

## A STUDY TO COMPARE THE CLINICAL FEATURES BETWEEN POST PULMONARY TUBERCULOSIS ASSOCIATED CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) WITH OTHER COPD PATIENTS

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### ABSTRACT

#### BACKGROUND

India is the highest TB burden country in the world and patients with treated TB may remain life-long sufferers of disabling sequelae. Many studies have shown that treated pulmonary tuberculosis can result in airflow obstruction. This study was designed to analyse the risk of Tuberculosis associated with Chronic obstructive pulmonary disease (COPD) among Chronic obstructive pulmonary disease patients.

#### MATERIALS AND METHODS

The patients of stable Chronic Obstructive Pulmonary Diseases will be picked up from outpatient and inpatient sections of the hospital at random. These COPD patients were divided into TB-associated COPD (only if their symptom of COPD started after the episode of pulmonary TB) and non-tubercular COPD group.

#### RESULTS

One hundred and thirty eight patients with COPD were enrolled during the study period. There were 107 males (77.5%) and 31 (22.4%) females. Of the total COPD patients, 58 (42.03%) had past history of pulmonary tuberculosis treatment. TB associated COPD were younger in age as compared to non-TB COPD group. This study also revealed that clinical symptoms of COPD are similar in both groups, except high percentage of haemoptysis in TB associated COPD group. On comparison, FEV1/ FVC ratio in both groups were almost similar.

#### CONCLUSION

The present study highlighted that pulmonary tuberculosis is definitely associated with pulmonary damage and constitutes a significant proportion of COPD patients.

#### KEYWORDS

Pulmonary Tuberculosis, Airflow Obstruction, Chronic Obstructive Pulmonary Disease.

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#### BACKGROUND

Chronic obstructive pulmonary disease is a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/ or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases.<sup>1</sup>

Chronic obstructive pulmonary disease (COPD) is estimated to affect 65 million people worldwide and it is currently the third leading cause of death, accounting for approximately 3 million deaths annually.

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Ninety percent of these deaths are in low- and middle-income countries, where the prevalence of pulmonary tuberculosis (PTB) remains high.<sup>2-3</sup>

Cigarette smoking is the leading environmental risk factor for COPD and fewer than 50% develop COPD during their lifetime. The other major risk factors are outdoor, occupational and indoor air pollution (resulting from the burning of wood and other biomass fuels).<sup>1</sup>

In the executive summary of the 2006 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, the role of tuberculosis in the development of chronic airways obstruction has been recognised.<sup>4</sup> According to the GOLD Workshop summary, chronic bronchitis or bronchiolitis and emphysema can occur as complications of pulmonary tuberculosis.<sup>5</sup>

Treated post tubercular patients are left with permanent changes in lung anatomy and are at higher risk of pulmonary sequelae and premature mortality.<sup>6-9</sup> These result in pulmonary sequelae that are characterised by bronchial and parenchymal structural changes including bronchovascular

distortion, bronchiectasis, emphysematous changes and fibrotic bands. Moreover, these changes remain permanently in the lungs after a microbiological cure.<sup>10</sup> The present study was done to know the prevalence of tuberculosis associated chronic obstructive pulmonary disease among total COPD patients and to compare the clinical features between post pulmonary tuberculosis associated COPD with other COPD patients.

### MATERIALS AND METHODS

We conducted a cross-sectional study in the Department of Internal Medicine and Department of Tuberculosis and Respiratory Diseases, GSVM Medical College, Kanpur, Uttar Pradesh, from July 2016 to June 2017. The patients of stable Chronic Obstructive Pulmonary Diseases will be picked up from outpatient and inpatient sections of the hospital at random.

#### Inclusion Criteria

COPD patients who are clinically stable will be included in the study.

#### Exclusion Criteria

1. Severe congestive heart failure.
2. Other respiratory diseases such as asthma, interstitial lung diseases, obstructive sleep apnoea, acute infections and severe hepatic failure and uncontrolled comorbidities such as malignancy.
3. Systemic Hypertension and Diabetes Mellitus.

#### Design of the Study

A detailed history and physical examination was carried out for every subject who entered in the study as per the pre-designed proforma. Patients were examined clinically and radiologically with a view to establish diagnosis and condition made as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. They were subjected to Haemoglobin, Total Leucocyte Count (TLC), Differential Leucocyte Count (DLC), Fasting and Postprandial blood sugar, serum creatinine, SGPT, Serum bilirubin, serum protein, serum albumin and spirometry. Echocardiography, ECG and other investigations if required will also be done.

Body mass index (BMI) (kg/ m<sup>2</sup>) of each patient was calculated by measuring weight and height. Dyspnoea was assessed by using the modified British Medical Research Council (mMRC) dyspnoea scale.

Data was compiled using Microsoft Excel and analysed using SPSS Statistics version 20.0. Categorical variables were analysed using percentage and chi-square test. Two tailed 'p' value less than 0.05 was considered significant. Quantitative variables were analysed using mean, standard deviation and student 't' test.

### Spirometry

Spirometry measures were done in every patient who had symptoms and signs suggestive of COPD along with history of exposure to risk factors. The diagnosis of COPD was confirmed by spirometry and they were allocated into stages as per criteria adopted and standardised by GOLD 2016. Spirometry was performed using techniques that meet published standards. Both FEV<sub>1</sub> and FVC were the largest value obtained from any of the three technically satisfactory curves and FVC and FEV<sub>1</sub> values in these curves did not vary by more than 5% or 100 mL, whichever was greater. Bronchodilator reversibility testing was also performed by inhaled salbutamol 200 µg by metered dose inhaler via spacer, after withholding inhaled short-acting bronchodilator for 6 hrs., long acting β<sub>2</sub> agonists for 12 hrs. and sustained-release theophylline for 24 hrs. Lung functions were again measured 10 - 15 minutes after the inhaled bronchodilator.

In present study 138 patients who have exertional dyspnoea with or without cough, expectoration and/ or having past history of pulmonary tuberculosis with complete anti-tuberculosis therapy were included. Patients were labelled 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.

### RESULTS

This study included 138 patients, 107 males and 31 females and their age ranging from 29 - 78 years with a mean age of 54.3 years. The mean ages among tuberculosis associated COPD and non-tuberculosis associated COPD were 46.8 and 59.8 years respectively. The mean body mass index among tuberculosis associated COPD and non-tuberculosis associated COPD were 17.74 and 19.25 respectively. Majority of the patients among TB associated COPD group had minimal chest x-ray changes (more U/L involvements and less fibrotic changes). The percentage of smoking among TB-COPD group and non-TB-COPD group were 58.62% (34/58) and 76.25% (61/80) respectively. Dyspnoea were associated in all the patients among both groups. The FEV<sub>1</sub>/ FVC ratio among TB-COPD group and non-TB-COPD group were 53.71 and 53.14 respectively. The mean FEV<sub>1</sub> (percentage predicted) among TB-COPD group and non-TB-COPD group were 46.03 and 47.15 respectively. The mean FVC (percentage predicted) among TB-COPD group and non-TB-COPD group were 58.20 and 58.57 respectively. The other features are summarised in table number 1 and 2.

Sl. No.	Interval between Tt Completion and Dyspnoea Starting (In Years)	Total Number of Cases (N= 58)	%
1	< 1	3	5.17%
2	1-2	6	10.4%
3	2-3	3	5.17%
4	3-4	6	10.4%
5	4-5	15	25.86%
6	>5	25	43.10%

Table 1

Sl. No.	Clinical Features		Cases (N= 58)	Control (N= 80)	%	P value	
1	Age in Years (Mean $\pm$ SD)		46.8 $\pm$ 5.55	59.8 $\pm$ 7.06		<0.0001	
2	Sex	Males	39	68	77.5 %	0.013	
		Females	10	12	15.9 %		
3	BMI (Mean $\pm$ SD)		17.74 $\pm$ 2.01	19.25 $\pm$ 2.11		<0.0001	
4	Smoking	Smokers	Yes	38	61	71.7 %	0.166
			No	20	19	28.3%	
		Pack Years (Mean)		15.94	19.25		
5	Clinical Features	Cough	Yes	34	50	60.8%	0.212
			No	24	30	39.1 %	
		Expectoration	Yes	26	45	51.5%	0.185
			No	32	35	48.5%	
		Dyspnoea	Yes	58	80	100	NA
			No	0	0	-	
		Haemoptysis	Yes	19	6	18.1%	0.0001
			No	39	74	81.9%	
Chest Pain	Yes	21	39	43.48	0.142		
	No	37	41	56.5%			
6	MMRC Grade	1	0	0	0	0.096	
		2	29	49	56.5 %		
		3	24	18	30.4 %		
		4	5	13	13.04 %		
7	FEV1/ FVC Ratio (Mean $\pm$ SD)		53.71 $\pm$ 7.03	53.14 $\pm$ 6.60		0.626	
8	FEV1 (% Predicted) (Mean $\pm$ SD)		46.03 $\pm$ 9.19	47.15 $\pm$ 9.96		0.501	
9	FVC (% Predicted) (Mean $\pm$ SD)		58.20 $\pm$ 7.89	58.57 $\pm$ 43.95		0.784	
10	GOLD COPD Stage	1	0	0	0	0.878	
		2	38	47	61.5 %		
		3	12	20	23.19 %		
		4	8	13	15.22%		

**Table 2. Comparison between TB associated COPD (Cases) and Non-TB associated COPD (Control)**

## DISCUSSION

According to the global burden of disease projections, chronic obstructive pulmonary disease (COPD) and tuberculosis (TB) are among the 10 leading causes of death and disability for low- and middle-income countries.<sup>11</sup>

The result in present study showed that 42.03% cases of COPD had associated with tuberculosis in the past. A recent study from India was conducted to find out hospital-based prevalence of TB-associated COPD and their results showed that almost one-third of COPD patients (32.4%) had associated TB in the past.<sup>12</sup> Another study from India which included 86 patients of COPD and showed that about 42% were associated with post pulmonary tuberculosis.<sup>13</sup>

A relationship between PTB and the development of COPD has been suggested in several reports. Willcox PA did a study to know the prevalence of chronic obstructive airways disease following treated pulmonary tuberculosis in seventy-one subjects who had previously been treated for tuberculosis. There was reported evidence of airways obstruction in 48 (68%) patients.<sup>14</sup>

Plit ML et al did a study to know the influence of antimicrobial chemotherapy on spirometric parameters and pro-inflammatory indices in severe pulmonary tuberculosis. They recruited seventy-six patients into the study, of whom 74 completed the treatment programme. They found that improvement in lung function occurred in 54% of patients, but residual airflow limitation or a restrictive pattern was evident in 28% and 24% of patients, respectively. They also highlighted that antimicrobial chemotherapy may lead to improved lung function in patients with pulmonary tuberculosis, a large proportion of patients has residual impairment.<sup>15</sup>

Lee and Chang found that CAO is a common finding owing to TB-destroyed lung.<sup>16</sup> Patricio Jiménez et al found that CAO is a common sequel with TB.<sup>17</sup> PLATINO study, a latest large population-based multicentre study, carried out in five Latin American countries (n= 5571 participants) included patients on the criteria of a past diagnosis of PTB by a physician and performed spirometry in the field. It included only those patients presenting to the hospital with dyspnoea. Along with the exclusion of other possible confounding factors, smokers and patients with age more than 65 years were also excluded. It was found that FEV1 is reduced compared with FVC in most cases.<sup>18</sup> Our study also revealed similar results (FEV1 more reduced in comparison to FVC). However, another study had found that after 15 years follow-up of 40 patients, there was a higher yearly decline in FVC compared with FEV1.<sup>19</sup>

Lamprecht B analysed data from 14 countries from the International Burden of Obstructive Lung Disease (BOLD) study to describe characteristics of COPD in never smokers and to identify possible risk factors in this population. They reviewed a total of 10,000 subjects, who completed questionnaires and had acceptable post bronchodilator spirometry data and had information on smoking status. Of this group, 4,291 (42.9%) were never the smokers. In their study, 5.3% COPD patients had a history of the previous TB.<sup>20</sup> While in present study, the numbers of TB associated COPD patients were on higher side. 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.<sup>21-22</sup> Moreover, it was a community-based study from low TB prevalence countries, which might have underscored the association between the two diseases. Ramakrishna R et al studied 100 cases of COPD diagnosed with FEV1/ FVC 0.7 or less presenting with symptoms of cough with expectoration

and breathlessness and among them 57 (57%) gave the history of tuberculosis. They also reported that age range of the patients was 41 to 81. Average age of post tubercular airway disease was 58.2.<sup>23</sup> While in present study, 42.03% had history of tuberculosis and mean age among TB associated COPD group was 46.8 years.

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.<sup>24-25</sup>

The development and subsequent disease progression seen both in TB and COPD result in characteristic destructive parenchymal lung changes. A common link to the pathogenesis of both conditions may lie in the destruction of pulmonary Extracellular Matrix (ECM) comprising of collagen and elastin, which is the key to the structural integrity of the lung.<sup>26</sup> The antigenic wall component of mycobacterium tuberculosis, lipoarabinomannan (LAM) stimulates the release of MMP-9 as well as up-regulating genetic expression of MMP-1 and MMP-9. This not only results in the breakdown of collagen in the ECM, but also stimulates further lung damage by activation of other immune mediators such as Interleukin-8 and other cytokines. Hrabec et al demonstrated that MMP-9 levels were three times higher in the serum of tuberculosis patients compared with controls with increasingly elevated levels seen in those patients exhibiting advanced disease compared to limited disease.<sup>27</sup> TNF alpha, which plays an important role in the formation of tuberculous granulomas has been demonstrated to stimulate MMP-9 secretion from granulomas cultured from patients with active tuberculosis.<sup>28</sup>

Risk of COPD has been found to increase with increase in radiological extent of TB, increase in number of previous TB episodes as well as with delay in initiating anti-TB therapy.<sup>14,29-30</sup> A study from India reported that 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).<sup>12</sup> Our study results are comparable to the above-mentioned study.

Lee SW did a study to know the Risk of Obstructive Lung Disease by Previous Pulmonary Tuberculosis in a Country with Intermediate Burden of Tuberculosis. Among 9,243 subjects, 3,687 enrolled for analysis and radiologists concluded that 294 (8.0%) subjects were classified as having TB lesion on chest x-ray. All TB lesions were classified as inactive and there was no subject with lesion indicative of active TB on chest x-ray. Two hundred and ninety subjects had minimal lesions and four subjects had moderately or far-advanced lesions. This study also showed lower FEV1 in TB patients with minimal chest x-ray changes.<sup>31</sup> Our study results are comparable to the above-mentioned study.

## CONCLUSION

In the present study, we have evaluated the Tuberculosis associated COPD and compared with non-TB associated COPD group. To the best of our knowledge, such types of comparative studies have been published in lesser number. The present study highlighted that TB associated COPD were younger in

age as compared to non-TB COPD group. This study also revealed that clinical symptoms of COPD are similar in both groups, except high percentage of haemoptysis in TB-COPD group. Our data also suggested that adequate durations of TB treatment might also help in reducing the prevalence of Tuberculosis associated COPD.

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