Pulmonary functional assessment: longitudinal study after treatment of pulmonary tuberculosis

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ABSTRACT

Even when treated adequately, pulmonary tuberculosis can lead to pulmonary sequelae. Patients treated for PTB between 2012 and 2016 answered a standardized questionnaire and underwent chest radiography and spirometry, measurement of absolute pulmonary volume, Diffusing Capacity for Carbon Monoxide (DLCO) and the 6-min walk test (6MWT) on two occasions: within the first year after the end of treatment (follow-up 1), and one and two years after follow-up 1 (follow-up 2). A total of 55 patients they underwent spirometry, 23 (41.82%) had obstructive ventilatory disorder (OVD) and eight (14.5%) had moderate OVD. In total, 29 patients underwent pulmonary function tests (PFTs) and 24 patients underwent the 6MWT on two occasions. The functional changes after PTB treatment appear not to have varied between one and two years of follow-up. There was a correlation between low FEV1 and low DLCO (p<0.001); low DLCO and low 6MWT (p<0.001) and radiographic abnormalities and low FEV1 (p=0.033). The most frequently observed change in spirometry was found in patients with OVD.

KEYWORDS: Spirometry. 6-minute walk test. Lung capacity. Tuberculosis sequelae.

INTRODUCTION

Tuberculosis (TB) is a global public health problem and its control has been a challenge in recent decades. In 2019, the incidence of the disease ranged from 8.9 to 11.1 million new cases of active TB and between 1.1-1.3 million deaths due to TB according to the World Health Organization (WHO), indicating that TB is currently the leading cause of death from infectious causes worldwide and is among the top 10 causes of death in general.

Even when treated adequately, pulmonary tuberculosis (PTB) can lead to pulmonary sequelae. Reduction in the total lung capacity (TLC) due to scar fibrosis is common. In addition, destructive changes in the pulmonary parenchyma can lead to airflow obstruction. These changes might affect the pulmonary compliance, resulting in peripheral airway collapse and, consequently, air trapping, leading to changes in pulmonary function.

Radiological sequelae of PTB might be related to dynamic changes in pulmonary function after the end of treatment. According to a longitudinal study by Chung et al., deterioration in the pulmonary function might occur up to 18 months after the end of treatment. Functional changes resulting from the sequelae might manifest as ventilatory restriction, ventilatory obstruction or a combined disorder (obstructive–restrictive together).
In a systematic review, after the evaluation of 156 articles, obstruction was mentioned in 52 (33%)\(^9\), and even in countries with low incidences of PTB, respiratory diseases are frequent after treatment of PTB\(^7\). The proportion of obstruction is variable and was related to the extent of radiological changes\(^8,9\). On the other hand, the restriction has been the most frequent disorder in recently published studies, observed in 52 to 68\%\(^10\)-\(^12\). A multicentric study in Brazil, that evaluated the functional changes in patients treated for PTB after excluding smoking patients and those with respiratory diseases prior to PTB treatment, the restriction has also been the predominant change\(^9\).

The 6-minute walk test (6MWT), used to evaluate an individual’s response to exercise, is reliable and has been validated according to the guidelines of the American Thoracic Society\(^13\). Some studies have reported patients with PTB who walked shorter distances during the 6MWT in comparison with healthy individuals; this was seen even in patients during treatment or who had successfully completed the treatment regimen\(^14\)-\(^16\). In recent years, a difference in the 6MWT distance has been noted after the end of treatment in patients with TB and human immunodeficiency virus (HIV) infection\(^17\).

Another test to assess the pulmonary function is the diffusing capacity of carbon monoxide (DLCO)\(^18\). Patients with PTB might have low DLCO and only a few studies evaluated the specific relationship between DLCO and PTB\(^8,18\). The mean DLCO varied from 74.1\% to 78.8\% in patients with TB sequelae, highlighting the importance of evaluating this parameter to assess pulmonary function\(^7,18\).

A recent review found an abundance of studies on the prevalence and proportion of post PTB disorders. On the other hand, there was a lack of studies on the disease progression and patients’ management\(^9\). There was consensus on the need for follow-up after PTB treatment as some evidences have emerged pointing to an increased risk of morbidity and mortality in the post PTB period\(^10\). Thus, this study aimed to evaluate the magnitude and progression of respiratory changes in spirometry according to the variables: absolute pulmonary volume, DLCO and 6MWT in patients treated for PTB.

**MATERIALS AND METHODS**

This prospective study included new cases of TB confirmed by smear microscopy or GeneXpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) and positive culture for *M. tuberculosis* in patients who sought the Tuberculosis Outpatient Clinic of the Clinical Hospital of the Federal University of Minas Gerais, who were successfully treated for PTB from January 1\(^{st}\), 2012 to December 30\(^{th}\), 2016. All patients signed an informed consent and received multiple treatments for PTB. Patients presenting with extrapulmonary TB, coinfected with the human the immunodeficiency virus (HIV) or presenting with unacceptable or non-reproducible spirometry curves were excluded.

Recruited patients answered a standardized questionnaire comprising questions on sociodemographic and clinical data, gender, age (≥ 18 years), history of smoking habit and comorbidities. Some of these patients participated in a previous study by the same authors\(^8\). The sociodemographic variables were self-declared skin color/ethnicity (white or non-white) and marital status (single or stable union). Regarding respiratory signs and symptoms, the presence of dyspnea, classified according to the modified Medical Research Council (mMRC) scale\(^20\), cough, sputum and wheezing was evaluated. These data were obtained on the day the pulmonary function tests (PFTs) were carried out. Individuals who smoked at least 100 cigarettes or the equivalent during their lifetimes were considered smokers, and individuals who had quit smoking for >12 months prior to study inclusion were considered ex-smokers\(^21\). Comorbidities were self-reported and valued when described in the medical records. Diagnosis of lung diseases (asthma, chronic obstructive pulmonary disease [COPD], bronchiectasis, interstitial lung disease and silicosis) prior to PTB treatment was reviewed by pulmonologists involved in this study, according to the definitions proposed by international guidelines such as the Global Initiative for Asthma, the Global Initiative for Obstructive Chronic Lung Disease and Pulmonology Practice\(^22\)-\(^24\).

PFTs were performed in the first follow-up within the first year after the end of treatment (follow-up 1) and repeated between one and two years after the follow-up 1 (follow-up 2). The Collins CPL system (Ferraris Respiratory, Louisville, CO, USA) was used to perform the tests. The acceptance and reproducibility criteria for PFTs were set according to the recommendations of the American Thoracic Society (ATS)\(^25\). Data were reported as absolute values and percentages in relation to the predicted values for the Brazilian population\(^26\). The following variables were analyzed: total lung capacity (TLC), residual volume (RV), RV/TLC ratio, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV\(_1\)), and FEV\(_1\)/FVC ratio\(^27\). DLCO was performed using the single-breath method, and the values suggested by Crapo and Morris\(^28\) were used.

OVD was considered when the FEV\(_1\)/FVC ratio was below the lowest limit of normal (LLN) and TLC was ≥ LLN; combined ventilatory disorder (obstructive–restrictive together) was considered when the FEV\(_1\)/FVC
Pulmonary functional assessment ratio was below the LLN and TLC was < LLN; RVD was considered when the FEV1/FVC ratio was above or equal to the LLN and TLC was < LLN; and the non-specific pattern (IVD) was considered when the FVC value was below the LLN, the FEV1/FVC ratio was equal to or above the LLN, and TLC was ≥ LLN.

To classify the severity of obstruction in the PFTs, a percentage of predicted FEV1 and FEV1/FVC was used, with ≥ 60% corresponding to mild, 41-59% to moderate, and ≤ 40% to severe obstruction; to predict the percentage of prediction, FVC ≥ 60% corresponded to mild, 51-59% to moderate, and ≤ 50% to severe restriction.

The 6MWT was performed in a 30-m corridor using a portable oximeter (Nonin Medical, INC. Plymouth, MN, USA) according to the recommendations of the ATS. All patients underwent two walking tests, with a minimum interval of 30 minutes; encouraging phrases were provided every minute. The following parameters were recorded: heart rate, respiratory rate and dyspnea score (Borg score of dyspnea); saturation was measured by pulse oximetry (SpO2) at the beginning and at the end of the test; and the walking distance at the end of the 6MWT. The test with the greatest distance covered in the 6MWT was selected. The 6MWTD findings were expressed as absolute values and percentages of the predicted values calculated using the reference equation proposed by Soares and Pereira for the Brazilian population.

Chest X-rays were performed on days close to the spirometry, they were evaluated by radiologists and classified by pulmonologists. Chest X-rays that showed no abnormalities were classified as normal. Chest X-rays that showed abnormalities were classified according to the National Tuberculosis Association (NTA), as follows: NTA I or minimum; NTA II or moderately advanced - the injury could be in one lung or in both lungs, its extension should not exceed the volume corresponding to an entire lung if the lesions are not confluent, and in the presence of confluent lesions, they should occupy no more than the equivalent of one-third of the lung; NTA III or very advanced - exceeding the moderately advanced limit.

The sample calculation considered a 95% confidence interval and a margin of error < 5%, including the average number of patients diagnosed with PTB evaluated per year at the Tuberculosis Outpatient Clinic of the Clinical Hospital of UFMG and the percentage of patients who developed pulmonary sequelae. The estimated minimum sample size resulted in 32 patients.

Data were collected using an Excel spreadsheet and analyzed using the Statistical Package software for the Social Sciences, version 24.0 (SPSS Inc, Chicago, IL, USA). The Kolmogorov–Smirnov test was used to assess the normality of continuous numerical variables distribution. C variables are expressed as means and standard deviations or as medians and interquartile intervals, while categorical variables are expressed as absolute and relative frequencies. The chi-square test was used for the comparison of categorical variables. To analyze the variables of lung function tests between follow-ups 1 and 2, the unpaired Student’s test or the Mann–Whitney test was performed, as indicated. To verify the direction and the degree of association between pulmonary function variables, either Pearson or Spearman’s coefficient was performed; as indicated. We set the significance level at 5% (p < 0.05).

This study is part of a project approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE Nº 14606113.7.0000.5149).

RESULTS

From the 57 selected patients, 55 were included in the analyses and two were excluded because they did not meet all inclusion criteria (Figure 1). Table 1 shows the main characteristics of the participants. The mean age was 50.4 years (22.2–77.1 years), 52.7% (29/55) were female, 43.6% (24/55) were non-white and 52.7% (29/55) patients had a stable union. Some comorbidities were observed in 60% (33/55) of patients, and systemic arterial hypertension.
was observed in 41.82% (23/55) of patients. Respiratory symptoms were reported by 81.8% (45/55) of patients, and 78.2% (43/55) reported dyspnea (Table 1). In total, 54.5% (30/55) of patients were smokers or ex-smokers. The smoking load was 33.9 packs-year, with a minimum of 2 packs-year and a maximum of 174 packs-year. Furthermore, 61.8% (34/55) of patients had minimal abnormalities on their chest X-ray (Table 1). Considering the 55 patients who underwent at least one examination with acceptable and reproducible spirometry curves, 36 patients underwent tests for absolute pulmonary volume and DLCO and 46 patients underwent the 6MWT (Figure 1). The absolute values and percentages of the predicted values obtained in the PFTs are shown in Table 2. The most prevalent ventilatory disorder was OVD; it was observed in 23/55 (41.82%) patients; 8/55 (14.5%) patients had moderate OVD (Table 3).

From the 55 selected patients, 29 underwent pulmonary volume and DLCO tests, and 24 patients underwent the 6MWT on two occasions (Table 4). The median duration between the end of treatment and follow up 1 was 147 days (range, 75-363), and between follow-up 1 and follow-up 2 was 634 days (range, 458-1127). When the results of PFTs and 6MWTD variables were compared in the two follow-ups, no statistical difference was observed between the

Table 1 - Sociodemographic and clinical characteristics of the sample (n=55).

| Characteristics               | n (55) | %   |
|-------------------------------|--------|-----|
| Gender                        |        |     |
| Male                          | 26     | 47.3|
| Female                        | 29     | 52.7|
| Age group (in years)          |        |     |
| Up to 29                      | 5      | 9.1 |
| 30-49                         | 20     | 36.3|
| 50-59                         | 13     | 23.6|
| ≥ 60                          | 17     | 30.9|
| Self-declared skin Color/Ethnicity |    |     |
| White                         | 19     | 34.5|
| Not White                     | 36     | 65.5|
| Marital status                |        |     |
| Single                        | 26     | 47.3|
| Not single (stable relationship) | 29 | 52.7|
| Comorbidities                 |        |     |
| SAH                           | 23     | 41.8|
| DM                            | 6      | 10.9|
| Silicosis                     | 5      | 9.1 |
| CKD                           | 5      | 9.1 |
| Cancer                        | 3      | 5.4 |
| RA or SS                      | 3      | 5.4 |
| Granulomatous polyangitis     | 1      | 1.8 |
| COPD                          | 7      | 12.7|
| Signs/Symptoms                |        |     |
| Cough                         | 19     | 34.5|
| Wheezing                      | 12     | 21.8|
| Dyspnea mMRC 0-1              | 32     | 58.2|
| mMRC 2 – 4                    | 23     | 41.8|
| Smoking                       |        |     |
| No                            | 25     | 45.5|
| Former smoker                 | 11     | 20.0|
| Yes                           | 19     | 34.5|
| Chest X-ray                   |        |     |
| Normal                        | 9      | 16.4|
| NTA I                         | 34     | 61.8|
| NTA II                        | 7      | 12.7|
| NTA III                       | 1      | 1.8 |
| Not informed                  | 4      | 7.3 |

SAH = systemic arterial hypertension; DM = diabetes mellitus; CKD = chronic kidney disease; RA = rheumatoid arthritis; SS = systemic sclerosis; COPD = chronic obstructive pulmonary disease; NTA = National Tuberculosis Association; mMRC = modified Medical Research Council.
Analyses of chest X-ray abnormalities and FEV1 values revealed that patients with X-ray changes had lower FEV1 values (p=0.033), (Supplementary Figure S2). A significant correlation was observed between FEV1 and DLCO (R=0.564; p<0.001), (Supplementary Figure S3), and between FEV1 and 6MWTD (R=0.506, p<0.001), (Supplementary Figure S4); between DLCO and 6MWTD (R=0.592, p<0.001), (Supplementary Figure S5). Thus, patients with lower FEV1 and lower DLCO had a worse performance in the 6MWT, i.e. walked shorter distances.

There was no significant correlation between chest X-ray abnormalities and DLCO (p=0.246), presence of symptoms and DLCO (p=0.163), FEV1 and DLCO (p=0.384) and 6MWTD and DLCO (p=0.357).

**DISCUSSION**

The main study results showed that the functional changes after PTB treatment seem not to vary between one and two years follow-up.

We did not find significant differences in pulmonary function of patients 12 and 24 months after PTB treatment. Allwood et al. showed that during treatment, lung volumes improved and computed tomography fibrosis scores decreased, but features of airflow obstruction and gas trapping emerged, while reduced DLCO seen in a majority of patients persisted. Furthermore, one year after the end of treatment, 18.6% of patients had residual restriction disorders, 16.3% had airflow obstruction, and 78.6% had reduced DLCO. Chung et al. found lower spirometry values 18 months after treatment; however, their study included patients in treatment for non-tuberculosis mycobacteria (NTM). Hnizdo et al. reported decreased values approximately 6 months after treatment, with stabilization of the changes between 7-12 months; despite the fact that their sample was composed of coal miners and included patients with more than one episode of PTB.

A strength of our study, in comparison with authors who evaluated parameters (Tables 4 and 5, and Supplementary Figure S1).

**Table 2 - Basal variables (follow-up 1) of pulmonary function tests in patients treated for pulmonary tuberculosis.**

| Spirometry (n=55) | Variable | Mean (SD) |
|-------------------|----------|-----------|
|                   | FVC, L   | 3.25 (0.94) |
|                   | FVC, %   | 87.79 (18.02) |
|                   | FEV1, L  | 2.37 (0.69) |
|                   | FEV1, %  | 78.39 (17.46) |
|                   | FEF25-75, L/S | 2.11 (1.01) |
|                   | FEF25-75, % | 72.65 (35.28) |
|                   | FEV1/FVC, % | 73.73 (19.07) |
| Absolute Pulmonary Volume (n=36) | TCL, L | 5.27 (1.37) |
|                   | TCL, %   | 101.21 (18.78) |
|                   | VR, L    | 1.81 (0.80) |
|                   | VR, %    | 100.96 (34.12) |
|                   | RV/TLC, %| 33.97 (9.87) |
| DCOb (n=36) | DCO, mL min⁻¹ mmHg⁻¹ | 25.46 (8.36) |
|                   | DCO, %   | 86.48 (23.59) |
| 6MWTD (n=46) | 6MWTD, m | 526.07 (95.07) |
|                   | 6MWTD, % | 90.31 (14.58) |

SD = standard deviation; L = liters; % = predicted percentage; m = meters; VC = vital capacity; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 s; FEF25-75 = forced expiratory flow between 25 and 75% of the forced vital capacity; TLC = total lung capacity; VR = residual volume; DCO = diffusing capacity for carbon monoxide; 6MWTD = 6-min walk test distance; 6MWTD% = 6-min walk test distance.

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**Table 3 - Functional classification of ventilator disorders detected during the follow-up of patients treated for pulmonary tuberculosis (n=55).**

| Ventilatory disorder | n | % | Graduation | n | % |
|----------------------|---|---|------------|---|---|
| No                   | 19| 34.54 | Mild | 11| 20 |
| OVD                  | 23| 41.82 | Moderate | 8| 14.55 |
|                      |   |        | Severe | 4| 7.27 |
| RVD                  | 8 | 14.54 | Mild | 8| 14.54 |
| MVD                  | 4 | 7.27 | Moderate | 2| 3.65 |
|                      |   |        | Severe | 1| 1.81 |
| NVD                  | 1 | 1.83 | - | 1| 1.81 |
| Total                | 55| 100.0 | - | -| - |

OVD = Obstructive Ventilatory Disorder; RVD = Restrictive Ventilatory Disorder; DVC = Mixed Ventilatory Disorder; NVD = Nonspecific Ventilatory Disorder.
have also evaluated lung function longitudinally, was to include patients who performed lung function after the end of treatment, thus reducing the interference of changes in lung function during the acute phase of PTB infection. In addition, as shown by Allwood et al., between 6 and 18 months after the diagnosis of PTB, tomography changes are more stable. Ravimohan et al. described the complexity of possible immunological and inflammatory pathways that can result in destruction of the lung tissue, consequently leading to changes in long term changes in lung function.

The most prevalent ventilatory disorder found in our study was of mild OVD, which is consistent with findings reported in most studies. The pathophysiological mechanism that leads to obstructive functional changes after PTB is not well established. One possibility would be the occurrence of bronchiectasis and bronchial stenosis. Another explanation is that they are caused by dysregulation of macrophage activity, leading to an initial destruction of

| Variable          | Follow-up 1 Mean (SD) | Follow-up 2 Mean (SD) | p-value |
|-------------------|------------------------|------------------------|---------|
| Spirometry        |                        |                        |         |
| VC, L             | 3.3 (1.0)              | 3.1 (0.9)              | 0.983   |
| VC, %             | 84.3 (19.6)            | 83.4 (20.1)            | 0.396   |
| FVC, L            | 3.1 (1.0)              | 3.1 (0.9)              | 0.767   |
| FVC, %            | 75.2 (27.8)            | 81.1 (17.4)            | 0.258   |
| FEV₁              | 2.1 (0.9)              | 2.2 (0.9)              | 0.666   |
| FEV₁, %           | 58.7 (29.8)            | 69.0 (23.4)            | 0.330   |
| FEF25-75%, L      | 1.6 (1.2)              | 1.9 (1.4)              | 0.360   |
| FEF25-75%, %      | 64.02 (36.06)          | 62.78 (42.95)          | 0.556   |
| FEV₁ / FVC        | 70.64 (14.53)          | 68.53 (19.83)          | 0.458   |
| Absolute Pulmonary Volume |                |                        |         |
| TLC               | 5.7 (1.4)              | 4.9 (1.1)              | 0.878   |
| TLC, %            | 102.3 (21.7)           | 93.1 (16.2)            | 0.878   |
| VR, L             | 2.1 (1.1)              | 1.8 (1.8)              | 0.919   |
| VR, %             | 112.1 (40.3)           | 101.8 (24.5)           | 0.646   |
| FRC, L            | 3.2 (1.1)              | 2.8 (0.8)              | 0.444   |
| FRC, %            | 100.7 (26.9)           | 91.1 (19.4)            | 0.799   |
| RV/TLC            | 38.6 (12)              | 37.6 (10.1)            | 0.889   |
| DLCO              |                        |                        |         |
| DLCO, mL min⁻¹ mmHg⁻¹ | 25.1 (9.2)         | 22.8 (9.78)            | 0.310   |
| DLCO, %           | 82.1 (26.1)            | 75.4 (21.7)            | 0.398   |

SD = Standard Deviation; L = liters; % = predicted percentage; RV = Residual Volume; FRC = Functional Residual Capacity; TLC = Total Lung Capacity; VC = Vital Capacity; FVC = Forced Vital Capacity; FEV₁ = Forced Expiratory Volume in 1s; FEF25-75% = Forced Expiratory Flow Between 25 and 75% of the CVF; DLCO = Diffusing Capacity for Carbon Monoxide.

| Table 4 - A comparison of pulmonary function tests results between follow-ups 1 and 2 (n=29). |

| Table 5 - Comparison of the 6-min walk tests results between follow-ups 1 and 2 (n=24). |

SD = standard deviation; SpO2 = saturation by pulse oximetry; HR = heart rate; RR = respiratory rate; bpm = breaths per minute; 6MWTD = 6-min walk test distance; bpm = beats per minute; 6MWTD % = 6-min walk test distance in predicted percentage.
pathogenic microorganisms, favoring tissue healing and playing a central role in tissue remodeling\textsuperscript{3}. Restrictive disorders could be due to destruction of pulmonary parenchyma by the deregulation of the mechanism of protease control, i.e., pulmonary damage caused by matrix metalloproteinases leading to fibrotic changes\textsuperscript{3}. Around 50% of restrictions take place one year after the PTB treatment\textsuperscript{10,11}.

Among patients who reported respiratory symptoms, dyspnea was the most frequent symptom, although it was not correlated with pulmonary function changes, since most patients had mild dyspnea (mMRC scale score: 0-1), similar to a previous study\textsuperscript{36}. Another study described self-reported symptoms, airflow obstruction and functional impairment 1-5 years after TB treatment with poor correlation between physiology, functional capacity and symptoms, although it was also a cross-sectional study\textsuperscript{34}.

Most patients did not show radiological abnormalities or had minimal lesions. However, patients with radiological changes had lower FEV\textsubscript{1}. Allwood \textit{et al.}\textsuperscript{2} showed that these changes may be secondary to the trapping of physiological gases, suggesting the development of airflow limitation at the level of the small airways.

A good correlation between FEV\textsubscript{1} and DLCO with 6MWTD is an interesting and new finding in our study; when FEV\textsubscript{1} and DLCO was lower in patients who walked shorter distances as shown by the 6MWT, suggesting worsening of gas exchange and greater severity of the disease in these patients\textsuperscript{18}. However, the equipment that measures DLCO is not widely available in most underdeveloped or developing countries, exactly in places in which the prevalence of post-PTB treatment changes is more significant\textsuperscript{6}.

In our study, patients walked distances close to the predicted value in two different times and without significant difference, which might demonstrate the stability of functional capacity. A South Africa cohort demonstrated similar 6MWTD results with respect to ours despite including patients that underwent up to six treatments for TB\textsuperscript{34}. In a previous study with only nine participants, five of the nine showed values below LLN after PTB treatment\textsuperscript{27}. Our results can be justified by the Latin American population included in this study, which are used to walk longer distances than Nordic populations, probably due to lifestyle habits\textsuperscript{38}. This study has some limitations. Firstly, this was a single-center trial; hence, the results cannot be generalized, however, to our knowledge, there are few studies that evaluated lung function at different periods after the end of TB treatment in the same patients. Secondly, this study included patients with COPD and smokers, which might have interfered with the results. Nevertheless, the high prevalence of smoking among these patients reflects the real-life clinical practice. People who are at higher risk to contract TB are often the same ones exposed to other risk factors for chronic respiratory diseases, including exposure to household smoke, ambient air pollution and occupational exposure to dust\textsuperscript{6}.

CONCLUSION

In the present study, 55 treated TB patients were evaluated. They underwent spirometry, 23 (41.82\%) had obstructive respiratory disorders (OVD) and eight (14.5\%) s had moderate OVD. Twenty-nine patients underwent pulmonary function tests (PFTs) and 24 the 6MWT on two occasions. Functional changes after PTB treatment appear not to have varied between one and two years of follow-up. There was correlation between low FEV\textsubscript{1} and low DLCO (p<0.001); low DLCO and low 6MWT distance (p<0.001) and X-ray abnormalities and low FEV\textsubscript{1} (p=0.033). The most frequently observed change in spirometry was found in patients with OVD.

Functional changes appear not to vary between one and two years after PTB treatment. The end of PTB treatment may represent the starting point of another disease with permanent changes in lung function. The importance of performing PFTs should be emphasized, especially in patients who have radiological sequelae.

Further studies should be conducted to identify and evaluate pulmonary changes that are clinically relevant and measures that can help patients with respiratory symptoms after PTB treatment, such as the use of inhaled drugs and pulmonary rehabilitation. Moreover, we emphasize the importance of PTB prevention since sequelae are irreversible despite adequate treatment, leading to clinical and economic losses that the patients would have to bear throughout their lives.

AUTHORS’ CONTRIBUTIONS

MPN: data collection, building the database, monitoring analysis and article writing; EVC: co-coordination of study conception and design, data analyses and article writing; NS: monitoring analysis, adjustment of the database, article writing; INA: verification of database, article writing; ALAC: verification of database, article writing; SSM: study conception and design, modeling the questionnaire, data analyses and article writing.

CONFLICT OF INTERESTS

The authors declare there is no conflict of interests.
ETHICAL APPROVAL

The study was approved by the Ethics Committee of the Federal University of Minas Gerais under protocol Nº CAAE 1460613.7.0000.5149 and all participants agreed to participate and signed a Free Informed Consent.

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Supplementary Figure S3 - Correlation between FEV$_1$ (liters) and DLCO (mL min$^{-1}$ mmHg$^{-1}$) during follow-up 1. DLCO = diffusing capacity for carbon monoxide; FEV$_1$ = forced expiratory volume in 1 second.

Supplementary Figure S4 - Correlation between FEV1 (liters) and 6MWTD (meters) during follow-up 1.

Supplementary Figure S5 - Correlation between DLCO (mL min$^{-1}$ mmHg$^{-1}$) and 6MWTD (meters) during follow-up 1.