

Pulmonary Functions' Assessment in Post-tuberculosis Cases by Spirometry: Obstructive Pattern is Predominant and Needs Cautious Evaluation in all Treated Cases Irrespective of Symptoms

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Abstract

Background: Approximately 30%–40% patients suffer with lung function issues in spite of successful treatment outcome; and these problems are less documented routinely. **Methods:** Prospective multicentric study conducted during July 2013–June 2017, to find pulmonary function assessment in posttuberculosis (TB) cases irrespective of their symptoms, included 500 cases in symptomatic and asymptomatic group and subjected to inclusion and exclusion criteria. All cases were subjected to spirometry analysis. Statistical analysis was done using Chi-square test. **Results:** In spirometry assessment of symptomatic post-TB cases, obstructive pattern was predominant type documented in 42% cases. In spirometry assessment of asymptomatic post-TB cases, obstructive pattern is documented in 32%, mixed pattern in 14%, and normal spirometry is documented in 46% cases. In spirometry assessment in symptomatic and asymptomatic cases, obstructive pattern is documented in 210 cases and 160 cases, respectively ($P < 0.00001$). Abnormal lung function is documented in 70% and 54% in symptomatic and asymptomatic post-TB cases, respectively ($P < 0.00001$). **Conclusions:** Lung function impairment is known to occur after pulmonary TB irrespective of duration of treatment and outcome of disease. Obstructive lung disease is the predominant lung function impairment in symptomatic cases. Significant number of asymptomatic cases are also having obstructive pattern of lung function in spirometry analysis.

Keywords: Obstructive pattern, posttuberculosis, pulmonary functions, spirometry

INTRODUCTION

Tuberculosis (TB), the disease caused by *Mycobacterium tuberculosis*, remains a major public health problem globally. In 2014, >9.6 million people are estimated to have fallen ill with TB, while 1.5 million people died of the disease.^[1] Of the 6.3 million notified cases of TB that occurred in 2014, 81% had lung TB.^[1] Over the past two decades, treatment of TB has significantly improved and 61 million patients were successfully treated for TB globally since 1995.^[1] However, such successful treatment of TB based on either documentation of bacteriological clearance of *M. tuberculosis* bacilli from the involved site or completion of the prescribed drug dose does not assess structural and functional effects on the involved organ which is the hallmark of the pathology of TB.^[2]

Based on recent trends in treatment outcomes, about 86% of the new and relapse pulmonary TB (PTB) cases notified

in 2014 were successfully treated. However, several studies have demonstrated the persistence of symptoms, reduced quality of life, abnormal radiological findings, and impaired pulmonary function tests (PFTs) in patients successfully treated for PTB.^[3-6]

The presence of extensive residual lung lesions may be a predictor of permanent disability following tissue destruction, cor pulmonale, and susceptibility to opportunistic infections, leading to reduced quality of life.^[7] In addition, the extent of disease is one of the risk factors involved in TB mortality rates.^[8]

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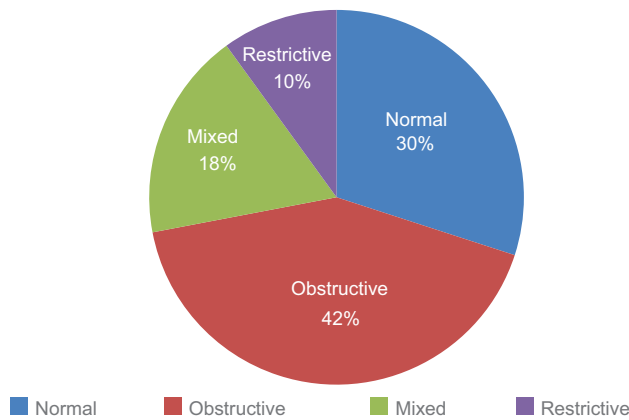


Figure 1: Pie diagram showing spirometry assessment in symptomatic posttuberculosis cases

The histopathological findings resulting from TB include the formation of caseous granuloma, tissue liquefaction, and formation of pulmonary cavities.^[7] From these changes, residual lesions remain in many patients, resulting in pulmonary sequelae that are characterized by impairments in the bronchial and parenchymal structure. These structural changes include bronchovascular distortions, bronchiectasis, emphysema, and fibrosis.^[2]

PTB can involve the airways, leading to mucosal edema, hypertrophy, and hyperplasia of mucous glands, increased mucus secretion, and smooth muscle hypertrophy. This affects the caliber of the airways, increases its strength, and decreases airflow.^[9] Through the mechanism of cicatricial fibrosis, there is also a reduction of total lung capacity.^[10] Post-TB patients may have limited exercise tolerance and significant disability which may affect daily activities.^[11]

Studies of pulmonary function in individuals with PTB demonstrated variable patterns and severity of impairment.^[2,12-16] Pulmonary function studies^[2,12-16] can show restrictive, obstructive, or mixed patterns and range from normal to severe impairment. These findings are currently incompletely characterized. The studies performed to date^[2,12-16] have been of highly selected populations, as follows: patients receiving only inpatient TB treatment; patients who have been referred for a symptom or preoperative evaluation; patients with an absence of other lung diseases; and persons sufficiently well to be currently employed in mining.^[2,12-16] These patients do not completely represent the populations affected by TB. PFTs objectively quantify lung function and impairment and are used to evaluate persons with chronic lung disease.^[17]

In this study, we observed pulmonary functions by spirometry by categorizing patients as asymptomatic and symptomatic previously treated PTB cases.

METHODS

A prospective multicentric observational study conducted in Venkatesh Chest hospital, and Pulmonary Medicine, MIMSR

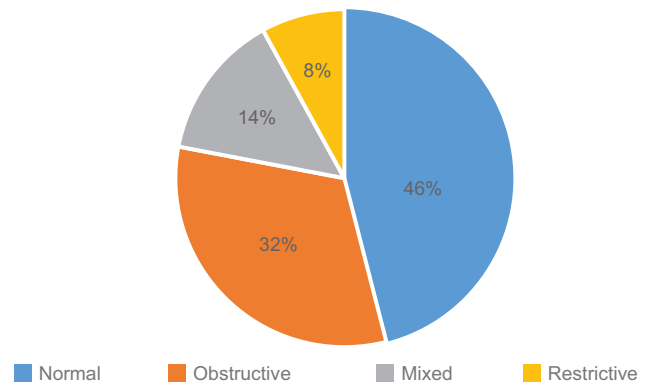


Figure 2: Pie diagram showing spirometry assessment in asymptomatic posttuberculosis cases

Medical College Latur during July 2013 to June 2017, to find out lung function assessment of previously treated PTB. We enrolled asymptomatic and symptomatic previously treated and declared cured as per national guidelines. A total of 500 asymptomatic and 500 symptomatic cases were enrolled in the study after IRB approval and written informed consent of the patient.

Inclusion criteria

1. PTB cases completed anti-TB treatment as per the standard guidelines for 6 months
2. PTB cases completed treatment as per national guidelines and declared cured.

Exclusion criteria

1. Extrapulmonary TB cases
2. Simultaneous involvement of lung and pleura
3. Multidrug resistant TB cases
4. Defaulted cases during treatment
5. History of irregular treatment
6. Cases with a history of smoking active or past to avoid spirometry analysis
7. Cases with diabetes mellitus, hypertension, and ischemic heart disease
8. Cases unable to cooperate during spirometry procedure or does not want to enroll in the study
9. Cases who failed to fulfill acceptability and reproducibility criteria of spirometry were excluded from the study.

All study cases were undergone following assessment to rule out other comorbidities from pure respiratory system involvement

1. Clinical assessment as vital parameters such as heart rate, respiratory rate, blood pressure, and documentation of respiratory adventitious sounds
2. Laboratory parameters such as hemoglobin, renal functions, blood sugar level, kidney functions, and electrocardiography
3. Spirometry performed.

Methodology of spirometry

Subsequently, spirometric evaluation was done by a portable spirometer, Spirolab II (manufactured by Medical International

Table 1: Spirometry assessment of symptomatic posttuberculosis cases (n=500)

	Total cases (%)
Normal	150 (30)
Obstructive	210 (42)
Mixed	90 (18)
Restrictive	50 (10)

Table 2: Spirometry assessment of asymptomatic posttuberculosis cases (n=500)

	Total cases (%)
Normal	230 (46)
Obstructive	160 (32)
Mixed	70 (14)
Restrictive	40 (8)

Table 3: Comparative spirometry analysis of symptomatic (n=500) and asymptomatic (n=500) cases in previously treated tuberculosis

	Symptomatic cases	Asymptomatic cases
Normal	150	230
Obstructive	210	160
Mixed	90	70
Restrictive	50	40

$\chi^2=27.21$, $df=4$, $P<0.00001$

Table 4: Spirometry abnormality in symptomatic (n=500) and asymptomatic (n=500) cases in previously treated tuberculosis

	Symptomatic cases (n=500), n (%)	Asymptomatic cases (n=500), n (%)
Normal	150 (30)	230 (46)
Abnormal	350 (70)	270 (54)

$\chi^2=27.16$, $df=1$, $P<0.00001$

Research, Italy) and meets American Thoracic Society and European Respiratory Society standards (ATS and ERS), before and 15 min after administration of 400 microgram salbutamol using pressurized metered-dose inhaler with small-volume spacer device. All patients were instructed not to use any bronchodilator on the preceding night and on the day of procedure. Spirometric procedure was carried out as per ATS/ERS task force recommendation for standardization of lung function testing.^[18] Subjects who were found to have postbronchodilator forced expiratory volume in first second (FEV1)/forced vital capacity (FVC) <0.7 were taken up for final analysis as this value indicates the cutoff for diagnosis of obstructive airway disease according to GOLD guideline. Bronchodilator reversibility was defined as an improvement in FEV1 by at least 12% and 200 ml over prebronchodilator value. FEV1/FVC \geq 0.7 was excluded as those patients had either a normal spirometry or a purely restrictive ventilatory abnormality. Furthermore, the individuals who failed to fulfill acceptability

and reproducibility criteria of spirometry were excluded. FVC, FEV1, and FEV1/FVC ratio values for case patients were compared with gender-specific and race-specific adult predicted normative population values and the control group.^[17]

Interpretive algorithms were used in determining restrictive or obstructive patterns and spirometry results were analyzed and categorized in four groups as follows:^[17-20]

1. Normal - FEV1/FVC ratio of >70% and an FVC of >80% predicted
2. Obstructive - airway obstruction was defined as an FEV1/FVC ratio of <70% and an FVC of >80% predicted
3. Mixed-combined defects were FVC of <80% predicted and an FEV1/FVC ratio of <70%
4. Restrictive-restrictive defects as an FEV1/FVC ratio of >70% with an FVC of <80% predicted.

The statistical analysis was done using Chi-squared test (three methods of Chi-squared test such as independence, goodness of fit, and proportion test). Significant values of Chi-squared were seen from probability table for different degrees of freedom required. *P* value was considered statistically significant if it was below 0.05 and highly significant in case if it was <0.001.

RESULTS

In this study, a total of 500 cases were in symptomatic and asymptomatic group of post-TB cases. In both the groups, males were predominant with 64% and 56%, respectively. Mean age was 42 ± 11 years and 48 ± 9 years, respectively. Main symptoms in symptomatic group were shortness of breath in 79% cases, cough in 48% cases, and sputum production in 39% cases.

In spirometry assessment of symptomatic post-TB cases, obstructive pattern was predominant type documented in 42% cases [Table 1 and Figure 1].

In spirometry assessment of asymptomatic post-TB cases, obstructive pattern is documented in 32%, mixed pattern in 14%, and normal spirometry is documented in 46% cases [Table 2 and Figure 2].

In spirometry assessment in symptomatic and asymptomatic cases, obstructive pattern is documented in 210 cases and 160 cases, respectively ($P < 0.00001$) [Table 3].

$\chi^2 = 27.21$, $df = 4$, $P < 0.00001$.

In spirometry assessment in symptomatic and asymptomatic cases, a significant difference is documented in normal and abnormal spirometry parameters in both groups ($P < 0.00001$) [Table 4].

$\chi^2 = 27.16$, $df = 1$, $P < 0.00001$.

DISCUSSION

Lung function pattern in symptomatic posttuberculosis cases

In this study, abnormal lung function is documented in 70% and 54% in symptomatic and asymptomatic post-TB cases,

respectively ($P < 0.00001$). Pasipanodya *et al.*^[7] conducted a study in the United States showed that 59% of patients treated for TB subsequently had abnormal pulmonary function. In that study, more than half of the patients treated for PTB evolved to significantly impaired pulmonary function. These data suggest that impaired pulmonary function after PTB is a major cause of chronic lung disease.^[7] Agarwala *et al.*^[21] conducted a study in India and observed that 52.7% of treated PTB patients had an obstructive ventilatory defect. Manji *et al.*^[22] conducted a study in Tanzania and observed the prevalence of abnormal lung functions in 74% of cases.

In the present study, spirometry assessment of symptomatic post-TB cases, obstructive, restrictive, and mixed pattern was observed in 42%, 10%, and 18%, respectively. Manji *et al.*^[22] documented in their study, the prevalence of individual patterns of impairment was 42%, 13%, and 19% for obstructive, restrictive, and mixed patterns of lung disease, respectively. A study by Pasipanodya *et al.*^[7] observed that the prevalence of individual subtypes of impairment for obstructive, restrictive, and mixed was 15%, 31%, and 13%, respectively. Studies by Long *et al.*,^[2] Willcox and Ferguson,^[14] Plit *et al.*,^[23] and Lee and Chang^[24] observed similar lung function abnormalities, and results are comparable to our study. Snider *et al.*^[13] found evenly distributed patterns of dysfunction among impaired patients, as follows: restrictive dysfunction, 24%; obstructive dysfunction, 23%; and mixed dysfunction, 19% cases. Verma *et al.*^[25] described similar findings in their study among 92 post-PTB individuals and they found restrictive pathology in 37 and mixed pattern in 21 patients as per spirometric criteria.

In the present study, spirometry assessment of symptomatic post-TB cases, mixed pattern was observed in 18% cases. Studies by Ramos *et al.*,^[26] Di Naso *et al.*,^[27] and Singla *et al.*^[28] observed predominantly mixed pattern of spirometric abnormality in the study population and such a high prevalence of mixed pattern can be explained by the extensive fibrosis coexisting with airflow obstruction.

Chushkin and Ots^[29] observed that approximately half of all PTB patients treated at the local TB dispensary suffered from impaired pulmonary function, a prevalence much higher than that observed in the general population. Pulmonary impairment was identified in 102 (47.7%) of the patients, the pattern being obstructive in 74 (34.6%), restrictive in 18 (8.4%), and mixed in 8 (3.7%) cases.

Lung function pattern in asymptomatic posttuberculosis cases

In this study, abnormal lung function is documented in 70% and 54% in symptomatic and asymptomatic post-TB cases, respectively ($P < 0.00001$). Guilani *et al.*^[30] in their study documented that 62% of asymptomatic post-TB cases were having spirometry abnormality. In their study,^[30] they concluded that all cases of cured PTB are prone to develop pulmonary function impairment. Even asymptomatic cases may have defective lung function.

Anno and Tomashefski^[31] in one of the early studies reported impairment of respiratory function in PTB patients. There was an increase in the residual volume (RV), RV/total lung capacity ratio, and a reduction in the maximal breathing capacity in a selected group of TB patients.^[31]

Obstructive is the most common abnormality documented in posttuberculosis cases?

In spirometry assessment in symptomatic and asymptomatic cases, obstructive pattern is documented in 210 cases and 160 cases, respectively ($P < 0.00001$). Overall prevalence of obstructive spirometry pattern in symptomatic and asymptomatic cases was 42% and 32%, respectively ($P < 0.0001$). The multicenter population-based PLATINO study^[32] also evaluated the relationship between past history of TB and development of airflow obstruction in five Latin American countries. The overall prevalence of airflow obstruction was 30.7% among those with a history of TB.^[32]

Gaensler and Lindgren^[12] in their study reported evidence of airflow obstruction in 61% TB patients. In a cross-sectional study performed in Chicago Municipal TB Sanatorium by Snider *et al.*^[13] reported airflow obstruction in 23% patients.

Indian studies by, Brashier *et al.*^[33] reported a 46% prevalence of airflow obstruction and the prevalence increased with the duration after treatment completion. In the Gothi *et al.*^[34] series, obliterative bronchiolitis was the cause of chronic airflow obstruction in 13% of patients and 78% of obliterative bronchiolitis was post-TB. Verma *et al.*^[25] reported a much lower prevalence of airflow obstruction. In fully treated PTB patients, obstructive spirometric pattern was seen in 15 (16.3%) patients and majority had irreversible airflow obstruction.

Baig *et al.*^[35] performed study in Pakistan and observed that 55.3% of treated PTB patients presenting with dyspnea and had an obstructive ventilatory defect. Study conducted by Patricio Jiménez *et al.*^[36] had also revealed that an obstructive pattern of pulmonary functional impairment following treated PTB was more common. In a larger study by Akkara *et al.*, the authors found that, of 257 participants with cured PTB, 86.8% had spirometry readings consistent with obstructive airway disease, that is, FEV1:FVC <70%.

Di Naso *et al.*^[27] conducted a study in Brazilian population with severe obstructive pulmonary disease found that 15.7% of patients had PTB sequelae. Zhou *et al.*^[10] found a higher prevalence of obstructive disorders (68%) in previously treated TB cases.

Other important clinical intrusions observed in this study

Does past history of tuberculosis as independent risk factor for obstructive airway disease?

In the present study, spirometry assessment in symptomatic and asymptomatic cases, obstructive pattern, is documented in 210 cases and 160 cases, respectively ($P < 0.00001$).

Allwood *et al.*^[38] in a systematic review assessed the relation between PTB and the development of chronic airflow

obstruction. A total of 19 studies including 1 case series, 3 case-control studies, 4 cohort studies, 8 single-center cross-sectional studies, and 3 multicenter cross-sectional studies were eligible for final analysis. The authors confirmed a positive association between a past history of TB and the presence of chronic airflow obstruction.^[38]

Lam *et al.*^[5] in a population-based study involving Guangzhou Biobank Cohort reported a past history of TB as an independent predictor of airflow obstruction with odds ratio of 1.37 after adjusting sex, age, and smoking exposure. Lee and Chang^[24] in a cross-sectional population-based study based on data from Second Korea National Health and Nutrition Examination Survey 2001, analyzed the effects of the previous TB on the risk of obstructive lung disease development.

Plit *et al.*^[23] and Chung *et al.*^[39] documented that PTB patients usually develop maximum loss of lung function within 6 months of the diagnosis of TB and it stabilizes 18 months after completion of treatment.

The burden of obstructive lung disease (BOLD) study^[40] had also shown past history of tuberculosis as a risk factor for developing airflow obstruction in later life with the adjusted odd ratio of 2.51. Two recent systemic reviews also confirmed this association.^[37,38,41]

Ehrlich *et al.*^[42] observed similar finding in their review of South African literature and showed a significant association between chronic airway obstruction and PTB. Inghammar *et al.*^[43] showed that impaired pulmonary function was associated with an increased risk of active TB. However, if decreased lung function is a risk factor for the development of TB, it is also possible that pulmonary impairment is a risk factor for its recurrence.^[43]

Indian studies by authors Verma *et al.*,^[25] Rajasekaran *et al.*,^[44] Krishna *et al.*,^[45] and Salvi and Barnes^[46] observed that the obstructive airway disease is common in previously treated TB cases and documented within 1–10 years of follow-up.

Posttubercular pulmonary impairment emerges as a distinct entity in various patterns but mainly as airflow limitation and previous TB is considered as risk factor for COPD.^[46,47]

Spirometry is less commonly used in routine evaluation of posttuberculosis cases!

In the present study, spirometry assessment in symptomatic and asymptomatic cases, abnormality was documented in 70% and 54%, respectively ($P < 0.00001$).

The presence of symptoms is not a sensitive and specific indicator of airway limitation, and the use of a symptom questionnaire appears to be an ineffective means of identifying pulmonary impairment.^[48]

However, evidence suggests that PFT is not used consistently. Even in developed countries, less than half of all patients newly diagnosed with chronic pulmonary diseases receive PFTs near the time of diagnosis.^[49]

In three large population studies, the authors Caballero *et al.*,^[50] Lam *et al.*,^[5] and Menezes *et al.*^[32] found a significant association between history of PTB and presence of airflow obstruction according to spirometry.

Using a mechanical peak expiratory flow meter or a pocket spirometer as a screening tool can reduce the number of diagnostic PFTs required.^[51] Although it has not been established that PFTs can predict recurrence, their use can probably help select a group of patients at higher risk of recurrence who require longer follow-up and prevention measures. This supports the idea that patients previously treated for PTB should undergo PFTs. However, PFTs has yet to be included in the guidelines for the treatment of TB.^[52]

CONCLUSIONS

Lung function impairment is known to occur after PTB irrespective of duration of treatment and outcome of disease. Routine use of spirometry is less utilized in these cases, and proportionate number of these cases were missed quality diagnosis and treatment, with simple spirometry technique.

Obstructive lung disease is the predominant lung function impairment in symptomatic post-TB cases. A significant number of asymptomatic post-TB cases are also having obstructive pattern of lung function in spirometry analysis. These cases are less evaluated and less efficiently treated in clinical setting. Prompt evaluation with the use of spirometry is must in all the cases of TB irrespective of symptoms.

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Conflicts of interest

There are no conflicts of interest.

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