



Research Article

## A Study on Identification of Different Phenotypes and Functional Status of Chronic Symptomatic Post Tuberculosis Patients

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### ABSTRACT

**Introduction:** It is estimated that in 2020 there were approximately 155 million TB survivors globally, of whom 18% had TB within the preceding five years. Although ICD10 includes a code for tuberculosis sequelae (B90.9), this code is rarely used. These findings call for strategies to address pulmonary impairment after TB (PIAT). Post-tubercular lung disease is defined as 'Evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to previous tuberculosis. Even after successful treatment, many patients suffer from post-TB sequelae. **Aims and Objectives:** To identify different lung function abnormalities and to assess pulmonary arterial hypertension, exacerbations, radiological involvement and factors associated with them in chronic symptomatic post TB lung disease patients. **Material and Methodology:** The present prospective observational study was carried out in Department of Respiratory Medicine of GMERS Medical College & Hospital, Gotri, Vadodara, Gujarat after obtaining the permission from Institutional Ethics Committee. All chronic symptomatic patients with past history of pulmonary tuberculosis were enrolled in the study from February 2023 to July 2024 after taking informed written consent. **Conclusion:** Post TB lung disease is more frequently observed in younger females and older males. The majority of PTLTLD patients have predominantly obstructive lung function impairment, followed by restrictive patterns. Pulmonary arterial hypertension (PAH) is more prevalent. Factors such as age, gender, smoking status, BMI, locality, socioeconomic status, chest X-ray findings and duration since past PTB do not markedly influence the severity of PAH in patients with PTLTLD.

**Keywords:** Pulmonary Tuberculosis, TB, Post TB Lung Disease (PTLD), Pulmonary Impairment After TB (PIAT), Post TB sequelae, PAH, Obstructive Lung Disease, Restrictive Lung Disease.

### INTRODUCTION

Tuberculosis (TB), is a preventable and usually curable disease, caused by Mycobacterium tuberculosis and infection is largely transmitted from person to person through inhalation of infected air droplets. The most common site of initial infection and disease is the lungs and spread to other intra-thoracic tissues such as hilar lymph nodes and pleura occur frequently. Yet in 2022, TB was the world's second leading cause of death from a single infectious agent, after corona virus disease (COVID-19), and caused almost twice as many deaths as HIV/AIDS. Based on modeling of global epidemiologic TB survival data, it is estimated that in 2020 there were approximately 155 million TB survivors globally, of whom 18% had TB within the preceding five years. [1,2]. Although ICD10 includes a code for tuberculosis sequelae (B90.9), this code is rarely used. [3] These findings call for strategies to address pulmonary impairment after TB (PIAT).

Post-tubercular lung disease is defined as 'Evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to previous tuberculosis. [4] Even after successful treatment, many patients suffer from post-TB sequelae. These may be parenchymal complications, airway diseases, mediastinal complications, vascular complications,

pleural/chest wall complications [5], systemic complications and psychosocial comorbidities (such as anxiety, depression, financial burden etc.) notable feature of lung involvement in TB is its striking heterogeneity. Patients may present with cavitation, fibrosis or nodular infiltrates, or have a mix of these pulmonary pathologies. Blood and sputum-derived neutrophil activation and inflammatory mediators will be examined in order to elucidate the predominant pathway of lung inflammation in TB and inform on future host-adjunctive therapy strategies. For example, polymorpho-nuclear neutrophilic granulocytes have been associated with active tuberculosis and the failure to control the infection, and likely contribute to exacerbated pathology and long-term sequelae and lung function loss. [6-8] Radiology plays an assisting role for detection of active tuberculous infection in correlation with laboratory results and strong clinical contact. The functional changes resulting from PTB that are observed after treatment manifest as restrictive lung disease (RLD), obstructive lung disease (OLD), or mixed obstructive-restrictive lung disease (MORLD), regardless of the history of exposure to smoking. [9]

Therefore, a planned observational study, aims to advance the understanding of the clinical, microbiological, immunological and socio-economical risk factors affecting long term outcome of pulmonary TB. It will also determine the occurrence of reversible and irreversible socio-economic consequences to patients, their households and the health sector related to post TB lung disease.

## **AIMS AND OBJECTIVES**

**Aim:** To identify different lung function abnormalities and to assess pulmonary arterial hypertension, exacerbations, radiological involvement and factors associated with them in chronic symptomatic post TB lung disease patients.

### **Primary Objectives:**

- To identify different phenotypes in chronic symptomatic patients of old pulmonary tuberculosis.

### **Secondary Objectives:**

- To analyze different lung functional abnormalities occurring in post TB patients by spirometry.
- To analyze cardiovascular manifestations occurring secondary to post TB complication.

## **MATERIALS AND METHODOLOGY**

The present prospective observational study was carried out in Department of Respiratory Medicine of GMERS Medical College & Hospital, Gotri, Vadodara, Gujarat after obtaining the permission from Institutional Ethics Committee and after CTRI (Clinical Trial Registry of India) registration to identify different phenotypes and functional status of chronic symptomatic post tuberculosis patients.

All chronic symptomatic patients with past history of pulmonary tuberculosis were enrolled in the study from February 2023 to July 2024 after taking informed written consent with the following inclusion and exclusion criteria.

### **Inclusion Criteria:**

- Patients with age  $\geq 18$  years
- Patients having history of pulmonary tuberculosis, whether treated with anti-tuberculosis treatment or not
- Willing to participate and give consent

### **Exclusion Criteria**

- Patients with active tuberculosis
- Patients with HIV positive
- Patients with associated systemic illness like acute myocardial infarction, unstable angina, chronic kidney disease, liver cirrhosis etc.
- Associated respiratory illness (Lung carcinoma, Lung abscess etc.)

After enrolment, detailed clinical history of all patients was taken and thorough physical examination was done. Patients were assessed for present complains, past history of pulmonary tuberculosis and its treatment, allergic history, smoking history, biomass exposure (if present) and history of exacerbations in last one year. Vitals (temperature, pulse, blood pressure, SpO<sub>2</sub>, respiratory rate) and BMI of all patients were recorded. Respiratory system was examined. After these all available blood investigations [Blood hemogram, differential leucocyte counts, ESR], sputum for AFB, sputum for culture and sensitivity were recorded. Pulmonary function test, radiological investigations and 2D-Echo reports were also recorded.

Different statistical tests like Chi squared test, comparison of mean, unpaired *t*-test with 95% confidence interval were used to derive 'p' value. The difference considered significant if the 'p' value was  $< 0.05$  and highly significant if the 'p' value was  $< 0.01$ .

## **OBSERVATIONS**

In the present study, 126 patients with past history of tuberculosis were assessed for eligibility and enrolled. Out of them, 16 patients were not able to perform pulmonary function test due to poor effort or severe dyspnea.

**Table 1: Baseline characteristics in obstructive and restrictive phenotype**

Variables	Total (n=126)	Obstructive (n=81)	Restrictive (n=26)	p value
	Mean +/- SD	Mean +/- SD	Mean +/- SD	
Age (years)	53.91 +/- 12.69	53.95 +/- 13.17	52.53 +/- 11.91	0.62
BMI (kg/m <sup>2</sup> )	19.86 +/- 4.48	19 +/- 4.22	20.94 +/- 5.08	<b>0.05</b>
Diabetes	13 (10%)	8 (10%)	2 (8%)	0.76
Hypertension	15 (11%)	9 (11%)	4 (15%)	0.58
HB	11.79 +/- 1.46	11.79 +/- 1.49	11.78 +/- 1.29	0.97
WBC	8391 +/- 2203	8328 +/- 2335	8484 +/- 1786	0.75
Platelet count	3.06 +/- 0.8	3.06 +/- 0.81	3.06 +/- 0.84	1.0
AEC	253.8 +/- 223	246.19 +/- 233	240.11 +/- 139	0.90
ESR	23.66 +/- 11.76	23.39 +/- 11.62	26.53 +/- 11.68	0.23
RVSP(mmHg)	54.42 +/- 18.38 (n=63)	46.29 +/- 12.68 (n=37)	57.53 +/- 18.98 (n=15)	<b>&lt;0.01</b>

The average age was similar between both the phenotypes. BMI was significantly lower in the obstructive group compared to the restrictive group ( $p=0.05$ ). The prevalence of diabetes and hypertension was comparable between both the phenotypes. HB, WBC counts, platelet counts, AEC and ESR levels did not differ significantly between the phenotypes. RVSP values were significantly lower in the obstructive phenotype than in the restrictive phenotype. ( $p=0.0008$ )

**Table 2: Distribution of age and gender**

Age (Years)	Male (n=79) n (%)	Female (n=47) n (%)	p value
<50 (n=42)	17 (21%)	25 (53%)	0.0002
>=50 (n=84)	62 (79%)	22 (47%)	0.0002

The table demonstrates a significant association between age and gender in chronic symptomatic post TB lung disease. In younger age group females were significantly associated ( $p=0.0002$ ) with this condition while in older age group males were significantly associated ( $p=0.0002$ ) with this condition. This suggests that chronic symptomatic post TB lung disease tends to manifest earlier in females and later in males.

In our study, spirometry results were available for a total of 110 patients. Among those, 3 patients (2%) exhibited normal spirometry, while 81 patients (74%) demonstrated an obstructive pattern (obstructive phenotype) and 26 patients (24%) had a restrictive lung function impairment (restrictive phenotype).

**Table 3: Distribution of symptoms between obstructive and restrictive phenotype**

Symptoms	Obstructive (n=81) n (%)	Restrictive (n=26) n (%)	p value
Breathlessness (n=106)	81 (100%)	25 (96%)	0.07
Productive cough (n=33)	24 (30%)	9 (35%)	0.63
Dry cough (n=24)	20 (25%)	4 (15%)	0.29
Loss of appetite (n=12)	9 (11%)	3 (12%)	0.88
Loss of weight (n=5)	3 (4%)	2 (8%)	0.41
Chest pain (n=4)	4 (5%)	0 (0%)	0.24
Fever (n=4)	3 (4%)	1 (4%)	1.0
Hemoptysis (n=3)	2 (2%)	1 (4%)	0.57
Pedal edema (n=1)	0 (0%)	1 (4%)	0.07

**Table 4: Distribution of radiological findings between PTLT phenotypes**

CXR	Post TB lung disease-Phenotypes		p value
	Obstructive (n=81) n (%)	Restrictive (n=26) n (%)	
Normal (n=14)	14 (17%)	0 (0%)	<b>0.02</b>
Emphysema (n=30)	26 (32%)	4 (15%)	0.09
Fibrosis (n=66)	45 (56%)	21 (81%)	<b>0.02</b>
Cavitary lesion (n=19)	11 (14%)	8 (31%)	<b>0.05</b>
Bronchiectasis (n=15)	8 (10%)	7 (27%)	<b>0.03</b>
Calcification (n=19)	15 (18%)	4 (15%)	0.72
Destroyed (n=11)	5 (6%)	6 (23%)	<b>0.01</b>

**Table 5: Factors affecting FEV1% in post TB obstructive phenotype**

Variables	Post TB obstructive phenotype		p value
	FEV1% of predicted (Mean +/- SD)		
Age (Years)	<50 (n=26)	>=50 (n=55)	0.01
	31.96 +/- 11.32	38.83 +/- 12.50	
Gender	Male (n=55)	Female (n=26)	0.64
	37.07 +/- 12.82	35.69 +/- 11.95	
Geography	Urban (n=31)	Rural (n=50)	0.95
	36.74 +/- 12.37	36.56 +/- 12.69	
Socioeconomic class	Middle (n=26)	Lower (n=50)	0.9
	36.88 +/- 11.35	36.50 +/- 13.09	
BMI (kg/m2)	<18.5 (n=43)	>=18.5 (n=38)	<0.001
	31.48 +/- 9.15	42.44 +/- 13.30	
Smoking	Smoker (n=39)	Non smoker (n=42)	0.71
	37.15 +/- 13.84	36.14 +/- 11.24	
Chest X-ray	Normal (n=14)	Abnormal (n=67)	0.12
	41.35 +/- 8.85	35.64 +/- 12.96	
PAH(RVSP mmHg)	<=50 (n=15)	>50 (n=15)	0.21
	37.4 +/- 13.78	31.93 +/- 9.48	
P/h/o PTB	<=10 (n=34)	>10 (n=47)	0.64
	37.38 +/- 14.09	36.08 +/- 11.33	
History of PTB	More than once (n=9)	Once (n=72)	0.05
	30 +/- 10.01	37.85 +/- 11.57	
MMRC	<2 (n=53)	>=2 (n=28)	0.2
	37.92 +/- 11.76	34.17 +/- 13.64	

Age was significantly associated with FEV1%, with patients aged  $\geq 50$  years had a higher FEV1% compared to those aged  $< 50$  years ( $p=0.01$ ). No significant differences were observed in FEV1% based on gender, geography, socioeconomic class, smoking status, or MMRC grade. However, BMI showed a strong association, with patients having a BMI  $\geq 18.5$  kg/m<sup>2</sup> displayed significantly higher FEV1% than those with BMI  $< 18.5$  kg/m<sup>2</sup> ( $p<0.0001$ ). Chest x-ray abnormalities and RVSP values did not show significant differences in FEV1%. Additionally, a history of PTB more than once was marginally associated with a lower FEV1% compared to those with only one episode ( $p=0.05$ ). Years since past history of PTB did not significantly affect FEV1%.

**Table 6: Factors affecting FVC% in post TB restrictive phenotype**

Variables	Post TB restrictive phenotype		p value
	FVC% of predicted (Mean +/- SD)		
Age (Years)	<50 (n=13)	>=50 (n=13)	0.91
	42.92 +/- 13.02	42.30 +/- 17.11	
Gender	Male (n=14)	Female (n=12)	0.74
	41.71 +/- 16.72	43.66 +/- 13.11	
Geography	Urban (n=16)	Rural (n=10)	0.33
	44.87 +/- 14.69	39 +/- 15.27	
Socioeconomic class	Middle (n=17)	Lower (n=9)	0.52
	44 +/- 15.85	40 +/- 13.38	
BMI (kg/m2)	<18.5 (n=8)	>=18.5 (n=18)	0.2
	37 +/- 11.40	45.11 +/- 15.86	
Smoking	Smoker (n=9)	Non smoker (n=17)	0.12
	36.44 +/- 15.05	45.88 +/- 14.17	
PAH(RVSP mmHg)	<=50 (n=7)	>50 (n=7)	0.38
	40.42 +/- 11.61	34.71 +/- 11.87	
P/h/o PTB	<=10 (n=13)	>10 (n=13)	0.91
	42.92 +/- 13.02	42.30 +/- 17.11	
History of PTB	More than once (n=4)	Once (n=22)	0.3
	35.5 +/- 12.39	43.90 +/- 15.19	
MMRC	<2 (n=18)	>=2 (n=7)	0.66
	42.38 +/- 16.02	39.57 +/- 8.92	

In patients with the post TB restrictive phenotype FVC% of predicted was analyzed across various demographic and clinical variables. Age did not significantly affect FVC%, with similar values observed in patients aged <50 years and those aged ≥50 years ( $p=0.91$ ). Gender also showed no significant difference ( $p=0.74$ ). Geography, socioeconomic class, and BMI did not significantly influence FVC%. While there was a trend towards lower FVC% in smokers compared to non-smokers ( $p=0.12$ ), this was not statistically significant. Patients with a history of PTB more than once tended to have a lower FVC% compared to those with one episode ( $p=0.3$ ), but again, the difference was not statistically significant. Additionally, PAH and MMRC grade did not show statistically significant associations with FVC%.

Additionally,

Our study suggests that restrictive phenotype is significantly more prevalent in urban settings (62%) compared to rural (38%), while obstructive phenotype is significantly more common in rural areas (62%) compared to urban areas (32%). ( $p=0.03$ )

Obstructive phenotype is significantly more prevalent among individuals from lower socioeconomic backgrounds (68%) compared to middle (32%), whereas restrictive phenotype is more common among those from middle socioeconomic backgrounds (65%) compared to lower socioeconomic class (35%), revealing a significant association ( $p=0.002$ ).

Obstructive phenotype is more significantly associated with lower BMI (53%) compared to higher BMI (47%) whereas restrictive phenotype is significantly more associated with higher BMI (70%) compared to lower BMI (30%) ( $p=0.04$ ).

There are 53 smokers and 73 non-smokers. Smoking status and smoking index do not play a decisive role in the development of either obstructive or restrictive phenotypes in post TB lung disease.

Our study highlights that restrictive phenotype has significantly higher mean RVSP value ( $57.53 \pm 18.98$ ) compared to obstructive ( $46.29 \pm 12.68$ ), ( $p=0.0008$ ) but patients with PAH are evenly distributed between the obstructive and restrictive phenotypes.

Among patients with an obstructive phenotype, 18% have normal CXR findings, while 82% have abnormal CXR findings. In contrast, all the patients with a restrictive phenotype are significantly associated with abnormal CXR. ( $p=0.02$ )

Our study indicates that the presence of exacerbations does not significantly differ between obstructive and restrictive phenotypes.

The duration since past history of tuberculosis does not markedly influence the distribution of obstructive versus restrictive phenotypes.

A number of PTB episodes in the past does not significantly differentiate between these two phenotypes in post TB lung disease patients.

Age is significantly associated with FEV1% in obstructive phenotype, with patients aged <50 years having a lower FEV1% ( $31.96 \pm 11.32$ ) compared to those aged ≥50 years ( $38.83 \pm 12.50$ ) ( $p=0.01$ ).

In obstructive phenotype patients having a BMI <18.5 kg/m<sup>2</sup> displaying significantly lower FEV1% ( $31.48 \pm 9.15$ ) than those with BMI ≥18.5 kg/m<sup>2</sup> ( $42.44 \pm 13.30$ ) ( $p<0.0001$ ).

In obstructive phenotype, history of PTB more than once is marginally associated with a lower FEV1% ( $30 \pm 10.01$ ) compared to those with history of PTB only once ( $37.85 \pm 11.57$ ) ( $p=0.05$ ).

In obstructive phenotype no significant differences are observed in FEV1% based on gender, geography, socioeconomic class, smoking status, MMRC grade, duration since past history of PTB, chest X-ray involvement and RVSP.

In restrictive phenotype no significant difference are observed in FVC% based on age, gender, geographical distribution, socioeconomic class, smoking, BMI, RVSP, MMRC, history of recurrent PTB and duration since past history of PTB.

In this study out of total 81 patients from post TB obstructive phenotype, 16(20%) patients has reversible and 65(80%) patients has non reversible post bronchodilator response.

Age and gender are not significantly associated with either the reversible or non-reversible obstructive phenotypes.

The duration since past history of pulmonary tuberculosis, chest X-ray findings and smoking status have no significant difference between the reversible and non-reversible obstructive phenotypes.

Patients with history of allergy are significantly more associated with obstructive reversible phenotype ( $p<0.0001$ ) whereas patients without history of allergy are significantly associated with obstructive non reversible phenotype ( $p<0.0001$ ).

Patients with episodic breathlessness are significantly more associated with obstructive reversible phenotype ( $p<0.0001$ ) whereas patients with persistent breathlessness are significantly more associated with obstructive non reversible phenotype ( $p<0.0001$ ).

2D Echo reports are available for 63 patients and out of which 8 (12%) patients has RVSP  $\leq 30$  mmHg considering normal and 23 (37%) patients have mild PAH (RVSP  $\leq 50$  mmHg) and 32 (51%) have moderate to severe PAH (RVSP  $> 50$  mmHg).

Our study suggests that older patients are more likely to have moderate to severe PAH compared to their younger counterparts.

Our study suggests a relatively higher prevalence of moderate to severe pulmonary hypertension in males compared to females.

Patients from rural community and those with lower socio economic class are more likely to experience moderate to severe PAH.

Those with higher BMI are more likely to experience moderate to severe PAH.

Smokers are more likely to exhibit moderate to severe PAH.

Chest X-ray findings, exacerbations and duration since past history of PTB do not markedly influence PAH.

There is no significant correlation found between RVSP and FEV1% (correlation coefficient of 0.25) as well as RVSP and FVC% (correlation coefficient of 0.11), implying that RVSP alone does not strongly predict FEV1% and FVC%.

Out of the total study population, 13% has normal chest x-rays and  $\leq 3$  zones and  $> 3$  zones involvement are present in 51% and 36% of patients respectively.

Younger patients are more significantly associated with  $\leq 3$  zones involvement ( $p=0.05$ ) and older patients with  $> 3$  zones involvement ( $p=0.01$ ).

Female patients are more significantly associated with  $\leq 3$  zones involvement ( $p=0.004$ ) and male patients with  $> 3$  zones involvement ( $p=0.009$ ).

Non smokers are more significantly associated with  $\leq 3$  zones involvement ( $p=0.008$ ) and smokers with  $> 3$  zones involvement ( $p=0.002$ ).

BMI, rural or urban community and socioeconomic class are not significantly associated with chest X-ray involvement. Age and gender have no significant association with post TB lung disease exacerbations.

Smokers are significantly more associated with an increased risk of exacerbations in post TB lung disease patients ( $p=0.05$ ).

BMI, socioeconomic status and geographical distribution do not significantly influence the occurrence of exacerbations. Patients with abnormal chest X-rays are significantly associated with a higher likelihood of exacerbations ( $p=0.03$ ). The duration since past history of PTB may not significantly influence the frequency of exacerbations.

## CONCLUSION

Post TB lung disease is more frequently observed in younger females and older males.

The majority of PTLTD patients have predominantly obstructive lung function impairment, followed by restrictive patterns. There are no notable differences in age, gender, smoking status, duration since past history of PTB, history of recurrent PTB or exacerbation frequency between obstructive and restrictive phenotypes. The obstructive phenotype is more common in rural communities, among individuals with lower BMI and within the lower socioeconomic class, while the restrictive phenotype is more prevalent in urban communities, in those with higher BMI and within the middle socioeconomic class.

Patients with a history of allergy and episodic breathlessness following PTB predominantly have reversible obstruction, resembling post-TB asthma.



Pulmonary arterial hypertension (PAH) is more prevalent in patients following PTB. Factors such as age, gender, smoking status, BMI, locality, socioeconomic status, chest X-ray findings and duration since past PTB do not markedly influence the severity of PAH in patients with PTLT. Patients with the obstructive phenotype have lower RVSP values compared to those with the restrictive phenotype.

Most of the patients have residual parenchymal involvement on chest X-rays. Patients with the restrictive phenotype have more diverse and structural lung parenchymal abnormalities. Greater radiological involvement is observed in older patients, males and smokers.

PTLD exacerbations are more frequent among patients with abnormal chest X-rays and smokers. No clear associations are found between age, gender, BMI, socioeconomic status, locality, or duration since past history of PTB and the frequency of PTLT exacerbations.

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