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Respiratory Medicine

AN OBLIVIOUS PLIGHT OF PULMONONARY TUBERCULOSIS: A LOOK AT THE AGENTS OF SEQUELAE

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ABSTRACT **Background:** The pathogenesis of pulmonary tuberculosis may cause chronic anatomical and pathophysiological changes even after attaining complete bacteriological cure — post tuberculosis lung disease. Preventative and control measures such as WHO end TB strategy and sustainable developmental goals have curtailed the expansion of the disease, but it still remains a global threat with its high incidence and mortality rate. As the programmes continue its focus on prevention and treatment, the long term sequelae is overlooked. This study aims to identify the factors associated with the development of post tuberculosis lung diseases. **Methods:** A hospital based cross sectional study was conducted among 50 patients during December 2022 - December 2023. All patients who were diagnosed with pulmonary tuberculosis above 18 years of age and completed treatment with no evidence of active pulmonary tuberculosis were evaluated. Data were entered into MS excel and SSPS software was used for analysis. **Results:** Out of 50 patient enrolled in the study, 60% of the patients presented with grade IV dyspnea according to MMRC grading. 90% of the patients developed. Bronchiectasis sequelae was significantly higher among males (p=0.003). The delay in diagnosis proved significant association in the advent of fibrosis (p=0.008). Male predominance (p = 0.010), history of hypertension (p=0.046) and high smoking index (p = 0.014) was associated in development of obstructive airway disease. **Conclusion:** Risk factors, such as, high smoking index, delay in diagnosis, hypertension proved to be costly in the evolution of sequelae. Hopefully, this endeavour may appeal to converge efforts to produce newer studies to investigate other risk factors, emphasise the need for follow up and monitoring of treated/cured patients.

KEYWORDS : delay in diagnosis, post tuberculosis lung disease, risk factors, smoking, sequelae

INTRODUCTION:

Tuberculosis is a public health problem of global concern. It has an estimated annual incidence of 10.6 million cases.[1-2] Among them, only 6 million cases are recognized and treated.[1-2] India has the highest tuberculosis burden in the world, accounting for 28% of global TB cases.[3] Pooled prevalence of TB infection in India is estimated to be 41%.[3] In addition, around half of the microbiologically cured TB cases develop moderate to severe long term pulmonary impairments.[4] Tuberculosis patients are declared cured if they turn sputum negative. However, there is a lack of attention on the long term effect of pulmonary TB.[5] Moreover, there is a lacunae in the post pulmonary TB sequelae in terms of policy making.[6] A scoping review of 212 guideline on TB noted that only three guidelines mentioned post TB sequelae.[7] There is a need to understand the problem of these sequelae for appropriate management.

Post TB sequelae are a range of pathological conditions occurring as a result of destructive pathological changes following pulmonary TB, even after bacteriological cure[8]. They include physical (post TB lung disease/PTLD) and psycho-social impairments (post TB economic, social, and psychological well being/Post TB ESP). They commonly affect lung and can show varied presentations from mild breathlessness to risk of death[8]. The prevalence of post TB lung disease vary between 18-87%[9-10]. The severity and pattern of PTLD varies between and within individuals.[9] The patterns depend on the compartments involved like airway, parenchyma, pleura, pulmonary vasculature, and others.[9] They can present with various clinical patterns such as TB associated obstructive lung diseases and parenchymal destruction leading to fibrosis, bronchiectasis, cavity, chronic pleural disease and pulmonary hypertension.[9-10]

Post tuberculosis sequelae attribute to 47% of the disability-adjusted life-years (DALY) total tuberculosis burden. 58 million DALY are attributed to post tuberculosis sequelae.[6] Out of the 12.1 DALY per incident TB case, 5.8 DALY is due to sequelae.[6] Two-third of the DALY occur after 15 years of incident cases. In addition, there is decreased quality of life among these cases.[11-12] Early detection of the disease and understanding the factors associated with the disease help in this process. While various host-immune response and pathogen diversity are postulated for the pathogenesis, there is need for further studies for improved understanding of the evolution of the disease.[13] Previous studies have noted association of HIV and other immunocompromised conditions, social factors like poor socio-economic conditions, long standing illness, and inadequate treatment as common risk factors.[4, 14] However, there is a need for study in different geographical location and study settings to provide evidence-based knowledge on them. There is lack of data from our study area regarding the incidence and risk factors for PTLD. Hence the current study was planned to provide evidence on PTLD and further strengthen the advocacy for follow-up and management of post tuberculosis lung disease.

METHODS:

This study was a hospital based cross sectional study on 50 post pulmonary TB patients, conducted over a period of 1 year.

Inclusion Criteria:

All patients who were diagnosed with pulmonary tuberculosis above 18 years of age and completed treatment with no evidence of active pulmonary tuberculosis.

Exclusion Criteria:

All pregnant women and patients with history of MDR Tuberculosis , recurrent TB, congenital lung diseases, chest Wall diseases and Post COVID structural lung diseases were excluded. After obtaining permission from institutional ethical committee and concerned authorities, patients satisfying the inclusion and exclusion criteria were approached for the study. All those adults above 18 years who were diagnosed with Pulmonary Tuberculosis and completed treatment were enrolled after taking informed written consent and informing about the study using patient information sheet. At the time of out patient visit/admission, a detailed clinical history, risk factor assessment, physical examination, baseline investigations, X-ray, Pulmonary function test, CT scan were done according to the treatment protocol in the department. The risk factors assessed were Age, Gender, BMI, Smoking, Diabetes, HTN, HIV/AIDS, PFT, time since diagnosis of PTB, treatment status (cured/completed), time since onset of symptoms to treatment. Details were entered in the predesigned proforma. Patients were diagnosed as post tuberculosis lung disease based on the working definition as follows: Anatomical and pathophysiological changes in the chest which are secondary to complications of pulmonary TB, whether primary or secondary, even after completion of treatment and complete bacteriological cure.

Data Analysis:

Data was enetered using MS Excel and analyzed using IBM-SPSS 20 software. Qualitative data was measured using frequency and percentage. Quantitative data was measured using mean and standard deviation. Association for qualitiative data was measured using Chi-square test and Fischer exact test was used wherever necessary. Association for quantitative data was measured using student t test. P value < 0.05 was taken as statistically significant.

RESULTS:

Presence Of Post Tuberculosis Sequelae Among Cases

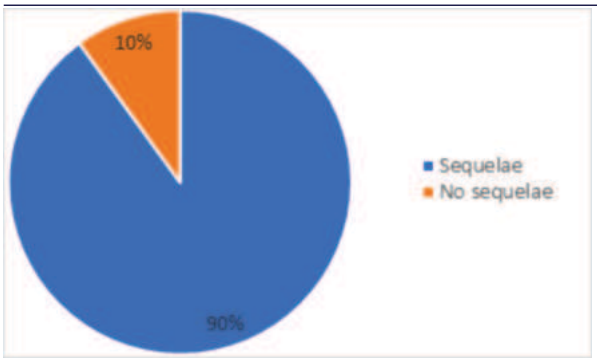

Fig.I

Post TB sequelae in participants

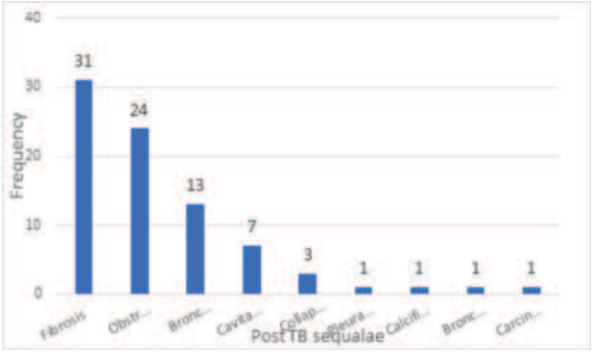

Fig. II

Association Between Fibrosis Sequelae With Risk Factors

Characteristics	Fibrosis (n=31)	No fibrosis (n=19)	P value
Age (Mean+SD) in years	64.03+8.7	64.6+10.7	0.906[a]
Gender Male Female	28 3	15 4	0.404[b]
BMI (Mean+SD) in kg/m^2	19.1+4.0	19.6+3.6	0.704[a]
Age of diagnosis of PTB (years) (Mean+SD)	45.4+15.9	42.7+14.7	0.555[a]
Gap between symptom to treatment (in weeks) (Median)	4	2	0.008[c]
Diabetes Mellitus (%)	32.3%	42.1%	0.552[b]
Hypertension (%)	48.4%	42.1%	0.773[b]
Cardiovascular disease (%)	25.8%	10.5%	0.282
Smoking index (Median)	500	400	0.534[c]
Silica exposure (%)	(7) 22.5%	(4) 21%	0.016[c]

Table I: The study noted significant association between delay in diagnosis and fibrosis as sequelae post TB (p=0.008). The median gap between symptom and treatment was 4 weeks for patients with sequelae and 2 weeks for patients without sequelae. Silica exposure among post pulmonary TB fibrosis patients was found to be significant (p = 0.016)

a: independent t test, b: Mann Whitney U test, c: chi-square test

Association Between Obstructive Airway Disease Sequelae With Risk Factors

Characteristics	Obstructive airway disease (n=24)	No obstructive airway disease (n=26)	P value
Age (Mean+SD) in years	63.6+6.1	65.2+11.7	0.544[a]
Gender Male Female	 24 0	 19 7	0.010[b]
BMI (Mean+SD) in kg/m^2	19.9+4.0	18.7+3.7	0.298[a]
Age of diagnosis of PTB (years) (Mean+SD)	40.1+12.3	48.3+17.0	0.058[a]
Gap between symptom to treatment (in weeks) (Median)	4	3.5	0.527[c]
Diabetes Mellitus (%)	33.3	38.5	0.774[b]
Hypertension (%)	62.5	30.8	0.046[b]
Cardiovascular disease (%)	20.8	19.2	0.887[b]
Smoking index (Median)	480	320	0.014[c]
Silica exposure (%)	(7) 29.2%	(4)15%	0.23

Table II: All the patients having obstructive airway disease were male, and in comparison 73% of patients without sequelae were male. This difference was statistically significant (p=0.010). Patients with obstructive airway disease had developed pulmonary TB at a younger age (40.1+12.3) compared to patients without obstructive airway disease (48.3+17.0). However, this difference was not statistically significant (p=0.058).

a: independent t test, b: Mann Whitney U test, c: chi-square test

Association Between Bronchiectasis Sequelae With Risk Factors

Characteristics	Bronchiectasis (n=13)	No Bronchiectasis (n=37)	P value
Age (Mean+SD) in years	62.04+8.7	65.3+9.6	0.290[a]
Gender Male Female	8 5	35 2	0.003[b]
BMI (Mean+SD) in kg/m^2	19.5+3.6	19.2+3.9	0.842[a]
Age of diagnosis of PTB (years)	41.9+16.3	45.2+15.1	0.506[a]
Gap between symptom to treatment (in weeks) (Median)	6	4	0.621[c]
Diabetes Mellitus (%)	38.5%	35.1%	0.830[b]
Hypertension (%)	23.1%	54.1%	0.104[b]
Cardiovascular disease (%)	7.7%	24.3%	0.258
Smoking index (Median)	625	0	0.000[c]
Silica exposure (%)	(5) 38%	(6) 16.7%	0.09

Table III: The study noted that bronchiectasis sequelae was higher among males compared to females and this difference was statistically significant (p=0.003). Smoking index was higher among patients without bronchiectasis sequelae compared with patients with sequelae, and this difference was statistically significant (p=0.000).
a: independent t test, b: Mann Whitney U test, c: chi-square test

DISCUSSION:

Post tuberculosis lung disease (PTLD) is a health concern globally. The need for research in the field was of concern due to non-uniformity of definition and criteria for evaluation of PTLD. The First International Symposium of post tuberculosis lung disease provided a uniform criteria to reduce this lacunae.[10] Due to the high lifetime burden of post tuberculosis sequelae, there is a need for global research on the topic for further advancement in approach and advocacy towards PTLD prevention and management.[6]

Prevalence Of Lung Disease

Our study noted 90% prevalence of PTLD among patients who attended the Pulmonary medicine department in a tertiary care hospital. 60% of the patients presented with grade IV dyspnea according to MMRC grading. These patients documented varied lung abnormalities including fibrosis (62%), obstructive airway disease (48%), bronchiectasis (26%), cavitation (14%), collapse (6%), pleural thickening (2%), calcification (1%) and Ca bronchus (1%). Previous systemic review by Dhamgaye TM et al noted that prevalence of PTLD varied from 18-87% across the globe.[15] Another meta-analysis by Maleche-Obimbo E et al noted that the congregated prevalence of abnormal radiological findings, abnormal lung function, and persistent respiratory symptoms was 64.6%, 46.7%, and 41.0%, respectively.[16] Various factors like study population characteristics, diagnostic modalities employed, and the duration of follow-up may have attributed to the variation. A high rate of PTLD in our study population may be related to the study area. Similarly, a tertiary care hospital study in Pakistan by Ali MG et al noted a prevalence of 91%.[17] As our study is conducted among patients attending a tertiary care hospital where majority of the participants may have attended due to symptoms. This may lead to a higher prevalence rate in our study.

Our study noted that fibrosis (62%) was the most common findings. Previous radiological studies have also noted that fibrosis and pleural thickening were the most common findings in post TB sequelae.[18]

Pathophysiology studies have noted that host immune responses including excessive inflammation and excess activation of lung matrix metalloprotease result in fibrosis.[19,20] Silica exposure was evident in fibrosis sequelae. 7 out of 31 patients with post pulmonary TB fibrosis were found to have silica exposure ($p = 0.016$). Both silica exposure and pulmonary TB may have contributed to the development of fibrosis.

In our study, obstructive airway disease was noted in around half of the participants. Previous studies have shown evidence on TB and COPD co-morbidity. In addition, O'Toole RF et al noted bi-directional relationship between the diseases.[21] A model based study in Africa by Johnson LF et al noted that co-morbidities are highest with COPD.[22] A 3-year follow up study in Malawi by Nightingale R et al noted airway obstruction in 15.8% cases.[23] Our study had a higher mean follow up period. Similarly, around one-fourth of our study participants were diagnosed with bronchiectasis. A previous study in Singapore by Fong I et al noted post-TB bronchiectasis in 31.1% cases. These cases were associated with higher hospitalization due to exacerbation of disease.[24] Another study by Al-Harbi A et al noted that among bronchiectasis due to various aetiology, 31% were due to post TB sequelae.[25] The study noted that post TB bronchiectasis had higher severity compared to other causes.[25,26] Choi H et al noted that they are also associated with poor outcome compared to non-TB bronchiectasis.[27]

Our study noted a single case of lung cancer as post TB sequelae. Similar results were noted in previous studies by Arulanantham A et al and Qin Y et al.[28-29] Squamous cell carcinoma lung was noted as post TB sequelae irrespective of other risk factors.[28-29] Additional factors like age and smoking can increase the risk of lung cancer in such cases.[28-29] Overall, there is a high prevalence of PTLD of varied aetiology. A comprehensive evaluation with regular follow up may help in early diagnosis and management of the cases are of utmost importance.

Risk Factors

The study explored various potential risk factors associated with the development of PTLD. There are documented evidence of host, immune, and environmental interaction in occurrence and severity of PTLD.[19,20] Our study attempted to add to the evidence.

Delay In Diagnosis Or Treatment

The current study found significant association between fibrosis and delay in diagnosis. It was noted that the mean delay between initiation of symptom and diagnosis was 4 weeks for PTLD cases and 2 weeks for post TB patients without sequelae. In addition, a model based study by Bastos HN et al noted that longer delay of more than 30 days was associated with PTLD and increased mortality.[30] Moreover, there is documented evidence that delayed diagnosis can lead to increased damage to lung tissue. Hence, early diagnosis and management is crucial.[31]

Co-morbidities

The current study did not find any significant association between PTLD and co-morbidities like Diabetes mellitus. However, hypertension was found to be associated with obstructive airway disease. Diabetes mellitus was noted in higher cases of PTLD (71.4%) compared to non-PTLD (30.2%) cases. While previous studies by Bisht MK et al[32] and Restrepo BI et al[33] documented that Diabetes Mellitus increase the risk of development of TB by 3 folds,[32-33] there is limited evidence on link between DM and PTLD. Kuziemski K et al noted that even in a healthy person, DM is associated with poor lung function and capacity for physical activity.[34]There is a need for focused study between these parameters.

Cardiovascular disease (CVD) is the most common cause of death worldwide. Association between TB and CVD can increase the burden to health care. During TB infection, the cytokines released from cholesterol plaques is postulated to destabilize the plaques, increasing the risk of CVD.[14] While no association was noted between hypertension and PTLD, our study noted that a significant association between hypertension and obstructive airway disease. There is lacunae in studies between PTLD and systemic hypertension. Post TB pulmonary hypertension is a global public health concern.[35] Group 3 pulmonary hypertension is also noted as Post TB sequelae.[36] There is a lacunae for further studies to provide evidence based data regarding the effect of co-morbidities on PTLD, and vice versa.

Smoking

The current study assessed the link between smoking with PTLD. Our study noted significant association between smoking index with diseases like bronchiectasis (post-TB) and obstructive airway disease (post-TB). Smoking is a documented risk factor for active TB, severe disease progression, and development of COPD.[37,38-39] It also affects the treatment outcome in TB.[40] They are associated with poor immune outcome in TB infection[38] and increases the symptomatic presentations in PTLD.[40] Cessation of smoking is an important component of management of TB. And current study shows that it is an important component of prevention and management of PTLD. Overall, the current study presents with known and unknown risk factors associated with PTLD.

Implications and Future Directions

This study has discovered that delay in diagnosis has strong association with the development of the most common sequelae, fibrosis. The role of smoking was also brought to attention pertaining to the advent of obstructive airway disease and bronchiectasis sequelae. Our study provides evaluation of the risk factors pertaining to the disease, and can help policy makers fulfil for need of well established follow up recommendations and evaluation of post TB pulmonary sequelae. Regular pulmonary function testing, imaging studies, and symptom monitoring should be implemented to detect and monitor PTLD, enabling timely interventions and supportive care. Furthermore, the identification of risk factors associated with PTLD development provides valuable insights for targeted prevention and management strategies. There is a need to disseminate the information on definition and diagnostic criteria for diagnosis of PTLD across various health care workers. It is ideal to educate the patients on preventable risk factors like smoking, delay in diagnosis in order to reduce the incidence and severity of PTLD. In short, this study serves as an appeal to the policy makers on the seriousness of the disease and need for it to be considered under health policy recommendations.

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