Burden, clinical features, and outcomes of post-tuberculosis chronic obstructive lung diseases

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Purpose of review
Post-tuberculosis lung disease (PTLD) is an increasingly recognized and debilitating consequence of pulmonary tuberculosis (PTB). In this review, we provide a comprehensive overview of PTLD with airflow obstruction (PTLD-AFO), focusing on its burden, pathophysiology, clinical manifestations, diagnostic methods, and management strategies.

Recent findings
The relationship between PTLD and airflow obstruction is complex and multifactorial. Approximately 60% of the patients with PTLD have some spirometric abnormality. Obstruction is documented in 18–22% of PTLD patients. The host susceptibility and host response to mycobacterium drive the pathogenic mechanism of PTLD. A balance between inflammatory, anti-inflammatory, and fibrotic pathways decides whether an individual with PTB would have PTLD after microbiological cure. An obstructive abnormality in PTLD-AFO is primarily due to destruction of bronchial walls, aberrant healing, and reduction of mucosal glands. The most common finding on computed tomography (CT) of thorax in patients with PTLD-AFO is bronchiectasis and cavitation. Therefore, the 'Cole's vicious vortex' described in bronchiectasis applies to PTLD. A multidisciplinary approach is required for diagnosis and treatment. The disability-adjusted life-years (DALYs) attributed to PTLD represent about 50% of the total estimated burden of DALYs due to tuberculosis (TB). Patients with PTLD require comprehensive care that includes psychosocial support, pulmonary rehabilitation, and vaccination against respiratory pathogens. In the absence of trials evaluating different treatments for PTLD-AFO, therapy is primarily symptomatic.

Summary
PTLD with airflow obstruction has considerable burden and causes a significant morbidity and mortality. However, many aspects of PTLD-AFO still need to be answered. Studies are required to evaluate different phenotypes, especially concerning *Aspergillus*-related complications. The treatment should be personalized based on the predominant phenotype of airflow obstruction. Extensive studies to understand the exact burden, pathogenesis, and treatment of PTBLD-AFO are needed.

Keywords
aspergilloma, aspergillosis, chronic pulmonary aspergillosis, post-tuberculosis lung disease, pulmonary tuberculosis

INTRODUCTION

Globally, over 10 million individuals developed tuberculosis (TB) in 2021 [1]. Pulmonary TB (PTB) is the most common form of TB, and antituberculosis therapy (ATT) successfully cures 85% of the patients affected with PTB [1]. There were an estimated 138–171 million TB survivors in 2020 [2▪]. Unfortunately, many PTB survivors remain symptomatic despite microbiological cure due to residual abnormalities of the airways, the lung parenchyma, or the pleura. The sequelae after recovery from pulmonary TB is called post-tuberculosis lung disease (PTLD) [3,4▪▪], defined as the presence of residual abnormalities on chest imaging in patients with previously treated

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Curr Opin Pulm Med 2024, 30:156–166

DOI:10.1097/MCP.0000000000001026

KEY POINTS

- There are over 150 million pulmonary tuberculosis survivors in 2020 and about 7–93% of TB survivors have some radiological residual abnormality, called as post-tuberculosis lung disease (PTLD).
- Approximately 60% of PTB survivors have spirometric abnormality. Roughly 20% have obstruction on spirometry.
- Several overlapping mechanisms are responsible for airflow obstruction in those with PTLD.
- Airflow obstruction (AFO) in PTLD could be due to underlying asthma or chronic obstructive disease, stenosis of large or small airways involvement (bronchiolitis), and bronchiectasis.
- The progression of PTLD-AFO can be due to persistence of mycobacterial RNA, recurrent secondary infections, aspergillus sensitization, and chronic pulmonary aspergillosis.
- The treatment is primarily symptomatic and requires comprehensive care according to the phenotype of PTLD-AFO.
- Treatment with airway balloon dilatation, inhaled bronchodilators, and oral antifungal azoles can be offered based on the underlying disease.

PTB, with or without symptoms [5,6]. The prevalence of residual abnormalities (nodules, parenchymal fibrosis, bronchiectasis, cavitation, pleural abnormalities, and others) ranges between 7.4 and 92.6% [7]. Patients with PTLD have a higher risk of developing lung function abnormalities, including obstructive, restrictive, or mixed [8▪▪].

EXISTING TERMINOLOGY FOR PTLD WITH AIRFLOW OBSTRUCTION

Several terminologies have been used to describe airflow obstruction associated with PTLD, such as tuberculosis-associated chronic obstructive pulmonary disease (TOPD, T-COPD), TB with obstruction, and others [9–11]. An airflow obstruction due to PTLD could be labeled as PTLD-AFO as this term captures the physiological changes due to PTB sequelae. Notably, the typical pathological findings of COPD are not encountered in PTLD-AFO [12,13]. Apart from the differences in pathogenesis, there are variations in the clinical profile, symptomatology, and treatment between COPD and PTLD-AFO (Table 1).

BURDEN OF POST-TUBERCULOSIS LUNG DISEASE-AIRFLOW OBSTRUCTION

The relationship between PTLD and airflow obstruction is complex and multifactorial, confounded by tobacco smoking, biomass fuel, and other environmental exposures. Recently, in a pooled analysis of 61 studies (42 reported spirometric abnormalities) with 41 014 patients with PTLD, 59% had spirometric abnormality compared to 5% of the controls. An obstruction, restriction, and a mixed pattern were reported in 18, 21, and 13% of the patients [8▪▪]. The odds of spirometric abnormality were fourfold higher in those with treated drug-resistant versus treated drug-sensitive TB. Notably, ever smokers had a higher occurrence of obstructive defect than nonsmokers. In another recent meta-analysis investigating spirometric abnormalities in PTLD, AFO was reported in 22 and 19% of those with previously treated drug-susceptible and drug-resistant TB,

Table 1. Key differences in post-tuberculosis lung disease with airflow obstruction and chronic obstructive pulmonary disease

	PTLD-AFO	COPD
Clinical profile	Mostly, young individuals with persistent symptoms after PTB	Mostly elderly with a prior history of smoking or environmental exposure (biomass fuel and others)
Symptoms	Cough, dyspnea, and hemoptysis (CPA or bronchiectasis)	Dyspnea and expectoration
Pathogenesis	Aberrant healing of airways, destruction of airway smooth muscles, peri-bronchiolar fibrosis, parenchymal destruction with cavitation	Mucous gland enlargement and goblet cell hyperplasia, airway smooth muscle hypertrophy, destruction of respiratory bronchioles, alveolar ducts, and alveoli
Spirometry	Fixed airflow obstruction	Fixed or partly reversible airflow obstruction
Imaging	Cavitation, nodules, mosaic attenuation, pleuroparenchymal fibrosis, and others	Airway wall thickening, emphysema
Natural history	Could be static or progressive, with multiple episodes of acute exacerbation	Progressive with recurrent episodes of acute worsening
Treatment	Depending on the phenotype, it involves airway stenting, inhaled bronchodilators	Inhaled bronchodilators

CPA, chronic pulmonary aspergillosis; PTB, pulmonary tuberculosis.

respectively [14▪▪]. In a recent population-based cross-sectional study from China comprising of 8680 participants, 610 (7%) had prior PTB. The odds ratio for AFO was 1.31 [95% confidence interval (95% CI), 1.05–1.62] in those with PTLD after adjusting for confounding factors such as tobacco smoking, exposure to household air pollution, sex, and others [15]. In another study of 4911 patients with previously treated PTB, Park *et al.* [16] found AFO in 27 and 13% of patients with and without chest radiograph abnormalities.

Most previous studies reporting spirometric abnormalities are limited by heterogeneity in inclusion criteria, confounding by tobacco smoking and other lung comorbid illnesses, and different definitions for reporting spirometric values. Also, most studies have included individuals at varying periods after completion of tuberculosis therapy. Therefore, the reported AFO could be an over or an underestimate [17]. Many studies were cross-sectional without longitudinal follow-up. A few studies have investigated the changes in lung functions over the course of treatment but have a short follow-up period [17,18]. Future longitudinal studies are warranted to know the true burden of AFO in PTLD.

PATHOGENESIS OF POST-TUBERCULOSIS LUNG DISEASE

The host susceptibility and host response to mycobacterium drive the pathogenetic mechanism of PTLD. Infection with mycobacteria incites both the innate and the adaptive immune responses by the host. Based on the bacterial burden and host response, there could be necrosis (pneumonia) or granuloma formation with or without fibrosis [19▪▪]. Neutrophils and macrophages are the critical effectors of innate immune response to mycobacterial infection. The neutrophils release matrix metalloproteinases (MMPs) that not only cause degradation of the mycobacterium but also damage the lung parenchyma [20,21]. MMP-1 polymorphisms are associated with lung fibrosis, extensive tissue damage, and cavitation in TB [22,23]. The neutrophils also release neutrophil extracellular traps (NETs) to control the spread of mycobacterial infection [24]. Unfortunately, these NETs cannot kill the mycobacteria, but cause inflammation-related tissue damage. The macrophages (classically activated macrophages), via the Th-1 mediated pathway, act to control the infection. Alternatively, during the later stage of infection, the macrophages, activated by interleukin (IL)-4 and IL-13 cytokines, have anti-inflammatory effects and promote wound healing by fibrosis [25]. Th-1 mediated production of interferon-gamma (IFN-ϒ) promotes healing without fibrosis by inhibiting tumor necrosis factor-alpha (TNF-α). A shift of $CD4^+$ T cell profile towards IFN-ϒ occurs after successful treatment [26].

The tuberculous granuloma typically controls the dissemination of mycobacterial infection. The classic granuloma has a necrotic central region surrounded by a rim of fibroblasts and lymphocytes. This granuloma calcifies and results in healing. Recent evidence suggests granuloma to evolve into a fibrotic, proinflammatory form (proinflammatory or permissive granuloma) [19▪▪,27]. Even within the granuloma, the central region has an inflammatory profile, while the peripheral region has an anti-inflammatory profile [28]. Healing in fibrotic granulomas is driven by fibroblasts and myofibroblasts mediated by the release of extracellular matrix, IL-10, and transforming growth factor-beta (TGF-β) [29]. Thus, an intricate balance between inflammatory, fibrotic, and anti-inflammatory pathways decides whether an individual with PTB would develop PTLD despite a microbiological cure.

PATHOPHYSIOLOGY OF POST-TUBERCULOSIS LUNG DISEASE-AIRFLOW OBSTRUCTION

The pathophysiology of AFO in PTLD is multifactorial and results from remodeling during healing and possibly host susceptibility [23,30–34]. The pathological changes typical of COPD, including the hypertrophy of mucosal and submucosal glands, increased smooth muscle mass, and emphysematous destruction, are not characteristically seen in PTLD (Fig. 1) [12,13]. The obstructive abnormality in PTLD-AFO is primarily due to airway destruction, with destruction of bronchial walls, aberrant healing, and reduction of mucosal glands. Airflow obstruction in PTLD is usually fixed. There are several mechanisms by which AFO can develop in PTLD as highlighted in the following section.

Tuberculosis complicating preexisting asthma or chronic obstructive pulmonary disease

Patients with COPD and asthma are at a higher risk of developing PTB due to inhaled corticosteroids [35–38]. The airflow obstruction due to the underlying airway disease could be further worsened by PTB (Fig. 1).

Endobronchial tuberculosis involving the large airways (trachea, mainstem, and segmental bronchi)

Occasionally, endobronchial TB heals with scarring and can cause fixed obstruction of larger airways due

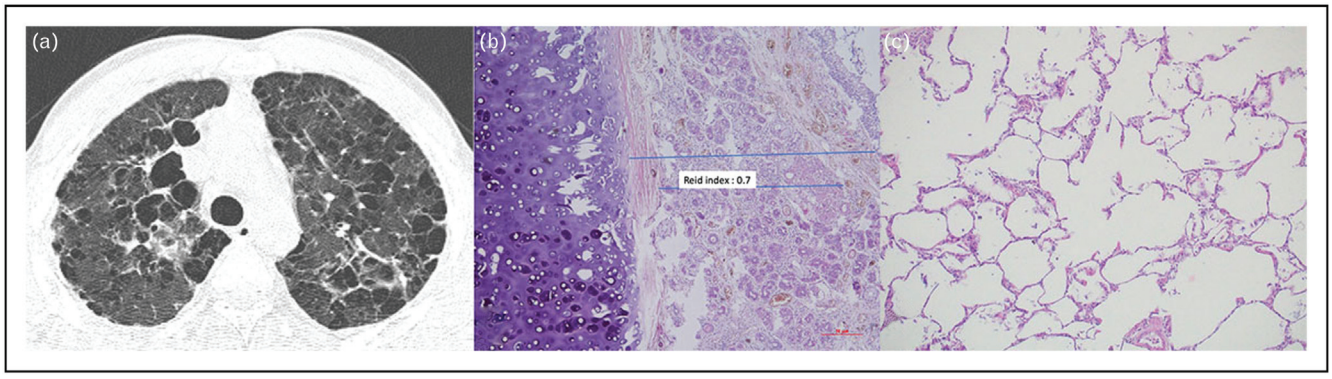

FIGURE 1. (a) Computed tomography (CT) of the thorax revealing centriacinar and paraseptal emphysema. There are linear opacities and some areas of ground glass opacification that represent residual changes of previous pulmonary tuberculosis. (b) Photomicrograph showing the thickness of the mucosa and its bronchial gland layer. The relationship is expressed as a gland/wall ratio (Reid index) in chronic bronchitis (H&E, x40). (c) Photomicrograph showing airspace enlargement and fragmented alveolar walls in emphysema (H&E, x100).

to abnormal healing. Patients with this phenotype present with exertional dyspnea, stridor, and rarely respiratory failure [39].

Endobronchial tuberculosis involving small airways

This type of PTLD-AFO manifests as bronchiolitis with or without bronchiectasis or cavitation (Fig. 2) [40–44]. This phenotype occurs due to fibrosis and persistent granulomas around bronchioles and smaller arterioles [43,45]. Additionally, there could be airway narrowing due to aberrant healing [17]. Patients present with dyspnea, cough, hemoptysis, and bronchiectasis or small airway involvement (mosaic attenuation) on computed tomography (CT) of the thorax.

MECHANISM OF PROGRESSION OF PARENCHYMAL AND SPIROMETRIC ABNORMALITIES IN POST-TUBERCULOSIS LUNG DISEASE

The cause of progressive lung damage in PTLD despite microbiological cure remains to be determined. Several plausible mechanisms can explain progressive lung damage in PTLD. The most common finding on CT of thorax in patients with PTLD is bronchiectasis and cavitation [7]. Therefore, the 'Cole's vicious vortex' described in bronchiectasis applies to PTLD [46].

Persistence of mycobacterium DNA or RNA

Although ATT is effective in eradicating the mycobacterial infection, there could be persistence of the

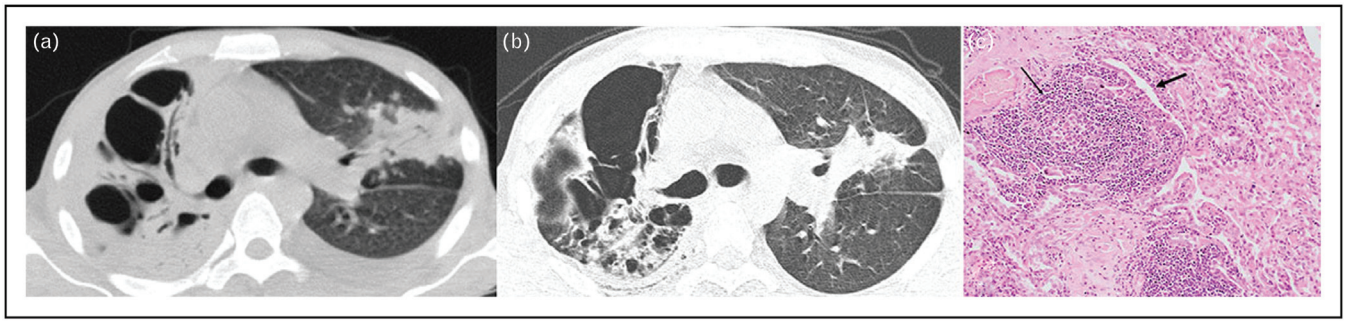

FIGURE 2. (a) Lung window (axial sections) of computed tomography (CT) of the thorax of a patient with active pulmonary tuberculosis revealing consolidation with cavitation involving the entire right upper lobe. (b) Lung window of CT thorax of the same patient six months after completion of antituberculosis therapy. The CT reveals PTLD with cavitation in the right upper lobe posterior segment. There is bronchiectasis in the right lower lobe apical segment. There is a resolution of consolidation. The consolidation in the left upper lobe is replaced by persistent mass-like consolidation with irregular margins suggestive of architectural distortion. The patient had an obstructive pattern on spirometry. (c) The patient had massive hemoptysis and underwent a right upper lobectomy. The photomicrograph of follicular bronchiolitis showing lymphoid follicle (Thin arrow) with germinal center compressing the bronchiolar lumen (Thick arrow) (H&E x400).

mycobacterial DNA or RNA in the airways that drive chronic inflammation [47]. In a recent study, Malherbe *et al.* [48] demonstrated persistent inflammation on PET CT of the thorax 1 year after ATT completion. Notably, mycobacterial mRNA persisted in bronchoalveolar lavage fluid for 1 year.

Recurrent exacerbations due to viral or bacterial pathogen

Due to structural damage and impaired mucociliary clearance, individuals with PTLD are at increased risk of exacerbations due to various infective pathogens [49]. Notably, the number of exacerbations is independently associated with lower FEV1 during follow-up [17]. Recurrent exacerbations cause progressive lung damage and worsening of bronchiectasis [50].

Chronic colonization with bacterial or atypical mycobacterial pathogens

Individuals of PTLD with bronchiectasis are at a higher risk of chronic colonization with bacterial pathogens. Chronic bacterial colonization causes perpetual airway inflammation and progressive worsening of lung functions and quality of life [51]. In a recent study, 29% of PTLD patients had an annual decline in FEV1 by 33 ml, with a cumulative decline of 100 ml three years after treatment completion. The median decline in this group was like those with COPD. The decline in FEV1 was attributed to chronic colonization with nontuberculous pathogens, biomass fuel exposure, and poor nutrition [52▪▪]. In another study, individuals with PTLD and bronchiectasis had a higher risk of infection with atypical mycobacterial pathogens and lower FEV1/FVC ratio than other causes of bronchiectasis [53].

Fungal sensitization and allergic bronchopulmonary aspergillosis

Genetically predisposed individuals with PTLD have an increased risk of allergic sensitization to *Aspergillus fumigatus*. Due to fungal sensitization, patients with PTLD can have recurrent exacerbations and continued airway inflammation like cystic fibrosis [54]. A perpetual state of inflammation could cause continuous airway damage and airflow obstruction. In a previous study, we found the prevalence of *Aspergillus* sensitization in 32% of PTLD individuals. Patients with *Aspergillus* sensitization were five times more likely to have an airflow obstruction on spirometry [55].

Chronic pulmonary aspergillosis

Chronic pulmonary aspergillosis (CPA, Fig. 3) is a chronic infection of the structurally damaged lung by *Aspergillus* spp. (most commonly *A. fumigatus*) that results in progressive damage (increase in the number and size of cavities, pleuroparenchymal fibrosis, and others) [56]. Patients with PTLD are at an increased risk of chronic *Aspergillus* infection, the commonest risk factor for CPA globally [57,58]. CPA is associated with morbidity and has a 5-year mortality of up to 80–85% [57]. Notably, studies on PTLD-AFO have not evaluated patients for CPA. Only four of the 61 studies reported the presence of simple aspergilloma on CT in a recent meta-analysis evaluating residual respiratory impairment in PTLD [8▪▪]. The pooled prevalence was shown to be 1.7%, a gross underestimate, as the individuals were not evaluated for CPA. Contrarily, more than 300 000 individuals were estimated to have CPA as a sequel to PTB in 2012 in India [59]. We routinely screen all patients with PTLD with cavitation or bronchiectasis for CPA using serum *A. fumigatus*

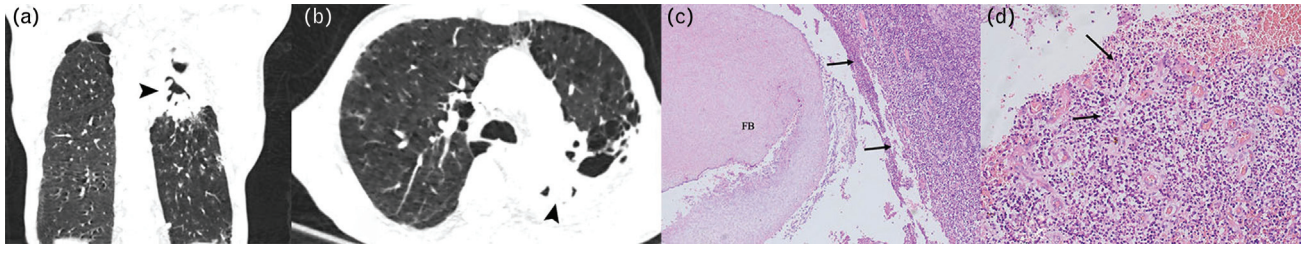

FIGURE 3. (a) Computed tomography of the thorax (coronal section) revealing consolidation with cavitation of the left upper lobe apico-posterior segment. There is a fungal ball (arrowhead) in one of the cavities. (b) The axial section of the same patient reveals a cavity with a fungal ball (arrowhead). There is also centriacinar emphysema. The serum for *Aspergillus fumigatus*-specific IgG was 198 mgA/l. These features are suggestive of chronic cavitary pulmonary aspergillosis. The patient had been treated for pulmonary tuberculosis 3 years prior. The patient was treated with oral itraconazole but had massive hemoptysis while on treatment. The patient underwent a left upper lobectomy. (c) photomicrograph of distended bronchi with ulcerated lining epithelium (black arrows), which is replaced by dense inflammatory infiltrate. The lumen shows an entangled mass of fungal hyphae forming a fungal ball (FB) (H&E x100). (d) the infiltrate is composed of dominantly plasma cells (black arrow) admixed with a few lymphocytes and neutrophils. (H&E x400).

specific IgG antibody. In a sample of 496 individuals with PTLD (cavities or bronchiectasis), we diagnosed CPA in 445 individuals (Table 2). PTLD-CPA individuals had a longer duration of symptoms and were more likely to be symptomatic than PTLD alone (Table 2). Notably, the proportion of individuals with airflow obstruction was similar in PTLD-CPA and PLTD alone. We suggest screening patients with PTLD (residual cavities or bronchiectasis) by performing serum *A. fumigatus* specific IgG.

In a recent study, we found the prevalence of *Aspergillus* sensitization and chronic *Aspergillus* infection of 29.5 and 76% in patients with bronchiectasis [60▪▪]. Notably, PTLD was an independent risk factor for *Aspergillus* sensitization and chronic *Aspergillus* infection [60▪▪]. Recently, Page *et al.* [61] found a CPA incidence of 6.5% in Ugandan PTLD patients on a resurvey after 2 years. Kim *et al.* [62] reported a CPA incidence of 2.9% during a 2-year follow-up in individuals with PTLD. Interestingly, patients with active PTB also have a higher occurrence of *A. fumigatus* coinfection. Setianingrum *et al.* reported *Aspergillus* coinfection during active TB in 30% of the individuals. About 7.5% (10/128) of their individuals had CPA at treatment completion [63]. In two different studies, the prevalence of CPA was 5 and 11% at the end of tuberculosis treatment [64,65].

Table 2. Demographics and clinical profile of the patients with post-tuberculosis lung disease with or without chronic pulmonary aspergillosis registered at authors' outpatient clinic

Demographic	PTLD with CPA ($n=445$)	PTLD without CPA ($n=51$)	*P*
Age (years)	43.5 ± 13.9	46.7 ± 15.3	0.133
Female sex, *n* (%)	198 (44.5)	17 (33.3)	0.128
Weight (kg)	50.9 ± 14.9	55.9 ± 18.6	0.042
No. of episodes of pulmonary tuberculosis, median (interquartile range)	1 (1–2)	1 (1–1)	0.035
Clinical findings			
Duration of symptoms, in years	0.7 (0.3–2)	0.5 (0.3–2)	0.020
Cough, *n* (%)	387 (87)	32 (62.7)	<0.0001
Dyspnea, *n* (%)	173 (38.9)	15 (29.4)	0.362
Wheezing, *n* (%)	178 (40.1)	20 (39.2)	0.904
Recurrent hemoptysis, *n* (%)	297 (66.9)	22 (43.1)	<0.0001
Fever, *n* (%)	131 (29.6)	11 (21.6)	0.228
Malaise, *n* (%)	166 (37.4)	7 (13.7)	<0.0001
SGRQ, total, median (interquartile range)	23.9 (15.7–38)	17.1 (8.6–27.9)	<0.0001
SGRQ, symptom, median (interquartile range)	35.8 (26.447.1)	28.8 (19–43.9)	0.026
SGRQ, activity, median (interquartile range)	35.7 (18.1–59.7)	23.8 (10.6–47.7)	0.010
SGRQ, impact, median (interquartile range)	12.6 (4.7–33.8)	5.5 (2.7–15.4)	0.001
Spirometry			
FEV1, % predicted, median (interquartile range)	57.4 (41.1–74.7)	50 (38.4–71.3)	0.097
FVC, % predicted, median (interquartile range)	62.5 (49.4–77.9)	65.3 (50.4–78.8)	0.783
FEV1:FVC ratio, % predicted, median (interquartile range)	89.3 (74.9–99.9)	78 (64.3–93.5)	<0.0001
Pattern on spirometry, *n* (%)			0.220
Normal	68 (15.3)	8 (15.7)	
Obstruction	361 (81.2)	42 (82.4)	
Mild	119	7	
Moderate	136	22	
Severe	106	13	
Restriction	16 (3.6)	1 (2)	

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; SGRQ, Saint George's Respiratory Questionnaire.

CLINICAL FEATURES

Patients of PTLD-AFO manifest with breathlessness, productive cough, and wheezing (Table 2) [15]. Hemoptysis occurs during secondary infections or could be a sign of bronchiectasis or CPA (Table 2) [55,60▪▪,66]. A large study comparing patients of PTLD-AFO with COPD found female preponderance and lower FEV1 and FEV1/FVC ratio in the former [49]. However, the annual frequency of exacerbations (acute worsening of respiratory symptoms) was similar in the two groups [49]. Chest auscultation could either be normal or reveal a monophonic (fixed airway obstruction) or polyphonic wheeze (airflow obstruction involving large or small airways), coarse (bronchiectasis) or fine crackles (parenchymal fibrosis) and bronchial breath sounds (cavitation). Individuals affected by PTLD have significant morbidity and mortality and a poor quality of life (Table 2).

DIAGNOSTIC APPROACH AND TREATMENT

Patients with PTLD-AFO should be comprehensively evaluated for the severity of airflow limitation and exclusion of other coexisting airway conditions and infections (Fig. 4). Chest CT should be done to assess the extent of residual lung damage. Spirometry

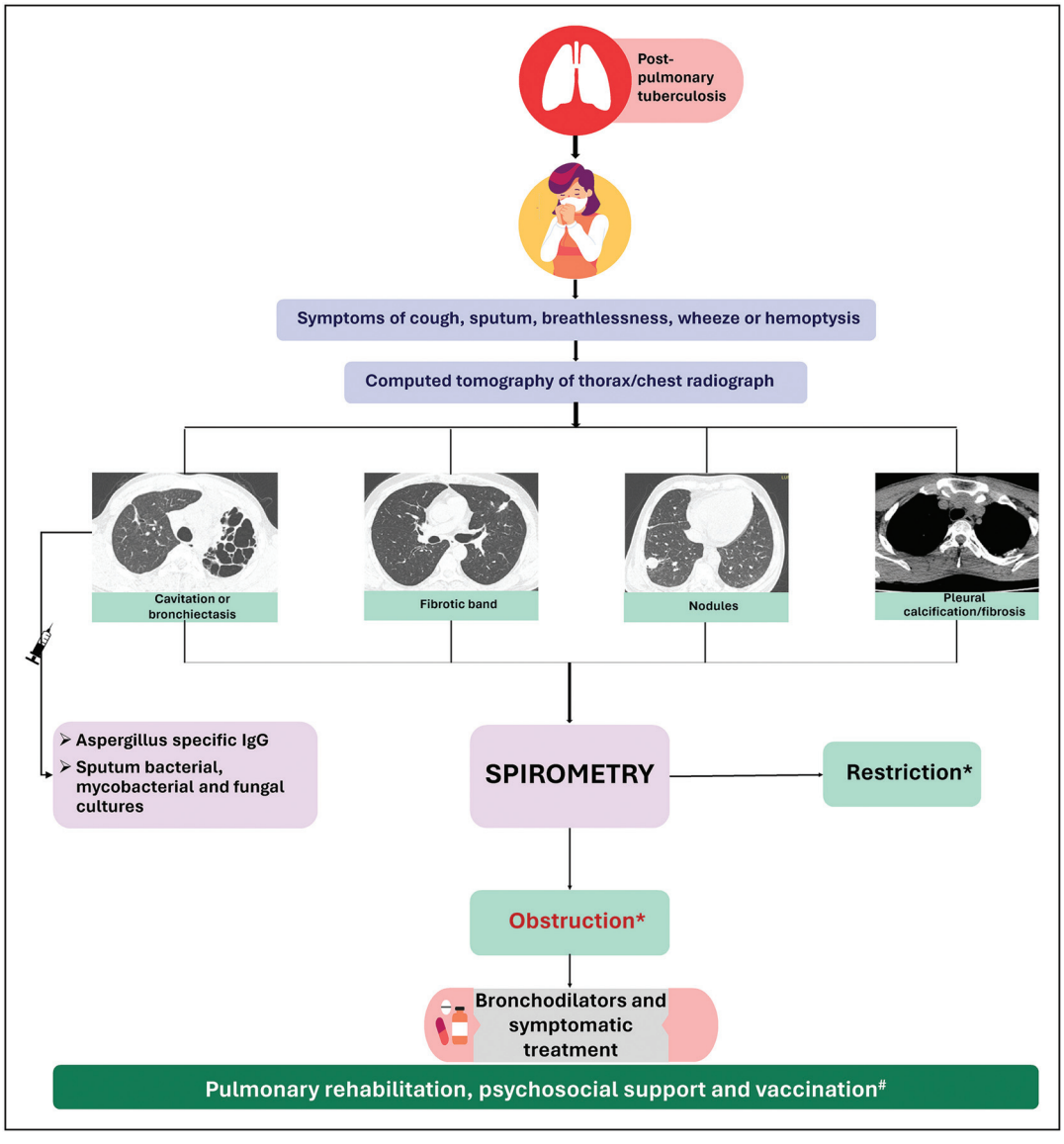

FIGURE 4. Proposed algorithm for the diagnostic evaluation and treatment of patients with postpulmonary tuberculosis lung disease (PTLD). *Those with normal, restriction, or mixed patterns on spirometry should be evaluated further by body plethysmography, impulse oscillometry, and dynamic computed tomography (CT) of the thorax. #Vaccination should be offered to those with cavitation or bronchiectasis on CT of the thorax or according to the existing guidelines.

should be performed to demonstrate airflow obstruction. An assessment of small airway involvement [dynamic CT scans, impulse oscillometry, body plethysmography, or diffusing lung capacity for carbon monoxide (DLCO), and others] is warranted in the presence of respiratory symptoms with normal spirometry [67]. Flexible bronchoscopy is warranted in patients with symptoms of central airway obstruction due to tracheal or main-stem bronchial stenoses. CPA should be excluded in patients with PTLD by performing serum *A. fumigatus* specific IgG [58,66,68–70]. Additionally, sputum cultures for mycobacterial and bacterial pathogens should be done at diagnosis and during exacerbations.

There is a paucity of literature on the treatment of PTLD with airflow obstruction, and the treatment strategy is extrapolated from other lung diseases such as COPD, asthma, or bronchiectasis (Table 3). A comprehensive care that includes psychosocial support, pulmonary rehabilitation, and vaccination against respiratory pathogens should be offered to all patients with PTLD-AFO. In the absence of trials evaluating different treatments for PTLD-AFO, symptomatic management is suggested as follows.

Post-tuberculosis lung disease-airflow obstruction with underlying asthma or chronic obstructive pulmonary disease

Patients with this phenotype of PTLD-AFO should be managed like asthma or COPD. In those with underlying asthma, inhaled glucocorticoids with or without long-acting β-2 agonists should be used per the prevalent guidelines [71]. For those with underlying COPD, treatment should be initiated with inhaled long-acting antimuscarinic agents and further changed according to the prevailing guidelines [72].

Post-tuberculosis lung disease-airflow obstruction with central airway obstruction

Here, the use of inhaled drugs is unlikely to help, as there is a fixed obstruction in the trachea and main-stem bronchi. Interventional bronchoscopic procedures such as bronchoscopic dilatation, airway stenting, argon plasma coagulation, electrocautery, or a combination of these procedures should be used in these patients [39,73,74].

Post-tuberculosis lung disease-airflow obstruction with airway obstruction due to bronchiectasis

The principles of treatment management are similar to those with other causes of bronchiectasis that include airway clearance strategies, use of mucolytic and mucoactive agents, eradication of chronic bacterial colonization (*pseudomonas aeruginosa* and *enterobacteriaceae* spp.), and vaccination against influenza, respiratory syncytial virus, coronavirus, and pneumococci [50,51]. Some patients with recurrent hemoptysis may require surgical resection of the affected segment or vascular embolization. We further recommend symptomatic treatment of this phenotype with inhaled bronchodilators (long-acting β-2 agonists or antimuscarinics or their combination) [75]. Cough suppressants may be used for treating the unrelenting cough. Whether inhaled glucocorticoids can be used in this subset of PTLD is not clear. There is limited role of systemic glucocorticoids in treatment in this phenotype of PTLD [76].

Post-tuberculosis lung disease with chronic pulmonary aspergillosis

The management of CPA involves the eradication of the fungi from the airways by using oral or systemic antifungal agents [66]. Oral itraconazole

Table 3. Treatment of phenotypes of post-tuberculosis lung disease with airflow obstruction

Phenotype	Treatment
PTLD-AFO with underlying asthma or COPD	Treatment with inhaled corticosteroids, long-acting β2 agonists, or long-acting antimuscarinic agents according to prevalent guidelines for asthma or COPD
PTLD-AFO with central airway obstruction	Airway dilatation with or without airway stenting, use of argon photocoagulation, electrocautery, or a combination of all
PTLD-AFO with bronchiectasis	Treatment with inhaled long-acting β2 agonists, or long-acting antimuscarinic agents, mucoactive agents, inhaled antibiotics, chest physiotherapy, and vaccination against influenza and pneumococci
PTLD-CPA	Oral itraconazole for 6–12 months. Other azoles, such as voriconazole, posaconazole, and others, may be tried
Treatment of exacerbations	Short course of antibiotics and short-acting bronchodilators. Oral glucocorticoids should be avoided

CPA, chronic pulmonary aspergillosis.

for 6–12 months is the preferred initial treatment [77]. Other antifungal agents may be used in those with itraconazole intolerance or failure [78]. Occasionally, patients may require prolonged therapy with antifungal agents.

Treatment of acute exacerbations

The natural history of PTLD is characterized by recurrent episodes of acute worsening, especially in those with bronchiectasis or CPA. The treatment for acute worsening involves a short course of antibiotics and short-acting bronchodilators. The role of systemic glucocorticoids is controversial.

OUTCOMES

Patients with PTLD continue to manifest symptoms and have functional limitations during follow-up [8▪▪,79▪]. About 25% of individuals with PTLD have activity-limiting dyspnea (a Medical Research Council score >2), and patients achieved only 79% of the predicted distance on 6-min walk test [8▪▪]. The estimated burden was higher for younger individuals and in high TB-burden countries [79▪]. In a recent study, 405 patients with PTB were followed prospectively for three years (299 completed 3 years follow-up) [52▪▪]. At ATT completion, 60% of the individuals still had some respiratory symptoms [52▪▪]. Around 20% of the patients had some respiratory symptoms 3 years after treatment. Notably, the disability-adjusted life-years (DALYs) attributed to PTLD represent 47% of the total estimated burden of DALYs due to TB [79▪].

FUTURE DIRECTIONS/CONCLUSION

Many aspects of PTLD with airflow obstruction remain unanswered. There is an urgent need for longitudinal studies to understand the true burden of PTLD-AFO. The mechanisms, including host susceptibility for airflow obstruction in PTLD, need further evaluation. Furthermore, predictors of developing airflow obstruction in patients with active PTB need to be investigated. More research is required to evaluate different phenotypes, especially with *Aspergillus*-related complications in PTLD. Randomized trials comparing different treatment strategies should be done to improve outcomes in patients with PTLD-AFO.

In conclusion, PTLD with airflow has a significant burden and is associated with significant morbidity and mortality. The etiopathogenesis of airflow obstruction in PTLD is multifactorial and results from airway and lung parenchymal scarring. The treatment should be personalized based on the predominant phenotype of airflow obstruction. Future studies are needed to understand the exact burden, pathogenesis, and treatment of PTBLD-AFO.

Acknowledgements

The authors thank Professor Amanjit Bal, Professor of Histopathology, PGIMER, Chandigarh for providing the histopathology images.

Financial support and sponsorship

None.

Conflicts of interest

All authors have no conflict of interest or disclosures.

REFERENCES AND RECOMMENDED READING

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