

Evaluation of tuberculosis-associated chronic obstructive pulmonary disease at a tertiary care hospital: A case-control study

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ABSTRACT

Context: Irreversible airway obstruction is important sequelae of pulmonary tuberculosis (TB) that might contribute to a significant proportion of chronic obstructive pulmonary disease (COPD). India has the highest TB burden in the world. However, there are limited data on the prevalence and presentation of TB-associated COPD from this region. **Aims:** This study aims to evaluate the prevalence of TB-associated COPD among COPD patients presenting to a tertiary care hospital. **Settings and Design:** It was a case-control study conducted in a tertiary care hospital. **Subjects and Methods:** Stable COPD patients presenting to chest OPD and an equal number of healthy controls were enrolled. COPD patients were subjected to detailed clinical evaluation and lung function test. History of pulmonary TB was evaluated from both groups through self-reporting and/or checking previous records. TB-associated COPD patients were identified and their prevalence and distinguishing features evaluated. **Results:** Of 74 COPD patients, 24 (32.4%) had previous history of pulmonary TB. The odds of having a previous TB in COPD patients was 3.96 (95% confidence interval: 1.64–9.55; $P = 0.002$) as compared to controls. Patients with TB-associated COPD were younger ($P = 0.02$), had lesser pack-years of smoking ($P = 0.027$) but had more number of hospitalizations ($P = 0.01$). The airflow limitation was similar in both groups. **Conclusions:** TB-associated COPD constitutes a significant proportion of COPD patients. It is a distinct clinical entity with preponderance in young. It may be associated with frequent hospitalizations as compared to other COPD patients.

KEY WORDS: Airflow limitation, chronic obstructive pulmonary disease, pulmonary tuberculosis

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is estimated to affect 65 million people worldwide and is currently the third leading cause of death. Of the total number of deaths, 90% are in low- and middle-income countries which also harbor maximum number of pulmonary tuberculosis (TB).^[1]

Apart from tobacco smoke, COPD has been known to occur in patients with previous pulmonary TB.^[2,3] This COPD phenotype has been variably termed as posttubercular obstructive airway disease or TB-associated COPD.^[3] Most of the evidence on the causative association between TB and COPD has been derived from studies on lung function evaluation in treated TB patients or from population-based

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surveys on COPD.^[4-8] The difference in the study designs, criteria used for COPD diagnosis and previous TB detection has led to variable results in these studies. Moreover, the presence of confounding factors such as tobacco smoking, exposure to biomass fuel, and childhood respiratory illnesses has limited the strength of their association.

India is the highest TB burden country in the world and hence is likely to harbor significant burden of TB-associated COPD. Furthermore, India has a growing population of COPD and is in second place for harboring the most number of morbidity and mortality cases from obstructive airway disease, after China.^[9] Ironically, there is paucity of studies on TB-associated COPD from this geographical region.^[10,11] Moreover, it is not known whether the clinical presentation of this COPD phenotype is different from smoking-related COPD that might necessitate a different approach to its management.^[12]

Hence, we planned to conduct a retrospective case-control study to find out hospital-based prevalence of TB-associated COPD among COPD patients and to evaluate its characteristic features.

SUBJECTS AND METHODS

It was a case-control study conducted in a tertiary care hospital over a period of 6 months (April 2016 to September 2016). Seventy-four consecutive patients of stable COPD attending chest OPD were enrolled as cases. An equal number of healthy subjects with similar age and gender distribution were taken as controls. Informed consent was taken from all subjects.

COPD patients with other pulmonary comorbidities such as obstructive sleep apnea, interstitial lung disease, lung cancer, congestive heart failure, unstable angina, recent myocardial infarction, and acute exacerbation of COPD in the past 4 weeks were excluded from the study. The study was approved by the Institutional Ethics Committee.

Detailed clinical history and medical examination were done with an emphasis on type and duration of symptoms, number of previous exacerbations, previous hospitalizations, tobacco smoke exposure, and occupational exposures to dust and smoke. The history of previous TB was elucidated through self-reporting by patients and/or by checking their medical records, if available. Specific points such as number of anti-tubercular treatment (ATT) courses, total duration of treatment, time elapsed since completion of treatment and their final outcome were recorded. Routine spirometry was performed as per the recent ATS guidelines^[13] using RMS Helios 401 PC-based Spirometer. Postbronchodilator forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), and FEV₁/FVC values were recorded based on which patients were categorized into four stages of airflow limitation as per recent GOLD guidelines.^[14] Room air oxygen saturation

level was noted, body mass index (BMI) and routine X-ray chest (CXR) posteroanterior view was done.

Patients were labeled as TB-associated COPD only if their symptom of COPD started after the episode of pulmonary TB. The prevalence of TB-associated COPD group was calculated, and its different parameters were compared with rest of COPD patients.

Statistical analysis

Data were statistically described in terms of mean \pm standard deviation, median with range or frequencies, wherever appropriate. Comparison of continuous variables between two groups was done using Student's *t*-test for independent variables. Correlation between different variables was carried out using Pearson correlation. $P < 0.05$ was considered statistically significant. All statistical calculations were done using computer program (IBM SPSS Statistics version 21.0).

RESULTS

Elderly males comprised the majority of COPD patients in our study. Out of 74 patients, 64 (86.5%) had a history of >10 pack-years of tobacco smoking, out of which 19 were current smokers [Table 1].

The distribution of patients among different COPD stages is shown in Figure 1. Median duration of onset of symptoms was 4 years (range: 2 months–25 years). History of exacerbation in the preceding year was present in 31% ($n = 23$) patients. Thirty-five patients had a history of the previous hospitalization related to COPD. There was a history of 51 COPD-related hospitalizations in 35 patients that occurred at any point during their illness.

Prevalence of tuberculosis-associated chronic obstructive pulmonary disease

Twenty-four patients (32.4%) in the COPD group and 8 patients in the control group had a history of TB. The unadjusted odds ratio for previous TB in the COPD group in comparison to controls was 3.96 (95% confidence interval: 1.64–9.55; $P = 0.002$). Median time elapsed since

Table 1: Baseline features of chronic obstructive pulmonary disease patients ($n=74$)

Patient parameter	Value
Age (years), mean \pm SD	60.2 \pm 8.9
Male:female	8:1
BMI (mean \pm SD)	19.56 \pm 5.02
Number of smokers (%)	86.5
Median pack years (range)	30.0 (0-120)
Exposure to chulha smoke (percentage patients)	19
Percentage oxygen saturation (mean \pm SD)	94 \pm 2.2
Percentage predicted FEV ₁ (mean \pm SD)	46.7 \pm 17.7
Percentage predicted FVC (mean \pm SD)	58.3 \pm 18.2

BMI: Body mass index, FEV₁: Forced expiratory volume in 1 s, FVC: Forced vital capacity, SD: Standard deviation

the completion of ATT was 4 years (range 1.5–35 years) in TB-associated COPD. Most of the patients (21/24) had taken a single course of ATT.

Comparison between tuberculosis-associated chronic obstructive pulmonary disease and other chronic obstructive pulmonary disease

TB-associated COPD patients were younger in age as compared to the rest of COPD patients ($P = 0.02$) with more proportion of females. They had similar symptoms except for high incidence of hemoptysis and frequent hospitalizations. Pack-years of smoking were less although airflow limitation was similar to other COPD patients [Table 2].

In TB-associated COPD patients, on univariate analysis, number of previous hospitalizations showed a positive correlation with age, duration of dyspnea, number of exacerbations in the last year and BMI [Table 3]. However, on multivariate analysis, duration of dyspnea retained positive correlation with hospitalizations ($r = 0.82$; $P = 0.022$) after adjusting for pack-years, age, and BMI. On the contrary, FEV₁ did not have shown correlation with any of the parameters [Table 3].

DISCUSSION

The present study was conducted to find out hospital-based prevalence of TB-associated COPD and to evaluate its characteristic features. The results showed that almost one-third of COPD patients (32.4%) had associated TB in the past. It was seen that patients with TB-associated COPD, despite being younger in age and having lesser pack-years of smoking, had similar grades of airway obstruction as compared to smoking-related COPD. This gives strong evidence in favor of casual association between TB and development of COPD.

In contrast to our study design, most of the published data on the association between TB and COPD has been derived from studies on previously treated TB patients. In a series of

cohort studies, airflow obstruction was found in the range of 28%–70% in previously treated TB patients^[4,15] whereas it was in the range of 11%–58%.^[16] in hospital-based cross-sectional studies. In one of the largest population-based PLATINO studies, airflow obstruction was seen in 30.7% patients with previous TB as compared to 13.9% among those without a history.^[7] In contrast, we evaluated “TB-associated COPD” among COPD patients at a tertiary care level in a case–control study design. We could not find other Indian study with a similar design in published literature.

Table 2: Comparison of features between tuberculosis-associated chronic obstructive pulmonary disease with other chronic obstructive pulmonary disease patients

	TB-associated COPD (n=24)	Other COPD (n=50)	P
Age (years), mean±SD	56.88±9.14	61.8±8.5	0.02
Gender			
Male	19	47	0.05
Female	5	3	
BMI (mean±SD)	18.76±4.08	19.9±5.4	0.34
Median duration (years) of dyspnea (range)	5 (1-25)	4.0 (0.15-15)	0.18
Grade of dyspnea			
Grade 1	4	12	0.80
Grade 2	15	27	
Grade 3	4	10	
Grade 4	1	1	
COPD stage			
Mild	1	3	0.59
Moderate	11	19	
Severe	7	21	
Very severe	5	7	
Cough (%)	66.6	64	0.82
Hemoptysis (%)	29.1	0.08	0.03
Smoking (%)	75	92	0.045
Pack years (mean±SD)	23.5±22.4	36.7±24.2	0.027
Percentage oxygen saturation (mean±SD)	94.9±2.22	94.8±2.26	0.79
Percentage predicted FEV ₁ (mean±SD)	46.3±18.4	46.9±17.6	0.90
Percentage predicted FVC (mean±SD)	56.2±18.4	59.3±18.2	0.51
Number of hospitalizations	21	30	0.01

BMI: Body mass index, FEV₁: Forced expiratory volume in 1 s, FVC: Forced vital capacity, SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, TB: Tuberculosis

Table 3: Correlation of forced expiratory volume in 1 s and number of hospitalizations with different parameters in tuberculosis-associated chronic obstructive pulmonary disease

	FEV ₁		Previous hospitalizations	
	Pearson coefficient (r)	P	Pearson coefficient (r)	P
Age	-0.104	0.63	0.818	0.007
Pack years	-0.233	0.28	-0.233	0.54
Duration of dyspnea	-0.313	0.14	0.90	0.001
BMI	0.368	0.08	-0.746	0.02
Time elapsed since last TB	-0.230	0.37	0.00	0.99
No of exacerbations	-0.272	0.20	0.767	0.01
Previous hospitalizations	-0.223	0.56	1	-

BMI: Body mass index, FEV₁: Forced expiratory volume in 1 s, TB: Tuberculosis

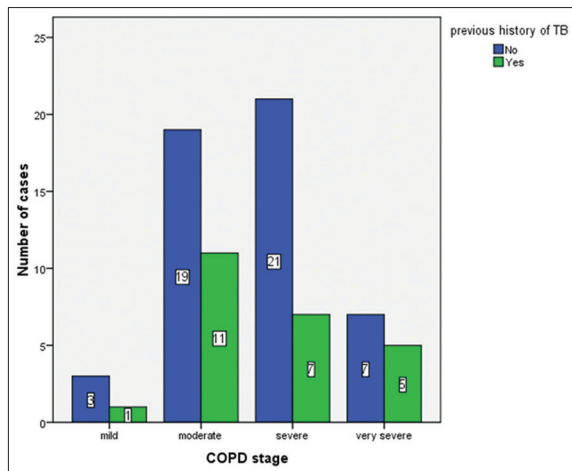


Figure 1: Distribution of patients among different stages of chronic obstructive pulmonary disease

In a landmark, population-based study (BOLD study)^[6] on COPD in never smokers, authors did not find any association of TB in the development of COPD. In their study, 5.3% COPD patients had a history of the previous TB which is significantly lower than our results. This is likely due to the fact that the study was done in never smokers which excluded the causative effect of smoking in both COPD and TB.^[17,18] Moreover, it was a community-based study from low TB prevalence countries which might have underscored the association between the two diseases. Our study enrolled COPD patients reporting to hospital with some symptoms and hence might have a higher chance of the previous TB. Another study from India enrolling patients with heavy pack years of smoking showed 57% prevalence of the previous TB in COPD patients.^[19]

Different mechanisms have been proposed for the development of COPD in TB patients. It includes endobronchial involvement causing airway obstruction, bronchiolar narrowing, and bronchiolitis obliterans resulting from peribronchial fibrosis and accelerated emphysematous changes caused by residual chronic or recurrent inflammation affecting lung compliance.^[16,20] A common link to the pathogenesis of both the conditions may lie in the destruction of pulmonary extracellular matrix due to increased activity of matrix metalloproteinases enzymes precipitated by TB.^[21]

Risk of COPD has been found to increase with increase in radiological extent of TB,^[4] increase in number of previous TB episodes^[22] as well as with delay in initiating anti-TB therapy.^[23] This could not be validated in our study as around 90% of patients with TB-associated COPD had a history of a single episode of TB as well as had minimal CXR changes (unilateral involvement and apical linear fibrotic strands). The results are similar to a Korean study which also showed lower FEV₁ in TB patients with minimal CXR changes.^[24] Moreover, our study did not include patients with mixed obstruction and restriction which are more likely to present with extensive CXR changes. The inclusion of these patients might have increased the prevalence of TB-associated COPD in our study.

Clinical behavior of TB-associated COPD in comparison to smoking-related COPD is not well defined. In our study, TB-associated COPD patients were younger in age as compared to other COPD which is likely due to the fact that TB is a disease of young adults as compared to smoking-related COPD which is uncommon in this age group.^[12] Furthermore, TB-associated COPD patients had similar symptoms in our study except for high frequency of hemoptysis. The results were in accordance with another Korean study that showed no difference in the presentation of COPD patients with and without previous TB.^[25] However, in contrast to our study, the authors showed a higher airway resistance in the TB-COPD group. In our study, there was no correlation between FEV₁ and duration of symptoms in TB-COPD patients which hints toward nonprogressive nature of airflow limitation

in TB-associated COPD. However, the fact can only be validated in longitudinal studies on TB-COPD patients with large sample size. Another interesting finding in our study was the higher number of hospitalizations seen in these patients that showed a positive correlation with age, BMI, and duration of symptoms. This was in contrast to a Korean study which did not show any difference in hospitalizations in the two groups.^[25] Structural changes such as fibrosis, bronchiectasis, cavity occurring as sequelae of TB may act as a nidus for recurrent infections in TB-associated COPD patients that warrant hospitalization.^[19]

Our study gave a real life picture of TB-associated COPD giving an insight into its prevalence encountered in a routine OPD. It also suggests that adequate TB control might also aid in reducing the prevalence of TB-associated COPD. However, being a case-control study with an inherent recall bias associated with it, the causal association between TB and COPD could not be confirmed. TB-associated COPD can occur after a variable period of TB occurrence, ranging from the point of TB diagnosis^[2] to several years after the treatment has ended. Moreover, airflow limitation seen in it may resolve with ATT and bronchodilators.^[15] Hence, following TB patients till any point of time in a cohort study design may not give a true picture of their association. Evaluating COPD patients for the previous TB in a retrospective study design, similar to our study, seem to be a better platform to evaluate this COPD phenotype. Effect of confounding factors notably tobacco smoking could not be excluded in our study. Nevertheless, it did not seem to affect the outcome as the number of pack-years was significantly less in patients with TB-associated COPD as compared to other COPD patients.

CONCLUSION

TB-associated COPD constitutes a substantial proportion of COPD in a hospital setting. It is a distinct clinical entity different from a larger smoking-related COPD and hence may require different management. Being a high TB burden country, there is a need to conduct large-scale studies and population surveys on COPD patients in India to find out the burden and course of TB-associated COPD. Further, longitudinal studies on TB-associated COPD in never smokers might help to formulate guidelines for its management.

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Conflicts of interest

There are no conflicts of interest.

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