Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

# Clinical significance of the COPD Assessment Test in evaluating treatment response in Mycobacterium avium complex pulmonary disease

**Naohisa Urabe**
naohisa.urabe@med.toho-u.ac.jp
Toho University
**Susumu Sakamoto**
Toho University
**Nozomi Tokita**
Toho University
**Takumi Kanokogi**
Toho University
**Hiroshige Shimizu**
Toho University
**Shion Miyoshi**
Toho University
**Takuma Isshiki**
Toho University
**Kazuma Kishi**
Toho University

**Research Article**

**Keywords:** Nontuberculous mycobacterial pulmonary disease, Mycobacterium avium complex, COPD Assessment Test, Health-related quality of life, Sputum culture conversion

**Posted Date:** April 1st, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-9091387/v1

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

**Additional Declarations:** No competing interests reported.

# Abstract

### Background

In *Mycobacterium avium* complex pulmonary disease (MAC-PD), sputum culture conversion is a key treatment endpoint but does not fully reflect symptom burden. We evaluated the clinical utility of the COPD Assessment Test (CAT) as a patient-reported measure of disease severity and treatment response in MAC-PD.

### Methods

We retrospectively analyzed 179 treatment courses in 174 patients with MAC-PD treated with guideline-based therapy at a single center. CAT scores were assessed at treatment initiation (CAT-Base) and at 6 and 12 months (Δ6 and Δ12). Associations between CAT-Base, baseline chest CT score, and baseline sputum culture status were examined. We evaluated whether Δ6 and Δ12 discriminated 12-month sputum culture status and overall treatment control, defined by radiological response at 12 months and microbiological course up to 24 months post-treatment initiation.

### Results

CAT-Base was associated with baseline chest CT score and was higher in baseline sputum culture-positive and poorly-controlled treatment courses. Neither Δ6 nor Δ12 discriminated 12-month sputum culture status. However, Δ12 was more favorable in well-controlled than poorly-controlled treatment courses and demonstrated modest discriminatory ability (area under the curve (AUC) 0.646), which improved in treatment courses with CAT-Base > 2 (AUC 0.682). In this subgroup, a Δ12 cut-off of − 3 yielded a specificity of 71.9% and a positive predictive value 85.5% for identifying well-controlled disease.

### Conclusions

CAT-Base reflects radiological severity and microbiological status in MAC-PD. In treatment courses with CAT-Base > 2, a 3-point CAT decrease at 12 months may help identify well-controlled disease, representing a pragmatic candidate threshold for clinically meaningful symptomatic improvement.

**Clinical trial number:** not applicable.


# Background

*Nontuberculous mycobacterial* pulmonary disease (NTM-PD) has been increasingly recognized worldwide, and the associated rise in mortality represents a growing major clinical concern [1]. In Japan, the incidence of NTM-PD has likewise

increased [2], with *Mycobacterium avium* complex pulmonary disease (MAC-PD) accounting for approximately 88% of cases, making it the most common prevalent form of NTM-PD in this setting [2].

Several outcome definitions for the treatment of MAC-PD have been proposed [3], among which sputum culture conversion is the most widely used endpoint in both clinical practice and clinical trials [4]. Sputum culture conversion is defined as at least three consecutive negative sputum cultures, collected at intervals of least four weeks or longer during treatment. However, in real-world practice, this definition is not applicable to all patients. Some patients are diagnosed by bronchoscopy and have negative sputum cultures at treatment initiation, whereas others are unable to expectorate adequate sputum specimens during follow-up.

To address this limitation, the concept of "*clinical cure*" has been proposed as an additional outcome category for MAC-PD [3]. Clinical cure is defined as symptomatic and/or objective improvement during treatment that is sustained until the end of therapy. Objective improvement can be assessed using serial chest computed tomography (CT); however, symptomatic improvement is more difficult to quantify because MAC-PD is associated not only with cough and sputum production, but also with reduced exercise tolerance, limitations in daily activities, and fatigue. Structured patient-reported outcome measures are therefore needed to evaluate symptomatic improvement as a component of clinical cure in a patient-centered manner.

Various instruments have been used to assess health-related quality of life (HRQoL) in patients with MAC-PD. Cross-sectional studies employing the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and the St George's Respiratory Questionnaire (SGRQ) have demonstrated substantial impairment across multiple HRQoL domains in patients with MAC-PD compared with the general population and other chronic diseases [5, 6]. The bronchiectasis-specific Quality of Life-Bronchiectasis (QOL-B) questionnaire has also been applied in patients with NTM-PD to assess symptoms and HRQoL [7–9]. Although the SF-36, SGRQ, and QOL-B provide detailed HRQoL assessments, they comprise numerous items and are relatively time-consuming, thus limiting their practicality in routine clinical practice.

The COPD Assessment Test (CAT) is a simple, freely available, eight-item questionnaire originally developed for chronic obstructive pulmonary disease [10]. The CAT correlates well with the SGRQ, and cross-sectional studies have reported impaired HRQoL as assessed by CAT in patients with NTM-PD and MAC-PD [11]. However, in MAC-PD, longitudinal data on changes in CAT scores during treatment are limited, and a disease-specific minimal clinically important difference (MCID) has not been established. Clarifying how CAT score trajectories relate to microbiological and radiological treatment control may help establish CAT as a practical, patient-centered endpoint in this disease.

Accordingly, we investigated the cross-sectional and longitudinal utility of the CAT in MAC-PD and explored whether changes in CAT scores during treatment are associated with microbiological and radiological treatment control and reflect clinically meaningful symptomatic improvement.

# Methods

# Study population

In this single-center retrospective cohort study conducted at Toho University Omori Medical Center, we analyzed 179 treatment courses of guideline-based, macrolide-containing multidrug therapy (GBT) administered to 174 patients with MAC-PD between April 2015 and August 2024. Eligible treatment courses were those in which GBT was continued for at least 12 months and CAT scores were available at both treatment initiation (baseline) and 12 months. When a new treatment course was initiated more than two years after completion of a previous course and MAC infection was reconfirmed by positive sputum or bronchoscopy culture, it was regarded as a separate treatment course. CAT scores at 6 months after treatment initiation were also available for 178 of the 179 treatment courses. All patients met the ATS/ERS/ESCMID/IDSA diagnostic criteria for NTM-PD [12] (Fig. 1).

# Definitions

**Baseline sputum culture-positive treatment courses** were defined as those in which at least one sputum culture was positive for MAC within the 12 months prior to, or at the time of, treatment initiation.

**Baseline sputum culture-negative treatment courses** were defined as those in which no sputum culture was positive for MAC during the 12 months prior to, or at the time of, treatment initiation. In these treatment courses, the diagnosis of MAC-PD had already been confirmed based on either positive bronchoscopic specimens, or positive sputum cultures obtained more than 12 months before treatment initiation.

For analyses based on microbiological response during the first 12 months of treatment, treatment courses were classified according to their overall sputum culture course.

**The sputum culture-negative treatment course group** included the following: (1) baseline sputum culture-positive treatment courses that achieved sputum culture conversion after treatment initiation, and (2) baseline sputum culture-negative course, in which sputum cultures for MAC remained negative or sputum samples could not be obtained throughout the first 12 months of treatment (dotted-fill boxes in Fig. 1).

**The sputum culture-positive treatment course group** included treatment courses with persistent sputum culture positivity without conversion during the first 12 months and treatment courses with reversion to sputum culture positivity within the first 12 months after initial conversion (gray-fill boxes in Fig. 1).

To evaluate overall treatment control, we created a composite outcome combining radiological response at 12 months and the microbiological course up to 24 months after treatment initiation.

**Well-controlled treatment courses** were defined as treatment courses that were classified as the sputum culture-negative group (as defined above) and showed radiological improvement on chest CT at

12 months compared with baseline (dotted outline in Fig. 1).

**Poorly-controlled treatment courses** were defined as treatment courses that showed no radiological improvement on chest CT at 12 months and met at least one of the following conditions: (1) classification as sputum culture-positive, or (2) classification as sputum culture-negative at 12 months with subsequent re-isolation of MAC from sputum or bronchoscopic specimens between 12 and 24 months after treatment initiation (thick outline in Fig. 1).

Treatment courses that did not meet the criteria for either well-controlled or poorly-controlled treatment courses were considered indeterminate and were excluded.

## Study design

First, to clarify the cross-sectional clinical significance of the baseline CAT score (CAT-Base), we examined its associations with baseline disease severity at treatment initiation. We assessed correlations between CAT-Base and continuous variables such as age, body mass index (BMI), and chest CT score, and compared CAT-Base and other clinical characteristics between treatment courses with and without baseline sputum culture positivity for MAC.

Second, to evaluate whether changes in CAT scores reflect microbiological response, treatment courses were classified according to their microbiological response during the first 12 months of treatment, using the sputum culture-negative and sputum culture-positive groups (Fig. 1). Changes in CAT scores from baseline to 6 months (Δ6 = CAT at 6 months − CAT-Base) and to 12 months (Δ12 = CAT at 12 months − CAT-Base) were compared between these two groups.

Third, to investigate the relationship between changes in CAT scores and overall treatment control, we applied the composite outcome definition to classify treatment courses as well-controlled or poorly-controlled. Treatment courses that did not meet either definition were considered indeterminate and so were excluded from this analysis. Also, CAT-Base, Δ6, and Δ12 were compared between well-controlled and poorly-controlled treatment courses.

Finally, because treatment courses with very low CAT-Base values (0–2 points) had limited room for symptomatic improvement, we conducted a sensitivity analysis excluding treatment courses with CAT-Base 0–2. In this restricted cohort, we re-evaluated the association between changes in CAT scores and overall treatment control.

When Δ6 or Δ12 differed significantly in any of the predefined between-group comparisons described above, receiver operating characteristic (ROC) analysis was performed to assess discriminatory performance and to explore candidate ΔCAT cut-off values.

## CAT score

CAT score was developed to evaluate HRQoL in patients with COPD [13]. In this study, we used the validated Japanese version of the CAT [14]. CAT scores range from 0 to 40, with higher scores indicating greater symptom burden.

## Chest CT score

Chest high-resolution CT (HRCT) findings in MAC-PD were scored as previously described [15, 16]. The lungs were divided into six zones at the levels of the carina and inferior pulmonary vein. Four types of pulmonary lesions characteristic of MAC-PD, cavities, bronchiectasis, nodules (< 10 mm), and infiltration (defined as an area of opacity ≥ 10 mm), were graded in each zone according to the extent of involvement using a five-point scale (0, no lesion; 1, 1–24%; 2, 25–49%; 3, 50–74%; 4, 75–100%). Chest CT scores were reviewed independently by two respiratory physicians, each with over 15 years of experience.

# Data collection

We collected data on age, sex, BMI, smoking history, comorbidities, concomitant medications, chest CT findings, sputum culture results, and CAT scores from electronic medical records. At our institution, all patients with MAC-PD routinely undergo chest CT scans and CAT assessments approximately 6 and 12 months after treatment initiation to evaluate therapeutic response. The data used in this study were retrospectively extracted from these assessments, which were performed as part of standard clinical care. Baseline chest CT scans were obtained within three months prior to treatment initiation. The variables included in the analyses are summarized in Supplementary Table 1.

# Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables as medians with interquartile ranges. Fisher's exact test was used to compare categorical variables, and the Mann–Whitney U test and Wilcoxon signed-rank test were used to compare continuous variables between independent and paired observations, respectively. Correlations between CAT-Base and baseline chest CT score, age, and BMI were assessed using Spearman's rank correlation coefficient. For contrasts in which changes in CAT scores (Δ6 or Δ12) differed significantly between groups, ROC curves were constructed, and areas under the curve (AUCs) with 95% confidence intervals (CIs) were calculated. For the contrast with the highest AUC, candidate cut-off values of ΔCAT were evaluated by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A two-sided p value of < 0.05 was considered statistically significant. All analyses were performed using R software with RStudio (Posit, Boston, MA).

## Use of Use of AI assistance during manuscript preparation

During manuscript preparation, the authors used ChatGPT (OpenAI, San Francisco, CA, USA) solely to improve the English language and readability of the manuscript. The authors reviewed and edited the output as needed and take full responsibility for the content of the article.

# Results

### Patient characteristics

The median age of the cohort was 67 years, and 161/179 (89.9%) treatment courses were observed in women (Table 1). Compared with baseline sputum culture-negative treatment courses (n = 88; median age, 64 years; 81 women), baseline sputum culture-positive treatment courses (n = 91; median age, 69 years; 80 women) had significantly higher CAT-Base values overall [12 (6–18.5) vs. 8.5 (4–16); p = 0.043] and higher scores for the CAT items “cough” [2 (1–3) vs. 1 (1–3); p < 0.001] and “confidence leaving home” [1 (0–2) vs. 0 (0–1); p = 0.005]. Cavitary lesions were also more frequent in baseline sputum culture–positive treatment courses than in baseline sputum culture-negative treatment courses (38.5% vs. 19.3%; p = 0.005).

### Baseline CAT score

CAT-Base showed a weak but significant positive correlation with baseline chest CT score (Spearman’s ρ = 0.204, p = 0.006; Supplementary Figure 1). In contrast, CAT-Base was not significantly correlated with BMI (ρ = −0.090, p = 0.233) or age (ρ = 0.014, p = 0.855; Supplementary Figures 2 and 3). As summarized in Table 2, CAT-Base did not differ significantly by sex, smoking history, presence of underlying lung disease, mixed infection with other respiratory pathogens, or presence of cavitary lesions.

### CAT scores according to sputum culture response

A total of 151 treatment courses were classified as sputum culture-negative and 28 as sputum culture-positive at 12 months (culture-negative: conversion by 12 months or sustained negativity; culture-positive: persistent positivity or reversion to positivity; see Figure 1) (Table 3). Compared with sputum culture-positive treatment courses, sputum culture-negative treatment courses had lower CAT-Base scores [9 (5–17.5) vs. 13 (8.5–20); p = 0.030] and lower scores for several CAT items, including cough, phlegm, breathlessness, activities, and energy (all p < 0.05). From baseline to 6 and 12 months, however, changes in CAT scores (Δ6 and Δ12) did not differ significantly between sputum culture-negative and sputum culture-positive treatment courses (Table 4): Δ6 [−2.0 (−5.0 to 1.0) vs. −1.0 (−5.0 to 1.3); p = 0.540] and Δ12 [−2.0 (−6.0 to 1.0) vs. −0.5 (−3.3 to 2.3); p = 0.166]. The distribution of Δ12 is presented in a waterfall plot (Figure 2).

### CAT scores according to treatment control status

A total of 123 treatment courses were classified as well-controlled and 33 as poorly-controlled (Table 5; classification schema is shown in Figure 1). Compared with poorly-controlled treatment courses, well-controlled treatment courses had lower CAT-Base scores [8 (4–16) vs. 13 (7–19); p = 0.004] and lower

scores for several CAT items, including cough, phlegm, breathlessness, limited activities, confidence leaving home, and energy (all $p < 0.05$). Changes in CAT scores from baseline to 6 months (Δ6) did not differ significantly between well-controlled and poorly-controlled treatment courses [−2.0 (−5.0 to 1.0) vs. −1.0 (−5.0 to 2.0); $p = 0.237$]. Conversely, Δ12 showed greater improvement in the well-controlled group [−2.0 (−6.0 to 0.0) vs. 0.0 (−3.0 to 3.0); $p = 0.010$] (Table 4).

**Changes in CAT scores according to treatment control status in treatment courses with baseline CAT score >2**

Because the median improvement in CAT scores (Δ6, Δ12) in well-controlled treatment courses was approximately −2 points, treatment courses with CAT-Base scores of 0–2 had limited room for further numerical improvement and were excluded in a sensitivity analysis. Among treatment courses with CAT-Base >2 (102 well-controlled and 32 poorly-controlled courses), Δ6 did not differ significantly between the two groups [−3.0 (−6.0 to 0.0) vs. −1.0 (−5.0 to 2.0); $p = 0.069$]. In contrast, Δ12 definitively showed greater improvement in the well-controlled group [−3.0 (−7.0 to −1.0) vs. 0.0 (−3.3 to 3.5); $p = 0.002$]. The distribution of Δ12 in this analysis is presented in a waterfall plot (Figure 3).

**ROC analysis of Δ12 for identifying well-controlled disease**

Because neither Δ6 nor Δ12 differed between the sputum culture-negative and sputum culture-positive groups, ROC analysis was not performed for microbiological response. For treatment control status, ROC analysis was restricted to Δ12 because Δ6 did not differ significantly between well-controlled and poorly-controlled treatment courses. Among treatment courses classified as well-controlled or poorly-controlled, Δ12 demonstrated modest discriminatory ability for treatment control (well-controlled vs. poorly-controlled), with an AUC of 0.646 (95% confidence interval [CI] 0.533–0.750) (Figure 4A). In the subgroup of treatment courses with CAT-Base >2, the discriminatory performance of Δ12 improved, yielding an AUC of 0.682 (95% CI 0.565–0.787) (Figure 4B). We therefore used the ROC curve for Δ12 in treatment courses with CAT-Base >2 to determine candidate cut-off values. Diagnostic indices were calculated for Δ12 cut-off values ranging from −7 to 0 (Table 6). A cut-off of Δ12 = −3 provided the best overall performance, with a sensitivity of 52.0%, specificity of 71.9%, PPV of 85.5%, and NPV of 31.9%.

Table 1. Baseline characteristics according to baseline sputum culture status

| Characteristic | No. of Treatment courses (n = 179) | Culture-positive treatment courses (n = 91) | Culture negative treatment courses. (n = 88) | p value |
|---|---|---|---|---|
| Age, years; median (IQR)[a] | 67 (60.0–74.0) | 69 (60–75) | 64 (59.8–72) | 0.292 |
| Sex, female; n (%) | 161 (89.9) | 80 (87.9) | 81 (92) | 0.458 |
| BMI (kg/m$^2$); median (IQR)[a] | 18.6 (17.4–20.1) | 18.5 (17.3–20.0) | 18.8 (17.6–20.1) | 0.285 |
| Smoking, never; n (%) | 136 (76) | 66 (72.5) | 70 (79.5) | 0.298 |
| Comorbidities; n (%) | | | | |
| Rheumatoid arthritis | 15 (8.4) | 7 (7.7) | 8 (9.1) | 0.792 |
| Current malignancy | 5 (2.8) | 3 (3.3) | 2 (2.3) | 1.000 |
| Past malignancy | 13 (7.3) | 6 (6.6) | 7 (8.0) | 0.780 |
| Underlying pulmonary disease; n (%) | | | | |
| Emphysema | 12 (6.7) | 7 (7.7) | 5 (5.7) | 0.767 |
| Interstitial pneumonia | 10 (5.6) | 4 (4.4) | 6 (6.8) | 0.531 |
| Concomitant drug; n (%) | | | | |
| Corticosteroids | 10 (5.6) | 4 (4.4) | 6 (6.8) | 0.531 |
| Immunosuppressant | 13 (7.3) | 7 (7.7) | 6 (6.8) | 1.000 |
| Biologic agent | 5 (2.8) | 3 (3.3) | 2 (2.3) | 1.000 |
| Chemotherapy | 2 (1.1) | 1 (1.1) | 1 (1.1) | 1.000 |
| Infecting MAC isolate; n (%) | | | | |
| *M. avium* | 145 (81.0) | 71 (78.0) | 74 (84.1) | 0.344 |
| *M. intracellulare* | 39 (21.8) | 20 (22.0) | 19 (21.6) | 1.000 |

| | | | | |
|---|---|---|---|---|
| Subjective symptoms; score (IQR)[a] | | | | |
| CAT score | 10 (5–18) | 12 (6–18.5) | 8.5 (4–16) | **0.043** |
| Cough[b] | 2 (1–3) | 2 (1–3) | 1 (1–3) | **<0.001** |
| Sputum[b] | 2 (1–3) | 2 (1–3) | 1 (0–3) | 0.062 |
| Chest tightness[b] | 1 (0–2) | 1 (0–2) | 1 (0–2) | 0.581 |
| Breathlessness[b] | 2 (1–3) | 2 (1–3) | 1 (0–3) | 0.269 |
| Limited activities[b] | 0 (0–1) | 0 (0–1) | 0 (0–1) | 0.290 |
| Confidence leaving home[b] | 0 (0–1) | 1 (0–2) | 0 (0–1) | **0.005** |
| Sleeplessness[b] | 1 (0–3) | 1 (0–3) | 1 (0–3) | 0.781 |
| Energy[b] | 1 (0.5–3) | 1 (1–3) | 1 (0–2) | 0.177 |
| Radiographical pattern; n (%) | | | | |
| Non-cavitary NBE type | 126 (70.4) | 57 (62.6) | 69 (78.4) | **0.023** |
| Cavitary NBE type | 45 (25.1) | 29 (31.9) | 16 (18.2) | **0.040** |
| FC type | 6 (3.4) | 5 (5.5) | 1 (1.1) | 0.211 |
| NC type | 5 (2.8) | 2 (2.2) | 3 (3.4) | 0.679 |
| Total chest CT score; median (IQR)[a] | 9 (7–13) | 10 (7–13) | 9 (6–12.2) | 0.127 |
| Cavitary lesion; n (%) | 52 (29.1) | 35 (38.5) | 17 (19.3) | **0.005** |
| Number of lobes with lesions; median (IQR)[a] | 4 (3–5) | 4 (3–5) | 4 (3–5) | 0.204 |
| Co-infection at baseline; n (%) | 42 (23.5) | 24 (26.4) | 18 (20.5) | 0.382 |

BMI, body mass index; MAC, *Mycobacterium avium* complex;

CAT, COPD Assessment Test; CT, computed tomography; IQR, interquartile range.

a, interquartile range; b,
CAT item score

Table 2. Baseline CAT score (CAT-Base) according to patient characteristics

| Characteristic | Level | n (%) | CAT-Base; median (IQR) | p value |
|---|---|---|---|---|
| Sex | Female | 161 (89.9) | 10.0 [5.0-18.0] | 0.952 |
| | Male | 18 (10.1) | 10.5 [6.0-14.5] | |
| Smoking | Never | 136 (76.0) | 10.0 [5.0-18.0] | 0.490 |
| | Ever | 43 (24.0) | 8.0 [5.5-16.5] | |
| Underlying pulmonary disease* | Absent | 157 (87.7) | 10.0 [5.0-17.0] | 0.204 |
| | Present | 22 (12.3) | 11.5 [8.0-20.5] | |
| Co-infection at baseline | Absent | 137 (76.5) | 10.0 [5.0-18.0] | 0.715 |
| | Present | 42 (23.5) | 9.0 [6.0-17.8] | |
| Cavitary lesion | Absent | 127 (70.9) | 10.0 [5.0-18.0] | 0.716 |
| | Present | 52 (29.1) | 9.5 [6.0-18.0] | |

Data are shown as median [(IQR) interquartile range] for CAT-Base and as number (%) for categorical variables.

*Underlying pulmonary disease includes idiopathic pulmonary fibrosis and/or COPD.

Ever smoking includes current and former smokers.

Table 3. Baseline CAT scores according to sputum culture status at 12 months after treatment initiation

| Characteristic | Sputum culture-negative treatment courses* (n = 151) | Sputum culture-positive treatment courses** (n = 28) | p value |
|---|---|---|---|
| Subjective symptoms (IQR)[a] | | | |
| CAT score | 9 (5–17.5) | 13 (8.5–20) | **0.03** |
| Cough[b] | 2 (1–3) | 3 (2–4) | **0.008** |
| Sputum[b] | 1 (0–3) | 3 (1–3) | **0.012** |
| Chest tightness[b] | 1 (0–2) | 1 (0–2) | 0.195 |
| Breathlessness[b] | 2 (0–3) | 3 (1–4) | **0.022** |
| Limited activities[b] | 0 (0–1) | 1 (0–1) | **0.049** |
| Confidence leaving home[b] | 0 (0–1) | 1 (0–3) | 0.225 |
| Sleeplessness[b] | 1 (0–3) | 1 (0–3) | 0.924 |
| Energy[b] | 1 (0–2) | 2 (1–3) | **0.037** |

*Sputum culture-negative treatment courses include those with sputum culture conversion or sustained culture negativity during the first 12 months of treatment.

**Sputum culture-positive treatment courses include those with persistent culture positivity or reversion to positivity during the first 12 months of treatment.

CAT, COPD assessment test; CT, Computed tomography

a, interquartile range; b, CAT item score

Table 4. Changes in CAT score from baseline to 6 and 12 months (Δ6, Δ12) according to sputum culture and treatment control status

| Comparison | Δ | Group 1; median (IQR) | Group 2; median (IQR) | p value |
|---|---|---|---|---|
| A. 12-month sputum culture status | | Culture-negative (n=151) | Culture-positive (n=28) | |
| | Δ6 | −2.0 [−5.0 to 1.0] | −1.0 [−5.0 to 1.3] | 0.54 |
| | Δ12 | −2.0 [−6.0 to 1.0] | −0.5 [−3.3 to 2.3] | 0.166 |
| | | | | |
| B. Treatment control status | | Well-controlled (n=123) | Poorly controlled (n=33) | |
| | Δ6 | −2.0 [−5.0 to 0.0] | −1.0 [−5.0 to 2.0] | 0.237 |
| | Δ12 | −2.0 [−6.0 to 0.0] | 0.0 [−3.0 to 3.0] | 0.01 |
| | | | | |
| C. Treatment control status (CAT-Base >2) | | Well-controlled (n= 102) | Poorly controlled (n=32) | |
| | Δ6 | −3.0 [−6.0 to 0.0] | −1.0 [−5.0 to 2.0] | 0.069 |
| | Δ12 | −3.0 [−7.0 to −1.0] | 0.0 [−3.3 to 3.5] | 0.002 |

**Definition of Δ**: Δ6 and Δ12 denote change in CAT score from baseline to 6 and 12 months, respectively.

Δ6 = CAT score at 6 months − Baseline CAT; Δ12 = CAT at 12 months − Baseline CAT.

CAT, COPD Assessment Test; IQR, interquartile range; Δ, change from baseline.

Table 5. Baseline CAT scores according to treatment control status at 12 months after treatment initiation

| Characteristic | Well-controlled treatment courses (n = 123) | Poorly-controlled treatment courses (n = 33) | p value |
|---|---|---|---|
| Subjective symptoms (IQR)[a] | | | |
| CAT score | 8 (4–16) | 13 (7–19) | **0.004** |
| Cough [b] | 2 (1–3) | 3 (1–3) | **0.003** |
| Sputum[b] | 1 (0–3) | 3 (1–3) | **0.001** |
| Chest tightness[b] | 1 (0–2) | 1 (0–2) | 0.140 |
| Breathlessness[b] | 1 (0–3) | 2 (1–3) | **0.045** |
| Limited activities[b] | 0 (0–1) | 1 (0–1) | **0.008** |
| Confidence leaving home[b] | 0 (0–1) | 1 (0–3) | **0.020** |
| Sleeplessness[b] | 1 (0–3) | 1 (0–3) | 0.663 |
| Energy[b] | 1 (0–2) | 2 (1–3) | **0.033** |

CAT, COPD assessment test.

a, interquartile range; b, CAT item score.

Table 6. Diagnostic performance of Δ12 for identifying well-controlled treatment courses (CAT-Base >2)

| Cut-off value (Δ12) | TP | FP | TN | FN | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|---|---|
| 0 | 82 | 18 | 14 | 20 | 0.804 | 0.438 | 0.82 | 0.412 |
| −1 | 77 | 15 | 17 | 25 | 0.755 | 0.531 | 0.837 | 0.405 |
| −2 | 66 | 12 | 20 | 36 | 0.647 | 0.625 | 0.846 | 0.357 |
| **−3** | **53** | **9** | **23** | **49** | **0.52** | **0.719** | **0.855** | **0.319** |
| −4 | 48 | 8 | 24 | 54 | 0.471 | 0.75 | 0.857 | 0.308 |
| −5 | 39 | 5 | 27 | 63 | 0.382 | 0.844 | 0.886 | 0.3 |
| −6 | 33 | 5 | 27 | 69 | 0.324 | 0.844 | 0.868 | 0.281 |
| −7 | 30 | 3 | 29 | 72 | 0.294 | 0.906 | 0.909 | 0.287 |

Only treatment courses with CAT-Base >2 were included; Δ12 ≤ cut-off was considered positive for predicting well-controlled treatment courses.

TP, true positive; FP, false positive; TN, true negative; FN, false negative; PPV, positive predictive value; NPV, negative predictive value.

# Discussion

In this study, CAT-Base was associated with disease severity in MAC-PD. CAT-Base showed a modest but significant correlation with baseline chest CT score and was consistently higher in treatment courses with baseline sputum culture positivity as well as in those that subsequently met the criteria for poor treatment control. These findings extend previous observations that symptom-based and HRQoL measures reflect physiological and prognostic disease severity in NTM-PD. Yagi et al. reported that six-minute walk distance, an objective marker of exercise capacity, correlated well with SGRQ scores in patients with MAC-PD,[17]. Other studies have demonstrated significantly worse SGRQ scores in MAC-PD than in age- and sex-matched general populations [18]. More recently, deterioration in QOL-B scores has been shown to parallel higher Body mass index, Age, Cavitary disease, Elevated erythrocyte sedimentation rate, Sex, (BACES) scores, indicating more advanced disease [9]. Consistent with these observations showing that HRQoL measures reflect disease severity, our findings suggest that CAT-Base may provide a simple symptom-based summary of overall disease burden in MAC-PD.

In our cohort, 84.4% of treatment courses achieved sputum culture negativity at 12 months (151/179), whereas only 68.7% (123/179) met the criteria for well-controlled disease based on the composite

outcome. When the analysis was restricted to treatment courses that were sputum culture-positive at baseline, the 12-month culture negativity rate was 72.5% (66/91), which is comparable to previously reported treatment success rates defined by sustained culture conversion under GBT (61.4%, 95% CI 49.7–72.5%) [19]. We also included baseline culture-negative treatment courses to reflect a real-world case mix; consequently, the overall 12-month culture negativity rate was 84.4%, similar to that reported by Saito et al. [20]. In their real-world cohort, 35 of 201 (17.4%) had refractory MAC-PD, whereas the remaining 82.6% achieved culture negativity after ≥ 6 months of GBT. Despite this rate of microbiological response, substantial heterogeneity in overall disease control was observed. Among the 151 treatment courses that achieved culture negativity at 12 months in our study, 19.9% (30/151) showed no radiological improvement at 12 months and 7.3% (11/151) had MAC re-detected from sputum or bronchoscopic specimens within the subsequent 12 months. Moreover, preventing progression of structural lung damage and avoiding long-term relapse are important therapeutic goals in MAC-PD. Even after culture conversion, some patients may show worsening radiological findings or symptoms, potentially due to replacement of MAC by other pathogenic organisms [21]. Accordingly, we defined treatment control using a composite outcome that incorporated sputum culture status, radiological change, and microbiological course up to 24 months.

A 3-point decrease in CAT score at 12 months (Δ12 = − 3) emerged as a candidate threshold for identifying well-controlled treatment courses with high specificity and PPV. Treatment courses with CAT-Base 0–2 were excluded from this analysis because the median Δ12 among well-controlled courses was − 2, making a larger numerical improvement unlikely in patients who were nearly asymptomatic at baseline. A 3-point change is consistent with findings in other chronic respiratory diseases, where an MCID of 3 points for CAT has been proposed in bronchiectasis [22] and an improvement MCID of approximately − 3 points has been reported in fibrotic interstitial lung diseases [23]. Prior NTM-PD studies using the SGRQ and QOL-B questionnaire have likewise demonstrated that symptom trajectories do not necessarily parallel microbiological outcomes. For example, culture conversion with amikacin liposome inhalation suspension (ALIS) in the CONVERT trial was not accompanied by improvement in SGRQ scores [4]. In the NTM-KOREA cohort, improvements in QOL-B scores and achievement of domain-specific MCIDs were limited and did not differ by culture conversion status [8]. Similarly, in a longitudinal MAC-PD cohort, QOL-B respiratory symptoms improved early, but only a subset of patients achieved a clinically meaningful (≥ 8-point) improvement [24]. Taken together, these findings indicate that symptomatic and HRQoL responses in MAC-PD do not necessarily mirror microbiological response, underscoring the value of a pragmatic symptom-based endpoint. Within this framework, a 3-point decrease in CAT score at 12 months may represent a reasonable candidate threshold for clinically meaningful symptomatic improvement, particularly in treatment courses with CAT-Base > 2 [3]. Notably, only 12.8% (23/179) of treatment courses in our cohort had CAT-Base 0–2, a lower proportion than the 41% of “asymptomatic” patients reported at diagnosis in a recent Japanese MAC-PD cohort [25]. This observation suggests that patients who self-identify as asymptomatic may nonetheless have measurable symptom burden when systematically assessed using the CAT, and that a 3-point decrease may represent a clinically relevant symptomatic target in MAC-PD with CAT-Base > 2.

This study has several limitations. First, it was a single-center retrospective study conducted in a relatively small cohort, which may limit the generalizability of the findings to broader clinical settings. Second, microbiological classification relied on routine clinical sputum sampling, and some patients were unable to expectorate. Consequently, assignment to sputum culture-negative or sputum culture-positive groups may have been influenced by specimen availability and sampling frequency rather than by true microbiological status. Third, we excluded treatment courses in which CAT could not be completed because of advanced age, visual impairment, or other difficulties, as well as treatment courses in which CAT assessments were inadvertently omitted by the investigators. Thus, treatment effects in frail older patients with poor performance status may not have been adequately captured in this cohort. Fourth, the composite definition of treatment control, combining radiological change at 12 months and microbiological findings up to 24 months, has not been externally validated thus its applicability beyond this cohort remains uncertain. Finally, the proposed Δ12 CAT cut-off of − 3 points demonstrated only modest discriminatory ability, was evaluated only in treatment courses with CAT-Base > 2 and should be regarded as exploratory pending confirmation in larger, prospective, multicenter studies.

## Conclusion

In this single-center MAC-PD cohort, higher baseline CAT scores were associated with greater radiological severity, poorer microbiological status, and inferior overall treatment control. Although 84.4% of treatment courses achieved sputum culture-negativity at 12 months, only 68.7% met the composite definition of well-controlled disease. Among treatment courses with CAT-Base > 2, a 3-point decrease in CAT score at 12 months (Δ12 = − 3) identified well-controlled disease with good specificity and high PPV. These findings suggest that CAT may complement microbiological and radiological endpoints as a simple patient-reported outcome measure, with Δ12 = − 3 representing a pragmatic candidate threshold for clinically meaningful symptomatic improvement in MAC-PD.

## Abbreviations

ALIS
amikacin liposome inhalation suspension
ATS
American Thoracic Society, AUC:area under the curve
BACES
Body mass index, Age, Cavitary disease, Elevated erythrocyte sedimentation rate, Sex
BMI
body mass index
CAT
COPD Assessment Test
CAT-Base
baseline CAT score

CI
confidence interval
COPD
chronic obstructive pulmonary disease
CT
computed tomography
Δ6
change in CAT score from baseline to 6 months
Δ12
change in CAT score from baseline to 12 months
ΔCAT
change in CAT score
ERS
European Respiratory Society
ESCMID
European Society of Clinical Microbiology and Infectious Diseases
GBT
guideline-based therapy
HRCT
high-resolution computed tomography
HRQoL
health-related quality of life
IDSA
Infectious Diseases Society of America
MAC
Mycobacterium avium complex
MAC-PD
*Mycobacterium avium* complex pulmonary disease
MCID
minimal clinically important difference
NTM
nontuberculous mycobacteria
NTM-PD
nontuberculous mycobacterial pulmonary disease
NPV
negative predictive value, PPV:positive predictive value
QOL-B
Quality of Life Questionnaire-Bronchiectasis
ROC
receiver operating characteristic

SF-36
36-Item Short Form Health Survey
SGRQ
St George’s Respiratory Questionnaire.

## Declarations

# Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Toho University Omori Medical Center (Approval No. T2025-036). The requirement for informed consent was waived because of the retrospective design and the use of anonymized clinical data. The study was conducted in accordance with the Declaration of Helsinki.

**Consent for publication**

Not applicable

# Competing interests

The authors declare that they have no competing interests.

# Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

# Author Contribution

Conceptualization: NU.Methodology: NU, SS, NT.Formal analysis: NU.Investigation: NU, SS, NT, TK, HS, SM.Data curation: NU, NT, TK, HS.Writing – original draft: NU.Writing – review and editing: SS, NT, TK, HS, SM, TI.Supervision: KK.All authors read and approved the final version of the manuscript.

# Acknowledgement

The authors acknowledge Dr. Florence Ene, MBBS, Ph.D., Platinum Medical Consulting Japan for professional medical English editing.

# Data Availability

All data generated or analyzed during this study are included in this article. For further inquiries, please contact the corresponding author.

# References


1. Harada K, Vu QT, Nishimura Y, Takeda T, Hamano H, Minato Y, et al. Trends in nontuberculous mycobacterial disease mortality based on 2000–2022 data from 83 countries. Int J Infect Dis. 2025;158:107932. https://doi.org/10.1016/j.ijid.2025.107932.
2. 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. https://doi.org/10.3201/eid2206.151086.
3. van Ingen J, Aksamit T, Andrejak C, Böttger EC, Cambau E, Daley CL, et al. Treatment outcome definitions in nontuberculous mycobacterial pulmonary disease: an NTM-NET consensus statement. Eur Respir J. 2018;51(3):1800170. https://doi.org/10.1183/13993003.00170-2018.
4. Griffith DE, Eagle G, Thomson R, Aksamit TR, Hasegawa N, Morimoto K, et al. Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by *Mycobacterium avium* complex (CONVERT): a prospective, open-label, randomized study. Am J Respir Crit Care Med. 2018;198(12):1559–69. https://doi.org/10.1164/rccm.201710-2028OC.
5. Mehta M, Marras TK. Impaired health-related quality of life in pulmonary nontuberculous mycobacterial disease. Respir Med. 2011;105(11):1718–25. https://doi.org/10.1016/j.rmed.2011.08.004.
6. 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. https://doi.org/10.1186/s12931-015-0304-5.
7. Quittner AL, Marciel KK, Salathe MA, O'Donnell AE, Gotfried MH, Ilowite JS, et al. A preliminary Quality of Life Questionnaire–Bronchiectasis: a patient-reported outcome measure for bronchiectasis. Chest. 2014;146(2):437–48. https://doi.org/10.1378/chest.13-1891.
8. Kwak N, Henkle E, Hwang H, Jeon D, Jhun BW, Jo KW, et al. Improvement in health-related quality of life following antibiotic treatment in nontuberculous mycobacterial pulmonary disease: initial analysis of the NTM-KOREA cohort, Clin. Infect Dis. 2024;78(6):1690–7. https://doi.org/10.1093/cid/ciae131.
9. Choi H, Kwak N, Jeon D, Jhun BW, Jo KW, Koh WJ, et al. BACES score as a predictor of health-related quality of life and associated factors in patients with nontuberculous mycobacterial pulmonary disease. Sci Rep. 2025;15:26257.
10. Jones PW, Tabberer M, Chen WH. Creating scenarios of the impact of COPD and their relationship to COPD Assessment Test (CAT) scores, BMC Pulm. Med. 2011;11:42. https://doi.org/10.1186/1471-

2466-11-42.

11. Hama M, Ushiki A, Kosaka M, Yamazaki Y, Yasuo M, Yamamoto H, et al. Health-related quality of life in patients with pulmonary nontuberculous mycobacterial infection. Int J Tuberc Lung Dis. 2016;20(6):747–52. https://doi.org/10.5588/ijtld.15.0820.
12. Daley CL, Iaccarino JM, Lange C, Cambau E, Wallace RJ Jr., Andrejak C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Eur Respir J. 2020;56(1):2000535. https://doi.org/10.1183/13993003.00535-2020.
13. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Leidy NK. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648–54. https://doi.org/10.1183/09031936.00102509.
14. Tsuda T, Suematsu R, Kamohara K, Kurose M, Arakawa I, Tomioka R, et al. Development of the Japanese version of the COPD Assessment Test. Respir Investig. 2012;50(2):34–9. https://doi.org/10.1016/j.resinv.2012.01.002.
15. Morimoto K, Yoshiyama T, Kurashima A, Sasaki Y, Hoshino Y, Yoshimori K, et al. Clinical features of pulmonary disease caused by *Mycobacterium avium* complex: proposal of criteria for radiological classification and its validation. Intern Med. 2014;53(5):397–401. https://doi.org/10.2169/internalmedicine.53.1668.
16. Urabe N, Sakamoto S, Tokita N, Yoshida H, Usui Y, Shimizu H, et al. Effectiveness of amikacin liposome inhalation suspension for refractory *Mycobacterium avium* complex pulmonary disease at 6 months post initiation. BMC Pulm Med. 2024;24:442. https://doi.org/10.1186/s12890-024-03261-w.
17. Yagi K, Asakura T, Namkoong H, Suzuki S, Asami T, Okamori S, et al. Association between six-minute walk test parameters and the health-related quality of life in patients with pulmonary *Mycobacterium avium* complex disease. BMC Pulm Med. 2018;18:114.
18. Ogawa T, Asakura T, Suzuki S, Okamori S, Kusumoto T, Sato Y, et al. Longitudinal validity and prognostic significance of the St George's Respiratory Questionnaire in *Mycobacterium avium* complex pulmonary disease. Respir Med. 2021;185:106515. https://doi.org/10.1016/j.rmed.2021.106515.
19. Diel R, Nienhaus A, Ringshausen FC, Richter E, Welte T, Rabe KF, et al. Microbiologic outcome of interventions against Mycobacterium avium complex pulmonary disease: a systematic review. Chest. 2018;153(4):888–921. https://doi.org/10.1016/j.chest.2017.12.026.
20. Saito T, Aono Y, Kono M, Ishige M, Sugiura T, Higasa M, et al. Predictive risk factors of treatment-refractory Mycobacterium avium complex lung disease: a single-center retrospective cohort study, Ther. Adv Infect Dis. 2025;12:1–10.
21. Urabe N, Sakamoto S, Shimanuki Y, Kanokogi T, Motohashi T, Anzai N, et al. Impact of chronic co-infection in pulmonary Mycobacterium avium complex disease after treatment initiation. BMC Pulm Med. 2022;22:157.

22. De la Carrillo D, Olveira C, García-Clemente M, Girón-Moreno RM, Nieto-Royo R, Navarro-Rolon A, et al. COPD Assessment Test in bronchiectasis: minimum clinically important difference and psychometric validation. A prospective study. Chest. 2020;157(4):824–33. https://doi.org/10.1016/j.chest.2019.12.030.
23. Matsuda T, Kondoh Y, Takei R, Sasano H, Fukihara J, Yamano Y, et al. Responsiveness and minimal clinically important difference of the COPD Assessment Test in fibrotic interstitial lung disease. Respir Investig. 2024;62(6):1088–93. https://doi.org/10.1016/j.resinv.2024.05.013.
24. Henkle E, Quittner AL, Dieckmann NF, Franklin H, Brunton AE, Daley CL, et al. Patient-reported symptom and health-related quality-of-life validation and responsiveness during the first 6 months of treatment for *Mycobacterium avium* complex pulmonary disease. Chest. 2023;164(1):53–64. https://doi.org/10.1016/j.chest.2023.02.028.
25. Fujiwara K, Watanabe F, Uesugi F, Furuuchi K, Ito M, Kodama T, et al. Beyond symptoms: radiologic identification of asymptomatic Mycobacterium avium complex pulmonary infections. Respir Med. 2024;226:107627. https://doi.org/10.1016/j.rmed.2024.107627.

# Figures

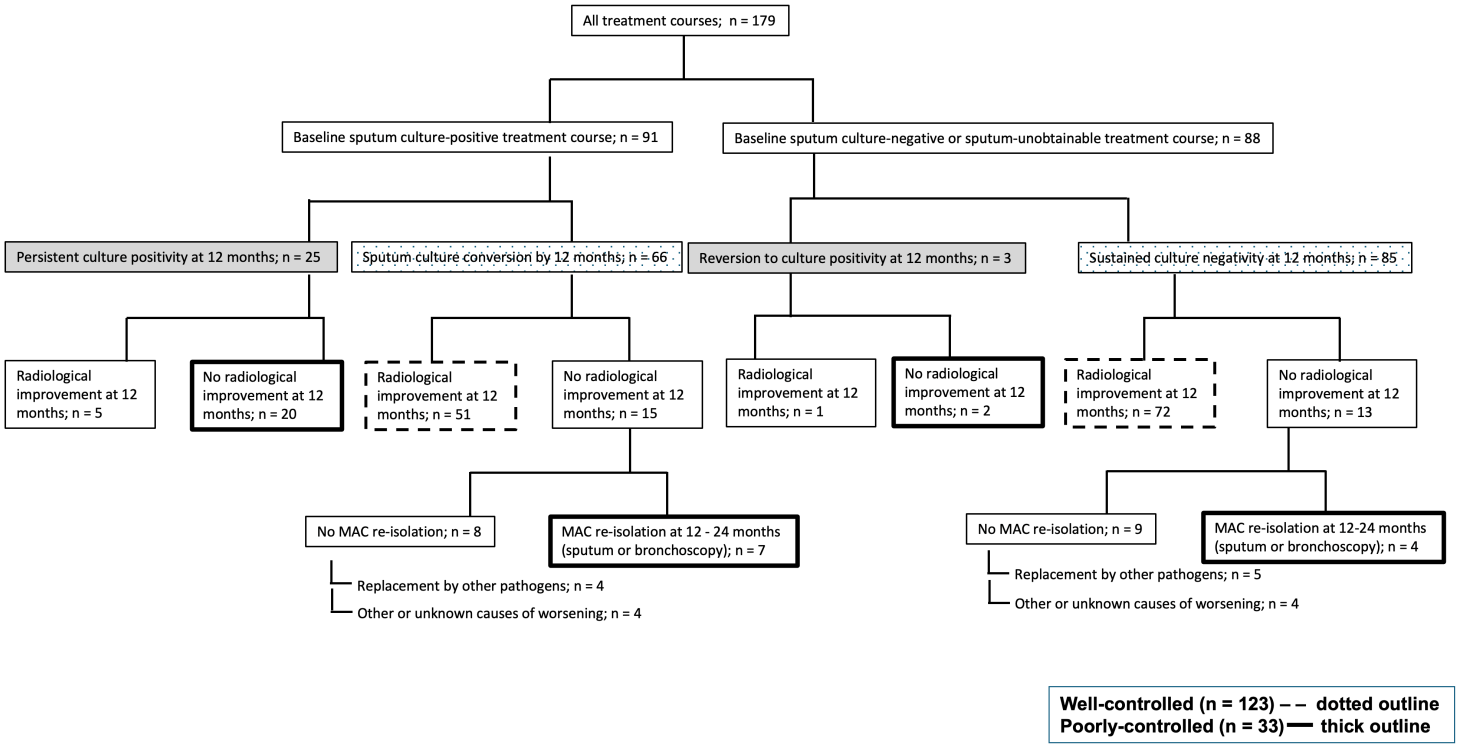



**Figure 1**

**Study flow and classification of treatment courses.**

Flow diagram showing the classification of 179 treatment courses in 174 patients with MAC-PD. At baseline, treatment courses were categorized as sputum culture-positive (n = 91) and sputum culture-negative or sputum-unobtainable (n = 88); and were subsequently classified according to sputum culture status during the first 12 months and microbiological course up to 24 months. Gray fill indicates sputum culture-positive treatment courses at 12 months. Dotted fill indicates sputum culture-negative treatment courses. Radiological improvement was assessed by changes in chest CT findings between baseline and 12 months. Boxes with dotted outlines indicate well-controlled treatment courses, thick solid outlines indicate poorly-controlled treatment courses, and remaining courses were classified as indeterminate.

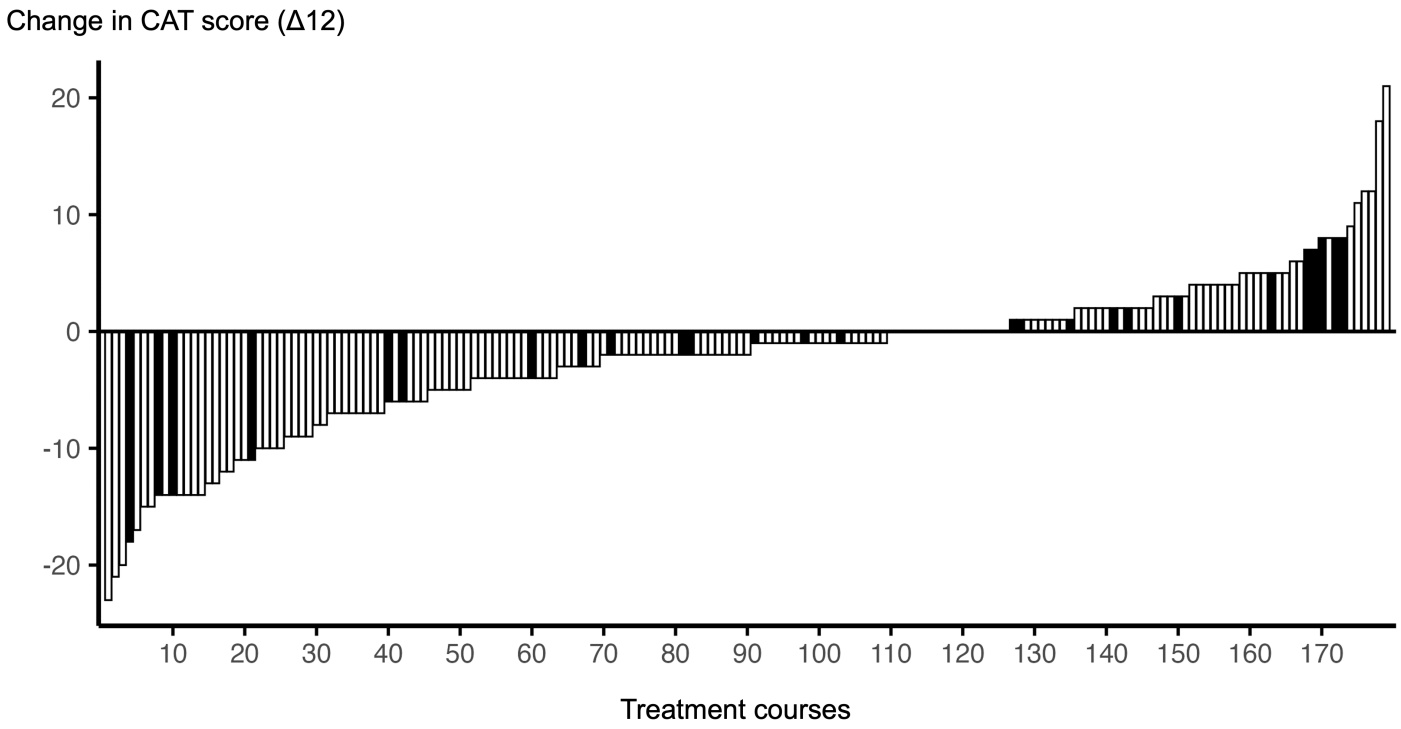



**Figure 2**

**Changes in CAT score at 12 months according to sputum culture response.**

Waterfall plot showing changes in CAT score from baseline to 12 months (Δ12), stratified by sputum culture status at 12 months: culture-negative treatment courses (open bars; n = 151) and culture-positive treatment courses (solid black bars; n = 28). Each bar represents one treatment course; negative values indicate improvement in CAT score.

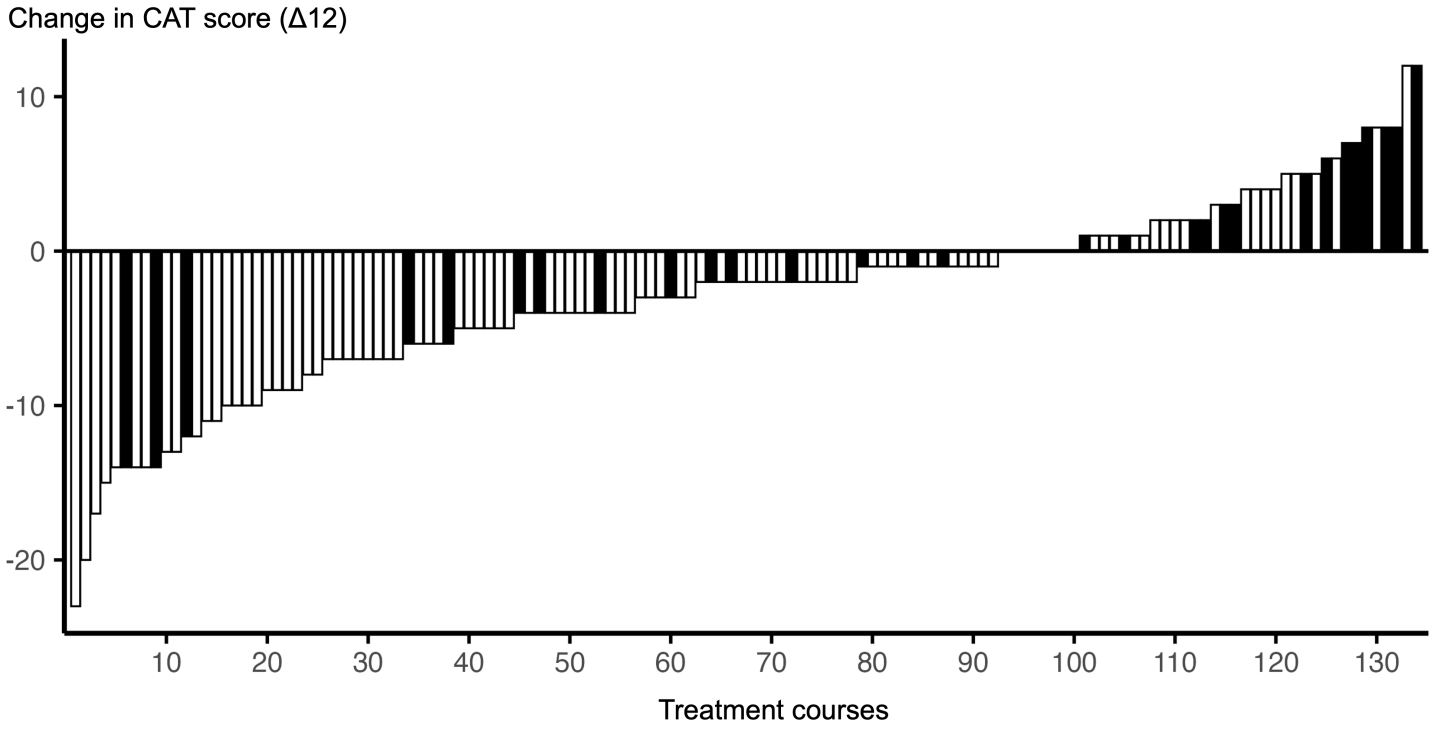



**Figure 3**

**Changes in CAT score at 12 months in treatment courses with CAT-Base >2.**

Waterfall plot showing changes in CAT score from baseline to 12 months (Δ12) in treatment courses with CAT-base >2, stratified by treatment control status: well-controlled treatment courses (open bars; n = 102) and poorly-controlled treatment courses (solid black bars; n = 32). Treatment courses with CAT-Base 0–2 were excluded. Each bar represents one treatment course; negative values indicate improvement in CAT score.

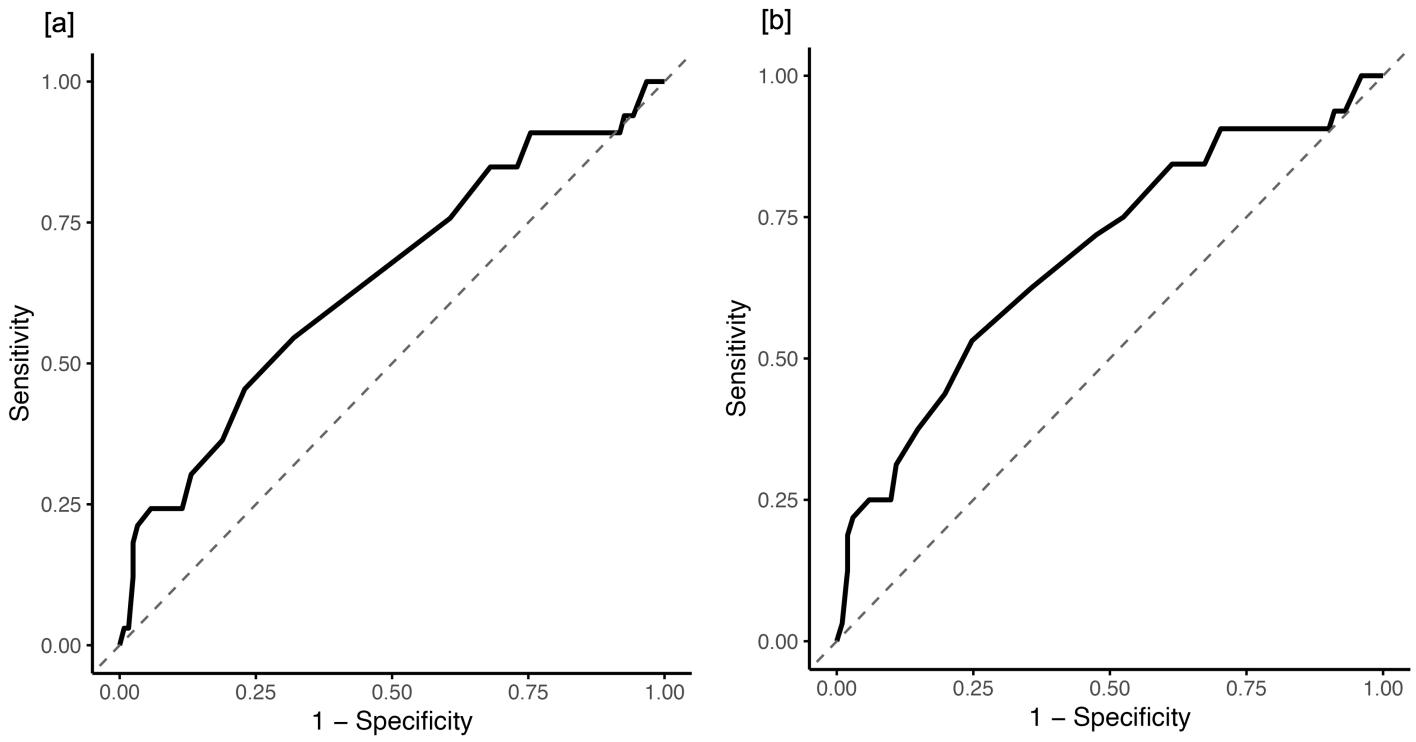



**Figure 4**

**ROC curves of changes in CAT score for discriminating treatment control status.**

Receiver operating characteristic (ROC) curves of changes in CAT score from baseline to 12 months (Δ12). (a) Discrimination between well-controlled (n = 123) and poorly-controlled treatment courses (n = 33), according to the composite definition based on radiological improvement at 12 months and microbiological course up to 24 months. The area under the ROC curve (AUC) was 0.646 (95% CI, 0.533–0.750). (b) Discrimination between well-controlled (n = 102) and poorly-controlled treatment courses (n = 32) in the subgroup with CAT-Base >2. The AUC was 0.682 (95% CI, 0.565–0.787).

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Figuresupplement1.tiff
- Figuresupplement2.tiff
- Figuresupplement3.tiff
- Tablesupplement1.xlsx