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Impact of Comorbidity in Pulmonary Tuberculosis Patients with Acute Respiratory Failure: Literature Review

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ABSTRACT

Pulmonary tuberculosis (TB) remains a global health concern, particularly in resource-limited settings, due to its high prevalence, significant morbidity, and emerging drug resistance. Acute respiratory failure (ARF) is a critical complication in TB, with mortality rates reaching 65–74%. Comorbidities such as diabetes mellitus (DM), HIV/AIDS, and chronic obstructive pulmonary disease (COPD) significantly contribute to the pathophysiology, incidence, and severity of ARF in TB patients. DM exacerbates TB through impaired immune responses, chronic inflammation, and heightened risk of secondary infections, while hyperglycemia-induced oxidative stress further damages lung parenchyma. HIV/AIDS accelerates TB progression by impairing immune defenses, increasing systemic and local inflammation, and predisposing patients to opportunistic infections, culminating in severe pulmonary damage. COPD, with its shared risk factors with TB, worsens ventilation-perfusion mismatch, promotes secondary infections, and amplifies respiratory distress through structural lung damage and inflammation. This review underscores the critical need for an integrated, multidisciplinary approach to managing comorbidities alongside TB to improve clinical outcomes. Effective strategies should include timely diagnosis, optimal management of comorbidities, and tailored interventions for ARF, particularly in developing nations. Future research is essential to develop targeted preventive and therapeutic protocols to mitigate the burden of ARF in TB patients, reduce mortality, and improve quality of life. These insights are crucial for advancing public health policies and clinical care for TB and its complications.

Keywords: pulmonary tuberculosis; acute respiratory failure; diabetes mellitus; HIV/AIDS; chronic obstructive pulmonary disease; comorbidities; respiratory complications.

INTRODUCTION

Pulmonary tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* (MTB), primarily affecting the lungs but capable of spreading to other organs [1]. According to a 2021 World Health Organization (WHO) report, approximately 10.6 million TB cases were reported globally that year, with the majority occurring in developing countries such as India, China, and Indonesia [2]. The disease spreads easily through airborne droplets, particularly in densely populated areas with poor ventilation [3]. Despite being treatable with effective anti-tuberculosis therapy, TB remains a significant public health issue due to delayed diagnosis, therapy non-compliance, and the emergence of drug resistance [4,5,6].

Patients with pulmonary TB are frequently burdened with comorbidities such as diabetes mellitus (DM), human immunodeficiency virus (HIV), and chronic obstructive pulmonary disease (COPD) [7]. These comorbidities exacerbate the progression of pulmonary TB and increase the risk of severe, life-threatening complications. One such complication is acute respiratory failure (ARF), a condition where the respiratory system fails to maintain adequate gas exchange, characterized by hypoxia or hypercapnia [8,9]. While ARF is rarely a direct result of pulmonary TB, it is a highly fatal emergency condition, with a mortality rate of 65–74% among TB patients [10,11]. This high fatality is often due to the lack of adequate intensive care facilities, particularly in developing nations [10].

These findings underscore the critical importance of comprehensive management of comorbidities and complications to improve the prognosis and quality of life for TB patients.

This literature review aims to comprehensively examine the role of comorbidities in ARF among pulmonary TB patients. It will explore how major comorbidities such as DM, HIV, and COPD influence the pathophysiology, incidence, and severity of ARF in these patients. Additionally, the review seeks to identify risk factors, clinical impacts, and management implications of comorbidities to improve clinical outcomes. Consequently, this review is expected to provide valuable insights and serve as a foundation for developing improved diagnostic and management strategies for pulmonary TB patients with ARF.

REVIEW CONTENT

Pulmonary Tuberculosis

Etiology

Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis*, an obligate intracellular pathogenic bacterium that is aerobic [1]. The bacterium's lipid-rich cell wall, primarily composed of mycolic acids, makes it acid-resistant and enables it to survive in harsh environments and persist in the host for extended periods [1]. MTB is transmitted via aerosol droplets produced when an individual with active pulmonary tuberculosis coughs, sneezes, or speaks. These droplets, containing the bacterium, can be inhaled by healthy individuals, with the bacteria settling in the alveoli of the lungs, initiating primary infection [3].

Risk factors for tuberculosis infection include conditions that impair host immunity, such as HIV infection, malnutrition, diabetes mellitus, use of immunosuppressive drugs, and crowded environments that increase transmission risk [12]. Individuals with weakened immune systems are at significantly higher risk of developing active TB from latent infection or progressing directly to active TB upon initial exposure [13].

Pathophysiology

TB is transmitted from patients with active disease to uninfected individuals through small droplet aerosols containing MTB. These droplets pass through the respiratory tract, where most of the bacilli are trapped by goblet cells secreting mucus. In some cases, the droplets bypass the first-line mucociliary defenses and reach the lungs. Upon reaching the alveoli, MTB is phagocytosed by alveolar macrophages [14]. However, MTB can inhibit phagosome-lysosome fusion, and survive, and replicate within macrophages by inducing interleukin-16 (IL-16) cytokine production. This mechanism triggers a cell-mediated immune response through T-cell activation, leading to the formation of granulomas [15].

Granulomas, a hallmark of pulmonary TB, are irregularly shaped masses of immune cells composed of activated macrophages, epithelioid cells, CD4+ and CD8+ T cells, and fibroblasts [16]. These structures function to isolate MTB while also providing a niche for the bacteria to persist in a dormant state [17]. In individuals with robust immune systems, granulomas may not eliminate MTB but can suppress its virulence, resulting in latent TB with no symptoms. Conversely, in individuals with impaired immunity, granulomas may exhibit increased necrotic activity in their centers, rupture, and release infectious bacteria into the airways, forming cavities [18]. This process characterizes the lung damage observed in TB patients.

Diagnosis

The diagnosis of pulmonary tuberculosis requires a comprehensive approach, including thorough anamnesis, clinical evaluation, and supplementary examinations such as radiology, microbiology, and immunology [19]. This approach aims to ensure an accurate diagnosis, enabling prompt initiation of treatment to prevent further transmission, severe complications, and death [20]. This is particularly critical as pulmonary TB is often misdiagnosed due to its resemblance to other pulmonary diseases, both in clinical symptoms and radiological findings, necessitating precise and timely examinations [21,22].

- *Anamnesis and Clinical Evaluations*

Anamnesis is the initial step in the diagnostic process for pulmonary tuberculosis and plays a crucial role in raising clinical suspicion. The primary symptom commonly reported by patients is persistent coughing lasting more than two weeks, often accompanied by sputum production [19]. In some cases, patients may also report hemoptysis (coughing up blood), indicative of lung tissue damage caused by the disease. Other systemic symptoms such as low-grade fever, night sweats, significant weight loss, and chronic fatigue are also frequently observed [23].

However, these symptoms are non-specific and can mimic other pulmonary conditions, such as bronchiectasis, lung cancer, or chronic pneumonia [14]. Therefore, anamnesis should include a detailed history of contact with individuals with active TB, exposure to crowded environments, and other risk factors such as HIV infection, diabetes mellitus, or immunocompromised states [19].

- *Radiological Examination*

Radiology plays a crucial role in detecting structural abnormalities in the lungs during the early diagnosis of pulmonary tuberculosis [24]. While chest X-rays are commonly used, they are largely subjective, making radiological results alone less sensitive and specific [25]. In urban settings, the specificity of radiological examinations is only around 63% [19]. Characteristic findings in pulmonary TB include infiltrates in the upper lobes, cavities, consolidation, or nodules [26]. However, these features are not specific to TB and can also appear in other infections or conditions, such as aspergillosis or lung cancer. Therefore, radiological findings must be confirmed through microbiological examinations [19,25].

- *Microbiology Examination*

Microbiological testing remains the definitive method for diagnosing pulmonary tuberculosis as it directly detects the presence of *Mycobacterium tuberculosis*.

- Acid-Fast Bacillus Microscopy (AFB): This test uses Ziehl-Neelsen staining to identify acid-fast bacilli in sputum. It is fast, inexpensive, and simple, making it suitable for screening pulmonary TB patients in developing countries [27].

- Mycobacterial Culture: Culture is the gold standard for TB diagnosis, allowing definitive identification of *M. tuberculosis* and drug susceptibility testing. Cultures are typically performed on solid media like Lowenstein-Jensen or liquid media such as MGIT (Mycobacterium Growth Indicator Tube) [28]. However, this method requires up to 6 weeks for results [20].

- Rapid Molecular Testing (GeneXpert MTB/RIF): This technology detects *M. tuberculosis* DNA and resistance to rifampicin. GeneXpert offers high sensitivity and specificity and provides results in approximately 2 hours, making it an essential tool for rapid diagnosis, especially in suspected cases of drug-resistant TB [28].

- *Immunological Examination*
  - Tuberculin Skin Test (TST): This test involves an intradermal injection of purified protein derivative (PPD), followed by the measurement of induration after 48–72 hours. While widely used, TST has limitations, including false-positive results in individuals vaccinated with BCG or infected with non-TB mycobacteria, and false-negative results in immunocompromised patients [29].

  - Interferon Gamma Release Assays (IGRA): Tests such as QuantiFERON-TB Gold measure the release of interferon-gamma by TB-specific T-lymphocytes. IGRAs are more specific than TST as they are unaffected by BCG vaccination. However, similar to TST, these tests cannot distinguish between latent and active TB infections [29,30].

Acute Respiratory Failure in Pulmonary TB

Signs of hypoxia or hypercapnia may indicate the respiratory system's failure to meet the body's oxygenation or carbon dioxide elimination needs in patients experiencing respiratory distress [9]. This condition can arise from impairments in ventilation, diffusion, perfusion, or a combination of these factors. In hypoxemic respiratory distress, the disruption is caused by ventilation-perfusion (V/Q) mismatch, whereas in hypercapnic respiratory distress, it stems from reduced ventilatory function, such as weakened respiratory muscles or airway obstruction [31].

In patients with pulmonary tuberculosis, ARF develops through interconnected mechanisms. Infection with *Mycobacterium tuberculosis* induces chronic inflammation that damages lung parenchyma, forming cavities, fibrosis, or segmental lung collapse [32]. These changes impair ventilation and oxygenation as lung tissue loses elasticity and functionality for gas exchange. Ongoing inflammation may also lead to pulmonary edema or consolidation, further exacerbating oxygen diffusion issues [33]. When secondary infections, such as pneumonia, or systemic complications, like sepsis, occur, the inflammatory burden increases, causing widespread alveolar dysfunction and eventual respiratory failure [34].

General management of ARF in pulmonary TB patients includes ventilatory support—ranging from non-invasive oxygenation to mechanical ventilation in severe cases—and addressing the underlying causes [9]. Treatment options include antituberculous therapy, antibiotics for secondary infections, and nutritional support. A multidisciplinary approach, including the management of comorbidities, is crucial to improving patient outcomes [11].

Comorbidities in Pulmonary TB

Diabetes Mellitus

Diabetes mellitus (DM) is a group of metabolic disorders characterized by chronic hyperglycemia due to insufficient insulin production, insulin resistance, or both [35]. DM significantly impacts various infectious diseases, including pulmonary TB. The prevalence of TB is higher in patients with DM compared to the general population, with DM increasing the risk of developing active TB by two to five times [36]. Additionally, patients with TB-DM have a worse prognosis and higher mortality rates than those with TB alone [37]. Diagnosing TB in patients with DM is often more complex due to atypical clinical presentations and immune dysfunctions that can affect diagnostic tests, such as tuberculin skin tests or interferon-gamma release assays (IGRA) [38]. Moreover, bacteriological examinations often reveal a higher bacterial load in TB-DM patients, indicating more severe infection [39].

DM exacerbates the risk of ARF in TB patients through several interconnected pathophysiological mechanisms. Chronic hyperglycemia in DM creates a pro-inflammatory environment that impairs immune responses to infection. Specifically, hyperglycemia reduces macrophage phagocytosis and chemotaxis, critical processes for controlling *Mycobacterium tuberculosis* replication [40]. Hyperglycemia also leads to the accumulation of advanced glycation end products (AGEs), which induce oxidative stress and increase the expression of pro-inflammatory cytokines such as TNF-α and IL-6. While these cytokines are essential for controlling TB, their excessive levels in DM patients cause uncontrolled inflammation in lung tissues [41,42]. Severe localized inflammation caused by DM, combined with TB-induced lung parenchyma dam, creates a susceptibility to pulmonary edema, alveolar collapse, and ventilatory failure.

Furthermore, chronic hyperglycemia heightens the risk of secondary infections, such as bacterial pneumonia, which can trigger severe complications like acute respiratory distress syndrome (ARDS) [43].

At the microvascular level, DM impairs endothelial function and increases pulmonary capillary permeability, exacerbating pulmonary edema commonly seen in ARF [44]. These processes collectively accelerate respiratory decompensation, increase the risk of ARF in TB-DM patients, and contribute to their higher mortality rates.

HIV/AIDS

Human Immunodeficiency Virus (HIV) is a virus that targets the immune system, particularly CD4+ T lymphocytes, causing progressive severe immunosuppression [45]. Untreated HIV infection progresses to acquired immunodeficiency syndrome (AIDS), rendering infected individuals susceptible to a variety of opportunistic infections, including pulmonary TB. HIV and TB aggravate each other, with TB prevalence being significantly higher among HIV-infected individuals than among the general population [19]. HIV increases the risk of latent TB developing into active TB by up to 20 times and contributes to the high mortality rate associated with TB-HIV coinfection [46]. Diagnosing TB in HIV patients is challenging due to non-specific clinical manifestations and insensitive microbiology results, particularly in patients with very low CD4+ counts [47].

ARF risk worsens in TB patients with HIV through a complex pathophysiological mechanism. HIV infection causes progressive destruction of CD4+ T cells, essential for controlling M. tuberculosis infection. Reduced CD4+ counts impair granuloma formation, structures required to contain and limit the spread of TB bacteria in the lung. Therefore, TB bacteria spread more extensively, and uncontrollable inflammation and more significant pulmonary parenchyma destruction occur in patients with TB and HIV [48]. The condition creates a lung parenchyma prone to respiratory complications, including pulmonary edema and alveolar collapse leading to ARF.

Moreover, TB-HIV patients often suffer secondary infections such as pneumonia [49]. Non-cardiogenic pulmonary edema can be caused by increased capillary permeability due to HIV-induced impact on the vascular endothelium [50]. Systemic inflammation induced by HIV worsens local inflammation in the lung. This will increase the expression of proinflammatory cytokines, such as TNF-α and IL-1β, resulting in excessive tissue injury [51]. When the above occurs in the alveoli, the gas exchange function is disrupted.

Hypoxemia from ARF in TB-HIV patients is frequently compounded by metabolic acidosis, lymphocyte poisoning by drugs like didanosine and stavudine, and lactic acidosis with the use of certain nucleoside reverse transcriptase inhibitors [52]. The combined effect of immunodeficiency, uncontrolled inflammation, and secondary complications comprises a vicious cycle that accelerates the progression of acute respiratory failure. Patients with TB-HIV and ARF have a dismal prognosis if not treated quickly and appropriately, with mortality rates far higher than TB patients without HIV.

COPD

Chronic Obstructive Pulmonary Disease (COPD) is a chronic lung disease characterized by progressive and irreversible airflow obstruction [53]. It is often associated with long-term exposure to lung irritants such as cigarette smoke, air pollution, or occupational dust. COPD induces chronic inflammation in the airways and lung parenchyma, leading to alveolar destruction (emphysema) and airway remodeling (chronic bronchitis) [54]. COPD is frequently observed in patients with pulmonary tuberculosis (TB) due to shared risk factors such as smoking exposure and low socioeconomic status [55]. The prevalence of TB is higher in COPD patients compared to the general population, and TB-COPD coinfection is linked to higher mortality, accelerated disease progression, and severe complications [56,57].

Diagnosing TB in COPD patients is challenging due to overlapping symptoms like chronic cough, breathlessness, and sputum production. Radiological examinations of TB patients with COPD comorbidity often reveal bronchiectasis, particularly if active TB lesions are present. Moreover, widespread emphysema is more commonly observed in the middle and lower lobes in these patients. Air trapping, where air becomes trapped in the alveoli due to small airway obstruction, is also more frequent in TB patients with COPD. This occurs as a result of permanent structural damage in the lungs caused by chronic inflammation and scarring from TB infection [58].

TB-COPD can lead to respiratory distress through a combination of parenchymal lung damage and ventilation-perfusion mismatch. Structural damage from TB, such as fibrosis, bronchiectasis, and parenchymal destruction, results in impaired lung elasticity, increased airway resistance, and air trapping, which exacerbate airway obstruction. These conditions worsen ventilation, potentially triggering ventilatory failure in severe cases, particularly during acute exacerbations [59]. COPD patients with a history of TB have poorer lung function due to chronic inflammation, recurrent infections, and reduced ventilatory capacity. This increases the risk of CO2 retention and hypoxemia, two primary factors that can induce respiratory distress, especially during exacerbations. These combined factors explain how TB-COPD leads to respiratory failure in patients with extensive lung damage [60].

Additionally, COPD increases mucus production and ciliary dysfunction, which impede bacterial clearance from the airways [61]. This heightens the risk of secondary infections like bacterial pneumonia, further aggravating inflammation and lung function [62]. At the vascular level, COPD often leads to pulmonary hypertension due to pulmonary artery wall remodelling, involving intimal changes and medial hypertrophy, thereby straining the right

ventricle of the heart [63]. This condition exacerbates hypoxemia by reducing pulmonary perfusion.

The combination of airway obstruction, parenchymal lung damage, secondary infections, and cardiopulmonary dysfunction creates a pathological cycle that accelerates respiratory decompensation. This explains why patients with TB-COPD are at higher risk of acute respiratory failure compared to TB patients without COPD. Multidisciplinary management, including optimal COPD care, appropriate antituberculosis therapy, and ventilatory support, is crucial for improving clinical outcomes in these patients.

CONCLUSION

Acute respiratory failure (ARF) in pulmonary tuberculosis (TB) represents a critical complication with high mortality, driven by a complex interplay of infection-induced lung damage and exacerbating comorbidities. This review highlights the significant roles of diabetes mellitus (DM), HIV/AIDS, and chronic obstructive pulmonary disease (COPD) in influencing the pathophysiology, incidence, and severity of ARF among TB patients. DM contributes to ARF through impaired immune responses, chronic inflammation, and an increased risk of secondary infections, while HIV-induced immunosuppression exacerbates TB progression and systemic inflammation, leading to severe pulmonary damage. COPD, on the other hand, amplifies the impact of TB through shared risk factors, impaired ventilation-perfusion, and secondary infections, further deteriorating lung function and increasing the risk of ventilatory failure.

The interactions between TB and these comorbidities underscore the importance of an integrated and multidisciplinary approach to diagnosis and management. Addressing comorbid conditions alongside TB treatment, coupled with timely interventions for ARF, is critical for improving clinical outcomes. Further research is needed to explore targeted strategies for early detection, preventive measures, and optimal management protocols to reduce the burden of ARF in TB patients, particularly in resource-limited settings where the disease burden is highest. This comprehensive understanding serves as a foundation for enhancing clinical care and public health policies for TB and its complications.

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