

Treatment outcome among Post TB obstructive airways diseases and COPD: A prospective cohort study

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ABSTRACT

Context: Post Tubercular Obstructive Airways Diseases (Post-TB OAD) is a sequela of Pulmonary TB but diseases progression may not same like Chronic Obstructive Pulmonary Diseases (COPD). **Aim:** To compare the frequency and severity of exacerbations, change of FEV1, frequency of hospitalization and mortality among COPD and post TB OAD patients. **Setting and Design:** Hospital-based prospective cohort study. **Methods and Material:** COPD cohort was diagnosed based on symptoms, history of exposure to risk factors and post bronchodilator FEV1/FVC ratio <70%. Post TB OAD cohort was diagnosed like COPD along with past history of Pulmonary TB. Both cohorts were followed up every 3-monthly intervals for up to 12 months. **Statistical Analysis:** Comparison of categorical variable was done by Chi-square test and continuous variable by unpaired *t* test. Longitudinal data of FEV1% were analyzed by repeated measure ANOVA test. **Results:** Totally, 68 patients with Post TB OAD and 66 COPD patients were taken into this study. The frequency of exacerbation (3.52 ± 1.84 verses 2.70 ± 1.37), number of severe exacerbation (56 verses 24) and frequency of hospitalization (1.37 ± 0.81 verses 0.97 ± 0.94) more seen in post-TB OAD cohort in compared to COPD cohort which is statistically significant. Mortality more seen in post-TB OAD group (14 verses 6). Rate of decline FEV1 per year more seen in Post-TB OAD (0.27 ± 0.28 lit verses 0.17 ± 0.26 liter) as compared to COPD. There was overall decreasing trend of FEV1% over period of 12 month but without any difference among two cohort. **Conclusion:** There was more in frequency of exacerbations, number of severe exacerbations, frequency of hospitalization and number of mortalities among post TB OAD compared to COPD.

Keywords: COPD, FEV1, post TB obstructive airway diseases

Introduction

Chronic obstructive pulmonary disease (COPD) was the second leading non-communicable cause of death and disability accounting for nearly 11% and 7% of all deaths and Disability Adjusted Life Years (DALYs) lost in India, respectively.^[1] There is increasing evidence to suggest lung injury can persist despite TB treatment, leading to chronic pulmonary sequelae like post TB Obstructive Airways Diseases (Post TB OAD).^[2,3]

Pathophysiologic process in both COPD and post TB OAD are different.^[3] So, there is a need to explore further. The objective of this study was to compare the frequency and severity of exacerbation, change of FEV1, frequency of hospitalization and mortality among COPD and Post TB OAD patients.

Subject and Methods

This study was conducted at both OPD and indoor setting of the Department of Pulmonary Medicine of Medical College Hospital during the period of November 2017 to October 2019. This study was a hospital based Prospective Cohort Study. Patient attending OPD and admitted to

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Pulmonary Medicine department having symptoms of cough with or without sputum production, breathlessness, and spirometry finding suggestive of persistent airflow obstruction (post Broncho-dilatation FEV₁/FVC <70%) were included as study population in this study. Patient with past history Pulmonary TB and presence of persistent airflow obstruction with spirometry (Post Broncho-dilatation FEV₁/FVC <70%) was named as Post-TB Obstructive Airways Diseases (Post-TB OAD) cohort. Past history of TB known by valid documentary evidence irrespective of anti-TB medication. Patient with no history of TB but history of risk factors like exposure to tobacco smoke, biomass fuels, occupational dusts, vapors, gases, and evidence of persistent airflow obstruction by spirometry (Post Broncho-dilatation FEV₁/FVC <70%) was named as COPD cohort. Patients age <18 yrs, subjects who were unable to perform spirometry, pregnancy (of any gestational age), having bacteriologically/radiologically active TB and patients those having contra-indication for spirometry^[4] were excluded from the study. Based on Previous study, rate of hospitalization per year was (2.46 ± 0.26) in post TB OAD and (1.56 ± 0.88) in COPD.^[5] Minimum sample size was around 25 in each cohort, which was calculated taking into α error 1%, 2 sided and power (1- β) of 99%. Convenience sampling method was followed.

Both COPD and Post-TB OAD patients' data were collected through structured questionnaire during the time of enrolment. Enrolment of study population was taken up to 1 yr. All patients were followed up for 12 months in 3 monthly intervals. Follow up data are collected through separate structured questionnaire. Particular emphasis was given for the change of symptoms signs, spirometry finding, frequency of exacerbation etc., All patients followed as per present GOLD guideline. Enrolled patient's un-scheduled visit (if any) data was also recorded. Enrolled Patients were reminded for scheduled follow up date by mobile phone call. Patients who lost to follow up were excluded from the analysis. After enrolling, a detail history, clinical examination, routine investigations, and spirometry were done. Spirometry with bronchodilator reversibility was done as per 2005 ATS/ERS guideline.^[6]

Severity of exacerbation was classified based on Global Initiative for Chronic Obstructive Lung Diseases (GOLD) 2017 guideline such as; mild (treated with short acting bronchodilator only), moderate (treated with short acting bronchodilator plus antibiotics and/or oral corticosteroid) and severe (required hospitalization or visit to emergency room).^[7]

Ethics: All participants of the study were being explained the objectives and protocols of the study. An informed written consent was taken from the patient or legal guardian of the patient (those unable to give consent due to sickness). During this study we followed the six-basic principle of medical ethics like; beneficence, non-maleficence, autonomy, justice, dignity and truthfulness and honest. Proper care has been taken for those patients developed acute exacerbation in form of treatment and

counselling. The study protocol was approved by institutional ethical committee (No. 2017/I-F-CT-01/077).

Statistical analysis

The continuous variables were expressed as mean values ± standard deviation. Comparison of continuous variable among Post-TB OAD and COPD was done by using the unpaired *t* test. The categorical data were expressed as percentage and comparison done by using the Chi-square test in parametric data and fisher's exact test in non-parametric data. Missing value were analyzed with Expectation Maximization method (Little's MCAR test). Longitudinal data of FEV₁ in percentages over period of 12 months were analyzed with repeated measure ANOVA with Greenhouse–Geisser correction method. For all statistical purposes *P* value less than 0.05 was considered to be statistically significant. All the statistical procedures were done with SPSS v 25 (IBM, New York).

Result

Totally, 68 patients of Post TB OAD as one cohort and 66 patients of COPD as another cohort was taken into study. The majority of the patients suffering from post-tubercular obstructive airway disease lie in the age group of 40-59 years and majority of COPD patients lie in the age group of 60-80 years. It has also been seen that age group below 40 year seen only in Post-TB OAD patients.

Table 1 shows mean age, mean BMI and frequency of male population lower in post-TB OAD than COPD group which is statistically significant. Co-morbidity among both cohorts were almost same prevalence. Totally, 11.8% of Post TB OAD patients also had exposure to tobacco smoking. Baseline post-bronchodilator FEV₁ slightly more in COPD cohort than post TB OAD but statistically insignificant. Whereas baseline post bronchodilator FVC less in post TB OAD in compared to COPD which is statistically significant. Baseline GOLD stage found in all most same frequency in both cohorts.

All the patients of both Post TB OAD and COPD presented to us as breathlessness. Post TB OAD patients had reported symptoms of cough (79.41% vs 96.97%), sputum production (67.65% vs 84.84%), hemoptysis (5.88% vs 3.03%), chest pain (23.53% vs 3.03%), chest tightness (26.47% vs 63.63%), and wheezing (26.47% vs 45.45%) as compared to the COPD.

Also, 41.18% of post-TB OAD patients developed respiratory symptoms after 6 years since completion of anti-tubercular therapy whereas 56% of patients developed respiratory symptoms within 6 years. One patient developed breathlessness due to obstructive airways pathology while on anti-tubercular treatment.

Table 2 shows, frequency of exacerbation, frequency of severe exacerbation, hospitalization rate more seen in post-TB OAD as compared to COPD. Though mortality rate more seen in post-TB OAD but statistically not significant.

The decline of absolute FEV1 value per year from time of enrolment to 1 year follow up was more marked in post TB OAD (0.27 ± 0.28 liter in Post-TB OAD and 0.17 ± 0.26 liter in COPD), which was statistically significant ($P < 0.05$).

There is overall significant change (decreasing trend) in mean FEV1% over a period of 12 months in both cohort as evidenced by Wilks' Lambda (4, 62) = 0.491, $F = 16.08$, $P < 0.001$, but the comparison of trend is not significant among two groups over a period of 12 months as evidenced by Wilks' Lambda (4, 62) = 0.980, $F = 0.323$, $P = 0.862$. Assuming unequal variances among all groups (Mauchly's test of sphericity $P < 0.001$), Greenhouse–Geisser correction was estimated [Figure 1].

Out of 68 post TB OAD patients 24 patients were on inhalational steroid as they were group D category based on GOLD. During 12 months follow-up period, 4 patients developed reactivation of TB and started re-initiation of anti-tubercular treatment. However out of 66 COPD patients, 44 patients were on inhalation steroid as they were group D category as per GOLD but none of them developed any active TB during follow up.

Discussion

Post TB OAD patients were younger than COPD patients in this study with a mean age of 51.8 years. Many other studies

showed similar finding that is mean age of post TB OAD patients were <65 yrs.^[8,9] Pulmonary tuberculosis is primarily a disease of young adults and the associated lung damage occurs during the acute disease process, which explains its relative contribution to post TB OAD being higher in the younger age group, especially in TB endemic areas. It has been seen that low BMI negatively influence prognosis of COPD.^[10] In our study, low BMI more seen in post-TB OAD, which may also negatively impact on prognosis.

Majority of patients in this study were male in both Post TB OAD and COPD group. In COPD cohort, male population were more as compared to Post-TB OAD. According to PLATINO study, males with history of TB were more likely to present with airflow obstruction than the female.^[11] In this country, smoking habit is predominant among males which not only results in COPD, but also increases the chance of acquiring PTB. Female patients are less likely to present to health facility with respiratory symptoms unless it is severe. These factors may be responsible for such a high percentage of male patients in this study population.

Totally, 11.8% of post TB OAD patients also had exposure to tobacco smoking. COPD patients also have history of exposure to biomass and outdoor pollution in addition of smoking. The effect of smoking and TB sequelae was undoubtedly additive in the development of chronic airflow obstruction in

Table 1: Baseline characteristic among COPD & Post-TB OAD

Variable	Post-TB OAD (n=68)	COPD (n=66)	P
Age (Years) Mean±SD	51.82±13.43	60.76±8.83	<0.001
BMI (kg/m ²) Mean±SD	18.52±3.65	20.02±3.87	<0.05
Male	44	58	<0.001
Alcoholic	10	12	>0.05
Co-morbidity			
Hypertension	4	10	>0.05
Diabetes Mellitus	8	10	>0.05
Cardio-vascular Diseases	4	6	>0.05
Chronic Kidney Diseases	2	2	>0.05
Exposure to risk factor			
Smoking	8	52	<0.0001
Biomass fuel Exposure	6	6	>0.05
Outdoor air pollution	4	10	>0.05
Baseline Post-bronchodilator FEV1% (Mean±SD)	33.82±14.14	38.42±23.06	>0.05
Baseline Post-bronchodilator FVC% (Mean±SD)	47.29±17.49	60.81±25.34	<0.05
Baseline GOLD Stage			
II	10	14	>0.05
III	26	18	>0.05
IV	32	30	>0.05

Table 2: Adverse events among Post- TB OAD & COPD

Types of Adverse Event	Post-TB OAD (68)		COPD (66)		P
	n (%)	Mean (SD)	n (%)	Mean (SD)	
Frequency of Exacerbation	-	3.52 (1.84)	-	2.70 (1.37)	<0.05
Severe Acute Exacerbation	56 (82)	-	24 (63)	-	<0.05
Hospitalization Rate	-	1.37 (0.81)	-	0.97 (0.94)	<0.05
Mortality rate	14 (20.59)	-	6 (9.09)	-	>0.05

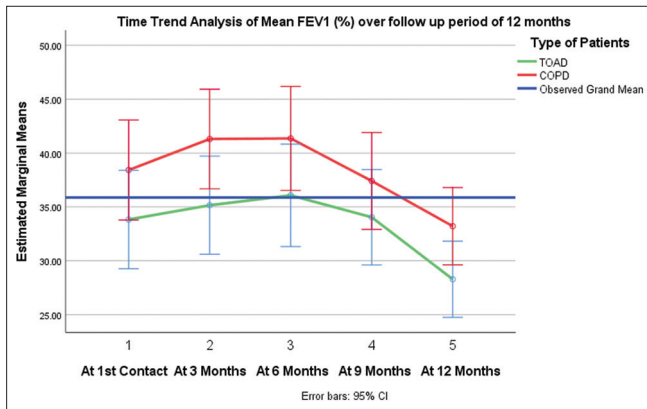


Figure 1: Time trend analysis of mean FEV1 (%)

this group of patients. Interaction with smoking is of particular interest, because it is a modifiable risk factor. Alcohol addiction, prevalence of co-morbidity, exposure to biomass fuel and outdoor pollution and baseline GOLD stage were equally seen in both Post TB OAD and COPD group that is matched in both cohorts. So, these factors cannot dissect the influences of these confounding factors.

Dyspnea was the commonest symptom both in Post TB OAD and COPD followed by cough and expectoration. Hemoptysis and chest pain seen mostly in Post TB OAD whereas chest-tightness and wheezing seen mostly in COPD. None of the symptoms were statistically dissimilar to each other. Similar finding noted in a Korean study in which no significant differences noted between the 2 groups in occurrence and frequency of symptoms of dyspnea and cough though there was a trend towards a greater frequency of hemoptysis in the Post TB OAD.^[12]

Majority of our post-TB OAD patients developed respiratory symptoms within 6 years of completion of anti-tubercular therapy. Study by Verma SK *et al.* and found that incidence of dyspnea in 27.7% cases within 1 year of stoppage of ATT, 50% developed within 1-5 years of stoppage of ATT and 13.3% after 5 years of completion of ATT which is similar to our finding.^[13] Whereas another study also mentioned that development of OAD and its impact is sustained for at least six years after TB diagnosis.^[14] Based on burden of tuberculosis, post-tubercular mortality and morbidity in India, it has been estimated that there is increased DALYs (Disability-Adjusted Life Years) from 54% to 174% which was due to post tuberculosis sequelae.^[15] These findings have important clinical impact for the management of TB and COPD, suggesting that some COPD cases may be preventable by controlling the TB epidemic and improving the quality of TB diagnosis and treatment. Moreover, follow-up care and early intervention for COPD may be necessary for TB patients after anti-TB treatment.

Baseline post-bronchodilator FEV₁ was lower in Post TB OAD (though statistically insignificant) as compared to COPD and also in decreasing trend during follow-up period. Similar finding was observed by other study like mean

post-bronchodilator FEV₁ values were lower in the group with past history of TB than in the other group.^[11,12] But some study showed opposite result i.e., COPD patients had more severe airflow obstruction than Post-TB OAD.^[16]

In this study the frequency of exacerbation, number of severe acute exacerbation and frequency of hospitalization were more seen in Post-TB OAD. As both group baseline line GOLD stage similar frequency, so frequency of hospitalization or exacerbation or decline rate of FEV₁ probably due to heterogeneity and separate phenotype. Similar observation found where; a greater number of hospitalization due to exacerbation among past history of TB in compared to without TB history.^[5] In this study there was more mortality among Post TB OAD compared to COPD. Other study noted that in-hospital mortality rates and hospitalization for the two groups were found to similar but 3-year overall mortality among past TB patients was higher compared to those without TB history.^[5] Though both COPD and Post-TB OAD patients have obstructive airways pathology but progression of diseases and outcome were different, this could be due to different causal pathway as cytokines inflammatory markers associated with two diseases were different.^[16]

The mean annual decrease post bronchodilator absolute FEV₁ value 270 ml in post TB OAD which was 100 ml more than to COPD in this study. More decrease in FEV₁ value in post TB OAD cohort could be due to more frequent exacerbation in this study. One study noted that the mean annual change of post bronchodilator FEV₁ in post-TB OAD was +48.52 ml/year while in COPD they was +108.28 ml/year.^[17] Recent study showed that around 14% of Post TB Lung diseases patients had declines in FEV₁ or FVC of ≥ 100 mL.^[18]

The trend of change of FEV₁% in each group was similar pattern. In first 3 month FEV₁% was increasing trend, 3rd month to 6th month almost no change but after 6 month decreasing trend was seen. The improvement of FEV₁% in first 3 month probably due to effect of bronchodilator but these effects gradually wear off. The overall decline of FEV₁% from baseline to 12-month follow up was significant in both cohort but difference among two cohort was not there. The declining lung function over period of time one of the important components of the natural history of COPD, which was seen in both cohorts.

Four of post-TB OAD patients developed relapse of Tuberculosis in contrast to none of patient from COPD in spite of use of inhalational corticosteroid. The hazard ratio for TB development in COPD was 2.47 (95% CI: 2.21,2.76) compared to control.^[10] COPD patient who subsequently developed TB had received higher daily dose of oral corticosteroid and oral β -agonists than COPD patients who did not develop TB.^[19] In another Taiwanese study, 10% of COPD patients develop pulmonary TB, those had received highest dose of fluticasone treatment (>500 mg/day) compared to 3% in lower dose and 1% in the no ICS group.^[20] Although there seems to be an

increased risk of PTB relapse in Post-TB OAD with chronic use of inhaled steroids, these patients could potentially benefit from treatment using only long-acting bronchodilators. Relapse in PTB, more likely towards drug resistance variety and also, Post TB sequelae more prevalent in drug resistance than to drug sensitive strain.^[21]

Further research required to identification of risk factors associated with development of Post-TB OAD and better potential treatment strategy, so that physician can attempt to prevent and effective management Post-TB OAD in pulmonary TB patients.

Strength of study was prospective cohort study, both cohorts were selected from same geographic, same ethnic population. So that we can able to interpret our data in better way than other cross sectional or retrospective study.

Limitation of this study as follows, first, though we have taken proper care for sample size calculation but still the sample size was less. So, interpretation of our data to be done with caution. Second, duration of follow up was up to 12 months, which may interfere towards outcome variable due to short duration of follow up. Third, though the treatment protocol was given as per GOLD guideline to both cohorts but we have not able to differentiate outcome based on the type of medication.

Relevant to the practice of primary care physicians

All the cases of post TB OAD patient should be examined for microbiological evidence to rule out active tuberculosis as there was evidence of relapse of PTB. Primary care physician's responsibility towards patients with PTB does not end with the microbiological cure but continues to show our future concern on functional abnormalities and good quality of life. So, after completion of treatment of PTB, we have to follow up the patient regularly not only to find out the relapse but also to look for early identification of any obstructive or restrictive abnormality to provide early treatment and prevention of bad outcome with available investigation tool like spirometry. As outcome of Post TB OAD and COPD were not same, so aggressive follow-up approach required for the treatment of Post TB OAD. Such an approach would be useful for public health purposes, so as to direct the attention for preventable causes.

Conclusion

Post-TB OAD patients are younger than COPD patients. There is significant more in frequency and severity of exacerbation, hospitalization rate, and rate of fall of FEV1 value per year among post TB OAD cohort than COPD cohort. Though the mortality rate was more seen among Post TB OAD compared to classical COPD. Both Post TB OAD and COPD had post-bronchodilator FEV1% in decreasing trend but no significant difference in the FEV1 decline rate among two group.

New Message: Treatment outcome of Post-TB OAD is worse than COPD in spite of almost similar presentation and treatment. Post TB OAD patients need more frequent follow-up for early identification and prevention of bad outcome. During the follow-up period physician should vigilant for relapse of TB also. After completion of anti TB drugs in Pulmonary TB patients, these patients need regular follow up for early identification of Post-TB OAD so that proper available treatment should be initiated for further progression of diseases.

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Conflicts of interest

There are no conflicts of interest.

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