Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Spl Issue [2] 2022 : 20-26
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Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Spirometry after Successful Treatment of Pulmonary Tuberculosis

Mahendran C.S[1*], Anuj K Bhatnagar[2], Prachi Saxena[3]
[1,3]Department of Respiratory Medicine, Santosh medical college and Hospital, Santosh Deemed to be University, Ghaziabad, UP
[2]Department of Respiratory Diseases &Tuberculosis, RBIPMT, Kingsway Camp, New Delhi
Email: dean.research@santosh.ac.in

ABSTRACT
Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis complex and among the leading cause of mortality and morbidity in India. India accounts for 23% of the global TB burden. Tuberculosis has been stated as a risk factor for development of COPD in GOLD guidelines. Post-tuberculosis respiratory morbidity is common and constitutes a significant subgroup of chronic lung disease patients presenting to medical out patients. Little is known about the prevalence of a restrictive pattern after PTB. Since the evaluation of true restriction requires the measurement of TLC, while majority of the studies only use spirometry. Most of those studies were conducted in countries where the incidence of tuberculosis is low; the prevalence and type of pulmonary impairment might differ in countries where that incidence is high. To describe the spirometry findings after successful treatment of pulmonary tuberculosis. To find out association between symptoms and variables including smoking, previous histories of tuberculosis with lung function as elicited by spirometry. To describe the response to therapeutic intervention for post tubercular lung disease. It was an observational prospective longitudinal study which enrolled 35 patients. Study was conducted in the Department of Respiratory Diseases & Tuberculosis, Rajan Babu Institute for Pulmonary Medicine and Tuberculosis (RBIPMT), North Delhi Municipal Corporation, GTB Nagar, Kingsway Camp, Delhi-110009. Spirometry evaluation was done on 0, 3rd and 6th month after successful completion of ATT. Cough and expectoration were main complaints which was significantly (p value 0.0001) associated with abnormal pattern of spirometry, mainly with obstruction without reversibility and restrictive pattern especially in males with significant difference (p-value-0.007). Despite of therapeutic intervention there was no significant change in the spirometric status and chest symptoms over the period of 6 months after completion of ATT. There is no role of inhaled bronchodilators in normal, restrictive and mixed pattern. Inhaled bronchodilators can be given in post PTB patients with obstructive spirometric pattern. Thus, in post PTB patients' spirometry has a pivotal role in diagnosing the abnormal spirometric patterns and devising the appropriate treatment with inhaled bronchodilators in selected (obstructive) spirometric pattern.
***Keywords**: Tuberculosis (TB), Spirometry, COPD*

Received 12.07.2022 Revised 08.08.2022 Accepted 13.10.2022

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis complex and among the leading cause of mortality and morbidity in India. India accounts for 23% of the global TB burden [1].Chronic obstructive pulmonary disease (COPD) and tuberculosis are among the world's ten most prevalent diseases, the main burden of the latter being in the developing countries, in the form of pulmonary tuberculosis. Burden of disease in India for tuberculosis have been ranked as sixth in terms of disability and death [2]. Tuberculosis has been stated as a risk factor for development of COPD in GOLD guidelines [3], however, the impact of pulmonary tuberculosis on the prevalence of COPD has often remained neglected.

Pulmonary tuberculosis patient who has taken complete course of anti-tubercular treatment (ATT) and cured [4] with sputum smear negative for acid fast bacilli (AFB) and X-ray chest showing inactive lesions are frequently left with respiratory disability due to impairment in pulmonary function, ranging from mild to severe often present to pulmonary medicine OPD. Pulmonary TB can involve the airways, resulting in mucosal edema, hypertrophy/hyperplasia of the mucous glands, increased mucous secretion and smooth muscle hypertrophy. This affects the caliber of the airways, increases their resistance and decreases airflow. The mechanism of fibrotic scarring can also result in reduced total lung capacity [5].

Post-tuberculosis respiratory morbidity is common and constitutes a significant subgroup of chronic lung disease patients presenting to medical out patients.

Patients with treated TB may remain lifelong sufferers of disabling sequela of the disease which subsequently impair their quality of life. There have been few studies on impaired pulmonary function in PTB survivors, and most such studies have involved highly selected populations. The patients in these study groups do not fully represent the populations affected by tuberculosis.

Based on the literature it is seldom known about the prevalence of a restrictive pattern after PTB. Since the evaluation of true restriction requires the measurement of TLC, while majority of the studies only use spirometry. Most of those studies were conducted in countries where the incidence of tuberculosis is low; the prevalence and type of pulmonary impairment might differ in countries where that incidence is high. Therefore, it the study was designed to describe the spirometry findings after successful treatment of pulmonary tuberculosis. Furthermore, to out association between symptoms and variables including smoking, previous history of tuberculosis with lung function as elicited by spirometry and drive the effectiveness based on response to therapeutic intervention for post tubercular lung disease.

MATERIAL AND METHODS

The current study was an observational prospective longitudinal study in which 46 patients (based on sample size calculation) have been enrolled. Study was conducted in the Department of Respiratory Diseases & Tuberculosis, Rajan Babu Institute for Pulmonary Medicine and Tuberculosis (RBIPMT), North Delhi Municipal Corporation, GTB Nagar, Kingsway Camp, Delhi-110009. Study period was taken from 1st Dec 2017 to 30th April 2018 where spirometry evaluation was done on 0, 3rd and 6th month after successful completion of ATT.

Inclusion of Study Subjects

Pulmonary tuberculosis patients aged above 18 years old those who have taken full course of Cat I, Cat II ATT under RNTCP and declared cured and Sputum Smear for AFB-ve were included in the present study.

Methods

Spirometry evaluation was done on 0, 3rd and 6th month after successful completion of ATT to evaluate the status of the lung health.

Statistical Analysis

Descriptive statistics were analyzed with SPSS version 18.0 software. Continuous variables were presented as mean (SD) or median if the data is skewed. Categorical variables were expressed as frequencies and percentages. Continuous variables were analyzed using repeated measures analysis of variance (ANOVA) and student t-test as appropriate. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

RESULTS AND DISCUSSION

All consecutively registered pulmonary TB patients who were declared cured/treatment completed at Kingsway Chest Clinic of RBIPMT and who met our inclusion and exclusion criteria were taken up as study group. A total of 50 patients were enrolled in this study between 1st December 2017 and 30th April 2018. Out of these 46 patients who had completed baseline, 3rd and 6th month follow-up visits and were consistently sputum smear negative were included in the final analysis of the study. Based upon the baseline spirometry findings, the study population was divided into Group A (Normal); Group B (Obstruction with significant reversibility); Group C(Obstruction with poor to partial reversibility); Group D (Restriction) and Group E (Mixed).

Table -1: Frequency distribution in various groups according to spirometry groups

GROUPS	Frequency (%)
A	13(28.3)
B	1(2.2)
C	15(32.6)
D	7(15.2)
E	10(21.7)
Total	**46(100)**

Maximum number of patients 47.8% (22) was in age group 20-40 constituting males more than females. Our study showed BMI of range 18.5 - 22.9 had highest frequency. Study revealed 37% participants were smokers with smoking index of $\geq$ 300.

In our study, maximum patients belonged to lower middle socio-economic status. Study revealed that out of 46 patients, 30 (65.2%) had chest symptoms; cough and expectoration were main complaints

constituting 65.2 % each, followed by dyspnea constituting 56.5% (26). out of these 26 patients, maximum patients had grade II mMRC breathlessness. 3 patients were diabetics.

In our study, out of 46 patients, 76.1% (35) had taken ATT once. These patients got their AFB sputum done at the initiation of ATT which showed that maximum 56.6% (26) patients had AFB direct smear in scanty/ 1+.

Out of 46 patients, therapeutic intervention was given to 33 patients who were continued on intervention over the period of 6 months. We compared age groups, gender, BMI, smoking status, socio-economic status with spirometry groups which showed no significant association. Chest symptoms were also being compared with baseline spirometry which showed significant association with spirometric group C, D, B+C, D+E, B+C+D+E compared to group A as shown in Table 2 below.

Comparison of mMRC grading and number of times ATT taken in past did not show any significant association with spirometric groups. We also compared patients baseline sputum AFB smear status at initiation of ATT with baseline spirometric groups which revealed that patients having low bacillary load at start of their ATT treatment were significantly associated with group C, Group D, Group B+C, Group D+E and Group B+C+D+E compared to group A as depicted in Table 3.

There was no change in the spirometric status of the patients over period of 6 months after completion of treatment. Our study also compared different variables with spirometry groups. All revealed insignificant association with some exceptions as mentioned further. There was significant association of male smoker with abnormal baseline spirometry compared to group A as shown in Table 4 below. There was significant association of cough with group C, B+C, D+E, B+C+D+E, compared to A in males and D+E, B+C+D+E compared to A in females with baseline spirometry as shown in Table 5.We also found significant association of baseline sputum smear status at initiation of ATT in males in group C, B+C compared to A. There was significant association of breathlessness, cough, sputum, wheeze at baseline, 3rd month and 6th month with baseline spirometry groups. Significant association was found in improvement of FEV1 with no change and worsening at 3rd month and 6th month in [group E, D+E, B+C+D+E] and group D+E as compared to group B+C respectively as depicted in Table 6,7.

In our study, we found that there was significant association in group A with improvement in group E, D+E, B+C+D+E in FVC at 3rd month as shown in Table 8.Also, there was significant association found between patients who had improvement in FVC at 6th month with group A as compared to abnormal spirometry pattern as depicted in Table 9.

Anti-tuberculosis treatment improves lung function in pulmonary tuberculosis patients but a significant proportion of patients are left with residual pulmonary impairment. After treatment of TB, the lung is left with residual fibrosis, scarring, cavitation and distortion of lung architecture leading to volume loss, and bronchiectasis. Pulmonary TB also involves airways leading to the edema, hypertrophy, and hyperplasia of mucous glands, thus affecting the caliber of the airways [6]. These patients form a large chunk of respiratory medicine department out as well as in patient. Unfortunately, because of simulation with clinico-radiological findings of PTB, such patients again had to take ATT from healthcare facilities. Moreover, there are no programmatic approach from government towards patient care in symptoms of post PTB patients. Post TB impairment can manifest as obstructive airway disease, restrictive or mixed defect. So, spirometry can be done to study the type of pulmonary impairment in these patients.

Our study was aimed at evaluating the spirometric changes in patients who had recently completed pulmonary TB treatment, factors significantly affecting spirometry and its correlation with symptomatology, also to study the response to therapeutic intervention. In this study among the total of 46 patients' abnormal spirometry was seen in 71.7% (33) of patients, and out of these 33, 2.2% had obstruction with significant reversibility, 32.6% had obstruction with poor or partial reversibility, 15.2% had restriction, 21.7% had mixed baseline spirometry. These findings indicate a huge burden of post tubercular pulmonary function abnormalities in patients of pulmonary TB. Similar study done by K. Sailaja *et al* shows that pattern of pulmonary function impairment was 62.5% obstructive, 16.07% restrictive and 21.42% mixed [7].

Demographic Characteristics

Body Mass Index (BMI): In our study, distribution of patients according to BMI was maximum in normal weight group (45.7%). Where as in study done by Singla et al [6]. It was found that maximum patients were in underweight group (52.3%). When BMI was compared in respective gender, it was seen that significant association (p value 0.03) found between females with BMI $\geq$18.5 and abnormal baseline spirometry groups when compared to males. This may be explained as females may have more extensive disease at time of presentation.

Smoking: In our study, maximum patients were nonsmoker (63%), followed by current (19.4%) and (17.6%) former smoker. Smoking index of >300 was seen in 76.4% among smokers. Of all the smokers, 41% had obstructive pattern, 11.7% had restrictive pattern and 29.4% had mixed pattern, 17.6% had

normal pattern at baseline spirometry. In a similar study done by Santhosh Kumar P.V *et al* there were 72% smokers and 28% nonsmokers. Among smokers 31.7% had obstructive, 14.6% had restrictive 19.5% had normal pattern on spirometry [8]. Males who have smoked had significantly (p= 0.04) abnormal spirometry (group B+C+D+E) as compared to males who have not smoked at base line. This may be explained by the fact that smoking is a known risk factor for COPD and may contribute to abnormal lung function in post pulmonary TB patients.

Socioeconomic Status: In this study it was seen that maximum patients were from lower middle (45.6%) followed by upper lower (34.7%), lower (15.25%) and upper middle (4.3%). No patients were in group of upper class. Similar study done by Singla et al[6] in post MDR TB patients, maximum patients were in upper lower class was 54.3% followed by lower middle 39.1%, upper middle 4.3% and upper 2.2% [9].

Chest Symptoms: In this study, 65.2% were symptomatic. Patients with chest symptoms were significantly associated with abnormal spirometric pattern. Among the symptomatic patients, main complaint was of cough (58.6%) and expectoration (58.6%) followed by breathlessness (56.5%). In a similar study done by Santra et. al, breathlessness was found to be the most common symptom (95.6%) followed by cough (89.8%) and expectoration (75.3%)[9.] Out of 16 asymptomatic patients 6 (37.5%) had abnormal baseline spirometry. Cough and expectoration were significantly (p value 0.0001) associated with abnormal pattern of spirometry, mainly with obstruction without reversibility and restrictive pattern especially males (p-value- 0.007).

Co-Morbidities: In our study, only comorbidity was diabetes mellitus. There were 3 patients with diabetes mellitus, 1 with restrictive and 2 with mixed pattern of spirometry.

Sputum AFB Smear Status at Initiation of AIT: In this study, it was found that patients having low bacillary load at start of their ATT were significantly (p value 0.02) associated with normal baseline spirometry at the end of their treatment as compared to obstruction with and without reversibility, restriction as well as combination of restriction and mixed pattern. Thus, it also can be inferred that patient with high bacillary load had more of restrictive and mixed pattern, possibly because of more parenchymal destruction.

It was also found in our study that males who had low bacillary load were significantly (P value 0.04) associated with normal pattern of spirometry as compared to obstructive pattern. In a similar study done by Santosh K. PV et al, revealed that sputum smear positive TB patients after completion of their treatment associated with pulmonary function decline and obstructive pattern on spirometry [9]. Hence early diagnosis and treatment is required in cases of pulmonary TB to reduce the pulmonary function impairment after treatment completion.

Therapeutic Intervention Group: In our study among the total 46 patients, 33(71.7%) were given the therapeutic intervention based on symptoms and further follow up was done at 3rd& 6th month along with spirometry. The medications included both inhaled and oral medications. However, in this study it was observed that despite therapeutic intervention there was no significant change in the spirometric status as well as chest symptoms of the patients over the period of 3rd and 6 months after completion of TB treatment.

At 3rd and 6thmonth of follow up cough and expectoration were significantly (p value 0.03) associated with combined group of restriction (group D) and mixed (group E) as compared to (group B and group C). In this study, change in follow up spirometry at 3rd month and 6th month parameters (FEV_1 and FVC) when compared to baseline spirometry parameters after therapeutic intervention revealed that there was a significant (P value 0.005) improvement of more than 100 ml in $FEV_1$and FVC in normal baseline spirometry group as compared to abnormal (groupB+C+D+E) as well group E defect. Also, it was found that there is significant association with no change (greater or less than 100 ml) and more than 100 ml worsening in FEV1and FVC in combined group of restriction and mixed (group D+E) as compared to normal baseline spirometry. Study done by Malherbe et al shown that PET-CT to evaluate local lung inflammation in PTB patients demonstrated that many patients have enhancement and/or development of new inflammatory lesions despite 6 months of ATT and following one year of treatment completion suggesting persistent inflammation leading to worsening in spirometry after completion of treatment. Patient who had a pure restriction or mixed pattern at baseline spirometry had significantly associated with no change in spirometry at follow up after therapeutic intervention given. As cure rate of pulmonary tuberculosis keeps improving the cases of post PTB also will increase causing significant increase in burden of these patients on health care system. These patients when have persistent symptoms may visit health care system and may be wrongly diagnosed and treated for Tuberculosis. Hence policies need to be put forwarded by government agencies to identify these patients correctly and as earliest as possible for their correct diagnosis and treatment for better quality of life even after successful completion of treatment of pulmonary tuberculosis. This study is pointer towards the need for large multicentric

studies involving various investigative modalities like spirometry in patient who recently completed the course of treatment.

Table -2: Comparison of individual chest symptoms with baseline spirometry groups

Groups	Breathlessness			Cough			Sputum			Wheeze			Chest Pain		
	No	Yes	P Value	No	Yes	P Value	No	Yes	P Value	No	Yes	P Value	No	Yes	P Value
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
A	13 (65)	0	-	10 (62.5)	3 (10)	-	10 (62.5)	3 (10)	-	13	0	-	13	0	-
B	0	1 (3.8)	-	0	1 (3.3)	-	0	1 (3.3)	-	1	0	-	1	0	-
C	5 (25)	10 (38.5)	-	4 (25)	11 (36.7)	**0.007**	4 (25)	11 (36.7)	**0.007**	13	2	-	15	0	-
D	2 (10)	5 (19.2)	-	2 (12.5)	5 (16.7)	**0.035**	2 (12.5)	5 (16.7)	**0.035**	6	1	-	6	1	-
E	0	10 (38.5)	-	0	10 (33.3)	-	0	10 (33.3)	-	8	2	-	10	0	-
B+C	5	11	-	4	12	**0.005**	4	12	**0.005**	14	2	-	16	0	-
D+E	2	15	-	2	15	**0.003**	2	15	**0.003**	14	3	-	16	1	-
B+C+D+E	7	26	-	6	27	**0.0001**	6	27	**0.0001**	28	5	-	32	1	-

Table 3. Comparison of patient's baseline sputum AFB smear status at initiation of ATT with baseline spirometry groups

Groups	Smear neg/scanty/1+(n)	2+/3+(n)	P value
A	12	1	-
B	1	0	
C	8	7	0.02
D	3	4	0.04
E	7	3	0.16
B+C	9	7	0.03
D+E	10	7	0.03
B+C+D+E	19	14	0.02
Total	31	15	

Table-4 Comparison of gender with smoking status in baseline spirometry groups

Groups	Smoking						P value (Male vs female)
	Male		P Value	Female		P Value	
	Non smoker	smoker		Non smoker	smoker		
A	6	3	-	4	0	-	-
B	0	1	-	0	0	-	-
C	2	6	0.08	7	0	-	-
D	1	2	0.31	4	0	-	-
E	2	5	0.13	3	0	-	-
B+C	2	7	0.57	7	0	-	-
D+E	3	7	0.10	7	0	-	-
B+C+D+E	5	14	0.04	14	0	-	-
Total	11	17		18			

Table - 5. Comparison of gender with cough in baseline spirometry groups

Groups	Cough						P value (Male vs female)
	Male			Female			
	No	Yes	P Value	No	Yes	P Value	
A	7	2	-	3	1	-	0.90
B	0	1	-	0	0		-
C	2	6	0.02	2	5	0.13	0.80
D	1	2	0.15	1	3	0.15	0.80
E	0	7	-	0	3	-	-
B+C	2	7	0.01	2	5	0.13	0.77
D+E	1	9	0.002	1	6	0.04	0.78
B+C+D+E	3	16	0.001	3	11	0.04	0.67

Table -6 Change in FEV1 at 3 rd. month in baseline spirometry groups.

Change in FEV_1 At follow up	3rd month		
Groups	Improvement	No change & worsening	P value
A	11	2	-
B	1	0	
C	10	5	0.27
D	0	7	-
E	2	8	0.001
B+C	11	5	0.32
D+E	2	15	0.00006
B+C+D+E	13	20	0.005
Total	24	22	

Table -7 change in FEV1 at 6th month in spirometry groups

Change in FEV_1	6th month		
Groups	Improvement	No change & worsening	P value
B+C	10	6	0.008
D+E	3	14	

Table 8 - Change in FVC at 3rd month in baseline spirometry groups

Change in FVC	3rd month		
Groups	Improvement	No change & worsening	P value
A	10	3	
B	0	1	
C	11	4	0.83
D	0	7	-
E	3	7	0.02
B+C	11	5	0.62
D+E	3	14	0.001
B+C+D+E	14	19	0.03
Total	24	22	

Table -9 Change in FVC at 6th month in baseline spirometry groups

Change in FVC	6th month		
Groups	Improvement	No change & worsening	P value
A	11	2	-
B	0	1	
C	11	4	0.46
D	0	7	-
E	3	7	0.007
B+C	11	5	0.32
D+E	3	14	0.0002
B+C+D+E	14	19	0.009
Total	25	21	

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CITATION OF THIS ARTICLE

Mahendran C.S, Anuj K Bhatnagar, P Saxena. Spirometry after Successful Treatment of Pulmonary Tuberculosis . Bull. Env.Pharmacol. Life Sci., Spl Issue [2]: 2022: 20-26