



Post-tuberculosis lung disease: a comparison of Brazilian, Italian, and Mexican cohorts

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ABSTRACT

Objective: To evaluate lung function in a cohort of patients with a history of pulmonary tuberculosis in Brazil, as well as to evaluate the decline in lung function over time and compare it with that observed in similar cohorts in Mexico and Italy. **Methods:** The three cohorts were compared in terms of age, smoking status, pulmonary function test results, six-minute walk test results, and arterial blood gas results. In the Brazilian cohort, pulmonary function test results, six-minute walk test results, and arterial blood gas results right after the end of tuberculosis treatment were compared with those obtained at the end of the follow-up period. **Results:** The three cohorts were very different regarding pulmonary function test results. The most common ventilatory patterns in the Brazilian, Italian, and Mexican cohorts were an obstructive pattern, a mixed pattern, and a normal pattern (in 58 patients [50.9%], in 18 patients [41.9%], and in 26 patients [44.1%], respectively). Only 2 multidrug-resistant tuberculosis cases were included in the Brazilian cohort, whereas, in the Mexican cohort, 27 cases were included (45.8%). Mean PaO₂ and mean SaO₂ were lower in the Mexican cohort than in the Brazilian cohort ($p < 0.0001$ and $p < 0.002$ for PaO₂ and SaO₂, respectively). In the Brazilian cohort, almost all functional parameters deteriorated over time. **Conclusions:** This study reinforces the importance of early and effective treatment of drug-susceptible tuberculosis patients, because multidrug-resistant tuberculosis increases lung damage. When patients complete their tuberculosis treatment, they should be evaluated as early as possible, and, if post-tuberculosis lung disease is diagnosed, they should be managed and offered pulmonary rehabilitation because there is evidence that it is effective in these patients.

Keywords: Tuberculosis; Tuberculosis, multidrug-resistant; Spirometry; Rehabilitation.

INTRODUCTION

Tuberculosis is a serious public health concern and one of the leading causes of death worldwide. According to the latest report by the WHO, 5.8 million people were diagnosed with tuberculosis and 1.3 million tuberculosis deaths occurred in 2020. In addition, COVID-19 has impacted tuberculosis control.^(1,2) The number of newly diagnosed tuberculosis cases fell from 7.1 million in 2019 to 5.8 million in 2020. In addition, reductions were observed in the number of people receiving multidrug-resistant tuberculosis (MDR-TB) treatment (a 15% reduction, from 177,100 people to 150,359 people) and tuberculosis preventive treatment (a 21% reduction, from 3.6 million people to 2.8 million people).⁽³⁾

Tuberculosis affects predominantly the lungs, and many patients, despite a bacteriologically confirmed cure, will have tuberculosis sequelae, with loss of lung function and chronic respiratory symptoms, as well as

decreased exercise capacity and quality of life.⁽⁴⁻¹⁰⁾ The prevalence of post-tuberculosis lung disease (PTLD) varies widely, from 18% to 87%,⁽¹¹⁾ depending on the population studied and the pulmonary function tests performed.

The International Union Against Tuberculosis and Lung Disease has recently published a core document on the importance of clinical evaluation of PTLD as soon as possible at the end of tuberculosis treatment.⁽¹²⁾ According to the document, one of the key research priorities is to describe the frequency and severity of PTLD in different populations.⁽¹²⁾ Indeed, although there is evidence that tuberculosis deteriorates lung function,⁽⁴⁻⁸⁾ the evidence regarding the type of damage, the severity of PTLD, and patient prognosis is not clear, and between-cohort comparisons have never been done.

Therefore, the objective of the present study was to evaluate lung function in a cohort of patients with a

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history of pulmonary tuberculosis in Brazil, as well as to evaluate the decline in lung function over time and compare it with that observed in similar cohorts in Mexico and Italy.

METHODS

In this study we compared three different cohorts to identify elements to improve screening and rehabilitation of post-treatment tuberculosis patients: a Brazilian cohort ($n = 114$), an Italian cohort ($n = 43$), and a Mexican cohort ($n = 59$). The study was approved by the local research ethics committees (Protocol nos. 2018-0682, 2215 CE, and C17-14 in Brazil, Italy, and Mexico, respectively).

The Brazilian cohort consisted of outpatients who were over 18 years of age, had a history of bacteriologically confirmed pulmonary tuberculosis, were evaluated right after the end of tuberculosis treatment, and were followed for a mean of 8.3 ± 4.9 years at the *Hospital de Clínicas de Porto Alegre* Outpatient Clinic, located in the city of Porto Alegre, Brazil. We retrospectively reviewed pulmonary function test results, six-minute walk test (6MWT) results, and arterial blood gas results at two different time points: right after the end of tuberculosis treatment and at the end of the follow-up period. Spirometry, lung volume measurements, and DL_{CO} measurements were performed with a MasterScreen Body-PFT device (Jaeger, Würzburg, Germany). All tests were performed in accordance with recommended standards⁽¹³⁻¹⁵⁾ and with the use of predicted values for the Brazilian population.⁽¹⁶⁻¹⁸⁾ Ventilatory patterns (obstructive, restrictive, and mixed) were defined in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) interpretative strategies for lung function tests.⁽¹⁹⁾ We also collected data on symptoms, BMI, smoking status, and bacteriological profile, as well as on radiological abnormalities, which were measured by using a scoring system proposed by Baez-Saldana et al.⁽²⁰⁾

The Italian cohort consisted of patients with a history of pulmonary tuberculosis and successful treatment, admitted for pulmonary rehabilitation between 2004 and 2017. Details on the study population and the study itself have been presented elsewhere.⁽⁵⁾ Pulmonary function tests were performed in accordance with the ATS guidelines⁽¹³⁻¹⁵⁾ and the ATS/ERS interpretative strategies for lung function tests,⁽¹⁹⁾ with the use of the ERS predicted values.⁽¹⁹⁾

In the Mexican cohort, as described previously,⁽⁶⁾ all patients had bacteriologically confirmed tuberculosis, and the functional impact of post-treatment sequelae was evaluated in those who were over 18 years of age and who had drug-susceptible tuberculosis (DS-TB) or MDR-TB. Pulmonary function tests were performed in accordance with the ATS/ERS guidelines and the ATS/ERS interpretative strategies for lung function tests,⁽¹⁹⁾ with the use of the National Health and Nutrition Examination Survey III reference values.⁽²¹⁾

Data analysis was performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). Data were presented as number of cases and percentage, mean \pm SD, or median (IQR). The three cohorts were compared in terms of age, smoking status, pulmonary function test results, 6MWT results, and arterial blood gas results. Categorical variables were compared by Pearson's chi-square test. Continuous variables were compared by ANOVA. In the Brazilian cohort, pulmonary function test results, 6MWT results, and arterial blood gas results right after the end of tuberculosis treatment and at the end of the follow-up period were compared by a t-test for paired samples. A two-sided p -value < 0.05 was considered significant for all analyses.

RESULTS

Description of the cohorts

Table 1 shows the characteristics of the three cohorts of patients with tuberculosis sequelae. In all three cohorts, males predominated (58.8% in the Brazilian cohort, 55.8% in the Italian cohort, and 52.5% in the Mexican cohort). The Italian patients were older than the Mexican patients (mean age, 72.3 ± 9.0 years vs. 41.1 ± 14.1 years, $p \leq 0.0001$). Current or past smoking was more common among the Italians (58.1%) and Brazilians (64.9%) than among the Mexicans (38.1%; $p = 0.011$).

Data on BMI and bacteriological profile were only available for the Brazilian and Mexican cohorts (Table 2). The mean BMI was 24.6 ± 4.9 kg/m² among the Brazilians and 25.6 ± 5.1 kg/m² among the Mexicans. Only 2 MDR-TB cases were included in the Brazilian cohort, whereas, in the Mexican cohort, 27 cases were included (45.8%).

Functional and radiological evaluation

The three cohorts were very different regarding pulmonary function test results. The most common ventilatory patterns in the Brazilian, Italian, and Mexican cohorts were an obstructive pattern, a mixed pattern, and a normal pattern (in 58 patients [50.9%], in 18 patients [41.9%], and in 26 patients [44.1%], respectively). DL_{CO} was lower in the Brazilian and Italian patients than in the Mexican patients ($p < 0.0001$). Mean PaO_2 and mean SaO_2 were lower in the Mexican cohort than in the Brazilian cohort ($p < 0.0001$ and $p < 0.002$ for PaO_2 and SaO_2 , respectively). The Mexican cohort showed a significant decrease in SaO_2 during the 6MWT in comparison with the other cohorts ($p < 0.0001$).

Data on respiratory symptoms, as well as radiological scores, were available for the Brazilian and Mexican cohorts only (Table 2). Cough was present in 68 (59.6%) of the 114 patients in the Brazilian cohort and in 9 (15.3%) of the 59 patients in the Mexican cohort. Some degree of dyspnea was reported by 96 (84.2%) of the 114 patients in the Brazilian cohort

and by 17 (28.8%) of the 59 patients in the Mexican cohort. The median radiological score was 5.0 (IQR, 4.0-7.3) for the Brazilian cohort and 6.0 (IQR, 3.0-10.0) for the Mexican cohort.

Evaluation of lung function over time in the Brazilian cohort

Pulmonary function tests were performed after the initial evaluation, although only in the Brazilian cohort. The mean time elapsed between the first and last tests was 8.3 ± 4.9 years. No intervention (pulmonary rehabilitation or surgical procedure) was performed between the first and last tests. As can be seen in Table 3, all functional parameters deteriorated over time, with the exception of RV in L, PaO_{2f} and SaO_{2f} , which decreased over time, albeit not significantly. Post-bronchodilator FEV_1 decreased from 1.7 ± 0.8 L to 1.4 ± 0.7 L ($p < 0.0001$). Post-bronchodilator FVC decreased from 2.6 ± 1.0 L to 2.3 ± 0.9 L ($p < 0.0001$). TLC decreased from 5.8 ± 1.8 L to 5.7 ± 1.7 L ($p < 0.0001$). DL_{CO} decreased from $49.1 \pm 16.7\%$ predicted to $41.8 \pm 19.9\%$ predicted ($p < 0.0001$). The six-minute walk distance decreased from 431.1 ± 105.3 m to 369.3 ± 107.9 m ($p < 0.0001$), and the lowest SaO_2 during the 6MWT decreased from 95.7 ± 2.2 to 94.6 ± 2.1 ($p < 0.0001$).

DISCUSSION

In the present study, tuberculosis was found to have a major impact on respiratory mechanics, gas exchange, and exercise tolerance in all cohorts. In the Brazilian cohort, all of the parameters evaluated

were found to have decreased over time. To our knowledge, this is the first comparison of cohorts of patients with PTLD in very different settings (North America, South America, and Europe).

A variety of sequelae can occur after tuberculosis, and many patients can present with persistent symptoms and reduced quality of life, as reported in the Brazilian and Mexican cohorts. Late diagnosis, increased number of treatments, extensive disease, MDR-TB, and untreated tuberculosis are usually associated with chronic impairment of lung function.⁽⁴⁾ However, even adequately treated patients (i.e., patients with microbiological cure) may be left with permanent pulmonary function abnormalities that will eventually impair exercise tolerance and quality of life, given the normal decline in lung volumes over the years.⁽²²⁾ Despite being young, the patients in the Mexican cohort were severely compromised, which

Table 2. Additional characteristics of the Brazilian and Mexican cohorts.

Characteristic	Cohort	
	Brazil (n = 114)	Mexico (n = 59)
BMI, kg/m ²	24.6 ± 4.9	25.6 ± 5.1
Cough	68 (59.6)	9 (15.3)
Dyspnea	96 (84.2)	17 (28.8)
DS-TB	112 (98.2)	32 (54.2)
MDR-TB	2 (1.8)	27 (45.8)
Radiological score	5.0 (4.0-7.3)	6.0 (3.0-10.0)

DS-TB: drug-susceptible tuberculosis; and MDR-TB: multidrug-resistant tuberculosis.

Table 1. Characteristics of the three cohorts of patients with tuberculosis sequelae.^a

Characteristic	Cohort			p
	Brazil (n = 114)	Italy (n = 43)	Mexico (n = 59)	
Age, years	65.3 ± 11.5 ^a	72.3 ± 9.0 ^b	41.1 ± 14.1 ^c	< 0.0001
Male sex	67 (58.8)	24 (55.8)	31 (52.5)	0.732
Current or past smoking	74 (64.9) ^a	25 (58.1) ^{ab}	16 (38.1) ^b	0.011
Post-BD FEV_{1f} , L	1.72 ± 0.83 ^a	1.36 ± 0.66 ^b	2.36 ± 0.86 ^c	< 0.0001
Post-BD FEV_{1f} , % predicted	59.3 ± 25.4 ^a	58.5 ± 24.5 ^a	79.9 ± 23.5 ^b	< 0.0001
Post-BD FVC, L	2.58 ± 1.04 ^a	2.37 ± 0.90 ^a	3.12 ± 1.06 ^b	< 0.0001
Post-BD FVC, % predicted	71.9 ± 23.9 ^a	77.9 ± 19.1 ^{ab}	88.3 ± 23.2 ^b	< 0.0001
Post-BD $\text{FEV}_{1f}/\text{FVC}$	66.5 ± 17.3 ^a	56.8 ± 17.3 ^b	76.2 ± 10.7 ^c	< 0.0001
Ventilatory pattern				
Obstructive	58 (50.9) ^a	11 (25.6) ^b	23 (39.0) ^{ab}	0.014
Restrictive	20 (17.5)	5 (11.6)	5 (8.5)	0.234
Mixed	15 (13.2) ^{ab}	18 (41.9) ^a	5 (8.5) ^b	< 0.0001
Normal	21 (18.4) ^a	9 (20.9) ^{ab}	26 (44.1) ^b	0.001
RV, % predicted	176.4 ± 78.8 ^b	140.8 ± 40.6 ^a	113.2 ± 41.6 ^a	< 0.0001
DL_{CO} , % predicted	50.3 ± 18.2 ^a	60.1 ± 20.5 ^a	88.6 ± 24.5 ^b	< 0.0001
PaO_2	78.6 ± 20.7 ^b	70.4 ± 7.5 ^a	65.3 ± 8.1 ^a	< 0.0001
SaO_2	94.4 ± 5.3 ^a	94.2 ± 2.3 ^a	91.9 ± 3.0 ^b	0.002
6MWD, m	430.6 ± 102.3 ^a	378.1 ± 122.5 ^b	536.7 ± 93.3 ^c	< 0.0001
Lowest SaO_2 during the 6MWT	95.7 ± 2.1 ^a	88.5 ± 5.2 ^b	86.2 ± 4.4 ^c	< 0.0001

BD: bronchodilator; 6MWD: six-minute walk distance; and 6MWT: six-minute walk test. ^aEqual letters mean no significant difference between cohorts, whereas different letters indicate a significant difference between cohorts.

Table 3. Decline in lung function over time in patients with tuberculosis sequelae in the Brazilian cohort.

Variable	Early follow-up	Late follow-up*	p
Pre-BD FEV ₁ , L	1.5 ± 0.8	1.3 ± 0.7	< 0.0001
Pre-BD FEV ₁ , % predicted	55.0 ± 25.0	48.9 ± 21.3	< 0.0001
Pre-BD FVC, L	2.4 ± 0.9	2.2 ± 0.9	< 0.0001
Pre-BD FVC, % predicted	66.9 ± 22.9	62.1 ± 20.0	< 0.0001
Pre-BD FEV ₁ /FVC	65.7 ± 16.8	61.3 ± 16.6	< 0.0001
Post-BD FEV ₁ , L	1.7 ± 0.8	1.4 ± 0.7	< 0.0001
Post-BD FEV ₁ , % predicted	59.2 ± 25.7	51.8 ± 21.8	< 0.0001
Post-BD FVC, L	2.6 ± 1.0	2.3 ± 0.9	< 0.0001
Post-BD FVC, % predicted	72.1 ± 24.1	65.5 ± 20.8	< 0.0001
Post-BD FEV ₁ /FVC	66.3 ± 17.2	62.1 ± 18.3	< 0.0001
TLC, L	5.8 ± 1.8	5.7 ± 1.7	< 0.0001
TLC, % predicted	103.8 ± 31.9	102.5 ± 27.5	< 0.0001
RV, L	4.3 ± 8.3	3.4 ± 1.4	0.089
RV, % predicted	178.6 ± 82.2	165.9 ± 70.4	< 0.0001
DL _{CO} , % predicted	49.1 ± 16.7	41.8 ± 19.9	< 0.0001
PaO ₂	71.1 ± 12.9	67.6 ± 16.5	0.125
SaO ₂	93.1 ± 6.2	91.9 ± 6.9	0.999
6MWD, m	431.1 ± 105.3	369.3 ± 107.9	< 0.0001
Lowest SaO ₂ during the 6MWT	95.7 ± 2.2	94.6 ± 2.1	0.007

*Mean time elapsed between the first and last tests: 8.3 ± 4.9 years. BD: bronchodilator; 6MWD: six-minute walk distance; and 6MWT: six-minute walk test.

is due to a high proportion of MDR-TB cases in that cohort. Although lung function was less compromised in the Mexican cohort than in the Italian and Brazilian cohorts, the Mexican cohort had more severe hypoxemia at rest and during exercise. Sometimes the combination of a restrictive pattern of sequelae (such as pulmonary fibrosis) with obstruction can lead to normal spirometry results or mild airway obstruction, with severe hypoxemia.⁽²³⁾

The most prevalent abnormal ventilatory pattern was an obstructive pattern in the Brazilian and Mexican cohorts, whereas, in the Italian cohort, it was a mixed obstructive and restrictive pattern. There is a wide variability in pulmonary involvement of tuberculosis. Pulmonary function tests can range from normal to severe dysfunction.^(24,25) The type of ventilatory defect is also quite heterogeneous.^(24,26) Actually, several studies have shown that lung function impairment is typically obstructive but occasionally restrictive.^(22,27-30) Host immune responses are probably a key component of this variable lung damage, but the specific factors associated with this damage remain unknown. An obstructive ventilatory pattern is related to excessive inflammation and, most frequently, to airway narrowing, pulmonary cavitation, and bronchiectasis. On the other hand, a restrictive ventilatory pattern is related to excessive fibrosis and presents radiologically as fibrotic bands, bronchovascular distortion, and pleural thickening.⁽¹¹⁾ Several studies have demonstrated that a history of treated tuberculosis is a risk factor for COPD.^(26,28,31,32) In a population-based study involving 14,050 patients from 128 countries, previous tuberculosis was associated with a 2.5-fold increased risk of COPD.⁽²⁸⁾ Furthermore, in a meta-analysis, treated tuberculosis

patients were shown to be approximately 3 times more likely to develop COPD.⁽²⁶⁾

Our study has some limitations. First, we compared different settings and clinical profiles. However, this becomes an opportunity to discuss how better to apply the new clinical standards for the assessment, management, and rehabilitation of PTLD.⁽¹²⁾ Second, it is difficult to estimate the role of smoking in lung function impairment because we had incomplete information on patient smoking habits (i.e., smoking history, in pack-years), which are difficult to assess because they are subject to memory bias. Despite these concerns, the strengths of our study are the completeness of functional evaluation in the three cohorts and the possibility (the first to our knowledge) to make an international comparison of PTLD patterns, including the evaluation of lung damage over time in one cohort.

In conclusion, the present study reinforces the importance of early and effective treatment of DS-TB patients, because MDR-TB increases lung damage. When patients complete their tuberculosis treatment, they should be evaluated as early as possible, and, if PTLD is diagnosed, they should be managed and offered pulmonary rehabilitation because there is evidence that it is effective in patients with PTLD.^(5,22,33-35) Preliminary data have shown that there is a significant improvement in the six-minute walk distance, lung function parameters (FEV₁ and FVC), and median SaO₂ after implementation of a comprehensive pulmonary rehabilitation program.⁽⁵⁾ Given that a decline in all lung function parameters was documented over a mean follow-up of 8.3 ± 4.9 years in the Brazilian cohort, additional prospective data are needed to determine whether pulmonary rehabilitation can improve the clinical history of PTLD.

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AUTHOR CONTRIBUTIONS

DRS: conceptualization, methodology, investigation, data curation, project administration, and drafting

of the manuscript. AAF, ARG, LD, RC, MMT, and DV: conceptualization, methodology, investigation, and drafting and revision of the manuscript. GBM: conceptualization, methodology, investigation, data curation, supervision, and drafting of the manuscript.

CONFLICTS OF INTEREST

None declared.

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