Review Article

Advanced Therapeutic Interventions Targeting *Mycobacterium Tuberculosis*

A. Razzak Mahmood, A[1], Rani, VI[2], Yadav, P[3], Patil, SS[4*]

1. *Department of Pharmaceutical Chemistry, College of Pharmacy, University of Baghdad. Bab Al-Mouadam, 10001. Baghdad, Iraq.*
2. *Assistant professor, Department of Community & Psychiatric Nursing, Faculty of Nursing, King Khalid University, Mahayil, Asir Region, KSA.*
3. *MD pharmacology, Professor, HOD, MGM Medical College, Vashi, Navi Mumbai.*
4. *Principal Scientist, ICAR-National Institute of Veterinary Epidemiology and Disease Informatics (NIVEDI), Bengaluru, Karnataka, India.*

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Corresponding Author's E-Mail:
sharanp094@gmail.com

ABSTRACT

Tuberculosis infection (TBI), caused by *Mycobacterium tuberculosis* (*M.tb*), presents with or without clinical signs of active TB and is a persistent global threat despite efforts to eradicate it. The emergence of HIV/AIDS is one of the problems to complete eradication. Recent research has focused on vaccines, diagnostics, and treatment. This review examines vulnerable populations, high-risk groups, and socio-economic factors influencing TBI prevalence. It also explores the intersection of TBI and the COVID-19 pandemic, including healthcare disruptions and transmission dynamics. Advances in TBI diagnosis, biomarkers, prophylactic therapies, and combination treatments are discussed, along with the integration of artificial intelligence (AI) in TBI therapy to optimize treatment and personalize care. Vulnerability to TBI varies based on age, socio-economic status, and immune status. High-risk groups include those with compromised immune systems, the elderly, and those in crowded or poorly ventilated settings. Socioeconomic factors such as poverty and limited healthcare access also contribute to TBI prevalence. The COVID-19 pandemic has disrupted TBI diagnosis and treatment, with limited healthcare access impacting outcomes. Changes in healthcare delivery, like telemedicine, may have long-term impacts on TBI care. Improved biomarkers, like interferon-gamma release assays (IGRAs), offer faster TBI diagnosis. Prophylactic therapies, such as isoniazid preventive therapy (IPT), reduce active TB risk in high-risk groups. Combination treatments are being evaluated for drug-resistant strains. AI integration in TBI therapy could lead to better outcomes by analyzing patient data for personalized treatment plans. In conclusion, TBI remains a global health threat requiring ongoing research and innovative approaches for diagnosis and treatment. Advances in diagnosis, prophylactic therapies, and combination treatments, along with AI integration, offer hope for improved outcomes and better patient care, In conclusion, traumatic brain injury (TBI) persists as a significant global health concern, necessitating sustained research efforts and the development of innovative diagnostic and therapeutic approaches. Advancements in diagnostic methods, prophylactic therapies, combination treatments, and the integration of artificial intelligence hold promise for enhancing outcomes and enhancing patient care.

Keywords: TuberculosisInfection (TBI), *Mycobacterium Tuberculosis (M.tb)*, Vulnerable Populations, High-Risk Groups, Socio-Economic Factors.

1. Context

Tuberculosis infection (TBI) is characterized by a sustained immunological response triggered by M. tuberculosis antigens, manifesting either with or without evident clinical symptoms of active TBI disease. A considerable proportion of individuals with TBI remain asymptomatic, exhibiting no overt signs of the disease, and therefore pose no risk of transmitting it. These individuals, however, are susceptible to active tuberculosis and potentially contribute to disease transmission. TBI is now recognized as a dynamic continuum of reactions to M.tb infection, influenced by the immunological response interactions between TBI bacteria and the host's immune system. A recent study suggests that persons diagnosed with TBI who showed no symptoms may have different infection levels. The infection may be eliminated, while, at the opposite end of the spectrum, active tuberculosis may be present in a subclinical state (1). It is estimated that 10% of the global population is infected with M.tb. However, the prevalence of resistance to fundamental anti-TB therapies, such as isoniazid and rifampicin, remains uncertain, primarily due to the challenges in isolating and testing infecting strains for resistance evaluation (2). Globally, there has been an increase in the prevalence of infections caused by strains resistant to isoniazid, which underscores the necessity to comprehend the dynamics of tuberculosis infection and the potential challenges posed by drug-resistant variants (3). The global efforts to eliminate TB have been hindered by the emergence of HIV and AIDS, perpetuating the problem as a continuous worldwide menace. The World Health Organization has classified tuberculosis as a "global emergency" due to its substantial severity. In 2010, Gandhi and colleagues underscored these concerns, highlighting the emergence of drug-resistant strains of tuberculosis due to the improper use of antibiotics during tuberculosis chemotherapy, noncompliance with anti-TBI medications, and inadequate monitoring of drug resistance (4). According to the World Health Organization (WHO), almost 9.6 million people were impacted by TBI, leading to 1.5 million fatalities and TBI-related deaths (5) There is a critical need for a method for effective TBI control that can rapidly and accurately diagnose *M.tb* and facilitate effective treatment on a global scale. However, existing point-of-care (POC) detection methods lack the speed and effectiveness required to reduce infection rates and TBI-related mortality significantly. These methods primarily focus on detecting active TBI infections. The diagnosis of active TBI involves detecting the presence of the causative *M.tb*, within the patient. While traditional microbiological culture methods are available, they suffer from slow growth rates and a higher risk of contamination, making them vulnerable to spreading the MDR strain. Sputum smear microscopy has traditionally been the main method for diagnosing TBI despite challenges in rapidly identifying TBI in a clinical setting (6). Patients suspected of having TBI may test negative in sputum smears, prompting the use of additional diagnostic procedures. Examples of diagnostic tests for tuberculosis include the TBI skin test (TST), interferon-gamma release assay (IGRA), culture examination, chest radiography, or amplification techniques to confirm the diagnosis. The cultural approach is the most precise and sensitive diagnostic technique, outperforming sputum smears' accuracy. Employed in clinical and research settings, the culture of *M.tb* proves to be a highly reliable method for diagnosing active tuberculosis. The growth in nanoscience and nanotechnology has greatly contributed to advancements in diagnostic procedures, especially in sample preparation and detection. The emphasis is on creating technologies that provide a direct, economical, sensitive, precise, and quick diagnosis of TBI at the POC levels. A conventional method entails using magnetic nanoparticles and antibodies in immune magnetic separation fields to diagnose viral and inflammatory diseases (7) which developed a diagnostic system that integrates microfluidics, magnetic nanoparticles tagged with anti-BCG antibodies, and nuclear magnetic resonance (NMR) equipment to analyze unprocessed biological materials. In addition, nanotechnology methods have been extensively used to create a highly responsive bio-sensing platform at both the micro and nanoscale using nanoparticles. This approach offers enhanced sensitivity, specificity, simplicity of assembly, and the ability to produce large volumes at a reasonable price for POC testing. Functionalized quantum dots combined with immune magnetic separation have shown exceptional sensitivity and specificity when used with clinical samples (8).

2. Evidence Acquisition

This review examines populations vulnerable to TBI, with a particular emphasis on demographics and socio-economic factors that contribute to disease prevalence. It also explores the relationship between TBI and the COVID-19 pandemic, analyzing how they mutually impact each other, including healthcare disruptions and patterns of TBI transmission. The review discusses advancements in TBI diagnosis, particularly the use of improved biomarkers for accurate identification, preventive therapies, and the effectiveness of combined treatments against drug-resistant strains. Additionally, it explores the integration of artificial intelligence in TBI therapy, highlighting its potential to enhance treatment approaches and personalized care strategies.

3. Results

3.1. Population Sensitive to TBI

Although not all persons infected with *M.tb* proceed to active tuberculosis infection the chance of disease progression varies among patients. Those with compromised immune systems exhibit a notably higher incidence of active TBI infection (9). This risk remains elevated even with effective antiretroviral treatment (ART). Household contacts (HHCs) of persons with bacteriologically confirmed cases proven for TBI are being

targeted for intervention. Those who tested positive for TBI but did not undergo tuberculosis preventive therapy (TPT) showed a markedly increased prevalence of active tuberculosis during the initial two years of observation compared to their TBI-negative counterparts. Irrespective of age or TBI status, individuals with household contacts (HHCs) are at a higher risk of getting active tuberculosis compared to the general population (10). Demographic factors that influence active TBI infection are those persons who have migrated from countries with a high incidence of tuberculosis, those experiencing homelessness, incarcerated individuals, illicit drug users, and patients receiving immunosuppressive treatment, medication such as TNF inhibitors, and long-term corticosteroids. Host genes affect a person's vulnerability to TBI. However, the identities of the implicated genes have remained unknown so far. Two complementary approaches to identifying those genes are association-based candidate genes and a comprehensive linkage screen While candidate gene studies could identify the precise gene or genes responsible for the onset of TBI, the linkage will only pinpoint the genes' chromosomal position. A substantial study is needed to switch from mapping age networks to finding genes. Still, it becomes simpler as the human genome project generates increasingly high-resolution physical and genetic maps. The genome-wide map of translated sequence tags (EST), a short length of coding DNA for which a PCR test is currently being developed, would substantially aid in identifying genes associated with TBI susceptibility. A substantial study is needed to switch from mapping age networks to finding genes. Still, it becomes simpler as the human genome project generates increasingly high-resolution physical and genetic maps. The genome-wide map of translated sequence tags (EST), a short length of coding DNA for which a PCR test is currently being developed, would substantially aid in identifying genes associated with TBI susceptibility. A substantial study is required to transition from the mapping of age networks to the identification of genes. However, as the human genome project progresses and generates increasingly high-resolution physical and genetic maps, the task becomes increasingly manageable. The development of a genome-wide map of translated sequence tags (EST), which are short fragments of coding DNA and for which a polymerase chain reaction (PCR) test is currently being developed, would facilitate the identification of genes associated with traumatic brain injury (TBI) susceptibility.

3.2. TBI Association with the COVID Epidemic

The regular TBI diagnostic and treatment services have been significantly affected by the COVID-19 pandemic. This is primarily attributed to the diminished capacity of healthcare systems, the reassignment of healthcare personnel to COVID-19-related duties, and the allocation of TBI diagnostic resources to address the similarity in symptoms between TBI and COVID-19. The enforcement and implementation of lockdowns and strict quarantine measures have caused delays in the diagnosis of TBI, interruptions in contact tracing attempts, and setbacks in the commencement of tuberculosis-preventative medication. These variables may have led to the increased spread of TBI within their homes (11). The number of reported TBI cases worldwide has significantly decreased, from 7.1 million in 2019 to 5.8 million in 2020, representing a remarkable historic fall. The southeast Asia and the western Pacific areas experienced the most significant reductions in TBI cases. Significant progress has been achieved in employing innovative strategies to address tuberculosis, as evidenced by recent research findings. (12) These approaches encompass a range of techniques for screening and diagnosing multiple diseases, such as utilizing GeneXpert, a diagnostic tool used for detecting TBI and COVID-19. They use automated technology to analyze chest X-rays and detect cough patterns directly at the point of service. An evident transition may be seen from specialist methodology to integrated approaches, such as using community health workers to enhance early identification, diagnosis, and treatment of tuberculosis patients. The regular TBI diagnostic and treatment services have been significantly affected by the ongoing pandemic of the novel coronavirus, SARS-CoV-2, also known as "covid-19." This is primarily attributed to the diminished capacity of healthcare systems, the reassignment of healthcare personnel to duties related to the management of the pandemic, and the allocation of TBI diagnostic resources to address the similarity in symptoms between TBI and the disease caused by the novel coronavirus. The enforcement and implementation of lockdowns and strict quarantine measures have caused delays in the diagnosis of TBI, interruptions in contact tracing attempts, and setbacks in the commencement of tuberculosis-preventative medication. These variables may have led to the increased spread of TBI within their homes (11). A notable decline in reported TBI cases worldwide was observed, with a decrease from 7.1 million in 2019 to 5.8 million in 2020, marking a substantial historic decrease. Notably, the southeastern Asia and the western Pacific regions have witnessed the most substantial declines in TBI cases. Recent research findings indicate significant progress in the implementation of innovative strategies to address tuberculosis. These approaches encompass a range of techniques for screening and diagnosing multiple diseases, such as the utilization of GeneXpert, a diagnostic tool employed for detecting TBI and COVD-19. These innovative approaches utilize automated technology to analyze chest X-rays and detect cough patterns directly at the point of service. A discernible shift is evident in the transition from specialized methodologies to integrated approaches, such as the utilization of community health workers to enhance the early identification, diagnosis, and treatment of tuberculosis patients. A deliberate and coordinated process guarantees that susceptible demographics in industrialized countries can get preventative screening by the ideals of health care. The COVID-19 pandemic has prompted progress in infection

prevention and control methods in healthcare systems, particularly in preventing TBI. This encompasses the increased use of masks by patients and personal protective equipment by healthcare workers. As a result, there has been a significant decrease in the spread of both COVID-19 and TBI (13). COVID-19 triggers diverse immune responses in individuals, ranging from asymptomatic to severe symptomatic cases marked by excessive cytokine release, potentially leading to fatal outcomes. The administration of immune-suppressing medications, like steroids, in COVID-19 treatment raises concerns about the potential reactivation of tuberculosis in the future. Although PCR and culture-based methods for TBI are considered the gold standard for diagnosing COVID-19, there is currently no ideal POC test available to determine active TBI infection. COVID-19 can manifest at any stage of TBI progression, posing higher risks for those with active pulmonary TBI. Identifying common signs and symptoms shared by both COVID-19 and TBI may contribute to the timely acquisition of imaging services, such as chest radiography or computed tomography, which can reveal evidence of pre-existing TBI before the onset of COVID-19. A deliberate and coordinated process ensures that susceptible demographics in industrialized countries receive preventive screening according to the principles of healthcare. The ongoing global pandemic has spurred advancements in infection prevention and control methodologies within healthcare systems, particularly in the realm of preventing traumatic brain injuries (TBIs). This has manifested in the increased utilization of masks by patients and the adoption of personal protective equipment by healthcare workers. Consequently, there has been a substantial decline in the transmission of both SARS-CoV-2 and traumatic brain injury (TBI) (13). The immune system of individuals infected with the novel virus exhibits a wide spectrum of responses, ranging from asymptomatic cases to severe symptomatic manifestations marked by excessive cytokine release, which can potentially lead to fatal outcomes. The administration of immune-suppressing medications, such as steroids, in the treatment of patients with COVDI-19 raises concerns about the potential reactivation of tuberculosis in the future. While PCR and culture-based methods are regarded as the gold standard for diagnosing TBI, there is currently no ideal point-of-care (POC) test available to determine active TBI infection. The potential for the manifestation of the novel virus at any stage of TBI progression underscores the heightened risks for those with active pulmonary TBI. The identification of shared signs and symptoms between these two conditions can facilitate the timely acquisition of imaging services, such as chest radiography or computed tomography, which can reveal evidence of pre-existing TBI before the onset of symptoms of both conditions. Key factors influencing mortality rates in cases of severe acute respiratory syndrome (SARS) due to the novel coronavirus (SARS-CoV-2), such as age and comorbidities, including human immunodeficiency virus (HIV) infection, poverty, diabetes, and malnutrition, contribute to tuberculosis (TB) mortality rates. Individuals with a compromised immune system, rendering them susceptible to TBI, face an elevated risk of contracting the virus. The implementation of control measures for TBI has been hindered by the ongoing challenges posed by the pandemic, underscoring the necessity of anticipating the possibility of coinfection. Despite advancements in technology and medicine, culture and antibiotic susceptibility testing remain the gold standard for diagnosing TBI. The ongoing outbreak of the novel strain of severe acute respiratory syndrome (SARS-CoV-2), which is the causative agent of the disease known as "coronavirus disease 2019" (henceforth referred to as "covid-19"), presents a valuable opportunity to explore the parallels between the epidemiology of the two diseases with regard to transmission. A comparative analysis of the challenges and insights gained from managing both diseases can be mutually beneficial. Swift and accurate diagnosis and widespread public awareness are essential for effective management of both conditions (Figure 1).

3.3. Diagnosis Improvement

The tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) are two critical diagnostic methods to detect tuberculosis infection (14). These tests indirectly detect the immune response to tuberculosis (TBI) and do not directly assess the existence or capacity to survive *M.tb* infection. Their capacity to differentiate between various phases of TBI is low, and they have a restricted ability to accurately anticipate the advancement of the infection to an active state of sickness (15). Therefore, a significant proportion of persons may need medical intervention to avoid a personal instance of active TBI. The IGRA QuantiFERON-TB Plus (QFT-Plus) includes recently developed antigens tailored to activate CD4+ and CD8+ T cells. QFT-Plus can detect recent infections and assess disease activity by measuring the intensity of the immune response. Compared to QFT-GIT, QFT-Plus emerges as a more accurate test for identifying TBI (16). The LIOFeron TB/TBI test, a novel IGRA test, potentially demonstrates greater sensitivity than the QFT-Plus assay. Due to their ability to assess a broader spectrum of immunological responses, IGRAs are less susceptible to the impact of immunosuppression. The choice of a diagnostic test for TBI is influenced by the clinical context, test availability, local TBI prevalence (whether high or low), and the fraction of the population vaccinated with BCG. Enhancing the deployment of TPT is a major challenge in streamlining and making screening procedures more accessible. The current challenges include the lack of a widely accessible and easily obtainable test that demonstrates both high sensitivity and specificity for diagnosing TBI, particularly in circumstances with limited resources. The dearth of a highly precise diagnostic instrument for definitively excluding TBI constitutes a substantial impediment in identifying the appropriate patient and determining the optimal time for initiating TPT. The World Health Organization (WHO) has proposed a set of algorithms that

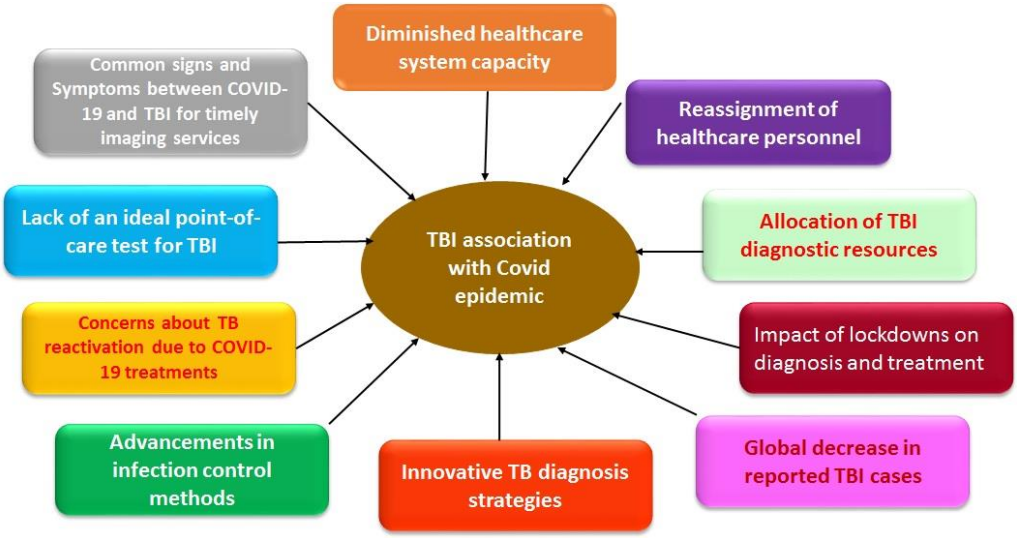

Figure 1: TBI association with Covid Pandemic

link different combinations of symptoms, such as chest X-rays, and quick nucleic acid amplification tests to exclude the potential of TBI (17). The paucity of these tests, particularly chest X-rays, in conjunction with the logistical challenges inherent in the regular implementation of TST (e.g., the necessity of storing tuberculin, the requirement of two visits, the potential for false positives in individuals vaccinated with BCG, and the possibility of negative results in immunocompromised individuals) and IGRA (which involves expenses and the need for laboratory facilities), poses a significant hurdle for treatment programs, particularly in resource-constrained environments. The "Xpert Mycobacterium tuberculosis/resistance to rifampicin assay" is a rapid nucleic acid amplification (NAA) method that has been developed for the specific purpose of identifying the presence of mycobacterium bacilli and assessing their susceptibility to the antibiotic rifampicin. (18). The assay's sensitivity is noteworthy, yet it is costly and necessitates considerable resources, including human capital and extended periods of time. This is of particular significance in pediatric settings, where the procurement of sputum samples can pose significant challenges. Imaging is paramount in the diagnosis of pulmonary TBI. The process entails the integration of two separate categories of information: structural data collected from CT scans, which identify lesions based on x-ray density, and functional data gained from PET scans utilizing 18fluorodeoxyglucose (18F-FDG), which highlight metabolic activity in inflammatory cells of mammals (19). In the rabbit model, the intensity of 18F-FDG peaks five weeks after infection, stabilizing or decreasing in the subsequent month as the disease progresses to a chronic state. The administration of isoniazid or rifampicin during chemotherapy has been shown to reduce the absorption of 18F-FDG, thereby diminishing the density and volume of CT lesions over time. Patients with active TBI exhibit elevated levels of Interleukin 18, directly correlating with the severity of the illness observed in radiographic imaging. Tuberculosis and Interleukin 18 have been shown to promote T-cell activation and generate interferon in chronic inflammatory conditions (20). The WHO has advocated for the implementation of advanced diagnostic techniques, including the use of liquid culture, drug susceptibility testing (DST), line probe assays (LPAs), and Xpert MTB/RIF, which facilitates the expeditious identification of multidrug-resistant tuberculosis (MDR-TBI). A range of non-commercial techniques have been developed for culture and drug susceptibility testing (DST), including microscopic observation drug susceptibility (MODS), thin-layer agar (TLA), colorimetric redox indicator (CRI), and the nitrate reductase assay (NRA). These techniques are distinguished by their rapidity and cost-effectiveness (21). The employment of cytospin slides and triton processing methods in the modified Ziehl-Neelsen (ZN) staining technique has been shown to enhance its diagnostic efficacy and sensitivity for TBI meningitis, surpassing the conventional ZN staining technique. Fluorescence microscopy (FM) with auramine O staining has been demonstrated to provide a 10% greater level of sensitivity compared to ZN, while maintaining a comparable degree of specificity. This enables expeditious and precise diagnosis (22). The integration of light-emitting diodes (LEDs) has further advanced the FM technique, rendering it more sophisticated and economical. To enhance the test's sensitivity, the use of substances such as bleach, sodium hydroxide, or a solution of N-acetyl L-cysteine and sodium hydroxide facilitates the process of converting sputum into a liquid form, thereby reducing the time required for collecting bacilli by centrifugation. It is imperative for technicians to analyze a minimum of two or three slides for

each patient on consecutive days. The establishment of a conclusive "smear-positive" diagnosis necessitates the demonstration of acid-fast bacilli (AFB) in both sets of evidence. The confirmation of an infection requires more than two days. An innovative and efficient approach for TBI diagnosis with high capacity involves the use of a TBDx automated microscopic system, developed by Signature Mapping Medical Sciences in Herndon, VA, USA (23). This automated smear microscopy system is capable of detecting and diagnosing TBI from sputum smears, thereby reducing the time required for diagnosis and enhancing its accuracy. The Tuberculin Skin Test (TST) and the Interferon-Gamma Release Assay (IGRA) are both diagnostic tests used to detect tuberculosis infection and are extensively used in diagnosing latent tuberculosis infection (LTBI) and active tuberculosis. The TST involves the intradermal injection of a minute quantity of TBI-purified protein derivative (PPD) of the bacilli into the dermis of the lower arm. The recipient of the TST is then required to return within 48 to 72 hours for a medical examination to ascertain the presence of any immunological reactions. A positive reaction is defined as an allergic reaction to a specific skin area that shows a measurable response to the antigen (24). The tuberculin skin test (TST) may provide erroneous positive outcomes in persons who have received the bacillus Calmette guérin (BCG) vaccine for TBI and false negative findings in patients with weakened immune systems. IGRA comprises the QuantiFERON-TBI Gold In-Tube test (QFT-GIT), which was created by Cellestis in Australia, and received FDA approval as indirect and adjunctive diagnostics for detecting TBI infection. The QFT-GIT test involves culturing a fresh blood sample that contains viable white blood cells with control samples and a unique mix of synthetic chemicals is analyzed using enzyme-linked immunosorbent assay (ELISA) to determine the quantity of IFN-α (25). Another diagnostic test, the T-Spot test (TST), involves placing peripheral blood mononuclear cells (PBMCs) in a controlled environment with two peptide combinations representing ESAT-6 and CFP-10 and allowing them to incubate. This test measures the number of cells that produce IFN-γ (spots) in response to certain antigens. TST findings indicate the existence of TBI infection, without providing information on the present infection status of the person. Supplementary diagnostic techniques such as IGRAs or chest radiographs are used to verify the presence of an active TBI infection. This is required because there is a higher probability of obtaining incorrect positive or negative results from the TST. Nucleic acid amplification tests (NAAT) for TBI provide prompt and precise molecular diagnosis and the capability to anticipate medication resistance (26). Semi-automated NAAT often utilizes polymerase chain reaction (PCR) to amplify and identify mycobacterial rRNA or DNA directly from different clinical samples, including blood, sputum, bone marrow, and tissue. The tuberculin skin test (TST) has been observed to yield false positive results in individuals who have received the bacillus Calmette-Guérin (BCG) vaccine for tuberculosis (TB) and false negative results in patients with compromised immune systems. The IGRA comprises the QuantiFERON-TB Gold In-Tube test (QFT-GIT), which was developed by Cellestis in Australia and received FDA approval as indirect and adjunctive diagnostics for detecting TBI infection. The QFT-GIT test involves culturing a fresh blood sample that contains viable white blood cells with control samples and a unique mix of synthetic chemicals. The sample is then analyzed using enzyme-linked immunosorbent assay (ELISA) to determine the quantity of IFN-α (25). Another diagnostic test, the T-Spot test (TST), involves placing peripheral blood mononuclear cells (PBMCs) in a controlled environment with two peptide combinations representing ESAT-6 and CFP-10 and allowing them to incubate. The T-Spot test quantifies the number of cells that produce IFN-γ (spots) in response to specific antigens. The TST's primary function is to indicate the presence of TBI infection; however, it does not provide information on the infection status of the individual. To verify the presence of an active TBI infection, supplementary diagnostic techniques, including IGRAs and chest radiographs, are employed. This is imperative because the TST has a higher probability of yielding inaccurate positive or negative results. Nucleic acid amplification tests (NAAT) for TBI provide a rapid and precise molecular diagnosis, as well as the capability to anticipate medication resistance (26). Semi-automated NAAT frequently employs polymerase chain reaction (PCR) to amplify and identify mycobacterial ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) directly from various clinical samples, including blood, sputum, bone marrow, and tissue. The implementation of these techniques has been limited due to the significant financial demands associated with operating in resource-intensive environments. The Xpert MTB/RIF assay is a sophisticated instrument that functions as a fully automated and integrated NAAT instrument (27). It encompasses sample preparation, amplification, and DNA detection processes. This assay has been shown to effectively overcome many of the constraints associated with current commercial NAAT techniques, including concerns around cross-contamination, time consumption, and laboratory challenges. The Xpert MTB/RIF test, when performed in a controlled environment, has the capacity to rapidly amplify and confirm the presence of M.tb infection. Furthermore, it can detect mutations that cause resistance to rifampicin within two hours. The GeneXpert Omni, developed by Cepheid, is still in the developmental phase. This device aims to perform point-of-care testing for tuberculosis and MDR-TBI using Xpert MTBI/RIF cartridges. The identification of volatile organic compounds (VOCs) in exhaled breath holds promise for expeditious detection of active pulmonary TBI at the point-of-care (POC) testing setting, where numerous significant breath biomarkers for TBI have been identified among VOCs. These biomarkers include oxidative stress products, such as alkanes and

alkane derivatives, and volatile metabolites of the TBI bacilli, such as cyclohexane and benzene derivatives (28).

3.4. TBI Biomarkers

At present, RNA sequencing is utilized to evaluate whole blood biomarkers, with the objective of accurately predicting the probability of acquiring active TBI in individuals exposed to the disease. Recent research has successfully identified genetic signatures indicative of the likelihood of developing tuberculosis within 6 to 12 months. A triad of genes has been demonstrated to be effective in distinguishing between active and latent TBI, with a correct classification rate of 91.5% for individuals. This represents a significant enhancement over earlier genetic signatures, which attained accuracies ranging from 80 to 85%. However, it should be noted that there are currently no available diagnostic tests capable of reliably detecting TBI or discerning between preclinical or early clinical illness and TBI. Furthermore, it is unable to identify TBI caused by drug-resistant strains of M.tb (29). However, analysis of TB pathways can reveal biomarkers associated with TBI in the blood of individuals with pulmonary TBI induced by interferon (IFN) and driven by neutrophils. This genetic profile involves type 2 (IFNγ) and type I (IFNαβ) IFN signaling. Unstimulated samples from children and adults with active TBI have shown significantly increased interferon (IFN)γ inducible protein 10 (IP10) in their plasma. This rise has been assessed using several approaches. The presence of immunological activation markers (CD38, HLA-DR) and the proliferation marker Ki-67 on Mtb-specific CD4+ T-cells demonstrated a direct relationship with the amount of Mtb present. In addition, multiparametric flow technology investigated polyfunctional T-cells as prospective biomarkers. The frequency of polyfunctional CD4+ T-cells in mice has been demonstrated to be significantly associated with the level of protection against Mtb infection that is induced by vaccination. Automated liquid culture equipment, such as the mycobacterial growth indicator tube, is widely used to diagnose TBI. These standardised approaches have emerged as promising frameworks for biomarker exploration, as they consistently yield information about the time required for growth detection. This timeframe has been observed to be significantly and inversely associated with the size of the initial sample, as evidenced by assessments with laboratory stock cultures (30). Furthermore, PCR-based techniques offer a precise means of quantifying viable mycobacteria. A notable instrument in this field is the GeneXpert MTB/RIF test, an automated molecular diagnostic instrument that is highly sensitive and efficient, specifically designed to diagnose pulmonary TBI. This technique employs real-time PCR amplification using molecular probes to identify MTBI DNA specifically. Lipoarabinomannan, a significant component of the mycobacterial cell wall, can be detected in a patient's urine using a commercially available enzyme-linked immunosorbent assay (ELISA). The sensitivity of the test is most effective for identifying TBI in individuals with advanced HIV infection. Notably, the levels of lipoarabinomannan decrease progressively after 1-2 months of concurrent TBI and HIV therapy, indicating the presence of urine lipoarabinomannan at the commencement of treatment. Exploration of lipoarabinomannan as a potential biomarker warrants further investigation, especially considering the potential of novel assays with improved sensitivity to broaden its applicability (31).

3.5. Prophylactic Therapy

Isoniazid has historically been the primary medication prescribed for tuberculosis preventive therapy. The isoniazid regimen, which typically spans a duration of 6 to 9 months, encounters challenges related to its limited acceptability and completion rates. This is primarily ascribed to the extended duration of therapy, inadequate compliance, and acceptability (32). Research indicates that rifampicin, or rifapentin, is a long-acting rifamycin in shorter treatment regimens and is equally effective compared to isoniazid-based regimens. These abbreviated regimens have been shown to exhibit higher treatment completion rates and enhanced safety. A study has shown that administering rifampicin on a daily basis over a period of four months has been demonstrated to be comparable in terms of efficacy to a nine-month course of isoniazid in preventing the onset prevalence of active TBI in adults and children (33). Both approaches have been shown to exhibit superior completion rates and reduced incidence of severe adverse effects. In select cases, preventive therapy might be recommended for household contacts with a high risk of contracting MDR-TBI, which should be identified as a personalised risk. The process of prophylactic therapy for TB involves a systematic approach to evaluating and treating individuals at risk of TB infection. Positive results from such evaluations prompt further examination to rule out active TB and assess risk factors. If prophylaxis is deemed appropriate, a suitable medication regimen is selected, such as isoniazid (INH) monotherapy or combination therapy, taking into account treatment duration and patient-specific factors. Education of the patient, monitoring for adverse effects, and regular follow-ups are crucial throughout treatment. Post-therapy assessments and reinforcement of preventive measures follow the completion of therapy. In the event of the emergence of TB disease symptoms, a comprehensive evaluation and treatment referrals are imperative. This systematic approach ensures proper evaluation, treatment initiation, monitoring, and completion, aiming to mitigate TB infection risks and prevent disease progression in high-risk individuals (Figure 2).

3.6. Combination Therapies

Clinical trials have provided substantial evidence indicating that the most effective strategy for tuberculosis treatment involves a prolonged course of a combination of medications. Achieving the desired outcome requires administering multiple drugs over an extended period. The current protocol for treating drug-sensitive tuberculosis spans six months, comprising two phases of drug therapy.

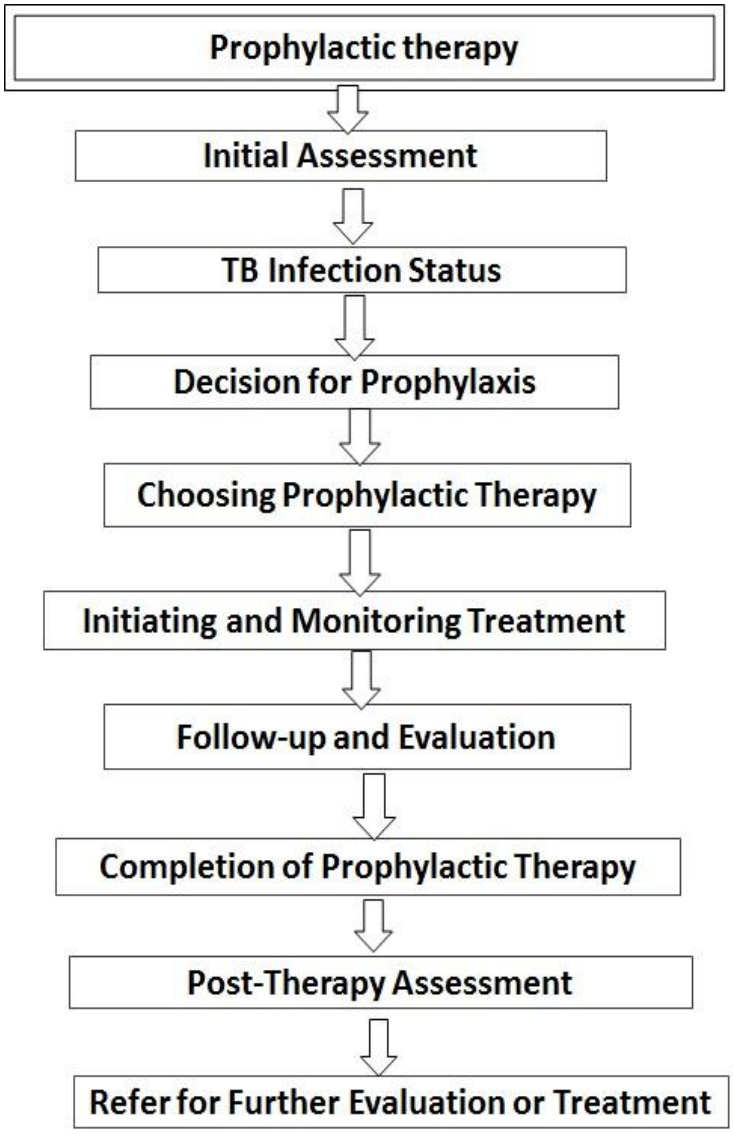

Figure 2. Prophylactic therapy

The initial treatment consists of a first phase of months with four medicines (isoniazid, rifampicin, pyrazinamide, and ethambutol), followed by a second phase of months with two medicines (isoniazid and rifampicin). This approach has been used for over four decades and established an estimated efficacy rate of 85% (34). However, the prevalence of tuberculosis cases resistant to existing medications, encompassing drug-resistant and multidrug-resistant cases, remains significant, exceeding 500,000 annually. Traditionally, treating drug-resistant tuberculosis involves administering more than four medications for up to 24 months due to the limited bactericidal capacity of the drugs, posing potential drug adverse reactions. The lack of treatment approach consistency has resulted in a suboptimal success rate of less than 50% in curing patients (35). Introducing innovative clinical trial designs and positive outcomes opens avenues for advancing more effective tuberculosis treatments. The pathogenesis of pulmonary TBI involves a synchronized immunological response, including several cell populations that undergo alterations over the course and treatment of the illness. Substantial evidence from clinical trials indicates that the most effective strategy for tuberculosis treatment involves a prolonged course of a combination of medications. Achieving the desired outcome necessitates the administration of multiple drugs over an extended period. The current protocol for treating drug-sensitive tuberculosis spans six months, comprising two phases of drug therapy. The initial phase of treatment consists of four medicines (isoniazid, rifampicin, pyrazinamide, and ethambutol) for a duration of months, followed by a second phase of two medicines (isoniazid and rifampicin) for a duration of months. This approach has been utilized for over four decades and has been found to demonstrate an estimated efficacy rate of 85% (34). However, the prevalence of tuberculosis cases resistant to existing medications, encompassing drug-resistant and multidrug-resistant cases, remains significant, exceeding 500,000 annually. The standard treatment for drug-resistant tuberculosis involves the administration of a minimum of four medications for a period of up to 24 months. This prolonged treatment duration is necessitated by the limited bactericidal efficacy of the medications, which can lead to adverse drug reactions. The absence of a uniform treatment approach has culminated in an unsatisfactory success rate, with cure rates falling short of 50% (35). The introduction of innovative clinical trial designs and positive outcomes has the potential to pave the way for the development of more effective tuberculosis treatments. The pathogenesis of pulmonary TB involves a synchronized immunological response, including several cell populations that undergo alterations over the course and treatment of the illness. The intricate and ever-changing characteristics of the infections necessitate that Mtb must withstand various stresses and possess physiological adaptability to cope with changing conditions. Elevated concentrations of extracellular Mtb are associated with necrotic and cavitating lesions, presenting significant challenges for treatment in both humans (36) and animal cases. Research in humans indicates that different lesions exhibit diverse responses to pharmacological therapy, potentially influenced by the amount of medication reaching Mtb. The response of Mtb to medications varies based on the lesion's location, mainly due to varied drug concentrations at specific sites. These findings influence the rationale for prolonged treatment duration and the enhanced effectiveness of therapy involving multiple medications and/or higher dosages. The intricate and ever-changing characteristics of the infections necessitate that Mtb must withstand various stresses and possess physiological adaptability to cope with changing conditions. Elevated concentrations of extracellular Mtb have been observed to be associated with necrotic and

cavitating lesions, which pose significant challenges for treatment in both human and animal cases. Research in human subjects indicates that different lesions exhibit diverse responses to pharmacological therapy, potentially influenced by the amount of medication reaching Mtb. The response of Mtb to medications varies based on the location of the lesion, primarily due to the varying drug concentrations at specific sites. These findings have significant implications for the rationale behind prolonged treatment duration and the enhanced effectiveness of therapy involving multiple medications and/or higher dosages. Certain antibiotics specifically target replicating cells, potentially limiting their efficacy against infections caused by non-replicating Mtb bacteria. However, additional medications in the treatment plan demonstrate the ability to eliminate actively proliferating and non-replicating Mtb. This attribute may contribute to the reduced length of therapy reported when integrating these medicines into the existing standard care regimen (37). Bedaquiline and pretomanid have shown good treatment effects in vitro against replicating and non-replicating Mtb. Tackling medication resistance is a formidable obstacle in managing several other ailments, such as bacterial infections and cancer. Prolonged exposure to medicine increases the probability of microbes acquiring resistance. Given the protracted duration of tuberculosis therapy lasting several months, the risk of resistance development is increased (38). Drug resistance may emerge when cells acquire specific factors that allow them to survive drug doses that would otherwise inhibit or kill cells lacking these factors. These traits have a genetic foundation, rendering the medicine ineffective at therapeutically beneficial quantities if resistance develops, enabling the resistant group to survive. It is evident that certain antibiotics have the capacity to target replicating cells, which may result in a limitation of their efficacy against infections caused by non-replicating Mtb bacteria. However, the addition of other medications to the treatment plan demonstrates the ability to eliminate both actively proliferating and non-replicating Mtb bacteria. This attribute may contribute to the reduced length of therapy reported when integrating these medicines into the existing standard care regimen (37). In vitro studies have demonstrated the in vitro efficacy of bedaquiline and pretomanid against both replicating and non-replicating Mtb. The ability to combat medication resistance, a formidable obstacle in the management of numerous ailments, including bacterial infections and cancer, is of significant importance. It has been demonstrated that prolonged exposure to a given pharmaceutical agent can increase the probability of microbes acquiring resistance. Given the protracted duration of tuberculosis therapy, which can last several months, the risk of resistance development is increased (38). The emergence of drug resistance can be attributed to the acquisition of specific factors by cells that enable their survival, thus allowing them to withstand drug doses that would otherwise be lethal to cells lacking these factors. These traits are genetically determined, thereby rendering the medicine ineffective at therapeutically beneficial quantities should resistance develop, thus enabling the resistant group to survive. A strategic approach involves employing a combination of medications that target distinct cellular mechanisms, proving effective in impeding resistance development in both experimental and clinical contexts. Multidrug therapies for tuberculosis have demonstrated improved efficacy compared to single-drug therapy, resulting in a decreased incidence of relapse with drug-resistant Mtb. Therefore, multidrug treatments comprising more than three medications are considered productive. This anticipation rests on the assumption that there would be fewer than one naturally occurring Mtb cell resistant to triple-drug therapy in severely infected patients, with infection severity measured by the bacillary load in cases of illness. The formulation of the selection of the three-drug combination consisting of pretomanid, moxifloxacin, and pyrazinamide was based on the encouraging outcomes obtained in preclinical models (39) and later assessed in a clinical study. The favorable clinical effectiveness of this three-drug combination led to the commencement of the current SimpliciTB clinical trial. The objective of this clinical trial is to assess the impact of adding bedaquiline to the treatment protocol that includes pretomanid, moxifloxacin, and pyrazinamide for both drug-susceptible (DS) and drug-resistant (DR) tuberculosis. By adding and substituting medications, researchers have adapted these therapeutic frameworks, leading to the identification of treatment regimens that have either been demonstrated to enhance treatment outcomes. A strategic approach involves the employment of a combination of medications that target distinct cellular mechanisms, thus proving effective in impeding resistance development in both experimental and clinical contexts. Multidrug therapies for tuberculosis have been shown to exhibit enhanced efficacy in comparison to single-drug therapy, resulting in a reduced incidence of relapse with drug-resistant Mtb. Consequently, multidrug treatments comprising more than three medications are regarded as effective. This assertion is predicated on the premise that the occurrence of Mtb cells demonstrating resistance to triple-drug therapy in severely infected patients would be infrequent, with infection severity gauged by the bacillary load in cases of illness. The selection of the three-drug combination consisting of pretomanid, moxifloxacin, and pyrazinamide was based on encouraging outcomes obtained in preclinical models (39) and was later assessed in a clinical study. The favourable clinical effectiveness of this three-drug combination led to the commencement of the current SimpliciTB clinical trial. The objective of this clinical trial is to assess the impact of adding bedaquiline to the treatment protocol that includes pretomanid, moxifloxacin, and pyrazinamide for both drug-susceptible (DS) and drug-resistant (DR) tuberculosis. Through the adaptation of these therapeutic frameworks, researchers have identified treatment regimens that have been demonstrated to enhance treatment outcomes.

3.7. Artificial Intelligence in TBI Therapy

Developing and implementing innovative and sustainable strategies is crucial for overcoming healthcare resource constraints linked to tuberculosis screening. Utilizing computer-aided detection and machine learning is a promising approach to address resource and diagnostic obstacles. The WHO has recently revised its recommendations for TBI screening. The amended guidelines now recommend using computer-aided detection tools to analyze digital chest radiography pictures in patients 15 years old and above. These software applications provide a numerical score that indicates the probability of tuberculosis infection (40). The "Stop TB" partnership and the "Foundation for Innovative New Diagnostics" (FIND) have created an online resource center for computer-aided detection methods in the diagnosis of TBI as a means of supporting this campaign. With advancements in technology and appropriate clinician training, artificial intelligence (AI) holds the potential to address lingering clinical challenges constrained by limited resources or technological barriers. The cost-effective nature of chest radiography provides a highly accurate means of screening patients. Furthermore, it is an easily accessible tool for detecting pulmonary tuberculosis, especially in cases where bacterial confirmation is challenging while utilizing minimal radiation. Common radiographic indicators of TBI include the presence of cavities, nodules, consolidation, pleural effusion, and enlarged mediastinal lymph nodes (41). Enlarged mediastinal lymph nodes are the prevalent manifestation. Most research investigating the recognition of certain radiographic findings by imaging modalities has shown a lack of agreement among observers. The diagnostic accuracy of mediastinal lymphadenopathy was poor, likely due to overlapping structures, even when lateral views were utilized. The development and implementation of innovative and sustainable strategies are imperative for surmounting healthcare resource constraints associated with tuberculosis screening. The utilization of computer-aided detection and machine learning emerges as a promising approach to address the existing challenges related to resources and diagnostics. The WHO has recently revised its recommendations for TBI screening. The updated guidelines now advocate for the incorporation of computer-aided detection tools to facilitate the analysis of digital chest radiography images in patients aged 15 years and above. These software applications provide a numerical score that indicates the probability of tuberculosis infection (40). The "Stop TB" partnership and the "Foundation for Innovative New Diagnostics" (FIND) have established an online resource center for computer-aided detection methods in the diagnosis of TBI, aiming to support this initiative. With technological advancements and the proper training of medical professionals, artificial intelligence (AI) has the potential to address persistent clinical challenges that are limited by resources or technological barriers. Chest radiography, a cost-effective diagnostic modality, offers a highly accurate means of screening patients. Furthermore, it is an easily accessible tool for detecting pulmonary tuberculosis, especially in cases where bacterial confirmation is challenging while utilizing minimal radiation. Common radiographic indicators of TBI include the presence of cavities, nodules, consolidation, pleural effusion, and enlarged mediastinal lymph nodes (41). Of these manifestations, enlarged mediastinal lymph nodes are the most prevalent. Research examining the recognition of specific radiographic findings by imaging modalities has revealed a lack of consensus among observers. The diagnostic accuracy of mediastinal lymphadenopathy was found to be poor, likely due to overlapping anatomical structures, even when lateral views were utilized. This issue persisted despite attempts to improve the accuracy (42). AI and computer-aided detection tools are vital in advancing and automating the analysis of digital chest radiography for TBI screening. AI involves the application of programming, training, and testing methods to empower computers with the ability to think and learn. Machine learning, a branch of AI, employs statistical methods to enhance the capabilities of robots and allow them to improve their performance. Deep learning, a specialized branch of machine learning, becomes particularly useful when dealing with vast amounts of data that require processing of input data. Deep learning networks employ artificial neural networks, which consist of multiple layers, to analyze data comprehensively. These networks, sometimes featuring multiple layers, possess the capability to autonomously learn from extensive datasets, enabling them to provide precise predictions for unfamiliar incoming data. Integrating machine learning and deep learning algorithms aims to enhance the efficiency of radiology operations, automating tasks such as lesion identification and providing valuable support to radiologists. While AI-driven computer-aided detection algorithms demonstrate enhanced efficacy, further clinical investigations are essential to address potential biases and validate results in real-world scenarios beyond controlled research environments. A groundbreaking research conducted by Mouton, pitcher, and Douglas pioneered the examination of AI for identifying anomalies in chest radiographs of pediatric patients within a population with an increased susceptibility to TBI cases. The development and implementation of innovative and sustainable strategies is of crucial importance in order to overcome the healthcare resource constraints linked to tuberculosis screening. The utilization of computer-aided detection and machine learning emerges as a promising approach to address the challenges posed by resource and diagnostic constraints. The WHO has recently revised its recommendations for TBI screening. The updated guidelines now advocate the utilization of computer-aided detection tools to analyze digital chest radiography images in patients aged 15 years and above. These software applications provide a numerical score that indicates the probability of tuberculosis infection (40). The "Stop TB" partnership and the "Foundation for

Innovative New Diagnostics" (FIND) have created an online resource center for computer-aided detection methods in the diagnosis of TBI as a means of supporting this campaign. With technological advancements and appropriate clinician training, artificial intelligence (AI) holds the potential to address lingering clinical challenges constrained by limited resources or technological barriers. The cost-effectiveness of chest radiography provides a highly accurate means of screening patients. Furthermore, it is an easily accessible tool for detecting pulmonary tuberculosis, especially in cases where bacterial confirmation is challenging while utilizing minimal radiation. Common radiographic indicators of TBI include the presence of cavities, nodules, consolidation, pleural effusion, and enlarged mediastinal lymph nodes (41). Of these, the most prevalent manifestation is that of enlarged mediastinal lymph nodes. Research into the recognition of specific radiographic findings by imaging modalities has shown a lack of agreement among observers. The diagnostic accuracy of mediastinal lymphadenopathy was found to be poor, likely due to overlapping anatomical structures, even when lateral views were utilized. The application of AI in TBI imaging, particularly in pediatric cases, faces various challenges commonly encountered in the context of other diseases. These challenges encompass the scarcity associated with AI models, which includes the use of varied training data, the absence of external validation, the possibility of biases, reliance on subjective reference standards (such as human interpretation of radiographic diagnosis instead of correlation with microbiological references), and a scarcity of real-world implementation data. To properly train AI models for TBI imaging, gathering a broad training dataset from many medical institutions, including equipment and modalities from different vendors and manufacturers, is critical. The focus on impartial training highlights the need to use initial data devoid of other influences that might conceal information, such as demographics or medical particulars influencing certain diagnoses. In the future, it will be essential to carry out randomized controlled trials across multiple centers, employing AI models and comparing their outcomes with those of trials without AI integration. The implementation of artificial intelligence (AI) in the domain of traumatic brain injury (TBI) imaging, particularly in pediatric cases, is confronted by numerous challenges that are pervasive in the context of other diseases. These challenges encompass the scarcity of AI models, which includes the use of varied training data, the absence of external validation, the possibility of biases, reliance on subjective reference standards (such as human interpretation of radiographic diagnosis instead of correlation with microbiological references), and a scarcity of real-world implementation data. To ensure the proper training of AI models for TBI imaging, it is essential to gather a comprehensive training dataset from multiple medical institutions, encompassing a range of equipment and modalities from various vendors and manufacturers. The emphasis on impartial training underscores the necessity to utilize initial data that is devoid of extraneous influences that might obscure information, such as demographics or medical particulars that influence specific diagnoses. In the future, it will be essential to carry out randomized controlled trials across multiple centers, employing AI models and comparing their outcomes with those of trials without AI integration. This approach is instrumental in gaining a comprehensive understanding of the potential advantages and efficiencies that AI could offer to patients. Advancements in computer-aided design (CAD) have made notable progress, particularly in developing a TBI detection algorithm. This algorithm initially segments lung areas and extracts specific characteristics, such as distinctive shapes, from the images. A classifier then evaluates these extracted features to determine the presence of TBI. Currently, the commercially available program for tuberculosis detection based on computer-aided design is CAD4TB, created by Delft Imaging Systems in Veenendaal, Netherlands (43). The algorithm's area under the curve (AUC) falls between 0.71 and 0.84, suggesting that commercially accessible products may not keep up with the latest breakthroughs in AI. The integration of clinical data into CAD4TB, along with its reconstruction, has resulted in its transformation from a CAD application to a deep learning model. AI deep learning networks, such as AlexNet, which were particularly developed for TBI detection, have become crucial. The AlexNet, a pre-trained deep learning network renowned for its efficacy in the ImageNet Large Scale Visual Recognition Competition, was first developed to categorize non-medical photos. The pretraining of AlexNet for picture recognition has been fully finished, necessitating modifications for medical imaging rather than starting the model training process again. Both the trained and untrained versions of GoogLeNet and AlexNet, which are highly acclaimed deep learning networks, have shown remarkable achievements in the ImageNet challenge, and a combination of both models, together with a radiologist, was used to address contradicting cases, leading to the most accurate approach (44). This approach is instrumental in gaining a comprehensive understanding of the potential advantages and efficiencies that artificial intelligence (AI) could offer to patients. Significant advancements have been made in the field of computer-aided design (CAD), particularly in the development of a TBI detection algorithm. This algorithm initially segments lung areas and extracts specific characteristics, such as distinctive shapes, from the images. Subsequent to this segmentation, a classifier is employed to assess the extracted features, thereby determining the presence of TBI. Currently, the commercially available program for tuberculosis detection based on computer-aided design is CAD4TB, created by Delft Imaging Systems in Veenendaal, Netherlands (43). The algorithm's area under the curve (AUC) ranges from 0.71 to 0.84, indicating that commercially available products may not fully align with the most recent

advancements in artificial intelligence (AI). The integration of clinical data into CAD4TB, along with its reconstruction, has resulted in its transformation from a CAD application to a deep learning model. AI deep learning networks, such as AlexNet, which were initially developed for TBI detection, have become instrumental. AlexNet, a pre-trained deep learning network that gained prominence for its effectiveness in the ImageNet Large Scale Visual Recognition Competition, was initially developed for the categorization of non-medical images. The completion of AlexNet's pretraining for picture recognition has rendered modifications for medical imaging obsolete, obviating the need to restart the model training process. The efficacy of both the trained and untrained versions of GoogLeNet and AlexNet, two of the most highly regarded deep learning networks, has been demonstrated in the ImageNet challenge. The combination of both models with a radiologist was used to address contradicting cases, leading to the most accurate approach (44). The method achieved a sensitivity of 97.3%, a specificity of 100%, and an AUC (area under the curve) of 0.99. Researchers are actively investigating AI for supplementary information analysis that surpasses human comprehension in several applications. The progress in tuberculosis detection models results in higher accuracy and effectiveness. The previously stated deep learning models, namely AlexNet and GoogLeNet, undergo pretraining on many pictures and can differentiate between several categories of images even before their application in radiology. Therefore, they need significant computer memory and hardware prerequisites to operate efficiently. Artificial Intelligence (AI) revolutionizes healthcare, aiding in early detection and treatment of diseases. In tuberculosis, AI contributes to diagnosing both active and latent infections through advanced imaging analysis. Chronic cough, weight loss, night sweats, and fatigue are common symptoms. AI's role lies in predictive analytics, helping healthcare professionals identify patterns and assess risks promptly. By leveraging technology, we enhance our ability to address tuberculosis and other health challenges, ultimately improving patient outcomes and streamlining healthcare processes (Figures 3 and Figure 4). The method demonstrated a sensitivity of 97.3%, a specificity of 100%, and an AUC (area under the curve) of 0.99. Researchers are currently investigating the use of AI for supplementary information analysis, with a view to achieving a level of comprehension that surpasses that of humans in a number of applications. The advancement in tuberculosis detection models has resulted in enhanced accuracy and effectiveness. The previously stated deep learning models, namely AlexNet and GoogLeNet, undergo pretraining on a multitude of pictures and are able to differentiate between several categories of images even before their application in radiology. However, it should be noted that these models require substantial computer memory and hardware prerequisites to operate efficiently. The advent of Artificial Intelligence (AI) has been instrumental in revolutionising the healthcare sector, aiding in the early detection and treatment of diseases. In the context of tuberculosis, AI plays a pivotal role in the diagnosis of both active and latent infections through advanced imaging analysis. Common symptoms associated with the condition include chronic cough, weight loss, night sweats and fatigue. The role of AI in this context lies in predictive analytics, aiding healthcare professionals in the timely identification of patterns and the assessment of risks. By leveraging technology, we enhance our ability to address tuberculosis and other health challenges, ultimately improving patient outcomes and streamlining healthcare processes (Figures 3 and 4).

3.8. Challenges

While TPT has demonstrated progress in specific countries and high-risk populations, it has yet to attain the targeted levels essential for fulfilling the objectives outlined in the end-TB plan. Regions with a high prevalence of TBI and limited resources tend to prioritize TBI treatment over prevention. A key obstacle to initiating isoniazid preventative treatment (45) is the concern about potential medication shortages, particularly in remote hospitals. The need for qualified healthcare professionals or inadequate training in prescribing TPT and encouraging patients with no symptoms to undergo screening or treatment for TBI might diminish confidence in healthcare practitioners. Regular assessment for TBI might lead to stigmatization among persons who do not exhibit any symptoms. The current diagnostic assays for TBI have intrinsic limitations and are not widely available in areas with limited resources. These obstacles hinder the broad control of TBI and might even lead to drug resistance if the administration of TPT needs to be done accurately. While immunotherapy enhances the immune system to fight cancer (46), it can pose challenges for individuals with latent tuberculosis, potentially reactivating the infection due to immune activation. Balancing these treatments requires careful monitoring and possibly adjusting immunotherapy regimens to prevent tuberculosis reactivation. Sputum analysis aids tuberculosis (TB) diagnosis through microscopy, culture, and molecular tests (47). While TPT has demonstrated progress in specific countries and high-risk populations, it has yet to attain the targeted levels essential for fulfilling the objectives outlined in the end-TB plan. Regions with a high prevalence of TBI and limited resources tend to prioritize TBI treatment over prevention. A significant impediment to the initiation of isoniazid preventive treatment (45) is the apprehension of potential medication shortages, particularly in remote healthcare facilities. The necessity for adequately trained healthcare professionals to administer TPT, as well as the encouragement of patients without symptoms to undergo screening or treatment for TBI, is a matter of concern, as it can potentially erode public confidence in healthcare practitioners. The regular assessment for TBI might lead to stigmatization among persons who do not exhibit any symptoms. The current diagnostic assays for TBI have inherent limitations and are not widely available in areas

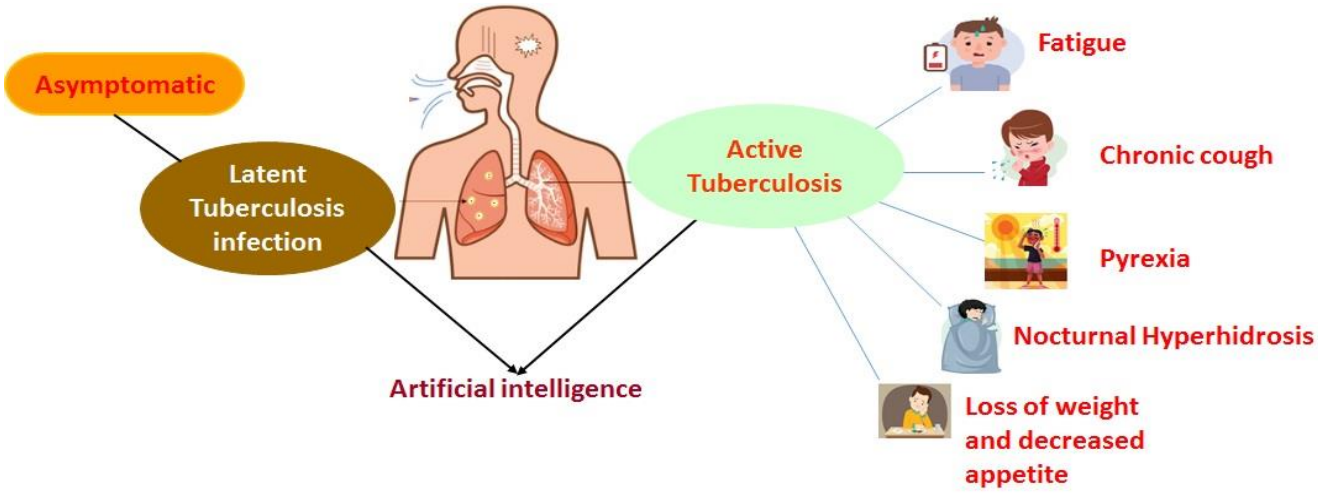

Figure 3. Tuberculosis symptoms of active and latent TB.

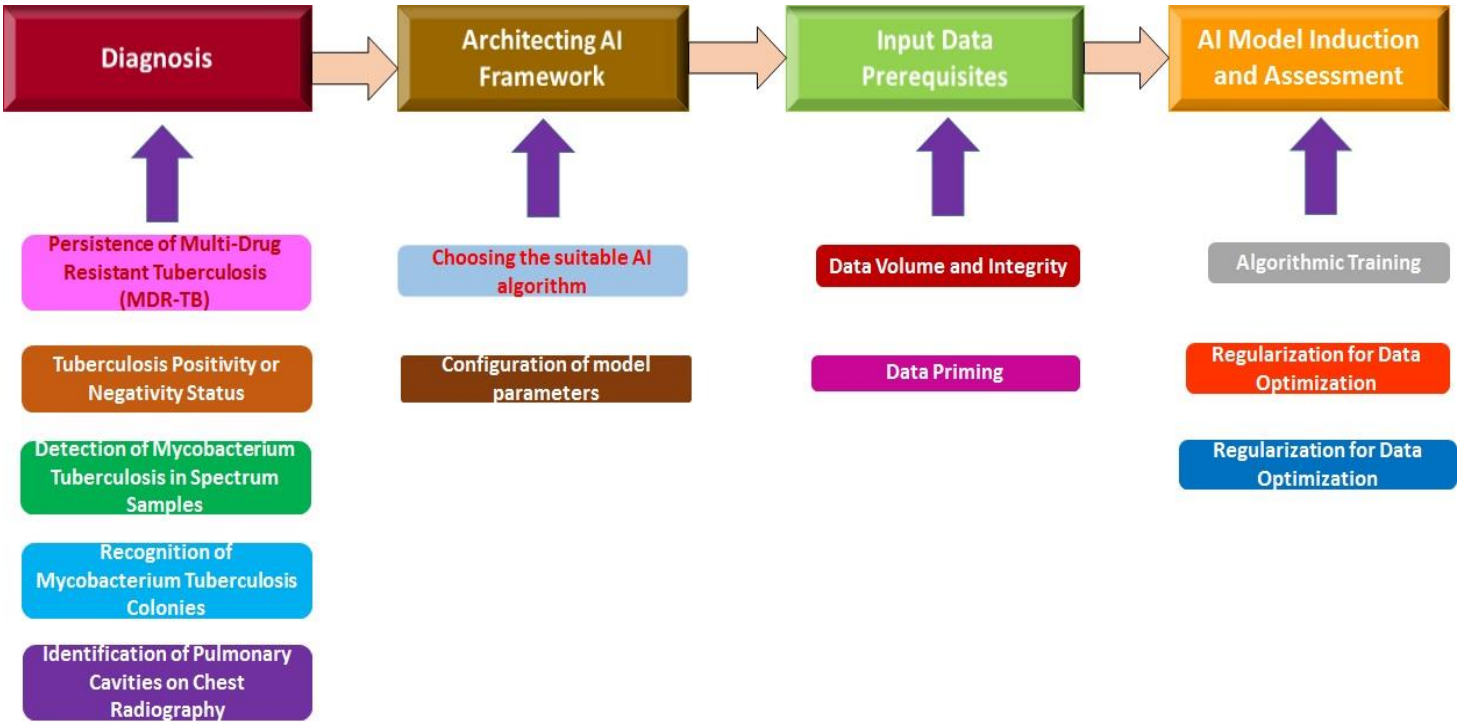

Figure 4. AI construction model for TB diagnosis

with limited resources. These challenges impede the comprehensive management of TBI and have the potential to induce drug resistance if the precise administration of TPT is required. While immunotherapy has been demonstrated to enhance the immune system's capacity to combat cancer (46), it has the potential to present challenges for individuals with latent tuberculosis, given the possibility of reactivation due to immune activation. Adequate monitoring and possible adjustments to immunotherapy regimens are essential to ensure the effective management of these treatments and avert potential tuberculosis reactivation. Sputum analysis is a

crucial component of TB diagnosis, facilitated by microscopy, culture, and molecular tests (47). AI faces challenges in TB detection due to sample variability, low bacterial load, and diverse strains. Interpreting complex sputum images accurately remains a hurdle, necessitating AI algorithms' robustness to detect TB features amidst contaminants. Integration with rapid, cost-effective testing methods is crucial to enhance AI's role in early TB diagnosis, treatment monitoring, and curbing. Extra-pulmonary TB's diverse manifestations beyond the lungs complicate diagnosis, leading to delayed treatment. Challenges for AI lie in analyzing atypical data sources, diverse clinical presentations, and limited datasets to accurately detect and manage extra-pulmonary TB (48). Treatment challenges also include drug resistance, lengthy treatment regimens, and the need to modulate the immune response effectively (49). The relevance of serological detection of animal viruses to tuberculosis lies in the broader context of infectious disease surveillance and control in animal populations (50). While these viruses primarily affect livestock, the principles and techniques used in serological detection can inform similar approaches for tuberculosis surveillance in animals, which are known reservoirs for Mycobacterium tuberculosis. Understanding the prevalence and spread of these viral infections can provide insights into managing tuberculosis ultimately benefiting both animal and human health. The utilization of artificial intelligence in the detection of tuberculosis (TB) is hindered by several factors. These include variability in samples, low bacterial load, and the presence of diverse strains. The interpretation of complex sputum images remains a significant challenge, necessitating the development of AI algorithms that are capable of detecting TB features amidst contaminants. Integration with rapid, cost-effective testing methods is imperative to enhance the role of AI in early TB diagnosis, treatment monitoring, and curbing. The diverse manifestations of extra-pulmonary TB, which are beyond the lungs, complicate the diagnosis process, leading to delayed treatment. The challenges associated with AI include the analysis of atypical data sources, diverse clinical presentations, and limited datasets, which hinders the accurate detection and management of extra-pulmonary TB (48). Treatment challenges also include drug resistance, lengthy treatment regimens, and the need to modulate the immune response effectively (49). The relevance of serological detection of animal viruses to tuberculosis lies in the broader context of infectious disease surveillance and control in animal populations (50). While these viruses primarily affect livestock, the principles and techniques used in serological detection can inform similar approaches for tuberculosis surveillance in animals, which are known reservoirs for Mycobacterium tuberculosis. A comprehensive understanding of the prevalence and dissemination of these viral infections can offer valuable insights into the management of tuberculosis, ultimately enhancing both animal and human health.

3.9. Future Scope

Enhanced POC diagnostic methods that accurately differentiate between inactive and active TBI while determining the probability of developing active TBI would undeniably constitute significant progress in global TBI prevention endeavors. IGRA testing is more effective than the TST in confirming and controlling TBI. Nevertheless, the present utilization of recent technology is restricted, and more investigation is crucial to improve the distinction between active and inactive TBI while uncovering prognostic indicators for the advancement of the illness. There is an ongoing need to further the progress of creating a TPT that is shorter or ultra-short in duration (<1 month) while being safe and well-tolerated. This therapy should be implemented without any potential medication interactions. Simultaneously, optimizing the utilization of existing technologies and strategically allocating resources to individuals at the highest risk of developing or reactivating active tuberculosis will significantly reduce the global tuberculosis burden. The development of advanced point-of-care (POC) diagnostic methods capable of accurately differentiating between inactive and active traumatic brain injury (TBI) while assessing the probability of developing active TBI would undoubtedly represent a substantial advancement in global TBI prevention efforts. IGRA testing has been demonstrated to be more effective than the TST in confirming and controlling TBI. However, the present utilization of recent technology is restricted, and further investigation is crucial to improve the distinction between active and inactive TBI while uncovering prognostic indicators for the advancement of the illness. There is an ongoing need to further the progress of creating a TPT that is shorter or ultra-short in duration (<1 month) while being safe and well-tolerated. The implementation of this therapy should be devoid of any potential medication interactions. Concurrently, the optimization of existing technologies and the strategic allocation of resources to individuals at the highest risk of developing or reactivating active tuberculosis will contribute to a substantial reduction in the global tuberculosis burden.

4. Conclusion

Each year, technological progress facilitates the development of more efficient diagnostic techniques for identifying active tuberculosis in patients. Failure to identify drug-resistant TBI may result in inefficient treatment and the possible dissemination of drug-resistant strains throughout the wider population. Consequently, the foremost requirement for tuberculosis diagnosis involves bacteriological confirmation of the disease and the identification of medication resistance. Many diagnostic methods for tuberculosis, which rely on antibody detection or assessment of immune system reactivity, prove unsuccessful in individuals with compromised immune systems. Given the prevalent physical and clinical conditions in regions affected by the TBI pandemic, there is an urgent demand for a highly effective diagnostic

approach. From a clinical perspective, it is crucial to pinpoint both the existence of TBI and any potential genetic alterations that could impede successful therapy to shorten the duration of therapy. Treatments need to eliminate the entire population of Mtb through sterilization rapidly. The diverse nature of TBI lesions and bacterial populations results in distinct subgroups of Mtb, each requiring specific antibiotic penetration. Annually, technological progress facilitates the development of more efficient diagnostic techniques for identifying active tuberculosis in patients. The failure to identify drug-resistant tuberculosis (TB) may result in inefficient treatment and the possible dissemination of drug-resistant strains throughout the wider population. Consequently, the foremost requirement for tuberculosis diagnosis involves bacteriological confirmation of the disease and the identification of medication resistance. Many diagnostic methods for tuberculosis, which rely on antibody detection or assessment of immune system reactivity, prove unsuccessful in individuals with compromised immune systems. In light of the pervasive physical and clinical conditions prevalent in regions grappling with the TBI pandemic, there is an urgent need for a highly effective diagnostic approach. From a clinical perspective, it is imperative to ascertain the presence of TBI and any underlying genetic alterations that could compromise the efficacy of therapy, thereby reducing its duration. The objective of treatment is the eradication of the entire population of Mtb through sterilization, which must be achieved expeditiously. The heterogeneity of TBI lesions and bacterial populations gives rise to distinct subgroups of Mtb, each requiring a tailored antibiotic regimen for effective penetration.

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Authors' Contribution
VIR and PY designed the project and wrote the manuscript text. AARM prepared figures. SSP supervised the project. All authors reviewed the manuscript. The design of the project and the composition of the manuscript text were the responsibility of VIR and PY. AARM was responsible for the preparation of the figures. SSP provided supervision for the project. All authors reviewed the manuscript.

Ethics
Not applicable.

Conflict of Interest
The authors declare that they have no conflict of interest.

Data Availability
The data that support the findings of this study are available on request from the corresponding author.

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