The Prevalence and Clinical Manifestations of Post-Tuberculosis Lung Disease in Immunocompetent HIV-Negative Individuals: A Scoping Review

Somasundram Pillay[1], Davashni Pillay[2]

[1]Internal Medicine Department, Nelson R Mandela School of Clinical Medicine, University of KwaZulu-Natal, Victoria Mxenge Hospital, 719 Umbilo Road, Durban, South Africa.

[2]University of Free State (UFS), 205 Nelson Mandela Dr, Park West, Bloemfontein, 9301Bloemfontein, South Africa.

Corresponding Author
Somasundram Pillay
Email:
drspillay@iafrica.com
Phone: +27 31 260 4182

Receive date:19/9/2024
Revise date:25/11/2024
Accept date:19/12/2024
Publish date:2/1/2025

Keywords: post-tuberculosis lung disease; immunocompetent; HIV-negative; prevalence; clinical manifestations; long-term outcomes

Background and study aim: Tuberculosis (TB) remains a leading cause of morbidity and mortality, particularly in low- and middle-income countries. Although TB treatment is generally effective, many patients develop long-term respiratory complications known as post-tuberculosis lung disease (PTLD). Most research has focused on HIV-positive individuals, leaving a gap in understanding PTLD in HIV-negative, immunocompetent individuals. This scoping review aims to assess the prevalence, clinical manifestations, diagnostic tools, and long-term outcomes of PTLD in HIV-negative individuals.

Patients and Methods: Following Arksey and O'Malley's scoping review framework, comprehensive searches were conducted in PubMed, Scopus, Web of Science, and Cochrane Library for studies published between 2010 and 2024. Inclusion criteria targeted studies examining PTLD in HIV-negative individuals. Ten studies were included in the analysis.

Results: The prevalence of PTLD in HIV-negative individuals ranged from 20% to 45%. Common clinical manifestations included chronic respiratory symptoms such as cough and dyspnoea, along with structural lung damage like pulmonary fibrosis and bronchiectasis. High-resolution computed tomography (HRCT) and spirometry were the most commonly used diagnostic tools. Long-term outcomes included persistent respiratory symptoms, recurrent infections, and chronic disability.

Conclusion: PTLD is a significant but under-recognized complication in HIV-negative TB survivors. Understanding its pathophysiology in immunocompetent individuals can improve diagnostic and treatment strategies, including pulmonary rehabilitation and long-term care. Further research and standardized care protocols are needed to manage this population better.

INTRODUCTION

Background and Rationale

Tuberculosis (TB) continues to be one of the leading causes of death worldwide, particularly in low- and middle-income countries. According to the World Health Organization (WHO), TB was responsible for an estimated 1.6 million deaths in 2021 [1]. In HIV-negative individuals, TB should be suspected in those presenting with persistent cough lasting more than 2 weeks, unexplained weight loss, night sweats, and fever. High-risk groups include individuals with a history of close contact with active TB cases, those residing or working in high TB prevalence areas, and individuals with predisposing conditions like diabetes mellitus or chronic kidney disease. Delays in diagnosis, which can range from weeks to several months, are often due to overlapping clinical features with other respiratory conditions, low clinical suspicion, and inadequate access to advanced diagnostic tools. Early use of high-resolution imaging and microbiological tests like GeneXpert can mitigate these delays [2]. Despite successful treatment of TB in most cases, many individuals suffer from long-term respiratory complications known as post-tuberculosis.

Tuberculosis lung disease (PTLD). PTLD encompasses a range of conditions, including pulmonary fibrosis, bronchiectasis, and chronic obstructive pulmonary disease (COPD) [3] These complications can significantly impair lung function and diminish the quality of life for survivors.

Much of the existing literature on PTLD focuses on individuals who are HIV-positive or immunocompromised. HIV-positive patients with TB often present with atypical clinical features due to compromised immune systems, which can result in more severe disease progression [4,5]. However, the pathophysiology of PTLD in HIV-negative, immunocompetent individuals may be different, as these patients generally mount a more robust immune response during active TB infection. Understanding how PTLD develops and manifests in immunocompetent individuals is critical for improving long-term outcomes in this population.

Objectives

This scoping review aims to address the gap in knowledge by focusing specifically on the prevalence, clinical manifestations, diagnostic criteria, and long-term outcomes of PTLD in HIV-negative individuals who have completed TB treatment. The primary objectives of this review are to:

1. Explore the existing literature on the prevalence and clinical manifestations of PTLD in immunocompetent, HIV-negative individuals.
2. Identify common diagnostic tools used to detect PTLD.
3. Assess the long-term health outcomes of individuals affected by PTLD.
4. Highlight gaps in the literature and propose areas for future research.

Research Questions

The scoping review seeks to answer the following questions:

1. What is the prevalence of post-tuberculosis lung disease (PTLD) in immunocompetent, HIV-negative individuals؟
2. What are the common clinical manifestations and comorbidities associated with PTLD in this population؟
3. What diagnostic tools and criteria are used to identify PTLD؟
4. What are the long-term outcomes for individuals with PTLD, and how are these outcomes managed؟

Methodology

Scoping Review Framework

The methodology for this scoping review followed Arksey and O'Malley's (2005) five-step framework [6:[

1. Identifying the research question.
2. Identifying relevant studies.
3. Study selection.
4. Charting the data.
5. Collating, summarizing, and reporting the results.

Eligibility Criteria

Inclusion Criteria:

- Studies that focus on PTLD in immunocompetent, HIV-negative individuals.
- Studies published between 2010 and 2024 that provide data on clinical outcomes, diagnostic methods, and treatment.
- Studies addressing PTLD as a post-TB complication, specifically pulmonary fibrosis, bronchiectasis, or COPD.

Exclusion Criteria:

- Studies involving HIV-positive individuals or those with compromised immune systems.
- Studies focusing solely on extra-pulmonary TB or unrelated post-TB lung complications.

Search Strategy

A systematic search was conducted using the following databases: PubMed, Scopus, Web of Science, and the Cochrane Library. The search was restricted to articles published in English between 2010 and 2024. The following Boolean search string was used:

")post-tuberculosis lung disease" OR "PTLD" OR "pulmonary complications after tuberculosis" OR "post-TB lung disease" OR "pulmonary fibrosis" OR "bronchiectasis" OR "chronic obstructive pulmonary disease") AND ("immunocompetent" OR "HIV-negative" OR "HIV seronegative") AND ("tuberculosis" OR "TB.("

Study Selection Process

The initial database search yielded 120 articles. After duplicates were removed, 94 articles remained. Two independent reviewers screened the titles and abstracts, excluding 52 articles. The remaining 42 full-text articles were further assessed for eligibility based on the inclusion criteria, leading to the exclusion of 32 studies. Discrepancies were resolved through consensus, and a third reviewer was consulted when necessary. Ultimately, 10 studies were included in this scoping review.

Data Extraction

Data were extracted using a standardized form to capture relevant information:

- Author(s), year of publication, study design, and country of study.
- Sample size, and population characteristics (age, sex, etc.(.
- Prevalence of PTLD, clinical manifestations, and diagnostic methods.
- Long-term outcomes and management strategies.

Results

Study Selection

The PRISMA Flow Diagram (Figure 1) outlines the study selection process. Of the 120 records initially identified, 10 studies were included in the final qualitative synthesis. Characteristics of

Included Studies

Table 1 provides a summary of the key characteristics of the included studies.

Figure 1: Flow Diagram

Records identified through database searching (n=120)

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Records after duplicates removed (n=94)

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Records screened (n=94)

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Excluded (n=60)

↓

Full-text articles assessed for eligibility (n=34)

↓

Excluded (n=24)

(Based on exclusion criteria)

↓

Studies included in qualitative synthesis (n=10)

DOI: 10.21608/aeji.2024.322332.1412

Table 1: Summary of study characteristics

Study Reference	Sample Size	Country	PTLD Prevalence	Main Clinical Manifestations	Diagnostic Tools Used
Hamusse (2017)	500	Ethiopia	30%	Chronic cough, dyspnoea	Chest CT, spirometry
Narayan (2019)	150	India	45%	Lung fibrosis, bronchiectasis	HRCT, pulmonary function tests
Saymaz and Özkara (2022)	Case report	Turkey	N/A	Bilateral micrographs, lung fibrosis	Chest CT
Diedrich (2012)	200	USA	40%	Fibrosis, bronchiectasis	Chest X-ray, spirometry
Du Preez (2020)	100	South Africa	32%	Persistent cough, reduced lung function	HRCT, pulmonary function tests
Veerasami (2013)	200	South Africa	28%	Dyspnoea, chronic productive cough	Chest CT
Shaw et al. (2020)	Review	Global	N/A	Post-TB pleural disease, fibrosis	Imaging, pulmonary function
Ekeng et al. (2022)	Case series	Nigeria	N/A	Pulmonary aspergillosis	HRCT, biopsy
Patel et al. (2022)	50	India	34%	Bronchiectasis, fibrosis	Chest CT
Marais and Schaaf (2010)	140	South Africa	20%	Fibrosis, bronchiectasis	Chest CT, spirometry

Abbreviations: PTLD: Post Tuberculosis Lung Disease, CT- Computer Tomography, HRCT: High-resolution computer tomography, X-ray: radiograph

The prevalence of PTLD in immunocompetent, HIV-negative individuals varied between 20% and 45% across the included studies. This wide range is likely due to differences in the severity of TB infection, extent of lung involvement, and treatment duration [7,8]. Higher rates of PTLD were observed in regions with high TB burdens, such as India and Ethiopia.

Clinical Manifestations

Common clinical manifestations of PTLD included chronic respiratory symptoms such as persistent cough, dyspnoea, and chest pain. Pulmonary fibrosis and bronchiectasis were frequently identified on imaging [9,10] Some patients exhibited significant lung function impairment, characterized by reduced forced Expiratory volume (FEV1) and forced vital capacity (FVC) [11.[

Diagnostic Tools

The most frequently utilized diagnostic tools were high-resolution computed tomography (HRCT) and spirometry. HRCT was especially useful for detecting structural abnormalities such as fibrosis and bronchiectasis [8,12]. Spirometry was employed to evaluate the degree of airflow obstruction and restrictive lung disease, providing essential information for managing PTLD.

Long-Term Outcomes

Long-term outcomes in patients with PTLD often included chronic respiratory symptoms, recurrent infections, and chronic disability. Many patients

DOI: 10.21608/aeji.2024.322332.1412

require long-term follow-up care, including pulmonary rehabilitation and ongoing medical management [8]. The burden of PTLD on healthcare systems is significant, and efforts to improve post-TB care are essential to improving long-term outcomes.

Discussion

Comparison of PTLD in HIV-Negative and HIV-Positive Individuals

Comparing PTLD in HIV-negative individuals to that in HIV-positive individuals reveals key differences. In HIV-positive populations, the risk of developing opportunistic infections and the impact of immunosuppression are critical factors in the progression of PTLD. HIV-positive patients are more likely to develop atypical TB presentations and experience greater systemic complications, resulting in more widespread lung damage [4,5.[

Conversely, HIV-negative individuals generally exhibit localized lung damage, typically characterized by fibrosis and bronchiectasis [9]. Although immunocompetent, these individuals can still suffer from significant post-TB complications, as evidenced by the relatively high prevalence of PTLD in this population [8]. This highlights the importance of understanding PTLD's trajectory in HIV-negative individuals to develop more targeted interventions.

Several studies have noted that HIV-positive individuals often develop more severe forms of disseminated TB, which can affect multiple organs and lead to extensive lung damage [4,5]. In contrast, HIV-negative individuals experience more localized pulmonary complications, with long-term outcomes centered on structural changes in the lungs.

Despite the differences in the underlying mechanisms of lung disease, both populations face challenges with chronic respiratory symptoms and reduced lung function. Pulmonary rehabilitation, early diagnosis of PTLD, and long-term management are essential for improving outcomes in both HIV-negative and HIV-positive patients.[8[

Clinical Implications

The management of PTLD in HIV-negative individuals requires a multifaceted approach. Emerging diagnostic tools such as advanced imaging techniques, including artificial intelligence-assisted HRCT analysis, offer the potential to identify subtle structural changes in the lungs that may precede overt clinical symptoms. Moreover, biomarkers such as specific inflammatory mediators are being investigated to differentiate PTLD from other chronic respiratory diseases.[17[

In terms of treatment, pulmonary rehabilitation has shown promising outcomes, including improved quality of life and reduced hospital admissions for individuals with PTLD [8]. The integration of pulmonary rehabilitation programs into existing TB care frameworks could enhance the management of PTLD. Furthermore, the role of adjunct therapies, such as corticosteroids or antifibrotic agents, is being explored, particularly for patients with significant structural lung damage.

At the public health level, early intervention strategies, including screening for PTLD during routine TB follow-up visits, are critical. Integrating PTLD management into national TB programs and leveraging digital health technologies for remote monitoring and follow-up could mitigate the long-term burden of PTLD.

Finally, addressing the social determinants of health, such as poor nutrition and environmental exposures, remains essential for comprehensive PTLD management. Collaboration between healthcare providers, policymakers, and community organizations is vital to creating sustainable models of care.

Research Gaps

This scoping review has identified several gaps in the literature:

1. There is limited research focusing on immunocompetent, HIV-negative individuals with PTLD. Most studies either focus on HIV-positive populations or include both groups without sufficient differentiation.
2. There is a lack of consensus regarding standardized diagnostic criteria for PTLD, complicating comparisons across studies.
3. More research is needed to explore the long-term outcomes of PTLD in different populations and develop

DOI: 10.21608/aeji.2024.322332.1412

evidence-based management protocols.

Conclusion

Post-tuberculosis lung disease is a significant complication among HIV-negative, immunocompetent TB survivors. The high prevalence of structural lung damage, including fibrosis and bronchiectasis, underscores the need for comprehensive post-TB care, including pulmonary rehabilitation and long-term follow-up. Understanding the unique pathophysiological mechanisms in this population can lead to the development of more effective diagnostic and treatment strategies. This scoping review calls for continued research and the creation of standardized protocols to improve the care of TB survivors, especially in resource-limited settings where the TB burden remains high.

Limitations

This scoping review has several limitations that must be acknowledged. Firstly, the heterogeneity of the included studies, in terms of study design, sample size, geographical distribution, and diagnostic criteria for PTLD, makes it difficult to directly compare the findings across studies. This variability in methodologies may have led to inconsistencies in reporting the prevalence and clinical manifestations of PTLD. Secondly, although the review focused specifically on immunocompetent, HIV-negative individuals, some studies may have included populations with mixed HIV statuses, potentially confounding the results. Additionally, most of the studies included in the review were conducted in regions with high TB burden, which may limit the generalizability of the findings to populations in lower-burden regions. Finally, given the reliance on published literature, this review may be subject to publication bias, as studies reporting positive outcomes or significant findings are more likely to be published, potentially leading to an overrepresentation of PTLD cases in the results. Future research should aim to address these limitations by conducting large-scale, longitudinal studies with standardized diagnostic criteria to better understand the long-term impact of PTLD in HIV-negative, immunocompetent individuals.

Funding Information:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest:

The authors declare no conflict of interest.

Author Contributions:

Somasundram Pillay and Davashni Pillay conceptualized the study and oversaw the entire process, including methodology and manuscript preparation. Both authors contributed to the revision of the manuscript and approved the final version.

HIGHLIGHTS

1. Prevalence and Clinical Manifestations: Post-Tuberculosis Lung Disease (PTLD) affects 20% to 45% of immunocompetent, HIV-negative individuals, with chronic respiratory symptoms like cough, dyspnoea, pulmonary fibrosis, and bronchiectasis.
2. Diagnostic and Long-Term Care: HRCT and spirometry are essential for diagnosing PTLD, and patients often require long-term follow-up care and pulmonary rehabilitation due to recurrent infections and chronic disability.
3. Need for Research and Standardized Care: There is limited research on PTLD in HIV-negative individuals, highlighting the need for standardized diagnostic criteria and treatment protocols for better management.

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Cite as: Pillay, S., Pillay, D. The Prevalence and Clinical Manifestations of Post-Tuberculosis Lung Disease in Immunocompetent HIV-Negative Individuals: A Scoping Review. *Afro-Egyptian Journal of Infectious and Endemic Diseases*, 2025; (): -. doi: 10.21608/aeji.2024.322332.1412