ISSN 2515-8260 Volume 09, Issue 09, 2022

Post-TB Airway Dysfunction Even In The Absence Of Radiologically Evident Lung Damage – An Unsuspected Aftermath

Adithya Vivek Sundar[1], Tushar Sahasrabudhe[2], Harshmeet Singh Gujral[3*]

1. Junior Resident, Department of Respiratory Medicine, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Dr. D.Y. Patil Vidyapeeth, Pune, Maharashtra, India.
2. Professor, Department of Respiratory Medicine, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Dr. D.Y. Patil Vidyapeeth, Pune, Maharashtra, India.
3. Junior Resident, Department of Respiratory Medicine, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Dr. D.Y. Patil Vidyapeeth, Pune, Maharashtra, India.

***Corresponding Author**

Dr. Harshmeet Singh Gujral, Junior Resident, Department of Respiratory Medicine, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Dr. D.Y. Patil Vidyapeeth, Pune, Maharashtra, India.

ABSTRACT:

BACKGROUND: Tuberculosis (TB) has been a major cause of suffering and death since time immemorial. Despite microbiological cure of TB infection, many patients develop long term lung impairment and functional disability which leads to their continued suffering. A proportion of treated TB patients suffer from Obstructive Airway Disease (OAD) which is usually attributed to structural lung damage like cavitation, bronchiectasis, lung fibrosis, bronchial stenosis, emphysema and resorptive collapse. However, in our clinical practice, we are observing many patients with history of pulmonary tuberculosis presenting with symptoms of airflow limitation despite no chest radiograph abnormality.

We therefore aim to study the spectrum of airflow obstruction and their severity in post TB patients with no residual structural lung damage and validate our clinical observation.

METHODS: This was a cross-sectional, observational study. We screened 509 patients, aged more than 18 years who had suffered from pulmonary TB (PTB) or extra-pulmonary TB (EPTB) in the past and were completely cured post-treatment. Those with radiologically evident lung scarring on chest X-ray (postero-anterior view) were excluded from the pulmonary group and those with residual mediastinal nodes or significant pleural thickening were excluded from the extrapulmonary group. Pre-existing OAD before onset of TB, active respiratory tract infection at the time of enrollment, TB treatment defaulters and tobacco smokers (smoking index > 50) were excluded. A total of 112 subjects with past PTB (group A) and 107 subjects with past EPTB (group B) were eligible. A detailed history and spirometry test were performed on them. Appropriate pre-requisites for the spirometry were

adhered to. Those who could not perform acceptable spirometry were excluded. The analyzable data consisted of 100 cases in each group (total = 200 cases).

RESULTS: Among the study population, 65% were males and 35% were females. Mean age of patients were 40.2 $\pm$ 13.4 years. On spirometry, obstructive pattern was seen in 27% (27/100) in group A as compared to 3% (3/100) in group B. There was strong correlation between PTB and presence of OAD ($p < 0.001$) with an Odd's ratio (OR) of 11.95 (95% CI 3.49 – 40.9). No such significant association was seen with EPTB group. Among PTB with OAD, 51.9% (14/27) had irreversible obstruction, 14.8% (4/27) had reversible obstruction and 33.3% (9/27) had small airway dysfunction. Among EPTB with OAD, 2 had irreversible obstruction and 1 had fixed extra-thoracic obstruction (past laryngeal TB leading to subglottic stenosis). Restriction was noted in 2% and 10% in group A and B respectively. 70.4% of patients with airflow obstruction had correlating symptoms, while 29.6% were asymptomatic. 74.1% of patients with airflow obstruction had history of TB within previous 5 years.

CONCLUSION: Our findings suggest development of airflow limitation in patients whose PTB got cured without radiologically evident structural damage. These cases may get undiagnosed till they develop symptoms. We recommend screening spirometry after the microbiological cure of pulmonary TB, even if there is no apparent lung scarring on chest radiograph.

KEYWORDS: Tuberculosis, spirometry, obstructive airway disease.

INTRODUCTION:

Tuberculosis has been one of the topmost infectious killer diseases over centuries with an estimated 115 million TB survivors globally as of 2020.[1] Managing post TB morbidity is gradually taking a front lead as the cure rate is increasing with the advent of potent drugs and regimens.[2,3] The rise in number of TB survivors can be attributed to early case detection and treatment initiation under the national TB programmes. Despite microbiological cure, it has been observed that many post TB patients develop long term lung impairment and functional disability which adds to continuing morbidity.[4] The spectrum of PTB sequelae includes cavitation, bronchiectasis, bronchial stenosis, lung fibrosis, emphysema and destroyed lung.[5,6] These structural changes may be responsible for the obstructive and restrictive pattern of airflow limitations in these patients.[7] Diffuse airway obstruction has been reported in 30%-60% of cases with PTB.[8,9] TB as a risk factor for obstructive lung disease later in life has been recently acknowledged by GOLD guidelines.[10]

In our clinical practice, we noticed many patients with symptoms of airflow obstruction with a history of TB, without chest X-ray abnormality. Interestingly, similar observations were seen in EPTB cases too. A pilot study published recently, showed significant positive correlation with TB and occurrence of airway obstruction even in those patients without radiologically evident lung scarring.[11] This study was therefore carried out with a much larger sample size (200 post TB cases) to assess the prevalence of airflow obstruction in

ISSN 2515-8260 Volume 09, Issue 09, 2022

cured PTB and EPTB patients with no radiologically evident structural lung damage and there by validate our clinical observation.

METHODS:

This was a single visit, cross-sectional, observational study that was performed in a tertiary care hospital in Pune. Institutional ethics committee approval was obtained before the start of study.

We screened 509 patients above 18 years of age with self-reported history of TB 509 patients We obtained documented evidence of TB treatment. Sputum smear examination was done for each participant and active PTB was thus excluded. All candidates were then subjected to chest radiograph (postero-anterior view) after obtaining their consent. Any lung scars on chest X-rays were assessed by Willcox classification.[12] Accordingly, each lung was divided into three zones and the extent of involvement were assessed as follows:

Degree I – Minimum involvement in only one zone without cavitation.

Degree II – Involvement of two/three zones with/without cavitation or involvement of one zone with cavitation.

Degree III – Severe involvement involving more than three zones with/without cavitation.

Only patients with normal to minimal post-TB lung scarring (degree I) on radiograph were included in study. Persons with active TB, symptoms or diagnosis of OAD before onset of TB infection, treatment defaulters, chronic lung disease due to any other condition, degree II and III lung involvement on radiograph, active lower respiratory tract infection at the time of enrollment and smokers (with smoking index >50) were excluded. Extent of smoking was assessed by 'Smoking Index' (SI) i.e., the number of beedi/cigarettes smoked per day multiplied by the duration of year smoked. Literature reports smoking as a risk factor for development of COPD in patients with smoking history of $\geq$10 pack years or smoking index of 200, considering one pack of 20 cigarettes/ bidis.[13] Adhering to the above criteria, a total of 112 subjects with past PTB (group A) and 107 subjects with past EPTB (group B) were considered eligible for the study.

All enrolled participants were subjected to spirometry. Appropriate pre-requisites for the spirometry were adhered to and those who could not perform acceptable spirometry were excluded. The analyzable data comprised of 200 post TB patients (100 cases in each group). Spirometry was performed by a trained technician with the patient in sitting posture using a turbine-based spirometer. Post bronchodilator reversibility was assessed after 15 minutes of inhaled salbutamol (400mcg). Each participant was made to perform a maximum of 8 forced expiratory maneuver test and values within 5% were considered acceptable. The best of the 3 results was used for grading lung function. The Chhabra (India) formula was used for the predicted values. Forced Expiratory Volume in 1st second (FEV1), Forced Vital Capacity (FVC), FEV1/FVC, Maximal Mid Expiratory Flow (MMEF) and Forced Expiratory Flow at 25% to 75% (FEF_{25-75}) were measured. Spirometry results were interpreted and their severity assessed as per relevant guidelines.[10,14,15,16] Small airway dysfunction was diagnosed when two of the spirometric indicators: MMEF and FEF_{25-75} were below 65% of predicted values.[17]

Data was entered in Microsoft excel. To analyse the data, SPSS (IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp. Released 2019) was used. Categorical variables were expressed in frequencies and proportions. Continuous variables were expressed in mean (SD). Chi-square test was applied to test the association between categorical variables. OR of PTB for OAD was calculated. Appropriate graphs and figures were made for the results. A p-value of <0.05 is considered statistically significant.

RESULTS:

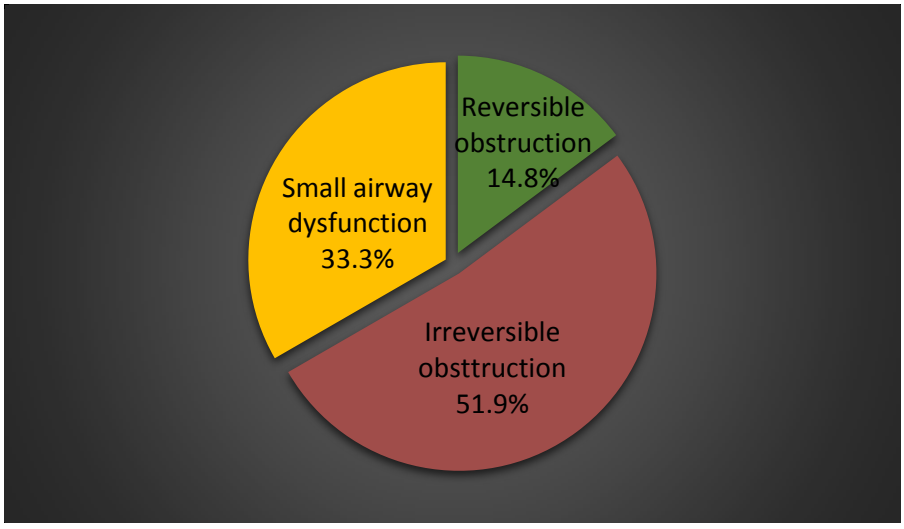
The study population comprised of 65% (130) males and 35% (70) females. The mean age of the patients was 40.2 $\pm$ 13.4 years. The frequency of airflow obstruction in group A patients was 27% (27/100) as compared to 3% (3/100) in group B, while restrictive defects were noted in 2% and 10% of group A and group B respectively (Table 1). Significant association was noted with group A and OAD (p <0.001) with an OR of 11.95 (95% CI 3.49 – 40.9). No positive correlation was observed with EPTB and OAD. Among the PTB with OAD, spirometric evidence of irreversible obstruction, reversible obstruction and small airway dysfunction were noted as 51.9%, 14.8% and 33.3% respectively (Fig 1). EPTB group recorded 2 cases of irreversible airflow obstruction and one with fixed extra thoracic airway obstruction (past laryngeal TB leading to subglottic stenosis). The mean FEV1, FEV1/FVC and FVC % in PTB group with OAD was 1.67L $\pm$ 0.52, 67.82% $\pm$ 10.5 and 80.19 $\pm$ 14.96 respectively.

Table 1. Spirometry pattern in treated pulmonary and extrapulmonary patients.

PATTERN OF SPIROMETRY	PULMONARY		EXTRA PULMONARY		p-value
	Frequency	Percent	Frequency	Percent	
Obstructive	27	27.0	3	3.0	<0.001 (Sig)
Restrictive	2	2.0	10	10.0	
Normal	71	71.0	87	87.0	
Total	100	100.0	100	100.0	

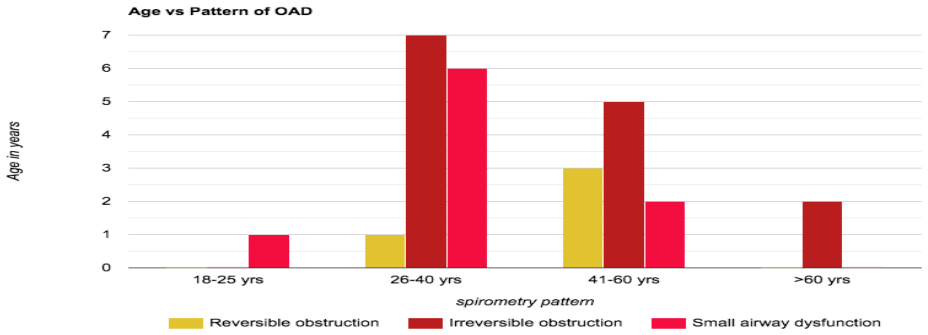
p-value calculated by Fisher test. p-value<0.05 is significant.

Fig 1. Pie-chart depicts type of obstructive defect in post PTB (group A) patients



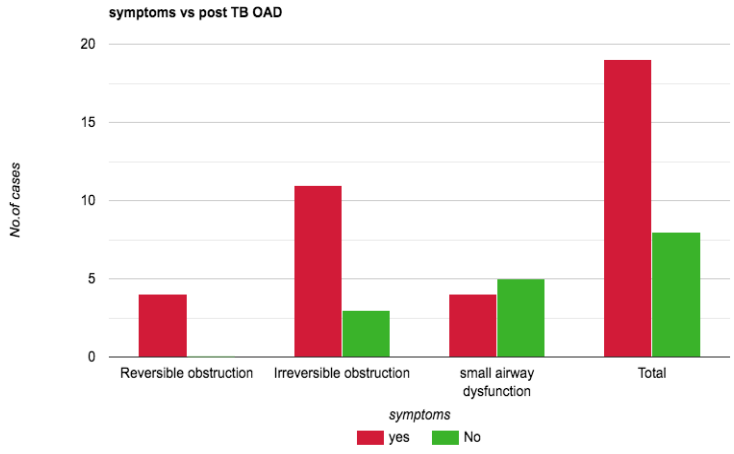
80% of study population were never-smokers, 16% were reformed smokers (SI < 50) and 4% were current smokers (SI < 50). Among group A, current smokers, reformed smokers and never smokers compromised of 5%, 15% and 80% respectively. In group B, 3% were current smokers, 17% were reformed smokers, 80% were never smokers. There was no significant association between smoking and onset of post-TB OAD. More than half of post-TB OAD cases (55.6%) were observed in younger age group (< 40 years age). 77.8% (7/9) of small airway dysfunction and 50% (7/14) of irreversible obstruction were noticed in patients under 40 years of age (Fig 2).

Fig 2. Bar diagram comparing age vs pattern of post TB obstructive airway disease.



We observed that, 29.6% of post TB OAD patients were asymptomatic and yet had lung impairment evident on spirometry. Among them, 55.6% had small airway dysfunction and 21.4% had irreversible obstruction (Fig 3). All cases of reversible obstruction (suggestive of asthma) had symptoms. The most common symptom at presentation was chronic cough (57.89%) followed by dyspnea (21.05%) and wheeze (15.78%). Despite evidence of clinical significance, since the sample size in the diseased group was small (n=27), statistical significance with chi square test was not done to avoid any misleading interpretations.

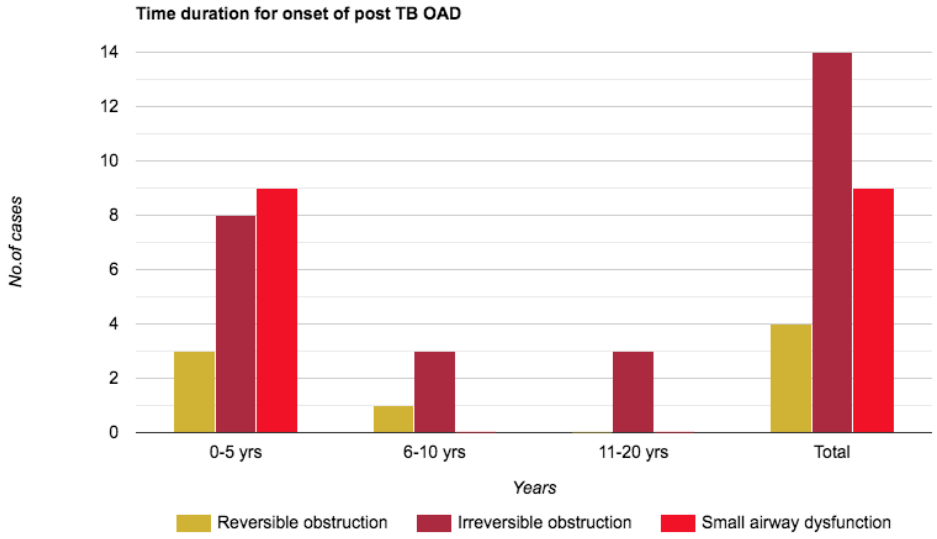
Fig 3. Bar diagram depicts prevalence of symptoms in post TB OAD patients.



ISSN 2515-8260 Volume 09, Issue 09, 2022

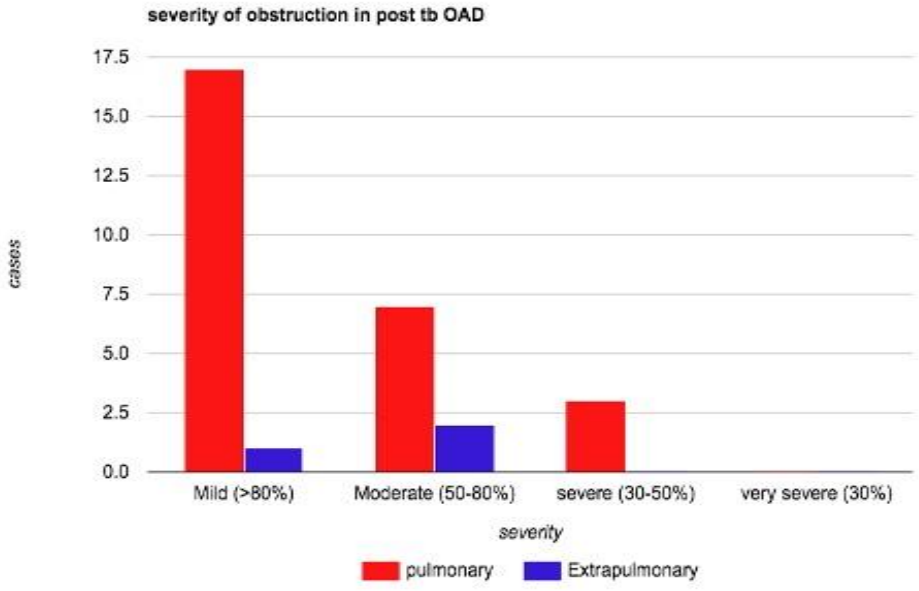
The duration of onset of OAD since completion of TB treatment was assessed. Strikingly, majority of airflow obstruction occurred within 5 years (74.1%) from treatment completion, while it developed within 6-10 years and 11-20 years in 14.8% and 11.1% of the cases respectively (Fig 4).

Fig 4. Bar diagram depicts duration of onset of post TB OAD since treatment completion.



Severity of obstruction was assessed, which revealed that 62.96% had mild (FEV1>80% predicted), 25.92% had moderate (FEV1 50%-80% predicted) and 11.1% had severe (FEV1 30%-50% predicted) obstruction (Fig 5).

Fig 5. Bar diagram showing severity of obstruction among group A and group B cases.



DISCUSSION:

'Post Tuberculosis sequalae' as an entity has seen progressive rise in recent years owing to the increase in the number of TB survivors. More than half of TB survivors develop some

form persistent lung dysfunction even after successful treatment completion.[7,18] These patients contribute significantly to the growing worldwide burden of COPD.[19] Although post TB OAD has been documented in several studies, these patients are seldom assessed or followed up for the same. National TB programmes are more focused on early case detection and treatment initiation, and are yet to address the issue of post tuberculosis sequalae. There is also a risk that these patients may end up restarting ATT in view of persistent symptoms and radiological shadows.

Our study focused on both PTB and EPTB cases with no radiologically evident lung damage. The prevalence of OAD in group A was 27% ($p<0.001$). Only 3% of group B developed obstruction, the prevalence of which was lesser than that observed in general population.[20] Hence, we considered group B as a proxy to control group. Significant association was established with PTB and onset of OAD, with OR of 11.95 (95% CI 3.49 – 40.9, $p = 0.0001$). Our findings were comparable with a multicentre, cross-sectional study done worldwide, in which the adjusted OR for airflow obstruction with history of PTB in Pune city was 11.173 (95% CI 1.72 – 79.97).[19] A systematic review of 19 studies reported a positive correlation between history of PTB and airflow obstruction.[21]

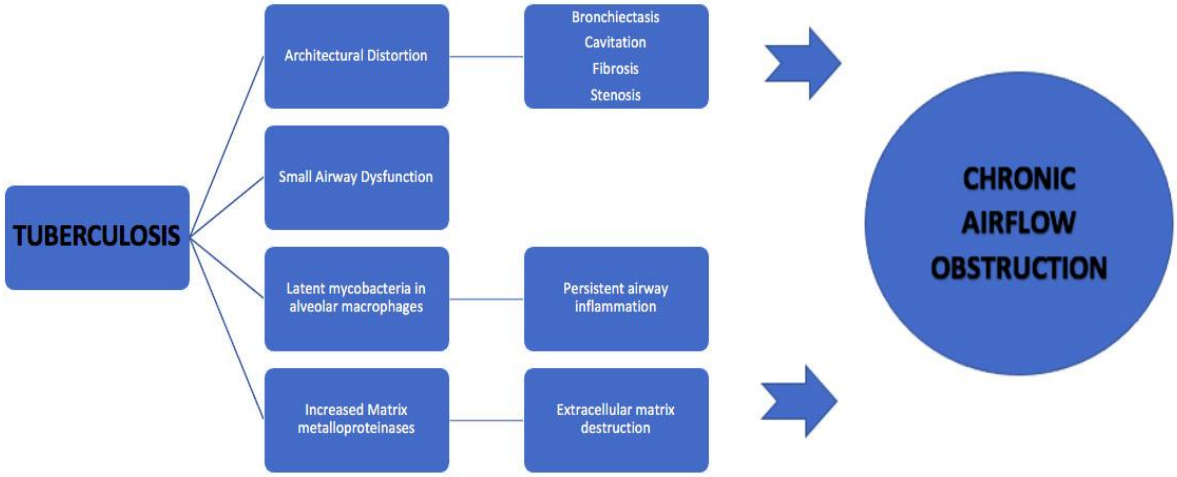
Obstructive ventilatory defect was the most common lung impairment in this study. These observations were in accordance with previous studies done in India.[22,23,24,25] Restrictive impairment was much lower compared to other studies, arguably due to the fact that patients with structural lung deformity were excluded. Although smoking is an independent risk factor for COPD and TB, there were no association with smoking and post TB OAD. Such association was not documented in earlier studies too.[26,27]

A notable finding in our study was that, 30% of the post TB OAD cases were asymptomatic (55.6% of small airway dysfunction and 21.4% of irreversible obstruction as depicted in fig 3). Studies done by Guilani et al[28] and Shital et al[22] showed that 62% and 54% of asymptomatic post TB cases had abnormal spirometry. This is of clinical significance because, these subsets of patients may be overlooked, and may present much later in life with severe disease which otherwise could have been well treated in advance. The time duration for onset of OAD after treatment completion was studied, a majority of the lung impairment occurred within 5 years of completion of TB treatment. Previous studies on duration of onset of post TB OAD showed variable results. Verma SK et al[29] in their study mentioned that most of the symptoms and lung dysfunction occurred within 5 years of treatment completion and Rajasekaran S et al[30] noticed development of post tb asthma in 50.9% patients in first year after treatment. These reports were comparable to our research findings. Conversely, Krishna K et al[25] and Baig IM et al[31] mentioned that post OAD was more common after 10 years of TB chemotherapy.

It is well known that tubercular lesions in lung heal by scarring that results in the loss of parenchymal tissue and hence a restrictive defect. The evidence that TB is associated with airflow obstruction tells us that parenchymal scarring is not the only pathological sequala and airways get injured to some extent too. However, it is unclear which mechanisms may

underlie airflow obstruction secondary to tuberculosis. It is hypothesised that host-pathogen interactions and immune hyperreactivity to TB antigen, persistent airway inflammation due to latent mycobacteria in alveolar macrophages and subsequent airway remodelling can be driving factors towards airflow limitation (Fig 6). These hypothesis need validation by evidence-based clinico-pathological studies.

Fig 6. Flow diagram representing the possible causes for airway obstruction in PTB



National TB policies do not adequately address the issue of post TB morbidity as the main focus is on reducing the transmission and hence the prevalence of TB. Since there are no standardized methods to follow up TB survivors, it is likely that these patients keep suffering and take treatment from private practitioners as a post-TB care is not a part of the public program. It is therefore only sensible to offer Post-TB Lung Disease (PTBLD) patients with symptomatic assessment, chest imaging and pulmonary function tests on routine follow up, either immediately or within few months after treatment completion. Greater awareness of PTBLD among policy-makers and practitioners is therefore warranted. Similar to GOLD strategy that has recognized TB as a potential risk factor for COPD, further work needs to be done for other post-TB sequalae such as asthma, bronchiectasis etc.

Despite the fact that our study contributes to the enriching literature on post TB lung function, it has few limitations. Firstly, there were no lung function test prior to TB infection, hence we could not ascertain the rate of decline of lung function or solely attribute TB as the cause for obstruction. Secondly, many cases in society reported as adult-onset asthma may be TB related as history of TB with complete radiological clearance is often not disclosed by the patients due to social stigma.

CONCLUSION:

Our responsibility towards TB patients does not end with microbiological cure. Our study demonstrates that airflow obstruction in treated PTB patients ensues largely in the initial years of treatment completion and can occur in the absence of structural lung damage, even in asymptomatics. Owing to the high prevalence of TB in developing countries like India,

this is a matter of considerable public health significance. We suggest routine screening lung function test in all TB survivors for early detection of obstructive airway disease for prompt treatment initiation, thus reducing further morbidity.

CONFLICTS OF INTEREST STATEMENT:

There are no conflicts of interest.

REFERNCES:

1. Dodd PJ, Yuen CM, Jayasooriya SM, van der Zalm MM, Seddon JA. Quantifying the global number of tuberculosis survivors: a modelling study. Lancet Infect Dis. 2021 Jul;21(7):984-992. doi: 10.1016/S1473-3099(20)30919-1.
2. Basham CA, Romanowski K, Johnston JC. Life after tuberculosis: planning for health. Lancet Respir Med 2019;7(12):1004–6. doi: 10.1016/S2213-2600(19)30371-6.
3. Marais BJ, Chakaya J, Swaminathan S, et al. Tackling long-term morbidity and mortality after successful tuberculosis treatment. Lancet Infect Dis 2020;20(6):641–2. doi: 10.1016/S1473-3099(20)30167-5.
4. Lee JH, Chang JH. Lung function in patients with chronic airflow obstruction due to tuberculous destroyed lung. Respir Med 2003;97:1273-42.
5. Kim HY, Song KS, Goo JM, Lee JS, Lee KS, Lim TH. Thoracic sequelae and complications of tuberculosis. Radiographics 2001;21:839-60.
6. Dheda K, Booth H, Huggett JF, Johnson MA, Zumla A, Rook GA. Lung remodeling in pulmonary tuberculosis. J Infect Dis 2005;192:1201-10.
7. Pasipanodya JG, Miller TL, Vecino M, et al. Pulmonary impairment after tuberculosis. Chest 2007; 131:1817–1824.
8. Hallett WY, Martin CJ. The diffuse obstructive pulmonary syndrome in a tuberculosis sanatorium. I. Etiological factors. Ann Intern Med 1961;54:1146-55.
9. Snider GL, Doctor L et al. Obstructive airway disease in patients with treated pulmonary tuberculosis. Am Rev Respir Dis 1971;103:625-40.
10. Global Strategy for Prevention, Diagnosis and Management of Chronic Obstructive Lung Disease 2022 report. Available from https://goldcopd.org/2022-gold-reports-2/
11. Mehta K, Balani KA, Sahasrabudhe TR. New onset adult asthma attributable to tuberculosis: A distinct phenotype? J Assoc Chest Physicians 2022;10:97-101.
12. Willcox PA, Ferguson AD. Chronic obstructive airways disease following treated pulmonary tuberculosis. *Respir Med* 1989; 83: 195–198.
13. ForeyBA, ThorntonAJ, LeePN. Systematic review with meta- analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. BMC Pulm Med 2011; 11: 36.
14. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019 Oct 15;200(8):e70-e88. doi: 10.1164/rccm.201908-1590ST. https://doi.org/10.1164/rccm.201908-1590ST
15. Timothy j. Barreiro et al. An Approach to Interpreting spirometry. *Am Fam Physician.* 2004;69(5):1107-1115.
16. 2022 GINA main report. https://ginasthma.org/gina-reports/
17. Xiao D, Chen Z, Wu S, *et al*. Prevalence and risk factors of small airway dysfunction, and association with smoking, in China: findings from a national cross-sectional study. *Lancet Respir Med* 2020;8:1081–93.
18. Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. Thorax 2000; 55: 32–38

19.Amaral AF, Coton S, Kato B, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. Eur Respir J 2015; 46: 1104–1112.
20. Murtagh, E., Heaney, L., Gingles, J. *et al.* The prevalence of obstructive lung disease in a general population sample: The NICECOPD study. *Eur J Epidemiol* **20**, 443–453 (2005). https://doi.org/10.1007/s10654-005-1248-8
21. Allwood B.W, Myer, et al. A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults. *Respiration.* 2013; **86**: 76-85
22. Shital patil, Rajesh patil, Anil Jadhav. Pulmonary functions' assessment in post-tuberculosis cases by spirometry: Obstructive pattern is predominant and needs cautious evaluation in all treated cases irrespective of symptoms. Int Journal of Mycobacteriology. 2018;7:128-33.
23. Agarwala A, Maikap MK, Panchadhyayee P, Mandal P, Roy PP. Chronic airway obstruction in post tubercular fibrosis cases: A serious lung function changes. Int J Res Med Sci 2016;4:5294-6.
24. Manji M, Shayo G, Mamuya S, Mpembeni R, Jusabani A, Mugusi F, *et al.* Lung functions among patients with pulmonary tuberculosis in Dar es Salaam – A cross-sectional study. BMC Pulm Med 2016;16:58.
25. Krishna K, Bond S, Artvinli M, Reid KDG, McHardy GJR, Crofton JW. Pulmonary function in treated tuberculosis; a long term follow-up. Am Rev Respir Dis. 1977;115:402-04.
26. Ramos LM, Sulmonett N, Ferreira CS, Henriques JF, de Miranda SS. Functional profile of patients with tuberculosis sequelae in a university hospital. *J Bras Pneumol.* 2006;32:43–7
27. Di Naso FC, Pereira JS, Schuh SJ, Unis G. Functional evaluation in patients with pulmonary tuberculosis sequelae. *Rev Port Pneumol.* 2011;17:216–21
28. Guilani A, Bhalotra B, Parakh U, Jain N. Even asymptomatic patients may have serious lung impairment after successful TB treatment. Am J Respir Crit Care Med 2014;189:A3203
29. Verma SK, Narayan KV, Kumar S. A study on prevalence of obstructive airway disease among post pulmonary tuberculosis patients. *Pulmon.* 2009; **11**(1): 4– 7.
30. Rajasekharan S, Savitri S, Jeyaganesh D. Post tuberculosis bronchial Asthma. Ind J Tub 2001; 48: 139.
31. Baig IM, Saeed W, Khalil KF. Post-tuberculous chronic obstructive pulmonary disease. J Coll Physicians Surg Pak. 2010;20:542-44.