

CLINICAL SCIENCE

Trends and predictors of changes in pulmonary function after treatment for pulmonary tuberculosis

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OBJECTIVES: The present study aimed to investigate the trends in changes in pulmonary function and the risk factors for pulmonary function deterioration in patients with pulmonary tuberculosis after completing treatment.

INTRODUCTION: Patients usually have pulmonary function abnormalities after completing treatment for pulmonary tuberculosis. The time course for changes in pulmonary function and the risk factors for deterioration have not been well studied.

METHODS: A total of 115 patients with 162 pulmonary function results were analyzed. We retrieved demographic and clinical data, radiographic scores, bacteriological data, and pulmonary function data. A generalized additive model with a locally weighted scatterplot smoothing technique was used to evaluate the trends in changes in pulmonary function. A generalized estimating equation model was used to determine the risk factors associated with deterioration of pulmonary function.

RESULTS: The median interval between the end of anti-tuberculosis treatment and the pulmonary function test was 16 months (range: 0 to 112 months). The nadir of pulmonary function occurred approximately 18 months after the completion of the treatment. The risk factors associated with pulmonary function deterioration included smear-positive disease, extensive pulmonary involvement prior to anti-tuberculosis treatment, prolonged anti-tuberculosis treatment, and reduced radiographic improvement after treatment.

CONCLUSIONS: After the completion of anti-tuberculosis TB treatment, several risk factors predicted pulmonary function deterioration. For patients with significant respiratory symptoms and multiple risk factors, the pulmonary function test should be followed up to monitor the progression of functional impairment, especially within the first 18 months after the completion of anti-tuberculosis treatment.

KEYWORDS: completion of treatment; disease extent; pulmonary function; pulmonary tuberculosis.

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INTRODUCTION

Pulmonary tuberculosis (TB) can cause parenchymal destruction by up-regulation of several proteases and dysregulation of protease control.¹ The histopathological abnormalities after treatment for pulmonary TB include fibrosis, bronchiectasis, and bronchial stenosis, all of which can cause pulmonary function abnormalities.²⁻³ Previous studies have evaluated the changes in pulmonary function before, during and after

pulmonary TB treatment.⁴⁻¹⁷ Between 48.7% and 76% of patients had pulmonary function abnormalities after completing pulmonary TB treatment.^{9-10,13-15,17} Although some studies have shown obstructive defects as the main abnormality, recent studies have shown that abnormalities could be obstructive, restrictive, or mixed defects.^{14-15,17} In a study performed on gold miners in South Africa, forced expiratory volume in the first second (FEV₁) and forced vital capacity (FVC) were found to be worse six months after tuberculosis treatment and were stabilized 13 to 18 months after treatment.¹⁶ The impairment in pulmonary function after completing pulmonary TB treatment is related to long-term respiratory symptoms, which affect quality of life.^{11-12,18}

It is important to identify patients with risk factors for pulmonary function deterioration after the completion of

pulmonary TB treatment. However, little is known about the trends in the changes in pulmonary function and the risk factors associated with pulmonary function deterioration. Therefore, we conducted a study to investigate the trends and predictors of the changes in pulmonary function in patients with pulmonary tuberculosis after the completion of treatment.

METHODS AND MATERIALS

Subjects

From January 2000 to December 2008, 2,789 patients with culture-confirmed pulmonary TB were identified at the National Taiwan University Hospital, a tertiary care referral center with 2,000 beds in northern Taiwan. Among these patients, 213 (7.6%) underwent pulmonary function tests after completing pulmonary TB treatment. Ninety-eight patients were excluded from further analysis due to the presence of the following conditions before the diagnosis of pulmonary TB: (1) pulmonary co-morbidities, including asthma, chronic obstructive airway disease (COPD) confirmed by spirometry, pneumoconiosis, interstitial lung disease, history of respiratory failure requiring mechanical ventilation, lung cancer, and lung resection; (2) congestive heart failure (New York Heart Association functional class >2); (3) autoimmune disease; and (4)

human immunodeficiency virus infection.¹⁹ The remaining 115 patients with 162 pulmonary function test results were analyzed. Tests performed within five years after the end of anti-tuberculosis treatment were selected to investigate the predictors of pulmonary function. This study was approved by the International Review Board of the National Taiwan University Hospital.

Mycobacteriological studies

Mycobacteriological studies were performed using standard procedures.²⁰⁻²² Briefly, sputum specimens were decontaminated with NaOH-citrate-N-acetyl-L-cysteine and then neutralized and centrifuged. The specimen sediments were inoculated onto Löwenstein-Jensen (LJ) slants and into Mycobacterium growth indicator tubes (MGIT) using a fluorometric BACTEC technique (BACTEC MGIT 960 system; Becton-Dickinson Diagnostic Instrument Systems; Sparks, MD). The LJ slants were incubated in a CO₂ incubator for an initial week and in ambient air for another seven weeks at 35°C. Growth in MGIT was observed for at least 42 days. *M. tuberculosis* was routinely identified using conventional biochemical methods.

Pulmonary function testing

The pulmonary function tests were performed using MasterScreen, (Jaeger, Germany) or Vmax 6200 (Sensormedics

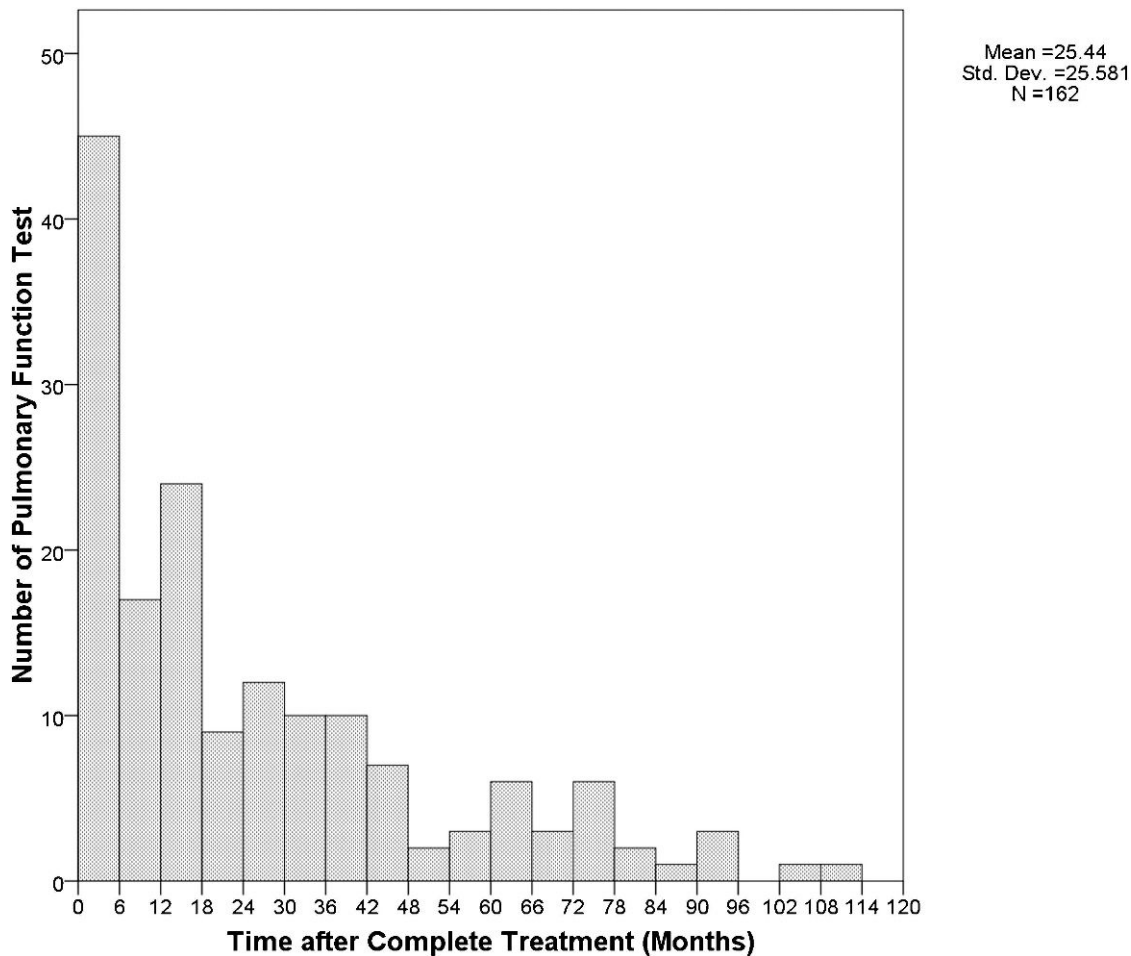


Figure 1 - Shows a histogram that describes the frequency of pulmonary function tests at each time interval after completion of anti-tuberculosis treatment.

Table 1 - Clinical data and pulmonary function results.

| Characteristic | Entire group (N = 106) | Patients with NTM isolates (N = 28) |
|---|------------------------|-------------------------------------|
| Clinical data | | |
| Age (years) | 59.3 [21.2] | 71.1 [14.8] |
| Male | 80 (75.5%) | 23 (82.1%) |
| History of smoking | 51 (48.1%) | 15 (53.6%) |
| Co-morbidity | | |
| Malignancy* | 11 (10.4%) | 3 (10.7%) |
| Diabetes mellitus | 10 (9.4%) | 5 (17.9%) |
| Smear-positive | 43 (40.6%) | 12 (42.9%) |
| Modification of anti-tuberculosis regimen | 20 (18.9%) | 5 (17.9%) |
| Treatment duration (months) | 9.2 [4.3] | 8.4 [2.9] |
| Radiographic score before treatment | 6.5 [4.6] | 7.0 [3.9] |
| Radiographic score after treatment | 3.4 [3.3] | 4.2 [3.9] |
| Non-tuberculosis mycobacterium isolate [†] | | |
| 0 | 78 (73.6%) | |
| 1 | 16 (15.1%) | |
| ≥ 2 | 12 (11.3%) | |
| Pulmonary function results[‡] | | |
| FEV ₁ (L) | 1.90 [0.79] | 1.77 [0.78] |
| FEV ₁ /predicted FEV ₁ (%) | 77.25 [26.44] | 86.37 [31.88] |
| FVC (L) | 2.71 [0.89] | 2.41 [0.97] |
| FVC/predicted FVC (%) | 87.94 [20.75] | 88.08 [26.92] |
| FEV ₁ /FVC (%) | 70.35 [15.40] | 74.67 [14.77] |
| Interpretation | | |
| Normal | 46 (32.9%) | 13 (33.3%) |
| Obstructive | 68 (48.6%) | 16 (41.0%) |
| Restrictive | 13 (9.3%) | 4 (10.3%) |
| Mixed | 13 (9.3%) | 6 (15.4%) |

The data are presented as number (percentage) or mean [standard deviation].

*The malignancies were head and neck cancer in 3, gastrointestinal cancer in 3, breast cancer in 2, and 1 each for hepatocellular carcinoma, prostate cancer and bladder cancer. All of these patients had no clinical evidence of pulmonary metastases before the pulmonary function test.

[†]Including 8 *Mycobacterium avium* complex, 17 rapidly growing mycobacteria, 2 *Mycobacterium gordonae*, and 1 *Mycobacterium scrofulaceum*.

[‡]For the entire group, 140 pulmonary function tests were recorded within 5 years after the end of anti-tuberculosis treatment, whereas 39 pulmonary function tests were recorded for patients with NTM isolates.

Corp., USA) spirometers in our pulmonary function laboratory, according to the recommendation by the American Thoracic Society.^{7,23-24} Daily calibration was performed for each machine before measuring pulmonary function. Patient data, including age, sex, weight, height, medication history, and smoking status, were collected via standard questionnaires prior to pulmonary function testing. Pulmonary function tests were performed by trained technicians with the patients in sitting postures. Each patient performed at least three acceptable forced expiratory maneuvers, which fulfilled the criteria of repeatability.²⁴ The reference equations for FEV₁, FVC, and FEV₁/FVC were obtained from a previous study of 354 non-smoking healthy Chinese patients (online supplement 1) and were used to calculate the predicted values of corresponding pulmonary function parameters.²⁵ Normal pulmonary function should have FEV₁ ≥80%, FVC ≥80%, and FEV₁/FVC ≥70% of predicted values. For abnormal pulmonary function, an obstructive defect was defined as FEV₁/FVC <70%, a restrictive defect as an FEV₁/FVC ratio ≥70% and FVC <80%, and a mixed defect as FEV₁/FVC <70% and FVC <80% of predicted values.

Data collection

From patients' medical records, we retrieved demographic data, smoking history, underlying co-morbidities, radiographic findings, laboratory results, pulmonary TB treatment courses, and results of pulmonary function tests. The standard anti-tuberculosis regimen consisted of oral isoniazid, rifampicin, and ethambutol, plus pyrazinamide

daily during the first two months and isoniazid plus rifampicin daily during the following four months.

According to previous studies, non-tuberculosis mycobacteria (NTM) are present in the respiratory tracts of 7.1% to 7.3% of patients with pulmonary tuberculosis.²⁶⁻²⁷ It was unknown whether these NTM isolates would cause pulmonary function deterioration. Therefore, we recorded the frequency of NTM isolates (0, 1 or ≥2) from sputum samples collected after beginning anti-tuberculosis treatment and before pulmonary function testing.

Chest radiographs that were obtained before and after anti-tuberculosis treatment were reviewed. Radiographic scores (RS) of chest radiographs⁹ that were taken before and after anti-tuberculosis treatment were recorded (in accordance with a previous study) to define the extent of the disease. Briefly, each lung was divided into three areas, and each area was rated on a four-point scale (0 to 3) for the extent of infiltration. The sum of the points from all six areas constituted the RS. A greater extent of infiltration resulted in a larger RS.

Statistical analysis

Continuous variables were reported as means (standard deviation) and categorical variables as numbers (percentage). Changes in pulmonary function over time after the completion of anti-tuberculosis treatment have been shown to be biphasic (non-linear).¹⁶ Therefore, we first established three generalized additive models for FEV₁, FVC, and FEV₁/FVC, with the Gaussian distribution selected.⁷ In

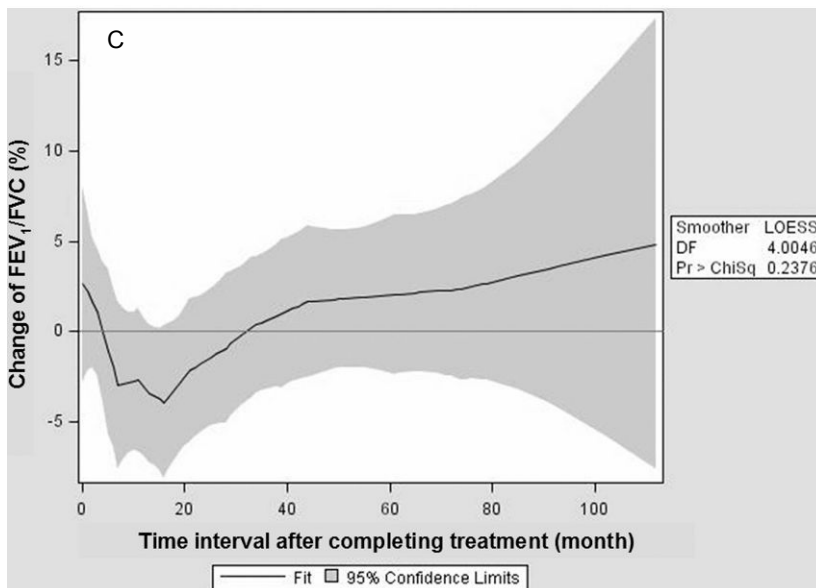
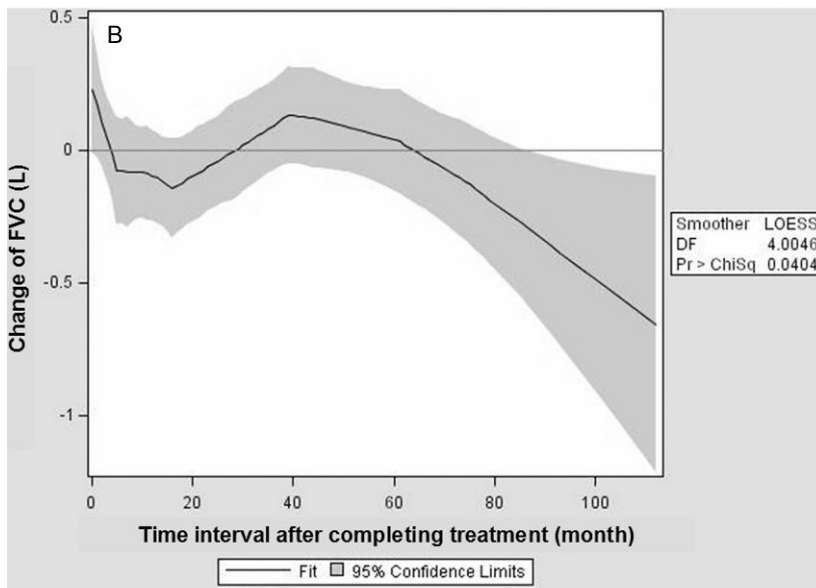
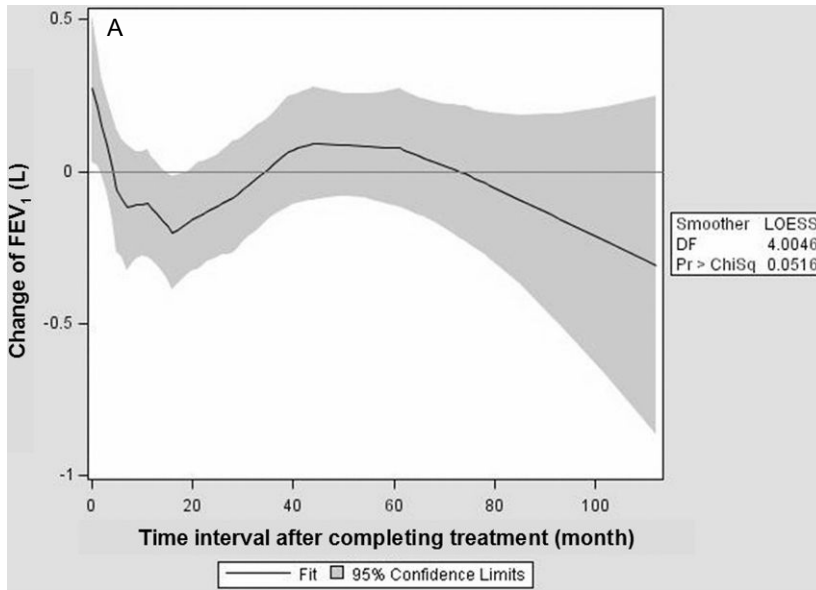


Figure 2 - Shows partial prediction curves that describe how the time after completing anti-tuberculosis treatment affected changes in pulmonary function, including FEV₁ (2A), FVC (2B), and FEV₁/FVC (2C). The y axis refers to the changes in FEV₁ (L) (2A), FVC (L) (2B), and FEV₁/FVC (%) (2C) at different time points after completing anti-tuberculosis treatment (time 0: end of anti-tuberculosis treatment). The shaded areas denote 95% confidence intervals. The maximal reduction in pulmonary function occurred approximately 18 months after completion of anti-tuberculosis treatment.

In addition to time after the completion of pulmonary TB treatment, we included 3 other covariates into these models: age, body weight, and height. Locally weighted scatterplot smoothing (LOESS) was selected as the smoothing technique for the smooth functions of the four covariates. From the partial prediction curves of the smooth functions of time after the completion of pulmonary TB treatment, we determined the time point at which the worst pulmonary function occurred.

Some subjects who were enrolled in this study performed repeated pulmonary function tests over time. The pulmonary function test results were not independent of each other, and a generalized linear model could not be applied for analysis. Therefore, we performed statistical analyses using generalized estimating equation (GEE) models with a stepwise variable selection procedure to identify the predictors of pulmonary function (FEV₁ and FVC) and the predictors of obstructive defect development within 5 years after completion of pulmonary TB treatment. The time interval (ΔT) between the date of each pulmonary function test and the timing of the worst pulmonary function (obtained by LOESS smoothing models) was included in the analysis. Other parameters with the potential to influence pulmonary function after completion of pulmonary TB treatment were also included in the analysis; these parameters were demographic data, smoking history, underlying co-morbidities, radiographic findings, laboratory results, and pulmonary tuberculosis treatment courses. A two-sided p value <0.05 was considered to be significant. All analyses were performed using SAS software (version 9.1.3, SAS Institute Inc., Cary, NC, U.S.A.).

RESULTS

Patients and pulmonary function

A total of 115 patients underwent 162 pulmonary function tests after they completed pulmonary TB treatment within the study period. Twenty-eight patients had more than one pulmonary function test result, and the time between repeated pulmonary function tests was at least six months (Figure 1). The median interval between the completion of pulmonary tuberculosis treatment and a pulmonary function test was 16 months (range: 0 to 112 months). Among these 115 patients, 106 (92.2%) underwent 140 (86% of all pulmonary function tests) pulmonary function tests within 5 years. Table 1 summarizes the baseline clinical characteristics of these 106 patients and the results of the 140 pulmonary function tests. The mean age at the first pulmonary function test was 59.3 years (range: 19 to 90). Ninety-four (67.1%) pulmonary function tests were abnormal, with obstructive defects being the most common problem (68 tests, 48.6%). Twenty-eight patients (26.4%) had at least one concurrent NTM isolate; these patients contributed 39 pulmonary function test results (Table 1). The mean age at which the patients underwent their first pulmonary function test was older in those patients with NTM isolates ($p < 0.001$ by Student's t -test, compared to those without NTM isolates). Otherwise, they had no

significantly different characteristics compared to those patients without NTM isolates.

From partial prediction curves, we observed trends of biphasic changes in FEV₁, FVC, and the FEV₁/FVC ratio with time after completion of pulmonary tuberculosis treatment (Figure 2A–C). Deterioration of pulmonary function occurred initially. The nadirs of the three smoothing curves occurred at 18 months.

Predictors of pulmonary function after completion of anti-tuberculosis treatment

The predictors of FEV₁ within 60 months after completion of anti-tuberculosis treatment are shown in Table 2 (for statistical details, please refer to online supplement 2). The time variable (ΔT), defined as the absolute time interval between the date of the pulmonary function test and the timing of worst FEV₁ (*i.e.*, 18 months), was significantly correlated with FEV₁. Patients who had smear-positive disease, longer treatment duration, higher RS before treatment, or less RS improvement after treatment had worse FEV₁ after completion of anti-tuberculosis treatment. From the end of the anti-tuberculosis treatment to the nadir of FEV₁, the estimated monthly reduction in FEV₁ was 18.83 mL (0.017 L/month * 1 month + 0.022 L/year * 1 month/12 = 0.01883 L) after adjusting for the other parameters.

The predictors of FVC within 60 months after completion of anti-tuberculosis treatment are listed in Table 3. Patients had worse FVC after completion of anti-tuberculosis treatment if they had longer treatment duration, a change in regimen during treatment, higher RS before treatment, or less RS improvement after treatment.

We also investigated the risk factors of obstructive defects (FEV₁/FVC ratio <70) after completion of treatment for pulmonary TB (Table 4). Patients with smear-positive disease had a higher risk of obstructive defects after completing anti-tuberculosis treatment (odds ratio 2.546, $p = 0.045$).

DISCUSSION

Our results showed that after completing pulmonary TB treatment, patients experienced gradual declines in pulmonary function until approximately 18 months. The risk factors for pulmonary function deterioration in association with TB included smear-positive disease, extensive pulmonary involvement with poor radiographic improvement after treatment, prolonged duration of treatment, and change in regimen.

Several co-morbidities could affect pulmonary function test results, including chronic lung diseases, severe congestive heart failure, autoimmune diseases, and HIV infection. Autoimmune diseases could have pulmonary involvement, possibly leading to significant changes in pulmonary function.²⁸ In addition, patients with HIV infection have a high risk of contracting respiratory diseases such as *Pneumocystis jirovecii* infection and recurrent bacterial pneumonia.²⁹ Therefore, in our study, we excluded

Table 2 - Predictors of FEV₁ within 60 months after completion of treatment for pulmonary tuberculosis.

| Parameter | Estimate (β _i) | Standard error | 95% confidence interval | p value |
|------------------------------|----------------------------|----------------|-------------------------|---------|
| Male | 0.607 | 0.212 | 0.192–1.024 | 0.004 |
| Height (cm) | 0.019 | 0.009 | 0.001–0.036 | 0.036 |
| Age (years) | -0.022 | 0.004 | -0.030– -0.013 | <0.001 |
| Smear-positive disease | -0.334 | 0.110 | -0.549– -0.120 | 0.002 |
| Treatment duration (months) | -0.023 | 0.010 | -0.043– -0.003 | 0.023 |
| RS before treatment | -0.074 | 0.019 | -0.112– -0.037 | <0.001 |
| ΔRS after treatment* | -0.055 | 0.025 | -0.104– -0.006 | 0.027 |
| ΔT (months) | 0.017 | 0.006 | 0.006–0.028 | 0.003 |
| One NTM isolate [†] | 0.361 | 0.148 | 0.071–0.651 | 0.015 |

Definitions of abbreviations: RS: radiographic score; ΔT: the absolute of the time interval between the date of the pulmonary function test to the time of the pulmonary function nadir (i.e., 18 months); NTM: non-tuberculosis mycobacterium.

*ΔRS = (RS after treatment) – (RS before treatment). Patients with more radiographic improvement had more negative ΔRS values.

[†]Only one NTM isolate was obtained from sputum samples during the time between the diagnosis of pulmonary tuberculosis and the pulmonary function test.

patients with these co-morbidities to give a more accurate description of the changes in pulmonary function and trends after completion of pulmonary TB treatment.

The time course for changes in pulmonary function after completing anti-tuberculosis treatment has never been well-studied. One previous study showed that the annual decrease in FEV₁ was 35.3 mL in patients with obstructive defects within 15 years after the end of anti-tuberculosis treatment.³⁰ However, the anti-tuberculosis treatment in this study was less effective than the modern four-drug combination regimen, and exposure to other noxious environmental factors may have contributed to changes in pulmonary function during long follow-up time periods. In a study performed in Cape Town, South Africa by Hnizdo et al., the pulmonary function of coal miners with pulmonary TB reached a nadir at approximately 6 months after completing anti-tuberculosis treatment (with a monthly FEV₁ reduction of 56.8 mL) and stabilized approximately 7 to 12 months later.¹⁶ Our results confirmed the biphasic change in pulmonary function over time after the end of anti-tuberculosis treatment, with a monthly FEV₁ reduction of 18.83 mL within the first 18 months. The greater declines in pulmonary function that were noted in the coal miners with TB were probably due to the concomitant presence of pneumoconiosis. In addition, without adjusting for smoking history or disease extent in the analysis, it is difficult to determine the contribution of each factor to the abnormalities in pulmonary function.

Smear-positive disease, which suggests either a high mycobacterial load or endobronchial involvement, has been shown to be an important predictor of pulmonary function

deterioration and obstructive defects after the completion of pulmonary TB treatment.³¹ In accordance with previous studies, we found that disease extent was a predictor of pulmonary function deterioration after the completion of pulmonary TB treatment.^{10,12–13} However, the previous studies did not consider the timing of the pulmonary function test. Smoking, which is the most important risk factor for COPD, increases the risk of active pulmonary tuberculosis.^{32–34} The impact of smoking on pulmonary function abnormalities after pulmonary TB infection is unknown, and previous studies have shown inconsistent results.^{9–10,15,17} In our study, smoking history was not a significant predictor of pulmonary function deterioration. The reason for this finding might be that most subjects with a history of smoking in our study had quit smoking before or immediately after their diagnosis with pulmonary TB, and subjects with COPD, as confirmed by spirometry, were excluded. It might also be the case that short-term changes in pulmonary function are mainly caused by post-tuberculosis pulmonary inflammation, which masks pulmonary function deterioration due to smoking.

It is not uncommon for patients with pulmonary TB to have NTM isolation from respiratory specimens.^{26–27} The clinical significance of NTM isolation, especially with respect to pulmonary function, is unclear in pulmonary tuberculosis patients; it might be the result of colonization, specimen contamination or true infection.³⁵ Patients with multiple NTM isolates were more likely to be symptomatic and had longer treatment times for pulmonary TB. Cavitations were more frequently visualized by chest radiographs in patients with NTM isolates.²⁶ Further study

Table 3 - Predictors of FVC within 60 months after completion of treatment for pulmonary tuberculosis.

| Parameter | Estimate (β _i) | Standard error | 95% confidence interval | p value |
|-----------------------------|----------------------------|----------------|-------------------------|---------|
| Male | 0.613 | 0.134 | 0.351–0.876 | <0.001 |
| Weight (kg) | 0.020 | 0.006 | 0.008–0.031 | 0.001 |
| Diabetes mellitus | -0.453 | 0.186 | -0.819– -0.088 | 0.015 |
| Malignancy | -0.588 | 0.185 | -0.951– -0.226 | 0.002 |
| Treatment duration (months) | -0.035 | 0.012 | -0.058– -0.012 | 0.003 |
| Change in regimen | -0.039 | 0.118 | -0.571– -0.107 | 0.004 |
| RS before treatment | -0.112 | 0.027 | -0.164– -0.059 | <0.001 |
| ΔRS after treatment* | -0.102 | 0.029 | -0.159– -0.045 | 0.001 |

Definition of abbreviation: RS: radiographic score.

*ΔRS = (RS after treatment)–(RS before treatment). Patients with more radiographic improvement had more negative ΔRS values.

Table 4 - Predictors of obstructive defect (FEV₁/FVC <70%) within 60 months after completion of treatment for pulmonary tuberculosis.

| Parameter | Odds ratio | 95% confidence interval | p value |
|------------------------|------------|-------------------------|---------|
| Diabetes mellitus | 0.186 | 0.034–1.030 | 0.054 |
| Smear-positive disease | 2.546 | 1.021–6.350 | 0.045 |
| Weight (kg) | 1.074 | 1.030–1.119 | <0.001 |
| Age (years) | 1.030 | 1.004–1.056 | 0.021 |

is needed to clarify the clinical significance of NTM colonization in changes in pulmonary function after completion of anti-tuberculosis treatment.

There are some limitations of our study. First, the study was limited by retrospective data and a relatively small sample size. Without longitudinal follow-up data, we could miss individual characteristics that might have significant impacts on pulmonary function. Second, selection bias might exist because our study population was treated in a tertiary medical center. Nevertheless, we believe that this is a minor concern because more than 90% of the patients with pulmonary TB were ambulatory and sought primary care in the outpatient department. Third, only 7.3% of our patients underwent pulmonary function tests after completing anti-tuberculosis treatment. Patients who received pulmonary function tests could have had more prominent respiratory symptoms and worse pulmonary function compared to patients who did not undergo such tests. Nevertheless, our results showed a prominent loss of pulmonary function after pulmonary TB infection. Pulmonary function follow-up analysis is recommended in patients with pre-existing lung disease who are at risk of pulmonary decompensation after pulmonary tuberculosis.

CONCLUSIONS

In conclusion, after completion of pulmonary TB treatment, the risk factors for pulmonary function deterioration include smear-positive disease, extensive disease before treatment, prolonged treatment duration, and less radiographic improvement after treatment. For patients with significant respiratory symptoms and multiple risk factors, the pulmonary function test should be followed up to monitor the progression of functional impairment and responses to treatment, especially within the first 18 months after completing anti-tuberculosis treatment.

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