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Understanding the Tuberculosis and COVID-19 Co-infection: A Comprehensive Review of Immunopathological Dynamics and Pandemic's Disruption in TB Services

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Abstract

Tuberculosis (TB) remains a significant public health challenge worldwide and its incidence has been exacerbated by the COVID-19 pandemic. The interaction between TB and COVID-19 poses significant risks to patients, leading to increased morbidity and complicating treatment strategies as both diseases share similar clinical manifestations, such as respiratory symptoms and immune effects. As the global health system continues to grapple with the impact of COVID-19 on existing infectious disease frameworks, it is imperative that researchers engage in research focused on understanding TB co-infection and COVID-19. The primary aim of this literature review is to contribute to the development of knowledge about the pathogenic etiology, clinical manifestations, risk factors, immunopathology of TB and COVID-19 co-infection, and the impact of the COVID-19 pandemic in TB services.

Keywords: TB; COVID-19; Co-infection; Immunopathology; Service

1. Introduction

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis*, primarily affecting the lungs, but it can also impact other organs. TB remains one of the leading causes of morbidity and mortality worldwide, particularly in low- and middle-income countries [1, 2, 3]. According to the World Health Organization (WHO), in 2021, tuberculosis became the second deadliest infectious disease in the world after COVID-19 and ranked thirteenth as the leading cause of death worldwide. There were an estimated 10.6 million new TB cases globally, with approximately 1.6 million deaths attributed to the disease. China is the third highest contributor among the eight countries that collectively account for two-thirds of the global TB cases, representing 8.4% of the total cases reported worldwide [4, 5].

On January 30, 2020, WHO received reports of 7818 new coronavirus disease cases worldwide and declared COVID-19 a pandemic on March 11, 2020 [6]. The emergence of the COVID-19 pandemic has further complicated the landscape of infectious diseases, particularly TB. COVID-19 and tuberculosis are transmitted through respiratory droplets, primarily affecting the lungs. Each disease activates T lymphocytes, particularly helper T cells, through distinct pathways, ultimately resulting in heightened production and release of interferon. The immune response to both infections can lead to severe complications as the body continues to face ongoing immune challenges [7].

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COVID-19, caused by the novel coronavirus SARS-CoV-2, has not only resulted in widespread illness and death but has also disrupted healthcare systems globally. TB and COVID-19 overlap can lead to diagnostic delays and mismanagement, complicating treatment protocols. Co-infection with COVID-19 can exacerbate the clinical course of TB due to the immunosuppressive effects of SARS-CoV-2. Patients with TB are at increased risk for severe COVID-19 outcomes, including hospitalization and mortality. Therefore, researchers are interested in conducting research about pathogenic etiology, clinical manifestations, risk factors, immunopathology of TB and COVID-19 co-infection, and the impact of the COVID-19 pandemic in TB services to provide convenient information.

2. Review content

2.1. Co-infection

Tuberculosis (TB) and COVID-19 co-infection are defined as diseases caused by both *Mycobacterium tuberculosis* and SARS-CoV-2 infection, and they have been reported globally [8]. Co-infection refers to the simultaneous infection of a host by multiple pathogens, including viruses, bacteria, fungi, and parasites [9]. This phenomenon is distinct from superinfection, where one infection follows another [10]. Co-infection can enhance disease transmission and progression through synergistic interactions between pathogens [9].

2.2. Pathogenic etiology

2.2.1. Mycobacterium tuberculosis

Tuberculosis is caused by a bacterium called *Mycobacterium tuberculosis*. This bacterium is classified under the *M. tuberculosis* complex group, which includes four other mycobacteria that can cause active tuberculosis, including *M. canettii, M. microti, M. bovis, and M. africanum*. *M. tuberculosis* and *M. bovis* are the two most frequent species and can cause sporadic or epizootic disease with high morbidity and mortality in this species. They are named for the nodular lesions found in the lungs, called tubercles [3].

M. tuberculosis is a nonmotile, non-spore-forming, catalase-negative intracellular bacterium. It can survive in dry and cold conditions (it can last for years in a refrigerator). The other trait is aerobic. This trait indicates that bacteria prefer tissues that have a high oxygen content. In this case, the pressure of the apical part of the lung is higher than the other parts, so this apical part is the preferred place for TB bacteria. The high lipid content of *M. tuberculosis* gives it many unique clinical characteristics, such as resistance to some antibiotics, difficulty staining with gram stain, and the ability to survive in extreme conditions such as extreme acidity or alkalinity, low oxygen situations, and intracellular survival (inside macrophages). These bacteria also take a long time to divide (about 16 to 20 hours), much slower than other bacteria that usually take less than an hour [11].

These organisms have a poor reaction to Gram stain. Thus, it is not classified as gram-positive or gram-negative. However, a weak gram positive can sometimes be observed on a Gram stain, referred to as a “ghost cell”. *M. tuberculosis* retains some staining even after being treated with acidic solutions. Hence, *M. tuberculosis* is considered an acid-resistant bacillus. Ziehl-Neelsen and Kinyoun stains are the most commonly used stains to identify *M. tuberculosis*. These tests stain acid-resistant bacteria a bright red colour, which makes them stand out against a blue background [12].

2.2.2. Sars-CoV-2

SARS-CoV-2 is a novel betaCoV that belongs to the same subgenus as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). The virus is spherical or elliptical and often pleomorphic, with a diameter of approximately 60-140 nm. Like other CoVs, it is sensitive to ultraviolet light and heat. In this case, even high temperatures can decrease the replication of any virus species. In contrast, this virus can survive at lower temperatures, even below 0°C. In addition, the virus can be effectively inactivated by lipid solvents, including ether (75%), ethanol, chlorine-containing disinfectants, peroxyacetic acid, and chloroform, except chlorhexidine [13].

Coronavirus is a type of single-stranded ribonucleic acid (RNA) that has a protective coating around it. The name “corona” comes from its appearance, which resembles the sun’s corona, with a surface that has spikes 9-12 nm long. In this virus structure, there are four main structural proteins produced by the coronavirus genome in its protective layer, namely N protein (nucleocapsid), M glycoprotein (membrane), S spike glycoprotein (spike), and E protein (envelope). The spike protein (S) interacts with the angiotensin-converting enzyme 2 (ACE2) receptor. It facilitates the union between the protective layer and the host cell membrane, thus allowing the virus to enter the host cell. Therefore, targeting therapy in COVID-19 patients is aimed at the S protein [14, 15, 16].

M proteins have a role in introducing the virus to the body and forming the envelope. E protein plays a role in the development, envelope formation, and spread of the virus. N proteins play a role in enhancing the transcription process and virus formation. The S protein is the main component responsible for binding the virus to the host cell and is crucial to the infection process. Human-to-human transmission can occur through the spread of airborne droplets or particles from an infected individual to a healthy individual within a short distance of about 2 meters [15, 16, 17]. Based on current data, it appears that bats initially served as COVID-19 hosts, possibly transmitted to humans through pangolins or other wild animals sold in seafood markets [14, 17].

2.3. Clinical manifestations

When infected, TB and COVID-19 share similar clinical manifestations. Common symptoms of the two infectious diseases include cough, chest pain, fever, fatigue, headache, and dyspnea. Each pathogen has systemic and local clinical manifestations.

2.3.1. TB

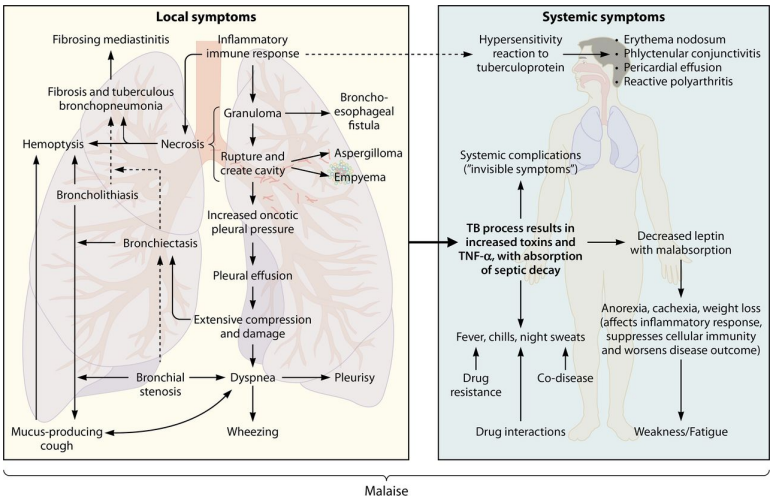

Figure 1 Local and systemic clinical manifestations in TB patients [2].

TB symptoms can be divided into two categories, namely systemic and local (pulmonary). The frequency of these symptoms differs according to whether the patient has primary or reactivated tuberculosis. Patients with primary tuberculosis are more likely to show no symptoms or minimal symptoms. The most commonly seen systemic symptom is fever, which is low-grade initially but becomes very marked as the disease progresses. Typically, fever develops in the afternoon and may not be accompanied by any apparent symptoms. Usually, during sleep, the patient will experience night sweats. Other signs also arise, such as weakness, unusual fatigue, headache, and weight loss [18].

With the simultaneous development of necrosis and liquefaction caseosa, patients will usually experience local symptoms such as cough and sputum, which are often associated with mild hemoptysis. Chest pain may be localized and pleuritic. Shortness of breath usually indicates extensive disease with widespread lung and parenchymal involvement or a form of tracheobronchial obstruction; therefore, it usually occurs in the late stages of the disease course [11, 18].

2.3.2. COVID-19

Systemic clinical manifestations of COVID-19 include fever, hypoxemia, lymphopenia, diarrhea, dyspnea, headache, fatigue, cough, and haemoptysis, while local clinical manifestations include rhinorrhoea, sneezing, sore throat, and others. Dizziness, abdominal pain, nausea, headache, vomiting and diarrhea are less common clinical presentations. During the first outbreak of the disease in Wuhan, 99 cases were reported that showed symptoms such as headache, dyspnea, abdominal pain, lymphopenia, diarrhea, mucus production and hemoptysis. About 74 infected people showed bilateral pneumonia. Similar symptoms were also found in non-pregnant and pregnant women. Individuals infected with the coronavirus showed prominent upper respiratory tract manifestations, including sneezing or sore throat, so the virus may have a higher affinity to lodge in the lower respiratory tract, as evident by upper respiratory tract symptoms such as rhinorrhoea, sneezing, and sore throat. In addition, based on results from chest radiographs upon admission, some of the cases show an infiltrate in the upper lobe of the lung that is associated with increasing dyspnea with hypoxemia [14, 15].

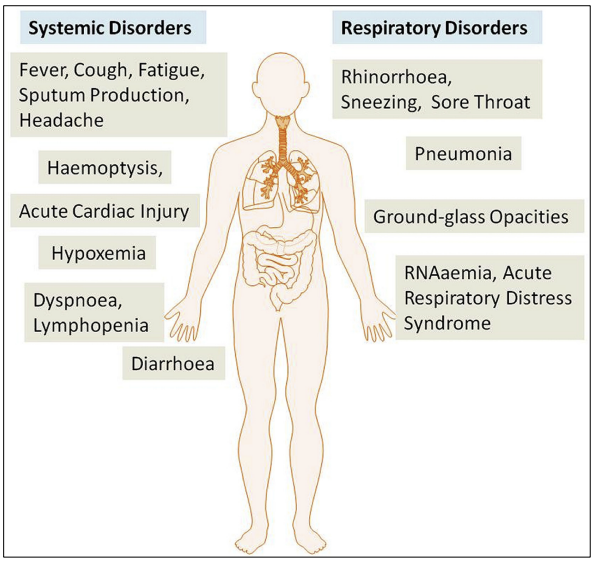

Figure 2 Local and systemic clinical manifestations in COVID-19 patients [15].

2.4. Risk factors

2.4.1. TB

Several factors that increase the risk of being infected with pulmonary tuberculosis, including:

1) Age: About 75% of pulmonary TB patients in Indonesia are in the economically productive age group (15-50 years). In addition, the risk of infection will increase again when a person approaches old age [19].
2) Gender: Tuberculosis is more common in men than women. This condition may be due to the fact that most men have a smoking habit [20].
3) Exposure to cigarette smoke: Smoking can lower the body's immune system, thereby increasing disease susceptibility. Likewise, passive smokers who inhale cigarette smoke will make passive smokers more easily infected with pulmonary TB [21].
4) Occupation: Occupation can be a risk factor due to direct patient contact. For example, health workers who interact directly with patients are at risk of tuberculosis transmission. However, other occupations, such as mine workers, may also increase the risk [19].
5) Economic status: Families earning below the Regional Minimum Wage consume food with nutritional levels that do not meet the needs of each family member. In a state of malnutrition, the immune response is reduced, decreasing the ability to defend against infection. In addition, poor socio-economic conditions can prevent patients from building a healthy or qualified house [19].
6) Environmental factors: The environment also affects the risk of tuberculosis, such as lighting, humidity, temperature, house building conditions, and occupancy density. M. tuberculosis bacteria can more easily enter homes that lack sunlight and have poor environmental conditions [19].
7) Diabetes mellitus: Active tuberculosis is most common in patients with poor glycemic control. In addition, insulin dependence is considered a risk factor for tuberculosis. Poorly controlled diabetes mellitus can lead to various complications, including increased susceptibility to tuberculosis through several mechanisms, including hyperglycemia and cellular insulinopenia, which have indirect effects on macrophage and lymphocyte function [21].
8) Other risk factors, such as HIV status and history of asthma, can also exacerbate the development of TB infection [20].

2.4.2. COVID-19

Several factors that increase the risk of being infected with COVID-19, including:

1) Age: The World Health Organization (WHO) states that people over 65 are included in the high-risk group for COVID-19 infection (WHO, 2020). Older age is associated with increased angiotensin-converting enzyme-2 (ACE-2) receptors, leading to high viral replication. In addition, a decreased immune system and increased comorbidities increase disease severity [22].

2) Gender: Males are at a higher risk than females. This condition is due to the high expression of ACE2 receptors in male testes, which makes it easier for the virus to enter and infect their bodies [23].
3) Exposure to cigarette smoke: Active smoking can increase the expression of ACE2 receptors, which is a mechanism used by the virus to enter cells [23].
4) Comorbid factors refer to other diseases suffered by patients infected with COVID-19. Some common comorbidities include diabetes mellitus, hypertension, heart disease, COPD (Chronic Obstructive Pulmonary Disease), asthma, kidney disease, cancer, liver disease, and tuberculosis [24].

2.5. Immunopathology

Commonly, *Mycobacterium tuberculosis* affects lung tissue by necrotic granuloma formation. Granulomas are the focus of the anti-tuberculosis immune response and are presented by macrophages, neutrophils, dendritic cells (DCs), natural killer (NK) cells, mast cells, and lymphocytes. Appropriate treatment and an effective immune response contribute to eliminating bacteria and resolving granulomas; however, some patient characteristics may make them susceptible to the chronic process. For example, due to the expression of cell death ligand 1 (programmed death ligand 1 or PD-L1), neutrophils cause loss of function and eventual death of lymphocytes. In some patients with active tuberculosis, there is a decrease in CD4+ percentage and absolute values in peripheral blood, which is associated with the severity of infection [25, 26, 27].

Initially, concurrent infection by TB and COVID-19 will delay or impair the response to the SARS-CoV-2 virus, while persistent inflammatory stimulation over time will lead to general T cell exhaustion. In both TB and COVID-19, lymphocytes act as mediators in the immune system, regulating the release of inflammatory chemicals (cytokines) and cell attractants (chemokines) at the site of infection; the decrease in lymphocyte count caused by co-infection directly affects the regulation of immune responses to these pathogens. The main impact of decreased lymphocyte counts is increased expression of cytokines, especially pro-inflammatory ones. Lung cell death due to necrosis and pyroptosis also results in local dispersion of DAMPs, which intensifies inflammatory feedback in the lower respiratory tract. The main cytokines contributing to bacillus containment, TNF and IFN-γ, also play a key role in the pro-inflammatory immunomodulatory response to SARS-CoV-2 [27, 28].

In most cases, the development of lymphopenia is characterized by a sharp decrease in the absolute content of CD4+ T cells, CD8+ T cells, B cells, and natural killer cells. It should be emphasized that the decrease in total T cells, CD3+CD4+, and CD3+CD8+ cells in COVID-19 patients is especially significant in older adults and patients requiring intensive care [27].

Changes in CD4+ T cell subsets during the infection process are closely related to the effectiveness of the effector phase of the immune response against specific types of pathogens. In both M. tb and SARS-CoV-2 virus infections, Th1 cells are considered the main effector T helper cells. Upon recognizing specific antigens in peripheral tissues, Th1 can produce IFNγ, which activates a wide variety of immunocompetent cells, including CD8+ cytotoxic T cells, ILC1, macrophages and B cells, involved in eliminating intracellular pathogens. However, the role of these Th cell populations in the pathogenesis of these diseases is somewhat controversial. The activation of T-helper 17 and neutrophils in the peripheral blood promotes mycobacterial invasion into the area of infection and, in addition to protective effects, damages surrounding tissues. Specifically, the relative number of Th2 cells in peripheral blood significantly increased among patients with tuberculosis. In contrast, the level of Th17 cells significantly decreased, whereas no significant difference between groups was observed in the Th1 and Tfh cells. Similar results were obtained in the analysis of peripheral Th subsets in tuberculosis using the method of nonspecific stimulation in vitro, which showed a decrease in the level of CD4+IL-17A+ cells against the background of infection. At the same time, the content of CD4+IL-4+ lymphocytes in patients was significantly increased. However, there were different observations made by Wang T. et al. (2011). Their results showed an increase in IL-17+CD4+ cell levels among tuberculosis patients compared to controls, confirming previous studies of increased IL-17 mRNA concentrations in peripheral blood lymphocytes among active tuberculosis patients. On the other hand, two independent research groups noted a decrease in Th17 content in the peripheral blood of patients. Moreover, the decreased level of IL-17 in the peripheral blood of tuberculosis patients is closely related to the low efficacy of treatment and the unfavourable outcome of the disease. In addition, the number of CD3+ is inversely proportional to the concentration of pro-inflammatory cytokines IL-6, IL-10 and TNFa in the peripheral blood serum [27].

Another mechanism of immune suppression is thought to be based on the role of T regulators (Tregs), which were shown to contribute to the development and persistence of infection. Anti-inflammatory processes were shown to be induced by CD8+ lymphocytes, which secrete IL-10 and TGF-β; in addition, the ESAT-6 Mtb protein causes the transformation of macrophages from the M1 phenotype, which produces IL-6, IL-12 and TNF-α, to M2, which is also

capable of stimulating IL-10 production. Currently, it is known that the SARS-CoV-2 virus penetrates the mucous membranes of the upper respiratory tract and replicates in ciliated epithelial cells, with further development of secondary viremia, immune compromise, hypoxia, and dissemination to target organs (heart, liver, kidneys, and sych others) leading to microangiopathy in the form of productive thrombovasculitis and hypercoagulable syndrome with immune system damage [27, 29].

During infection with the COVID-19 virus, there is direct damage to the respiratory system cells and damage mediated by impaired blood circulation. The direct cytotoxic effect of the virus is due to the penetration of the virus into cells expressing angiotensin-converting enzyme 2 (ACE2)-alveolates, which leads to the development of pneumonia. Some cytokines expressed upon co-infection also have adverse effects, such as increased expression of ACE2 receptors on the cell surface, which IFN-γ stimulates. The unrestricted inflammatory infiltration of immune cells observed in the lungs, in addition to direct viral damage, also contributed to more significant tissue damage due to excessive secretion of proteases and reactive oxygen species. Diffuse alveolar damage is characterized by the desquamation of alveolar cells, formation of hyaline membranes and development of pulmonary oedema. Extensive microcirculation disorders due to vascular damage and increased thrombus formation aggravate lung tissue damage and reduce the effectiveness of reparative processes [27].

2.6. Impact of COVID-19 pandemic on TB services

Most centers saw a decline during their national lockdowns in the first four months of 2020 in several areas, such as a decrease in TB-related hospital discharges, newly diagnosed active TB cases, total active TB outpatient visits, and new latent TB infections diagnosed (along with related outpatient visits). WHO noted a 21% decrease in individuals who began TB preventive treatment in 2020, marking a reversal of the positive trend sustained until 2019 [30]. Conversely, articles indicated that the proportion of latent tuberculosis infection (LTBI) among TB contacts increased during the pandemic, showing a difference ranging from 5.9% to 14.3% [31].

In certain centers, staff originally designated for TB services were reassigned to focus on COVID-19. Additionally, the reduced attendance at TB clinics was linked to patients' fears of COVID-19 exposure in the community, disruptions in services, and difficulties accessing healthcare during lockdowns. On the other hand, national lockdowns led to a rise in the use of telemedicine. In the TB centers surveyed in Australia, Russia, India, and the United Kingdom, there was an increase in telehealth service utilization [32].

There is an immediate need to develop strategies for screening, preventing, and treating *M. tuberculosis* in patients with COVID-19. Real-time PCR and the Xpert/MTB RIF assay should be conducted on all samples collected in areas where TB is endemic. It is crucial to rethink TB diagnosis and apply the successful approaches used for COVID-19 to TB as well. Additionally, TB surveillance and case notifications should be digitized, incorporating real-time data aggregation similar to that used for COVID-19 to guide public health responses effectively [15].

3. Conclusion

In conclusion, the literature review calls for urgent research efforts better to understand the dynamics of TB and COVID-19 co-infection since the pandemic affects TB services, such as a decrease in TB-related hospital discharges, newly diagnosed active TB cases, total active TB outpatient visits, and new latent TB infections diagnosed. The immune response can lead to severe complications. It emphasizes that both diseases stimulate T lymphocyte activity through different mechanisms, ultimately increasing interferon production. Besides, CD4+ and CD8+ T cells also lead to immune dysregulation characterized by lymphopenia and increased pro-inflammatory cytokine levels. This understanding is essential for developing effective treatment strategies and public health interventions to mitigate these diseases' impact on vulnerable populations. As global health systems continue to adapt to the challenges posed by COVID-19, prioritizing research on co-infections will be vital in enhancing patient outcomes and improving overall public health responses.

Compliance with ethical standards

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Disclosure of Conflict of Interest

No conflict of interest is to be disclosed.

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