24. Simpson JL, Baines KJ, Horvat JC, Essilfie AT, Brown AC, Tooze M, et al. COPD is characterized by increased detection of *Haemophilus influenzae*, *Streptococcus pneumoniae* and a deficiency of *Bacillus* species. *Respirology*. 2016;21(4):697–704.
 25. Wilson CB, Jones PW, O'Leary CJ, Hansell DM, Cole PJ, Wilson R. Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. *Eur Respir J*. 1997;10(8):1754–60.
 26. Chen AC, Martin ML, Lourie R, Rogers GB, Burr LD, Hasnain SZ, et al. Adult non-cystic fibrosis bronchiectasis is characterised by airway luminal Th17 pathway activation. *PLoS One*. 2015;10(3):e0119325.
 27. Hector A, Kroner C, Carevic M, Bakele M, Rieber N, Riethmuller J, et al. The chemokine CCL18 characterises *Pseudomonas* infections in cystic fibrosis lung disease. *Eur Respir J*. 2014;44(6):1608–15.
 28. Dimakou K, Triantafyllidou C, Toumbis M, Tsikritsaki K, Malagari K, Bakakos P. Non CF-bronchiectasis: Aetiologic approach, clinical, radiological, microbiological and functional profile in 277 patients. *Respir Med*. 2016;116:1–7.
 29. Faverio P, Stainer A, Bonaiti G, Zucchetti SC, Simonetta E, Lapadula G, et al. Characterizing non-tuberculous mycobacteria infection in bronchiectasis. *Int J Mol Sci*. 2016;17(11):E1913.
 30. Asakura T, Yamada Y, Namkoong H, Suzuki S, Nijima Y, Kamata H, et al. Impact of cavity and infiltration on pulmonary function and health-related quality of life in pulmonary *Mycobacterium avium* Complex disease: a 3-dimensional computed tomographic analysis. *Respir Med*. 2017;126:9–16.
 31. Gochi M, Takayanagi N, Kanauchi T, Ishiguro T, Yanagisawa T, Sugita Y. Retrospective study of the predictors of mortality and radiographic deterioration in 782 patients with nodular/bronchiectatic *Mycobacterium avium* Complex lung disease. *BMJ Open*. 2015;5(8):e008058.
 32. Takeda K, Imamura Y, Takazono T, Yoshida M, Ide S, Hirano K, et al. The risk factors for developing of chronic pulmonary aspergillosis in nontuberculous mycobacteria patients and clinical characteristics and outcomes in chronic pulmonary aspergillosis patients coinfecting with nontuberculous mycobacteria. *Med Mycol*. 2016;54(2):120–7.
 33. Song JW, Koh WJ, Lee KS, Lee JY, Chung MJ, Kim TS, et al. High-resolution CT findings of *Mycobacterium avium*-Intracellulare Complex pulmonary disease: correlation with pulmonary function test results. *AJR Am J Roentgenol*. 2008;191(4):1070.
 34. Binder AM, Adjemian J, Olivier KN, Prevots DR. Epidemiology of nontuberculous mycobacterial infections and associated chronic macrolide use among persons with cystic fibrosis. *Am J Respir Crit Care Med*. 2013;188(7):807–12.
 35. Bar-On O, Mussaffi H, Mei-Zahav M, Prais D, Steuer G, Stafler P, et al. Increasing nontuberculous mycobacteria infection in cystic fibrosis. *J Cyst Fibros*. 2015;14(1):53–62.
 36. Aksamit TR, O'Donnell AE, Barker A, Olivier KN, Winthrop KL, Daniels ML, et al. Adult bronchiectasis patients: a first look at the United States bronchiectasis research registry. *Chest*. 2016;151(5):982–92.
 37. Hwang JA, Kim S, Jo KW, Shim TS. Natural history of *Mycobacterium avium* complex lung disease in untreated patients with stable course. *Eur Respir J*. 2017;49(3):1600537.

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