ORIGINAL RESEARCH

Impact of latent tuberculosis infection on pulmonary function: A longitudinal study

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Received: 25 September, 2021 Accepted: 29 October, 2021

ABSTRACT
Objective: To assess the impact of latent tuberculosis infection (LTBI) on pulmonary function, focusing on reductions in FEV1, FVC, and PEF, and identifying factors influencing this decline. **Methodology:** A cohort of 50 participants aged under 18, with confirmed LTBI via tuberculin skin tests or interferon-gamma release assays (IGRA), was enrolled in the study. Exclusion criteria included individuals with active tuberculosis, pre-existing pulmonary conditions, and those undergoing immunosuppressive therapy. Participants underwent baseline pulmonary function tests, including spirometry, and were followed for 24 months with regular assessments of pulmonary function, clinical status, and lifestyle factors. Data were analysed using descriptive statistics, repeated-measures analysis, multivariate regression, Kaplan-Meier survival analysis, and Cox proportional hazards models. **Results:** The study revealed a gradual decline in pulmonary function over time. The mean FEV1 decreased from 85.2% to 80.3% over the 24 months. Similarly, FVC and PEF also showed reductions. Multivariate regression analysis identified age, smoking history, and severity of LTBI as significant predictors of pulmonary decline, with severe LTBI having the most pronounced effect. Kaplan-Meier survival analysis showed that participants with severe LTBI developed active tuberculosis more rapidly, with a median time of 12.2 months compared to 18.4 months in those with mild LTBI. Cox proportional hazards models confirmed that older age, smoking history, and severe LTBI were associated with an increased risk of pulmonary decline. **Conclusion:** LTBI is associated with a gradual and significant decline in pulmonary function over time, with severe LTBI and smoking history being key risk factors. The study emphasizes the importance of early detection and monitoring of LTBI to prevent long-term respiratory complications and progression to active tuberculosis. Further research is needed to explore interventions to mitigate pulmonary impairment in LTBI patients.

Keywords: Latent Tuberculosis Infection, Pulmonary Function, Longitudinal Study, Forced Expiratory Volume, Peak Expiratory Flow

BACKGROUND

Tuberculosis (TB) is transmitted via the air and is caused by the mycobacterium tuberculosis. Inhaled germs may cause a tuberculosis infection if the airways are diseased. Lung sickness is a condition that manifests itself when the immune system of the body is unable to eliminate the germs(1). In the year 2021; there were about 10.6 million people who were afflicted by TB, with 11% of those cases affecting children and adolescents under the age of 15. In the second place, tuberculosis may manifest itself in a variety of ways; the most common manifestation is pulmonary disease in children. Obtaining bacteriological data in cases involving babies and young children continues to be challenging, regardless of the organ being investigated. It is estimated that between thirty and forty percent of babies who are less than one year old who have a primary infection will acquire pulmonary tuberculosis (PTB) because of that individual infection. Getting older is the primary factor determining the likelihood of a disease (2). Even though there have been efforts made to improve the diagnosis and treatment of juvenile TB, it is still possible that children who have had tuberculosis in the past may still be at risk for experiencing long-term repercussions from the illness. There is a lack of understanding about the occurrence and severity of post-TB lung disease (PTLD) in adolescents and young adults. Several well-documented changes in lung function and post-TB bronchiectasis have been seen in individuals who have pulmonary transportation lung disease (PTLD)(3).

Lung injuries that occur in children, such as those caused by pneumonia or respiratory infections, can cause impairments while the lungs are still growing normally throughout infancy. Considering this, it is of the utmost importance to possess data specific to PTLD in juveniles. A dozen times, when compared to the outcome of catching tuberculosis (PTB) as an adult who has never had tuberculosis (TB), it is very probable that being infected with PTB during childhood has a more harmful effect on the lung function of the individual in the future(4). In a recent study, the objective assessment of pulmonary tetralogy of the lungs (PTLD) by testing was suggested to detect post-TB pulmonary alterations earlier. These may reduce healthcare costs, reduce the strain placed on patients, their families, and healthcare systems, and maybe cause treatment to be started sooner to avoid permanent loss of lung function(5).
This systematic longitudinal study evaluates the impact of latent tuberculosis (TB) on pulmonary function, this research aims to fill that gap by conducting a comprehensive review and meta-analysis.

AIM OF THE STUDY

To assess the LTBI results in significant reductions in lung function over an extended period via a longitudinal study.

Objective

To evaluate the long-term impact of latent tuberculosis infection (LTBI) on pulmonary function in affected individuals.

Methodology

A longitudinal cohort study was conducted to examine the effects of latent tuberculosis infection (LTBI) on pulmonary function over time. Participants had regular evaluations and follow-ups to ascertain the presence or no changes in lung function.

Inclusion Criteria

The longitudinal study was conducted involving 50 participants with latent tuberculosis.The inclusion criteria for this study required participantsaged <18 who had tested positive for latent tuberculosis infection (LTBI), as confirmed by either a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA). Eligible participants were those who did not exhibit signs of active tuberculosis, as verified through negative chest X-rays and clinical evaluations. Only individuals with no previous history of active tuberculosis treatment were considered. Furthermore, participants and their legal guardians, where applicable, had to provide informed consent (or assent, with parental consent) and demonstrate a willingness to adhere to the study's follow-up protocols throughout its duration.

Exclusion Criteria

The following criteria were used to exclude patients from the study:

- Individuals with active tuberculosis at the time of screening.
- Participants with pre-existing pulmonary conditions (e.g., COPD, asthma) that could affect lung function assessments.
- Pregnant women, due to potential health risks during the study.
- Individuals currently undergoing immunosuppressive therapy, such as corticosteroids or chemotherapy.
- Participants who failed to attend follow-up appointments or adhere to study protocols.

Data Collection

Participants in longitudinal research were those whose clinical or diagnostic testing has shown that they have a latent tuberculosis infection (LTBI). The effects of LTBI on lung function are the focus of this investigation. Information gathering is the goal of this line of action. Ideally, before beginning research, all relevant demographic information should be gathered, including but not limited to age, gender, smoking history, socioeconomic status, medical history, and extensive medical background. After that, the patientunderwent several tests to determine how well their lungs work. The treatments would include a spirometry evaluation, which includes the examination of FEV1, FVC, and other lung function metrics; chest X-rays; and blood testing to detect indicators of LTBI (long-term brain damage).
The participants were closely watched for a certain period, ranging from twelve to twenty-four months. During this time, they will be checked for changes in lung function, symptoms of active tuberculosis, or any other respiratory problems that may develop. The study gathered information on lifestyle variables like exercise levels, food intake, and alcohol consumption. The study design entailed regular monitoring for symptoms of active tuberculosis, such as decreased body weight, fever, and coughing.
Individuals would have their pulmonary function evaluated at the start and at certain intervals during the trial. These assessments would be carried out at regular intervals to guarantee continuous and dependable data collection throughout the experiment. The results would only be considered credible at that point. Individuals were categorized according to their risk profile for LTBI to make it easier to study the possible relationships between various factors and lung health over time.

Data Analysis

The data analysis for the longitudinal study began with descriptive statistics to summarize baseline characteristics of the study cohort, including demographics, comorbidities, and baseline pulmonary function measures. The primary outcome was changes

in pulmonary function over the study period, which were measured through longitudinal analysis techniques. These changes were examined using repeated-measures analysis of variance (ANOVA) or mixed-effects models, accounting for within-subject correlations due to the repeated nature of the data. The analysis explored potential predictors of pulmonary decline, including the severity of LTBI (measured by clinical biomarkers, chest X-ray findings, and immunological tests), age, sex, smoking history, and other relevant factors. Multivariate regression models were used to determine the influence of these variables on pulmonary function outcomes, controlling for potential confounders. A Kaplan-Meier survival analysis was also conducted to determine the time to the development of active tuberculosis, if relevant.

Cox proportional hazards models were employed to identify factors associated with an increased risk of deterioration in lung function or progression to active tuberculosis. Data were assessed for normality, and transformations or non-parametric tests were applied where necessary to ensure the robustness of the results. Additionally, sensitivity analyses were performed to test the stability of the findings, considering different methods of data handling and assumptions. Longitudinal data allowed for the tracking of individual changes over time, providing a clearer understanding of the relationship between LTBI and pulmonary function progression. The results were validated against known risk factors and compared with external data sets or studies, ensuring external validity and generalizability.

RESULTS

Table 1: Characteristics of the Study Cohort

Variable	Category	Frequency (%)	Mean (SD)
Age (years)	-	-	45.3 (±12.6)
Gender	Male	30 (60%)	
	Female	20 (40%)	
Smoking History	Smoker	18 (36%)	
	Non-smoker	32 (64%)	
Presence of Comorbidities	Yes	22 (44%)	
	No	28 (56%)	
LTBI Severity	Mild	15 (30%)	
	Moderate	25 (50%)	
	Severe	10 (20%)	
Baseline Pulmonary Function (FEV1, % of predicted)	-	85.2% (±10.5%)	

Table 1 displays the demographic and clinical data of the fifty patients who participated in the research. Half of the people who participated in the research were men; their average age was 42.3% (±12.6). A third of those who participated said they had smoked at some point in the past. Mild LTBI was reported by 30% of patients, moderate LTBI by 50%, and severe LTBI by 20%. Almost half of the population had several chronic diseases. The estimated baseline pulmonary function, measured by forced expiratory volume in one second (FEV1), was 85.2%, with a standard deviation of 10.5%.

Table 2: Pulmonary Function Changes over Time

Timepoint	Mean FEV1 (% of predicted)	Mean FVC (% of predicted)	Mean PEF (% of predicted)
Baseline (T0)	85.2 (±10.5)	90.3 (±8.1)	95.1 (±12.0)
6-month Follow-up (T1)	83.5 (±11.2)	88.9 (±7.5)	93.6 (±11.3)
12-month Follow-up (T2)	81.8 (±12.1)	87.4 (±6.9)	91.2 (±10.7)
24-month Follow-up (T3)	80.3 (±13.0)	85.8 (±7.2)	89.0 (±11.5)

Table 2 displays the average changes in pulmonary function measurements (FEV1, FVC, and PEF) at the beginning of therapy, six months later, twelve months later, and twenty-four months later. During the investigation, there was a gradual but consistent decline in the quality of pulmonary function. Over 24 months, the forced expiratory volume in one second (FEV1) had decreased to 80.3% (±13.0%) from its baseline value of 85.2% (±10.5%). There was a decline in the mean FVC from 90.3% (±8.1%) at the beginning of the study to 85.8% (±7.2%) at the end. Similarly, the mean PEF fell from 95.1% (±12.0%) at the beginning of the study to 89.0% (±11.5%) at the end. At the same time, both the FVC and the PEF showed a little decrease.

Table 3: Multivariate Regression Analysis of Predictors of Pulmonary Decline

Variable	Coefficient (β)	Standard Error	p-value
Age (years)	-0.23	0.08	0.005
Smoking History	-4.51	1.85	0.015
LTBI Severity (Moderate)	-3.20	1.55	0.046
LTBI Severity (Severe)	-7.15	2.30	0.003
Comorbidities	-2.65	1.78	0.144

Table 3 displays the results of a multivariate regression analysis conducted to identify the variables linked to a decline in lung function. A reduction in pulmonary function was significantly associated with an individual's age (γ = -0.23, p = 0.005), suggesting that age plays a substantial role in outcome prediction. A cigarette smoking history was also shown to be a strong predictor of pulmonary impairment (-4.51, p 0.015). Reduced lung function was shown to be associated with both moderate and severe traumatic brain injuries (TBI) (moderate: β = -3.20, p = 0.046; severe: β = -7.15, p = 0.003). The result was significantly affected by the degree of TBI. Despite investigating it, the existence of comorbidities did not have a statistically significant impact (p = 0.144).

Table 4: Kaplan-Meier Survival Analysis of Time to Active Tuberculosis Development

LTBI Severity	No. of Events	Median Time to Active TB (Months)	Log-Rank Test p-value
Mild	0	-	-
Moderate	5	18.4	0.042
Severe	8	12.2	0.008

Table 4 displays the findings of a Kaplan-Meier survival analysis conducted to ascertain the probability of contracting active TB. The median duration for active TB to emerge was 18.4 months for mild long-term brain damage compared to 12.2 months for severe. No active tuberculosis among the individuals who had moderate LTBI was found. More severe LTBI was linked to a shorter time to progression in the groups with moderate vs. severe (p = 0.008) and mild versus mild (p = 0.042), respectively, according to the log-rank test, which showed a significant difference in the amount of time it took for active tuberculosis to develop.

Table 5: Cox Proportional Hazards Model for Risk of Pulmonary Function Decline

Variable	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Age (years)	1.02	1.01 - 1.04	0.002
Smoking History	2.31	1.12 - 4.78	0.022
LTBI Severity (Moderate)	1.74	0.96 - 3.15	0.070
LTBI Severity (Severe)	3.12	1.61 - 6.06	0.001

The results of applying a Cox proportional hazards model to determine the likelihood of a decline in pulmonary function are shown in Table 5. Both those who smoked (hazard ratio = 2.31, p = 0.022) and those who were older (hazard ratio = 1.02, p = 0.002) were shown to have a greater possibility of seeing a drop in their risk of developing the condition. In situations of severe traumatic brain injury (LTBI), pulmonary function impairment was more likely to occur, as shown by a significantly higher hazard ratio (HR = 3.12, p = 0.001) for this scenario. This happened because of the risk being affected. Even though there was a tendency toward a slightly greater frequency of mild LTBI, this trend did not meet the criteria for statistical significance (hazard ratio = 1.74, p = 0.070).

DISCUSSION

The research was conductedto understand the long-term effects of latent tuberculosis infection (LTBI) on lung function. This researchwas conducted using a longitudinal cohort approach, the sample consisted of 50 participants. The forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF) measurements were used to assess lung function throughout the program. These measurements showed a gradual reduction in lung function. The results of this study are consistent with the hypothesis that long-term brain injury (LTBI) might produce progressive lung damage even in the absence of any illness. The fact that lung function has been slowly deteriorating is a significant factor that highlights the need to keep a close check on those who have sustained long-term traumatic brain injuries for the development of respiratory difficulties.

The multivariate regression analysis revealed that several variables caused pulmonary function loss. Age was shown to be a major predictor of a decline in lung function, with older people seeing bigger declines in lung function than younger people. According to Schneider et, al. long-term brain injury (LTBI) may expedite the normal loss of lung function that happens

with increasing age(6). This conclusion is consistent with findings from past studies. In this instance, the findings support the idea. According to Chaudhary et al., a history of smoking was shown to be strongly related to decreased lung function(7). This is in addition to the fact that smoking is a well-established risk factor in the general population for the worsening of respiratory illnesses among the general population. Because it sheds light on the compounding impact that smoking has on these people, this further highlights the importance of targeted therapy among smokers who have a history of being exposed to tuberculosis.

The severity of the chronic traumatic brain injury was one of the major characteristics that related to the loss of lung function. Other relevant factors were the severity of the damage. According to a prior studyPai et.al conducted on the subject, individuals who have suffered from severe LTBI are more likely to have a pulmonary impairment and post-TB lung disease (PTLD). According to the findings of their investigation, severe LTBI was linked to decreases in FEV1, FVC, and PEF, which were the most significant. It was shown that individuals who had several comorbidities had a higher incidence of traumatic brain injuries, which might range from moderate to severe(8). According to the findings of this study, there was no statistically significant connection between the existence of comorbidities and the decline in lung function. The fact that this is the case underscores the need to do larger research to study this link in more depth, even if the low sample size is the reason.

The Kaplan-Meier survival analysis found that a considerable risk of long-term brain damage (LTBI) was associated with an earlier onset of active tuberculosis (TB). The median period elapsed before the participants began showing sickness symptoms was twenty-two months. Concerningly, active tuberculosis (TB) is more common among those with severe types of long-term bacterial infection (LTBI) compared to those with less severe LTBI(9). Past and present research, including this study, indicates that the severity of LTBI significantly predicts whether tuberculosis will advance to an active state. The results of this analysis corroborated these earlier findings. Significant differences were found between the groups with moderate and severe long-term effects of illness (LTBI) using the log-rank test. The need to closely observe these individuals for signs of active TB cannot be overstated.

The findings from the Kaplan-Meier analysis were corroborated by the Cox proportional hazards model findings, which demonstrated that age and smoking history were significant predictors of pulmonary function decline. This discovery is consistent with the overall literature on aging and the loss of lung function and the hazard ratio for age, demonstrating that the likelihood of experiencing a decline in lung function increases with each passing year(10). According to the hazard ratio for smoking (HR = 2.31), it is concerning that someone who smokes and has a long-term brain injury is more than twice as likely to have a serious deterioration in their pulmonary function as someone who does not smoke. It is very necessary for those who have LTBI to give up smoking to reduce the likelihood of developing long-term lung issues.

The findings of this study are consistent with those of earlier research that showed that individuals who do not initially have active tuberculosis may nonetheless develop post-TB lung disease (PTLD). As stated by Pasipanodya et al., it is essential to monitor lung function in individuals who have been diagnosed with long-term tuberculosis infection (LTBI), particularly those who are of advanced age or have a historical smoking habit(11).

CONCLUSION

To conclude, this longitudinal research offered significant insights into the long-term consequences that LTBI has on lung function. Given the evidence, it seems that individuals who have a history of smoking, advanced age, and a history of severe traumatic brain injury (TBI) may have a gradual deterioration in lung function after the injury. The findings of this research highlight the need for early detection and treatment of long-term brain injury (LTBI) to lower the risk of long-term respiratory difficulties or prevent them from occurring in the first place. In addition, they stress the need to make sure that persons who are impacted by the condition have their lung health monitored constantly.

REFERENCES

1. Wong YJ, Noordin NM, Keshavjee S, Lee SWH. Impact of latent tuberculosis infection on health and wellbeing: a systematic review and meta-analysis. Eur Respir Rev. 2021 Mar 31;30(159):200260.
2. Leung CC, Chan KCW, Chan WK, Lin AWC, Lee SS, Wong NS. A longitudinal study on latent TB infection screening and its association with TB incidence in HIV patients. Sci Rep. 2019 Jul 12;9(1):10093.
3. Lew YL, Tan AF, Yerkovich ST, Yeo TW, Chang AB, Lowbridge CP. Pulmonary function outcomes after tuberculosis treatment in children: a systematic review and meta-analysis. Arch Dis Child. 2024 Mar 1;109(3):188.
4. Kim SH, Lee SO, Park JB, Park IA, Park SJ, Yun SC, et al. A Prospective Longitudinal Study Evaluating the Usefulness of a T-Cell-Based Assay for Latent Tuberculosis Infection in Kidney Transplant Recipients. Am J Transplant. 2011 Sep;11(9):1927–35.
5. Guo T, Tian S, Xin H, Du J, Cao X, Feng B, et al. Impact of fine particulate matter on latent tuberculosis infection and active tuberculosis in older adults: a population-based multicentre cohort study. Emerg Microbes Infect. 2014 Dec 31;13(1):2302852.
6. Schneider JL, Rowe JH, Garcia-de-Alba C, Kim CF, Sharpe AH, Haigis MC. The aging lung: Physiology, disease, and immunity. Cell. 2004 Apr 15;184(8):1990–2019.

7. Chaudhuri R, Livingston E, McMahon AD, Lafferty J, Fraser I, Spears M, et al. Effects of Smoking Cessation on Lung Function and Airway Inflammation in Smokers with Asthma. Am J Respir Crit Care Med. 2006 Jul 15;174(2):127–33.
8. Pai M, Zwerling A, Menzies D. Systematic Review: T-Cell–based Assays for the Diagnosis of Latent Tuberculosis Infection: An Update. Ann Intern Med. 2008 Aug 5;149(3):177.
9. Andrews JR, Noubary F, Walensky RP, Cerda R, Losina E, Horsburgh CR. Risk of Progression to Active Tuberculosis Following Reinfection With Mycobacterium tuberculosis. Clin Infect Dis. 2012 Mar 15;54(6):784–91.
10. Occhipinti M, Larici AR, Bonomo L, Incalzi RA. Aging Airways: between Normal and Disease. A Multidimensional Diagnostic Approach by Combining Clinical, Functional, and Imaging Data. Aging Dis. 2017;8(4):471.
11. Pasipanodya JG, Miller TL, Vecino M, Munguia G, Garmon R, Bae S, et al. Pulmonary Impairment After Tuberculosis. Chest. 2007 Jun;131(6):1817–24.