Review

Risk Factors for Tuberculosis Treatment Failure: A Literature Review

Karolina Kėvelaitienė *, Valerija Edita Davidavičienė, Edvardas Danila

Posted Date: 3 December 2024

doi: 10.20944/preprints202412.0263.v1

Keywords: tuberculosis management; tuberculosis risk factors; tuberculosis treatment outcome

 doi:10.20944/preprints202412.0263.v1

Review

Risk Factors for Tuberculosis Treatment Failure: A Literature Review

Karolina Kėvelaitienė [1,2,*], Valerija Edita Davidavičienė [3] and Edvardas Danila [1,2]

[1] Institute of Clinical Medicine, Clinic of Chest Diseases, Immunology and Allergology, Vilnius University Faculty of Medicine, LT-03101 Vilnius, Lithuania; edvardas.danila@santa.lt

[2] Centre of Pulmonology and Allergology, Vilnius University Hospital Santaros Klinikos, LT-08661 Vilnius, Lithuania

[3] Programs and Tuberculosis State Information System Department, Vilnius University Hospital Santaros Klinikos, LT-08661 Vilnius, Lithuania; edita.davidaviciene@santa.lt

* Correspondence: karolina.kevelaitiene@santa.lt

Abstract: Tuberculosis (TB), induced by Mycobacterium tuberculosis, continues to be a significant global health concern. It affects approximately 25% of the global population and ranks among the primary causes of mortality from infectious diseases. Notwithstanding progress, TB treatment and diagnosis continue to encounter substantial obstacles, such as restricted access to precise diagnostics and efficacious therapies. By 2035, international objectives seek to diminish tuberculosis-related fatalities by 95% and enhance treatment accessibility. Multiple factors affect the success of TB treatment, including personal behaviors, social and demographic circumstances, and concurrent health conditions. Critical risk factors for suboptimal treatment outcomes encompass low body mass index, tobacco use, substance abuse, and various demographic variables including gender, age, unemployment, geographic location, and migration status. Co-infections with HIV, diabetes, chronic kidney disease, COVID-19, and rheumatic diseases are associated with increased rates of treatment failure. Supplementary challenges, including loss to follow-up, drug-resistant TB, and household contacts, elevate the probability of treatment failure. This review's findings intend to furnish essential insights for policymakers, healthcare professionals, and TB control programs, thereby enhancing strategies and interventions. The primary objective is to improve the efficacy of TB management globally, with an emphasis on attaining superior treatment outcomes, particularly in the most underserved regions.

Keywords: tuberculosis management; tuberculosis risk factors; tuberculosis treatment outcome

1. Introduction

Tuberculosis (TB) remains a significant public health challenge globally, particularly in developing countries where healthcare resources are often limited [1,2]. It is caused by the bacterium *Mycobacterium tuberculosis* (MTB), primarily affecting the lungs but can also impact other body parts. A bacterium that can survive harsh environments mainly due to the presence of an unusually thick, lipid-rich cell envelope [3,4], infects approximately ¼ of the world's population [5].

The World Health Organization (WHO) highlights that TB is one of the leading causes of death from infectious diseases, second only to COVID-19 in recent years [5,6]. Globally, TB has likely resumed its position as the foremost cause of death from a singular infectious agent, after three years, it was supplanted by coronavirus disease (COVID-19) [7]. Despite significant advancements in research and control efforts, the global fight against TB still faces critical challenges. Current diagnostic, therapeutic, and preventive measures are often inadequate, and without a substantial increase in research and development, we are unlikely to meet our ambitious goals for 2035. Specifically, we aim to reduce TB-related deaths by 95%, decrease the incidence rate by 90%, and ensure that 90% of patients receive effective first-line treatment [8]. Strengthening health systems is vital for enhancing the early detection of TB and improving the overall quality of care, diagnosis, and treatment [9].

 doi:10.20944/preprints202412.0263.v1

TB treatment coverage is a crucial indicator in the End TB Strategy, reflecting significant progress from 51% in 2013 to 70% in 2017. However, this increase is tempered by a concerning decline in the treatment success rate, which fell from 86% in 2013 to 82% in 2016. Particularly alarming are the success rates for multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), which remain alarmingly low at 55% and 34%, respectively, as of 2015. These figures highlight the ongoing challenges in effectively treating more resistant strains of TB and underscore the need for intensified efforts in research, improved treatment protocols, and better access to care [10].

This situation may be linked to the limited evaluation of treatment outcomes in resource-limited, constrained countries and various factors that can impact TB treatment efficacy. Comprehensive assessments of TB treatment outcomes are essential for enhancing programmatic management.

We believe that the findings of this review will offer valuable insights for policymakers, healthcare providers, and TB control programs, enabling them to refine strategies and interventions. Ultimately, this research aims to contribute to improving the effectiveness of TB management globally, with a focus on ensuring better treatment outcomes in regions where they are needed most.

2. Malnutrition

Low body mass index (BMI) is a well-established risk factor for the development of TB [11]. At the same time, growing evidence suggests that a high BMI may serve as a protective factor against TB. Epidemiological studies have previously shown that obesity is linked to a reduced risk of developing active TB, with an inverse dose-response relationship [12–15]. Adipose tissue plays a role in inflammation and immunity by producing a range of pro-inflammatory and anti-inflammatory factors, which may influence an individual's susceptibility to infections, including TB [16]. For instance, one study found that a BMI above 28 kg/m² was independently associated with reduced susceptibility to TB in rural China [17]. However, while some research suggests an inverse logarithmic relationship between TB incidence and BMI, this relationship becomes less clear at BMIs above 30 kg/m² [13]. Overall, the impact of overweight and obesity—particularly a BMI greater than 30 kg/m²—on TB development remains unclear. While these conditions might offer some protection against TB, they could also represent a target for TB control strategies. Therefore, several other studies have also found similar results, indicating that being underweight or having a low BMI is a significant risk factor for developing active TB [18,19].

Cai et al. conducted an observational study involving 199 patients and explored the causal relationship between waist circumference and TB through a two-sample Mendelian randomization (MR) analysis. Their findings suggest that increased waist circumference may be a significant risk factor for developing TB, highlighting the importance of considering abdominal obesity in TB risk assessments [20].

In another observational study involving 264 patients, Oyewusi et al. [21] found that a low BMI at the start of treatment for rifampicin- or multidrug-resistant tuberculosis (MDR/RR-TB) is associated with poorer treatment outcomes. Specifically, patients with low BMI demonstrated a moderate correlation with a lower frequency of treatment success. This suggests that nutritional status plays a critical role in the efficacy of TB treatment. Importantly, the study also indicated that improving BMI could potentially accelerate culture conversion and enhance end-of-treatment outcomes. These findings highlight the necessity of integrating nutritional support into treatment plans for TB patients, particularly those with MDR/RR-TB, to optimize their recovery and overall health [21].

Summarizing important findings from Yerezhepov et al.'s [22] observational study on the association of various risk factors with pulmonary TB. The study highlights that underweight status, diabetes, and unemployment are significantly correlated with the incidence of TB, supported by strong statistical evidence ($p < 0.001$). The emphasis on the underweight population (22.3%) underscores the public health concern, as low body weight can compromise immune function, making individuals more susceptible to infections like TB [22].

These findings confirm the results of other studies in different countries [23,24]. For instance, a population-based study in China, involving 27,807 individuals, investigated risk factors for incident

 doi:10.20944/preprints202412.0263.v1

TB. Over a 7-year follow-up period, 108 individuals developed TB. The analysis found that a BMI less than 24 kg/m² had a significantly higher risk of TB (adjusted hazard ratio 2.68; P = 0.006) [23]. Similarly, J.R. Koethe's review of the literature on protein-calorie malnutrition (PCM) and low body mass index (BMI) as risk factors for TB. PCM is a well-established risk factor for the development of TB disease, although evidence linking malnutrition to the risk of acquiring tuberculous infection is limited. Malnutrition is associated with increased mortality and relapse rates in active TB patients. Clinical trials of macronutrient supplementation during TB treatment have shown modest benefits, including a 2-3 kg weight gain after 2 months and potential improvements in physical function, sputum conversion, and treatment completion [24].

Malnutrition or a low BMI plays a significant role in TB outcomes. As previously highlighted in earlier studies, the analysis revealed that individuals with a BMI lower than 24 kg/m² faced a notably higher risk of developing TB, with an adjusted hazard ratio of 2.68 (P = 0.006) [23]. This aligns with findings from other countries, reinforcing the idea that socio-economic and health-related factors contribute significantly to the burden of TB globally [25].

3. Tobacco Smoking

The relationship between cigarette smoking and TB has been a topic of ongoing debate since at least 1918 [26]. A 2010 editorial [27] highlighted that numerous epidemiological studies and meta-analyses have identified both active and passive smoking as independent risk factors for TB infection, with relative risks estimated at approximately 1.5 to 2. Smoking is also associated with an increased risk of reactivation of TB infection (relative risk of 2 to 3), progression of primary TB, exacerbation of cavitary disease, and higher mortality rates from TB (relative risk of 1.5 to 3).

While a few studies report negative findings regarding smoking and certain TB outcomes, these are largely attributed to various confounding factors [28,29]. Given the substantial evidence linking smoking to TB, it is recommended that TB control programs incorporate tobacco control as a preventative strategy [30].

The narrative review, authored by Charles Feldman and colleagues, synthesizes relevant publications in English, accessed via PubMed and Google up until July 2023. The review begins by addressing the epidemiological evidence linking smoking to an increased risk of TB development. Subsequent sections explore the mechanisms by which alveolar macrophages attempt to eliminate intracellular *Mycobacterium tuberculosis* along with the countermeasures employed by the pathogen to evade host defenses. The review also examines the harmful effects of smoking on macrophage-mediated antimycobacterial responses and highlights how smoke directly impacts *M. tuberculosis*, promoting the pathogen's persistence within the airways [114].

Kaliner et al. [31] performed a retrospective cohort analysis analyzing 50 TB patients who smoked in comparison to a matched random sample of 100 TB patients who did not smoke, spanning the years 2007 to 2017. Among the smokers, 68,8 % (n = 20) experienced treatment failure. The findings revealed that smokers had longer hospital stays and extended treatment durations. They also had higher rates of multidrug-resistant strains, increased treatment failure rates, and elevated mortality. Overall, TB patients who were smokers were significantly more likely to experience treatment failure [31].

In another observational study involving 252 patients, Amoori et al. [32] collected data from thirty-six health centers in Ahvaz, southwest Iran, from January to October 2021. Their findings indicated that cigarette smoking was identified as a significant factor affecting TB, with an impact rate of 42.5% based on the evaluation criteria used in the study [32].

In a prospective observational study conducted by Vyawahare et al. [33], 189 patients diagnosed with pulmonary TB were assessed over two years at tertiary care centers. Data were collected to investigate risk factors associated with the development of drug-resistant TB through multivariate analysis. Among the participants, 36 were diagnosed with drug-resistant TB, while 153 had drug-sensitive strains. The study found that patients with drug-resistant TB were 7.77 times more likely to be tobacco users compared to those with drug-sensitive TB [33].

 doi:10.20944/preprints202412.0263.v1

Tobacco smoking has a significant impact on TB treatment outcomes. In Kaliner et al.'s study, nearly 70% of patients were smokers [31]. This finding aligns with numerous other studies conducted in diverse settings, all of which have consistently shown a clear association between smoking and poorer TB outcomes [34–36].

4. Alcohol Use

Heavy alcohol consumption is a well-known risk factor for both the development of TB and negative treatment outcomes [37]. In 2022, approximately 700,000 new TB infections were linked to alcohol use disorders. Research indicates that alcohol use increases the risk of developing TB by 35% compared to non-drinkers (relative risk: 1.35; 95% confidence interval: 1.09–1.68). Furthermore, reducing alcohol consumption could potentially prevent up to 17% of new TB cases and 15% of TB-related deaths [38]. Moreover, high alcohol consumption—characterized by a volume or pattern that leads to negative health effects—has been linked to delayed culture conversion and increased relapse rates in patients undergoing treatment for TB [39,40]. The causal pathways behind these poorer outcomes remain unclear. However, low exposure to TB medications, potentially due to pharmacokinetic changes, may contribute to suboptimal treatment responses, suggesting an opportunity for therapeutic intervention [41–43]. Finally, both alcohol use disorder (AUD) and TB are marked by social marginalization and stigma. Their coexistence further exacerbates the disadvantages faced by individuals, making it more difficult for them to seek and maintain care [44].

The study conducted by Bayigga J et al. [45] performed an explanatory sequential analysis in two large urban districts in Uganda. They assessed the prevalence of AUD using the Cut, Annoyed, Guilty, Eye Opener (CAGE) tool and employed a Poisson regression model with robust variance to identify factors associated with AUD. Of the 325 individuals with TB examined, 62 (18.7%, 95% confidence range [CI] 18% to 31%) were identified as having AUD, with a predominant majority being male (82.3%, or 51 out of 62). This analysis revealed that being male (adjusted prevalence ratio [aPR] 2.32, 95% CI 1.19 to 4.49) and residing in an urban area (adjusted odds ratio [aOR] 1.79, 95% CI 1.10 to 2.92) were significantly associated with AUD. Among those with AUD, there was a trend toward suboptimal TB treatment outcomes, although this did not achieve statistical significance (aPR 1.65, 95% CI 0.95 to 2.85) [45].

Khaitan A. et al. [46] study included TB patients who had completed their treatment and those who had been lost to follow-up (LTFU), as well as staff from the National TB Elimination Program (NTEP), healthcare providers, family members, and community members from the Ballabgarh block in Haryana, India. In-depth interviews (IDIs) and focus group discussions (FGDs) were conducted to explore stakeholders' perceptions of the reasons for LTFU, particularly about alcohol use. Using grounded theory, they performed an inductive analysis of the transcripts to identify key themes and sub-themes. A conceptual framework linking TB and AUD was developed, highlighting potential areas for intervention. In mid-2018, they conducted fifty-eight IDIs and four FGDs. Almost all key informants, along with many patient participants, believed that alcohol use significantly increases the risk of LTFU among TB patients. The main themes identified included shared personality traits and attitudes, the combined side effects of antitubercular medications and alcohol, lack of family support, and adverse financial circumstances [46].

In a global observational study by Jinyi W et al. [47], data on TB deaths and age-standardized death rates attributable to alcohol were collected from the Global Burden of Disease 2019 public database across 204 countries and territories. The study found that the global age-standardized death rate for TB related to alcohol consumption declined from 5.35 (95% uncertainty interval [UI] = 3.51, 7.00) in 1990 to 2.54 (95% UI = 1.65, 3.33) in 2019. Significant declines were observed in Andean Latin America (average annual percent change [AAPC] = −7.59; 95% confidence interval [CI] = −8.00, −7.16, $P < 0.05$), East Asia (AAPC = −7.32; 95% CI = −8.00, −6.62, $P < 0.05$), and Central Latin America (AAPC = −7.31; 95% CI = −7.63, −6.99, $P < 0.05$). However, increases were noted in certain regions, particularly parts of Central Asia. The age-period-cohort model indicated that TB attributable to alcohol consumption was most prevalent in older adults aged 60-80 years. Machine learning projections

 doi:10.20944/preprints202412.0263.v1

suggested that by 2035, the age-standardized mortality rate for TB linked to alcohol intake would be 1.29 per 100,000 individuals [47].

Alcohol use significantly affects TB treatment outcomes. Kaliner et al. [31] conducted a retrospective cohort study between 2007 and 2017, comparing 50 TB patients with alcohol use to a matched sample of 100 non-alcoholic TB patients. The study found that alcohol use was a significant predictor of TB treatment failure, with an odds ratio of 4.0 (95% CI: 1.06–15.2, P = 0.04) in multivariate analysis. Kaplan–Meier survival analysis further revealed that TB patients who consumed alcohol had shorter survival times compared to those who abstained from alcohol (P = 0.03). Additionally, the average age at death was significantly younger for alcohol users (42.9 years vs. 77.3 years, P < 0.01) [31].

These findings suggest that alcohol use increases the risk of poor TB treatment outcomes, with alcohol users being four times more likely to experience treatment failure than non-users [31].

5. Drugs Abuse

To achieve the global strategy for eliminating TB, the WHO has identified specific high-risk populations due to biological or behavioral factors. These include individuals who engage in substance use [6].

Drug use is rising globally and has become a significant public health concern. Among individuals aged 15 to 64, the prevalence increased from 4.8% in 2009 to 5.3% in 2018 (United Nations Office on Drugs and Crime [UNODC], 2021). In 2021, over 296 million people reported using at least one drug, reflecting a 23% increase since 2011. According to projections from the UNODC (2020), the number of drug users is expected to rise by 40% by 2030.

In addition to addiction, injecting drugs can facilitate the transmission of infectious diseases, including TB. In Canada, active TB cases are primarily seen among migrants from endemic countries and Indigenous populations. However, since 2003, Greater Montréal has reported instances of active TB among substance users and homeless individuals, with 35 cases documented over 10 years. Notably, 86% of these cases involved non-indigenous individuals born in Canada. Among them, 28 individuals had multiple risk factors, with 93% reporting substance use [48].

The study conducted by Mbayang Ndiaye aimed to identify factors associated with TB among injecting drug users at the addiction treatment center in Dakar. This cross-sectional, descriptive, and analytical research took place at the Addictology Unit of Fann Hospital from January 1, 2015, to September 30, 2022. A total of 300 patients participated, and heroin emerged as the predominant injectable drug used (99.7%), followed closely by tobacco (96.7%). The prevalence of TB among this population was found to be 24.7% [49].

In another observational study, Zhang L et al. [50] aimed to assess the prevalence and correlates of latent tuberculosis infection (LTBI) in Malaysia's largest prison, Kajang Prison. From October 2019 to January 2023, involving 601 patients. Independent risk factors for LTBI included opioid use disorder (OUD) (adjusted odds ratio [AOR] = 1.95; 95% CI [1.25-3.05]). Interestingly, pre-incarceration cannabis use was negatively associated with LTBI (AOR = 0.69; 95% CI [0.39-0.96]). The high prevalence of LTBI in Malaysia's largest prison underscores the urgent need for routine screening and the implementation of TB preventive therapy in high-risk settings such as prisons [50].

Sandra Eugênia Coutinho and colleagues in Brazil conducted a retrospective cohort study involving outpatients aged over 18 who were smokers and starting TB treatment at two outpatient TB clinics. The study included 111 patients, with a smoking cessation rate of 26.8% (19 out of 71) at the end of the 6-month TB treatment period. However, 40 patients could not be evaluated at the end of treatment due to loss to follow-up (36 patients) or death (4 patients), resulting in a high loss to follow-up rate of 40.5%. Patients identified drug use (n = 15, 19.2%) as a major barrier to smoking cessation during the study [51].

Drug use has a significant impact on TB treatment outcomes. In Coutinho et al.'s study, nearly 20% of smoking patients also reported using drugs [51]. Given the poorer treatment outcomes observed in TB patients who use substances, collaborative efforts are essential to address these

 doi:10.20944/preprints202412.0263.v1

challenges in the effort to eliminate TB. Establishing joint initiatives focused on TB and drug use is recommended to enhance treatment success [52].

6. Sex Factor

Globally, adult males exhibit significantly higher rates of TB compared to females. In many countries, TB notification rates for HIV-negative men are approximately 1.6 to 2.7 times greater than those for HIV-negative women [53]. Epidemiological data consistently reveal sex-based differences in TB, including variations in infection prevalence, progression rates, clinical incidence, and morbidity and mortality, all of which tend to place men at greater risk [54]. The underlying reasons for this gender bias remain unclear. Key contributing factors may include socio-economic and behavioral influences, underreporting of female cases, and disparities in access to healthcare. Additionally, there may be genetic differences that affect susceptibility to TB infection [53].

In one of the largest population-based studies conducted in Germany, self-reported lifetime prevalence estimates for TB revealed minimal differences between men and women. However, this finding, along with potential biases in data collection and cohort selection, may reflect the generally shorter survival rates observed in men diagnosed with TB [55]. As a result, there is a need for well-designed, systematic studies to investigate the factors contributing to sex-based differences in TB case fatality rates across Europe [56–58].

Stephanie Pape conducted an extensive search of electronic databases and gray literature up to December 2020 to identify studies reporting sex-stratified TB mortality data in Europe. Using random-effects meta-analysis, she estimated pooled relative risks associated with sex-related TB fatalities. Out of a total of 17,400 screened records, 117 studies met the criteria for quantitative analysis. Among these, 75 studies provided absolute participant data, demonstrating moderate quality but limited sex stratification, and reported between 33 and 235,000 TB cases and 7 to 27,108 deaths. The analysis revealed a pooled male-to-female TB fatality risk ratio of 1.4 (95% CI [1.3–1.5]). Notably, higher male TB fatality rates were observed in studies with greater levels of homelessness (coefficient 3.18, 95% CI [-0.59 to 6.94], $p = 0.10$) and a lower proportion of migrants (coefficient -0.24, 95% CI [-0.5 to 0.04], $p = 0.09$). These findings suggest that TB case fatality rates for males in Europe are 30–50% higher than those for females [59].

In a study conducted in Afghanistan by Shayan N. et al., a total of 422 TB patients and 514 controls were recruited from Herat Regional Hospital and associated TB laboratories between October 2020 and February 2021. The findings indicated that male sex was significantly associated with an increased likelihood of TB infection ($p = 0.023$) [60].

Similarly, in an observational study in South Africa, Oshiomah P. et al. [61] recruited 1,126 participants with suspected TB from 12 community health clinics, ultimately forming a cohort of 774 individuals. The results revealed that males had three times the odds of active TB compared to females (OR = 3.01 [2.20, 4.12], $p < 0.001$) [61].

In a registry-based retrospective cohort study conducted by Hind M. AlOsaimi and colleagues at King Fahad Medical City in Riyadh, Saudi Arabia, from January 1, 2018, to December 31, 2023. The study used data from the National Tuberculosis Registry of Saudi Arabia to evaluate treatment outcomes for 427 patients with pulmonary tuberculosis (PTB). Treatment outcomes were categorized as success or failure based on clinical evaluation, chest X-ray changes, and sputum examination results during follow-up. The study found that 88.5% of patients had successful treatment outcomes. Additionally, males were more likely to experience treatment failure compared to females, with an adjusted odds ratio (aOR) of 1.3 (95% CI 1.2–1.5, $p < 0.001$) [115].

These studies highlight the significant role of sex in influencing TB treatment outcomes. In particular, males are more likely to experience both TB infection and treatment failure compared to females. In the study by M. AlOsaimi et al.'the findings indicated that males were 1.3 times more likely to have TB treatment failure compared to females (OR = 1.3 [1.2, 1.5], $p < 0.001$) [115]. Given these findings, future research should prioritize the examination of sex- and gender-related factors that affect TB mortality and fatality. This focus will enhance the synthesis of empirical evidence and support informed decision-making for health interventions in this area [62–64].

 doi:10.20944/preprints202412.0263.v1

7. Age Factor

The highest incidence of TB cases is found in individuals aged 25 to 54 years. However, in the WHO regions of the Eastern Mediterranean, South-East Asia, and Western Pacific, the epidemic predominantly affects the elderly population, with notification rates increasing steadily with age. The peak incidence of TB occurs in individuals aged 65 years and older [65].

In the elderly population, several factors contribute to the heightened concern regarding TB. These include age-related immunodeficiency, the potential for compounded immunosuppression from coexisting age-related conditions, and possible interactions between antituberculosis medications and drugs prescribed for other health issues. Systematic screening of high-risk groups for early TB diagnosis has proven effective in advancing global efforts to combat the TB epidemic [66].

A study conducted by Jiang H. et al. in China, which followed participants for seven years, found that 246 individuals developed TB, resulting in an incidence rate of 92.21 cases per 100,000 person-years (95% CI: 81.2–104.3). Increasing age was correlated with a higher risk of active TB, with an adjusted hazard ratio of 1.03 for each additional year (95% CI: 1.01–1.04, $P < 0.001$). These findings underscore the alarmingly high incidence of TB among the elderly population in China [67].

In Iran, Golsha R. et al. [68] analyzed data from the TB registry program in the Gorgan health district between 2013 and 2018. The mortality rate was notably higher in individuals over 65 years old ($p < 0.001$). The study highlights that age is a significant risk factor for active TB and its treatment outcomes [68].

Globally, the incidence of TB among elderly populations varies significantly between countries with high and low burdens of the disease. For individuals aged 65 and older, the reviewed literature reported an average annual incidence rate of 10.9 cases per 100,000 in the United States [69] and 11.2 cases per 100,000 in Germany [70].

These studies collectively highlight the significant role of age in influencing TB outcomes. In particular, increasing correlates with a higher risk of developing active TB and experiencing treatment failure, with an adjusted hazard ratio of 1.03 for each additional year of age (95% CI: 1.01 -- 1.04, $P < 0.001$) [67]. Given these findings, future research should prioritize understanding how age-related factors contribute to TB mortality and fatality to improve treatment strategies and outcomes for the elderly.

8. Sociodemographic Factors

Despite ongoing efforts to improve case identification and treatment adherence, the incidence of TB remains alarmingly high in many low-income countries. The WHO has set a target to reduce this incidence rate by 4% to 5% annually in these regions [71]. The impact of TB on patients' quality of life is intricate and multifaceted, encompassing physical, psychological, and social well-being [72,73]. Physical manifestations, including chronic coughing, fever, and weight loss, may result in considerable deterioration of physical functioning and general health [74]. Moreover, the psychological and social consequences of TB—including stigma, discrimination, and social isolation—further detract from patients' quality of life [75]. Patients often grapple with heightened levels of anxiety and depression stemming from their diagnosis and treatment. These mental health issues may affect their capacity to work, support their families, and sustain social relationships [76,77]. Consequently, the interplay between psychological distress and physical symptoms creates a vicious cycle, exacerbating both health issues and the overall quality of life for individuals affected by TB [72].

In a retrospective study conducted by Sanchez-Perez et al. in Mexico, the researchers analyzed data from the National Epidemiological Surveillance System (SINAVE) to assess TB incidence rates. The study used TB case registration data and estimated annual populations to calculate these rates. It also explored factors influencing the success and failure of anti-TB treatment, focusing on sociodemographic variables, the concentration of indigenous populations in municipalities, and admission data from SINAVE. The analysis included 233 TB cases, with the following distribution of outcomes: 175 (75.1%) were classified as successful cases (cured or completed treatment), 40 (17.1%)

 doi:10.20944/preprints202412.0263.v1

were classified as treatment failures or lost to follow-up, 6 (2.6%) died from TB, 10 (4.3%) died from other causes, and 2 (0.9%) were still undergoing treatment (both registered in 2022). The study found that several factors were associated with lower treatment success rates. Individuals with a higher level of education—specifically, those with at least a secondary education—had a significantly higher success rate (88.3%) compared to those with only primary education or less (24.2%). Additionally, individuals not engaged in agricultural work had a higher treatment success rate (83.6%) compared to those working in agriculture (29.1%). Key sociodemographic factors linked to poorer treatment outcomes included residing in municipalities with high or very high concentrations of indigenous populations, identifying as indigenous, having a lower level of education (primary school or less), and working in agriculture. These findings underscore the need for targeted interventions addressing these disparities to improve TB treatment outcomes [78].

In another observational study, Oshiomah et al. [79] investigated the epidemiological risk factors for TB in the Northern Cape Province of South Africa, an area with an extreme TB incidence rate of 926 per 100,000 people. Capitalizing on the region's high TB prevalence and community transmission dynamics, the researchers designed a case-control study with similar exposure mechanisms across both groups. They recruited 1,126 participants with suspected TB from 12 community health clinics, ultimately forming a cohort of 774 individuals (374 cases and 400 controls) after applying their enrollment criteria. The findings revealed that residing in a town significantly increased the risk of TB, with an odds ratio of 3.20 (95% CI: 2.26–4.55). Additionally, the study examined demographic factors that may reflect historical health trends in South Africa. Notably, being born in a rural area and later moving to a town was associated with a heightened TB risk, while individuals born in towns and currently living in rural areas appeared to have a protective advantage. These interaction effects highlight rapid demographic changes, particularly socioeconomic status and mobility, that have occurred over recent generations in South Africa. The models demonstrated that these risk factors accounted for 19% to 21% of the variance in TB case/control status [79].

In another study, Cotugno Sergio and colleagues conducted a systematic review and meta-analysis to examine TB outcomes among migrants compared to non-migrants in Europe. Six researchers searched PubMed, SCOPUS, and Web of Science up to March 2024 and screened the abstracts of potentially eligible articles. Of the 1,109 papers screened, 34 studies met the inclusion criteria, encompassing a total of 601,293 participants (459,670 non-migrants and 141,623 migrants). The meta-analysis, adjusted for potential confounders, revealed that migrants had a significantly lower risk of mortality (RR=0.391 95% CI: 0.276-0.554, I^2=71.6%), a lower rate of treatment completion (RR=0.313, 95% CI: 0.163-0.600), and a higher rate of loss to follow-up (RR=4.331 95% CI: 1.542-12.163, I^2=55.8%). Migrants in Europe experience lower mortality rates from TB, yet their management of the disease is challenged by a higher risk of loss to follow-up and treatment discontinuation [101].

Yerezhepov et al. conducted a case-control study involving 1,555 participants in Kazakhstan. The study found that specific epidemiological risk factors, such as unemployment ($\chi^2 = 81.1$, $p < 0.001$), were significantly associated with pulmonary tuberculosis (PTB) [80].

This finding aligns with prior research indicating reduced non-compliance with anti-tuberculosis treatment attributable to poverty and exclusionary conditions, including low educational attainment and low-wage employment, such as agricultural labor. These factors, consistent with this study, also encompass the scarcity of health services, geographical distance to these services, financial constraints for accessing health units, negative perceptions fostering distrust in health services, and inter- and intra-community conflicts [80].

These studies collectively highlight the significant role of factors such as urban living, unemployment, and migrant status in influencing TB outcomes. Oshiomah et al. [79] found that residing in a town significantly increased the risk of developing TB, with an odds ratio of 3.20 (95% CI: 2.26–4.55). Migrants, particularly in Europe, are also at higher risk of losing follow-up and discontinuing treatment, with an RR of 4.33 (95% CI: 1.54–12.16, I^2=55.8%), as reported by Cotugno Sergio [101]. In a case-control study conducted by Yerezhepov et al. in Kazakhstan, involving 1,555 participants, specific epidemiological risk factors, such as unemployment, were strongly associated with poor TB outcomes ($\chi^2 = 81.1$, $p < 0.001$) [80].

 doi:10.20944/preprints202412.0263.v1

This finding aligns with previous studies that indicate lower compliance with anti-tuberculosis treatment is often linked to poverty and social exclusion. Factors such as low educational attainment and low-paying jobs, particularly in agriculture. Additionally, challenges such as limited access to health services, the distance to healthcare facilities, financial constraints for transportation, distrust in health services due to negative perceptions, and conflicts within and between communities further exacerbate the issue [81,82].

9. Co- Morbidity

9.1. Human Immunodeficiency Virus

In order to implement the global strategy for eradicating TB, the WHO has pinpointed certain high-risk groups based on biological or behavioral factors. One such group is individuals living with HIV [6].

The study conducted by Adakun et al. explored the feasibility of assessing and referring to adults who successfully completed TB treatment for comorbidities, risk factors, and disabilities at health facilities in Kenya, Uganda, Zambia, and Zimbabwe. Health workers evaluated 1,063 patients, finding that 476 (44%) had HIV co-infection, while 172 (16%) had other comorbidities. Notably, seven out of ten patients who completed TB treatment had at least one comorbidity, risk factor, or disability. This highlights the critical need for early, patient-centered care—including pulmonary rehabilitation—to enhance quality of life, reduce the risk of TB recurrence, and improve long-term survival rates [83].

In a study conducted by Barreto-Duarte, the aim was to investigate factors associated with unfavorable outcomes in anti-tuberculosis treatment (ATT) among patients undergoing retreatment in Brazil. This observational study included patients aged 18 and older who were reported to the Brazilian National Notifiable Disease Information System between 2015 and 2022. Out of 743,823 reported TB cases during the study period, 555,632 were eligible for analysis, comprising 462,061 new cases and 93,571 retreatment cases (44,642 recurrent cases and 48,929 cases following loss to follow-up). Regarding mortality, advanced age and living with HIV were significant risk factors, with HIV presenting an OR of 6.28 (95% CI, 6.03–6.54) [84].

Similarly, Matulyte E et al. [116] conducted a retrospective chart review in Lithuania to analyze the characteristics of TB-HIV co-infected adults registered in the State Information System of Tuberculosis from 2008 to 2020. The study included 345 cases involving 311 patients (239 new cases and 106 previously treated cases). The researchers used multivariable logistic regression to identify factors associated with drug-resistant TB and unsuccessful treatment outcomes. The primary aim of the study was to explore the socio-demographic and clinical characteristics of TB-HIV co-infected patients in Lithuania and their relationship with TB outcomes. The findings revealed that the treatment success rate was notably low among both drug-susceptible and drug-resistant TB cases, at 61.4% and 34.6%, respectively. A significant proportion of cases were drug-resistant, with 38% of new cases and 61% of previously treated cases showing resistance to TB drugs. Overall, the unsuccessful treatment outcome was observed in 38.6% of drug-susceptible TB cases and 65.4% of drug-resistant TB cases, indicating a substantial challenge in managing TB-HIV co-infection in this population [116].

These studies collectively reinforce the critical role of HIV in influencing TB treatment outcomes. As demonstrated in the research by Matulyte et al., the presence of HIV significantly exacerbates the likelihood of unsuccessful treatment outcomes, with higher rates of failure observed in drug-resistance cases (patience of the unsuccessful treatment outcome was observed in 38.6% of drug-susceptible TB cases and 65.4% of drug-resistant TB cases) [116]. This emphasizes the need for tailored approaches to manage TB-HIV co-infection, focusing on early detection, comprehensive care, and addressing drug resistance to improve treatment success.

9.2. Diabetes Mellitus

TB and diabetes mellitus (DM) present a significant dual burden to public health worldwide. In 2021, an estimated 10.6 million individuals were living with TB, while approximately 537 million adults aged 20 to 79 had DM [6,85]. The WHO emphasizes the importance of collaborative efforts to address both TB and DM as essential components of the End TB strategy [86]. A systematic review

 doi:10.20944/preprints202412.0263.v1

found that nearly 15% of TB patients also had diabetes, with a notably higher prevalence of comorbidity in countries with a high TB burden [87,88]. As a major risk factor for TB, diabetes impacts disease control and treatment effectiveness at multiple levels. Numerous studies have highlighted the unfavorable outcomes of TB in patients with diabetes, underscoring the critical need for integrated approaches in managing these interconnected health issues [89,90].

Li et al. conducted a study to examine the prevalence and identify risk factors for diabetes among individuals with TB in economically affluent cities in China. Among the 322 patients diagnosed with TB, 54 individuals (16.8%) were found to have DM, including 43 males (13.4%) and 11 females (3.4%). The average age of patients with DM was 55.44 ± 12.36 years, compared to 46.09 ± 16.87 years for those without DM. Multivariate logistic regression analysis indicated that male gender (adjusted odds ratio [aOR] = 3.29, 95% confidence interval [CI]: 1.05–10.30), age over 47 years (aOR = 1.04, 95% CI: 1.01–1.07), a family history of diabetes (aOR = 5.09, 95% CI: 1.28–20.32), and elevated random blood glucose levels (aOR = 1.6, 95% CI: 1.38–1.86) were significant risk factors for DM in patients with TB. Diabetes is prevalent among patients with TB. The study recommends targeted screening and increased awareness of DM, particularly for men over middle age with a family history of diabetes and elevated random blood glucose levels [91].

In a study by Shi et al., patients with DM and TB who visited the hospital between January 2020 and January 2023 were compared to a control group of simple diabetes patients. A total of 315 participants were included. Univariate analysis revealed that poor glucose control, hypoproteinemia, lymphopenia, a history of TB contact, high infection rates, smoking, and alcohol consumption were positively associated with TB in DM patients. Multivariate stepwise regression analysis identified poor glycemic control (OR = 3.37) as significant risk factors for developing TB in DM patients [92].

On one hand, the high sugar content in tissues, along with metabolic disorders and decreased immune function in patients with DM, can lead to increased production of drug-resistant strains of *M. tuberculosis*, negatively impacting the prognosis for DM and TB patients. On the other hand, tuberculosis can exacerbate glucose metabolism disorders in DM patients, raising the risk of ketoacidosis and leading to more severe health outcomes. As a result, DM and TB present significant challenges in global public health due to their severity, treatment complexities, and poor prognosis [93].

Adam Nowiński and colleagues conducted an analysis of a national cohort of 19,217 adult TB patients diagnosed between 2011 and 2016 in Poland. The study aimed to compare treatment success and mortality rates between patients with comorbidities and those without in order to assess the impact of various comorbidities on TB outcomes. The researchers calculated odds ratios (OR) to quantify the relationship between comorbidities and TB treatment success and mortality. The results revealed that patients with comorbidities had significantly lower treatment success rates and higher mortality rates compared to those without. Specifically, diabetes was identified as a significant risk factor, with an OD 1.9 for increased TB-related mortality. These findings underscore the critical need for managing comorbid conditions, such as diabetes, in TB patients to improve treatment outcomes and reduce mortality risks [117].

Together, these studies highlight the critical role of diabetes in influencing TB treatment outcomes. As demonstrated in Nowiński et al.'s research, the presence of diabetes significantly increases the likelihood of unsuccessful TB treatment outcomes and raises the risk of TB-related mortality (OD 1.9) [117]. This underscores the urgent need for integrated management strategies for TB and diabetes co-infection, focusing on early detection, comprehensive care, and addressing drug resistance to improve treatment success and reduce the dual burden of these diseases.

9.3. Chronic Kidney Disease

Chronic kidney disease (CKD) is a major global health concern, affecting approximately 8–16% of the population worldwide [119]. TB is a major contributor to infectious disease-related illness and death globally. A recent systematic review and meta-analysis revealed that the overall mortality rate in TB patients was almost three times higher than in those without the disease [120]. Previous research

 doi:10.20944/preprints202412.0263.v1

has indicated that individuals with CKD, particularly those undergoing hemodialysis (HD), experience a higher rate of TB compared to the general population [121,122].

Xiao J et al. conducted a retrospective study involving 167 patients diagnosed with active TB at two tertiary medical centers in Chongqing over a six-year period. The study gathered data on the clinical characteristics and treatment outcomes of TB patients with and without CKD, analyzing factors associated with mortality. Among the 167 patients, 66.7% (44/66) of those on hemodialysis (HD), 41.1% (21/51) of pre-dialysis (pre-HD) patients, and 32.0% (16/50) of non-CKD patients had extrapulmonary TB, with the pleura and lymph nodes being the most common affected sites in CKD patients. Mortality rates were higher in CKD patients, with non-CKD, pre-HD, and HD patients having mortality rates of 6.1%, 31.9%, and 37.3%, respectively. Multivariate Cox analysis identified age ≥40 years (HR: 5.871; p=0.019), hypoalbuminemia (HR: 2.879; p=0.004), CKD stage 4–5 (HR: 4.719; p=0.018), and HD treatment (HR: 6.13; p=0.005) as significant factors associated with increased mortality. Patients with CKD and TB have a higher mortality rate. Factors such as CKD stages 4–5, and HD were identified as independent predictors of increased mortality [123].

In a similar study conducted by Pradhan R et al. in Nepal, the prevalence, clinical features, and outcomes of TB in patients with CKD. The study was a hospital-based cross-sectional analysis performed at Tribhuvan University Teaching Hospital (TUTH), a tertiary care center in Kathmandu. Patients aged 16 and older with CKD stages 3, 4, 5, and 5D (on maintenance dialysis) were included. A total of 401 CKD patients were included. The prevalence of TB in CKD patients was found to be 13.7% (55 patients), with 49 new cases of TB. After two months of anti-tubercular treatment, 29 out of the 49 newly diagnosed patients (59.2%) showed improvement. However, mortality at two months was 28.6% (14 deaths among the 49 patients). Four patients (8.2%) showed no improvement, and two (4%) were lost to follow-up. The study concluded that the prevalence and mortality of TB were higher among CKD patients [124].

Taken together, these studies underscore the critical impact of CKD on TB treatment outcomes. As demonstrated in Xiao et al.'s research, factors such as CKD stage 4–5(HR: 4.719; p=0.018), and HD treatment (HR: 6.13; p=0.005) [123] were significantly associated with higher mortality rates in TB patients. These findings highlight the urgent need for integrated management strategies that address both CKD and TB co-infection, with an emphasis on early detection. Such approaches are essential to improve treatment success and mitigate the dual burden of these diseases.

9.4. COVID – 19

Globally, TB has likely regained its status as the leading cause of death from a single infectious agent, following a three-year period during which COVID-19 temporarily took the top spot [7]. Since the onset of the pandemic, cases of co-infection with TB and COVID-19 have been reported. These infections can occur simultaneously, with COVID-19 preceding TB, or in patients with TB-related sequelae. Both diseases predominantly affect the lungs and share common symptoms, such as fever and cough, which can complicate diagnosis and lead to delays in treatment [125]. Research has shown that co-infection with TB and COVID-19 is associated with higher mortality rates and an increased risk of long-term lung complications [126,127].

Migliori G et al. conducted a comprehensive study across 174 centers in 31 countries, collecting data on patients affected by both COVID-19 and TB between March 1, 2020, and September 30, 2022. Patients were followed until they either recovered, died, or the cohort period ended. All participants had concurrent TB and COVID-19, and deaths were classified based on whether they were attributed to TB, COVID-19, or both. Survival analysis was performed using Cox proportional hazards regression models, with the log-rank test applied to compare survival and mortality outcomes attributed to either TB, COVID-19, or both diseases. The study included 788 patients with active or sequelae TB and COVID-19 from 31 countries. During the observation period, 10.8% (85 patients) died. Survival rates were significantly lower for those whose deaths were attributed to both TB and COVID-19, compared to those who died from either TB or COVID-19 alone ($p<0.001$). The study concluded that over 10% of patients with both TB and COVID-19 died during the observation period [128].

 doi:10.20944/preprints202412.0263.v1

Similarly, Nalunjogi J et al. conducted a study aimed at comparing the number of new or recurrent TB diagnoses, the incidence of drug-resistant TB (DR-TB), and TB-related deaths in 2020 versus 2019 across 11 countries in Europe, North America, and Australia. TB managers or directors from national reference centers in these countries provided data on key variables through a validated monthly questionnaire. A descriptive analysis was performed to compare the incidence of TB, DR-TB, and mortality between the pre-COVID-19 year (2019) and the first year of the COVID-19 pandemic (2020). The results revealed a decrease in the number of TB cases (both new diagnoses and recurrences) reported in 2020 compared to 2019, with the exception of Virginia (USA) and Australia. Fewer notifications of DR-TB were also observed in most countries, except in France, Portugal, and Spain. TB-related deaths were higher in 2020 than in 2019 in most countries, though three countries—France, the Netherlands, and Virginia (USA)—reported minimal changes in TB mortality. The study concluded that a comprehensive evaluation of the medium-term impact of COVID-19 on TB services would benefit from similar research conducted in various settings. Additionally, the global availability of treatment outcome data from patients co-infected with TB and COVID-19 would provide valuable insights [129].

Taken together, these studies highlight the significant impact of COVID-19 on TB treatment outcomes. As shown in Migliori et al.'s research, survival rates were considerably lower for patients whose deaths were attributed to both TB and COVID-19, compared to those who died from either TB or COVID-19 alone ($p<0.001$) [128]. These findings underscore the urgent need for integrated management strategies that address both TB and COVID-19 co-infection, with a focus on early detection and timely treatment. Such approaches are essential to improve patient outcomes and reduce the dual burden of these diseases.

9.5. Inflammatory Rheumatic Diseases

As survival rates among patients with rheumatic diseases continue to improve, the significance of comorbidities, particularly infections, has become more pronounced—especially with the introduction of biologic therapies into treatment regimens. These patients are widely recognized as being more susceptible to a variety of infections, primarily due to the immunosuppressive effects of both the disease itself and the treatments used to manage it [130–132]. TB infection has long been a major concern in patients with rheumatic diseases (RD), due to the heightened risk associated with both the disease itself and the immunosuppressive treatments commonly used in its management [133–136].

The aim of Miltinienė D et al. [137] study was to assess the incidence of TB in a cohort of patients with inflammatory RD and compare it to the general population. The study included patients with a first-time diagnosis of RD between January 1, 2012, and December 31, 2017, identified from the Lithuanian Compulsory Health Insurance Information System. TB cases were verified using national health databases and the Tuberculosis Register at Vilnius University Hospital. A total of 8,779 patients with newly diagnosed RD were included, with 458 using biologic disease-modifying antirheumatic drugs (bDMARDs). The cohort was predominantly female (70%) and consisted mostly of rheumatoid arthritis (RA) patients (53%), with a mean age of 56 years. Over a follow-up period averaging 2.71 years, 9 TB cases were identified among 23,800 person-years of follow-up, with two cases occurring in patients treated with bDMARDs. The calculated annual TB incidence in the RD cohort was 37.81 per 100,000 person-years, which aligned with national estimates, resulting in a sex- and age-standardized incidence ratio (SIR) of 0.90. The study also found an unadjusted hazard ratio of 4.54 for TB risk in bDMARD users versus non-users, though this was not statistically significant [137].

Similarly, Yamada T with colleagues analyzed data from a large, single-institute cohort of patients with rheumatoid RA at the Institute of Rheumatology, Tokyo Women's Medical University, Japan. Information on TB history was collected through patient self-reports during the period from April to October 2003. The study aimed to investigate the age-adjusted incidence rate of TB and the relative risk of TB infection in RA patients. Among 5,044 RA patients, 483 (9.6%) reported a history of TB prior to October 2002. The frequency of reported TB history increased with age. Over the course of one year, four new cases of TB were identified among the 5,544 RA patients. The age-adjusted

 doi:10.20944/preprints202412.0263.v1

incidence of TB was 42.4 per 100,000 RA patients. The relative risk (RR) of TB in RA patients was 3.21 (95% CI: 1.21–8.55), with men having a significantly higher risk (RR 10.59, 95% CI: 3.42–32.78) compared to women (RR 1.41, 95% CI: 0.2–10). The study found a higher risk of TB among RA patients compared to the general population, with men particularly at greater risk [138].

Both studies highlight the elevated TB risk in RA patients and emphasize the need for vigilant monitoring and management of TB in this population. As demonstrated in Yamada T et al.'s research, factors such as the relative risk (RR) of TB in RA patients was 3.21 (95% CI: 1.21–8.55), with men having a significantly higher risk (RR 10.59, 95% CI: 3.42–32.78) compared to women (RR 1.41, 95% CI: 0.2–10) [138]. Were significantly associated with higher mortality rates in TB patients. They underscore the importance of early detection and integrated care strategies to manage both RA and TB.

10. Loss to Follow-Up During Tuberculosis Treatment

A significant barrier to achieving the goal of TB in India by 2025 is the issue of treatment discontinuation, often referred to as loss to follow-up (LTFU). Research indicates that LTFU rates in India vary between 15% and 25% across different studies [94–98].

Anwita Khaitan and colleagues conducted a study in the Ballabgarh block of Haryana, India, involving TB patients who had been LTFU, as well as staff from the National TB Elimination Program (NTEP). The research aimed to explore stakeholder perspectives on the factors contributing to LTFU, with a particular focus on alcohol use. Almost all key informants, along with many patient participants, believed that alcohol consumption was a significant factor increasing the likelihood of TB patients being lost to follow-up. The study identified several key themes, including shared personality traits and attitudes, the combined negative effects of antitubercular drugs and alcohol, lack of family support, and financial difficulties [99].

Similarly, Beatriz Barreto-Duarte and colleagues conducted an observational study analyzing patients aged 18 and older with TB reported to the Brazilian National Notifiable Disease Information System from 2015 to 2022. The study compared clinical and epidemiological variables between new cases and retreatments, using regression models to identify factors associated with unfavorable treatment outcomes. Out of 743,823 reported TB cases during the study period, 555,632 cases were eligible, comprising 462,061 new cases and 93,571 retreatments (including 44,642 recurrent cases and 48,929 cases following LTFU). LTFU emerged as a significant risk factor for unfavorable treatment outcomes, with an odds ratio (OR) of 3.96 (95% confidence interval [CI], 3.83–4.1). Additionally, LTFU was the primary risk factor for subsequent loss to follow-up (OR, 4.93 [95% CI, 4.76–5.11]). The findings highlight that retreatment is a considerable risk factor for adverse treatment outcomes, particularly following loss to follow-up. Treatment success rates among individuals with RLTFU fall short of the targets set by the WHO End TB Strategy across Brazil. These results emphasize the urgent need for targeted interventions to enhance treatment adherence and improve outcomes for individuals who experience LTFU [100].

The 2020 revised guidelines categorize TB treatment outcomes as either successful or unsuccessful, with the latter including patients who are LTFU. This classification underscores a significant challenge: physicians often struggle to ensure that patients complete their treatment regimens. Examining the outcomes of TB can provide valuable insights into the readiness of healthcare systems to tackle the interplay between social determinants and disease [102].

Taken together, these studies underscore the critical role of LTFU in determining TB treatment outcomes. As demonstrated in Barreto-Duarte et al.'s research, LTFU is a significant risk factor for unfavorable outcomes, with an odds ratio of 3.96 for poor treatment outcomes and an even higher risk (OR = 4.93) for subsequent loss to follow-up [100]. These findings reinforce the urgent need for comprehensive management strategies to address LTFU, including early detection, patient-centered care, and addressing social and economic barriers to improve treatment adherence and reduce the burden of TB.

11. Drug-Resistance Mycobacterium Tuberculosis

 doi:10.20944/preprints202412.0263.v1

The rising prevalence of rifampicin-resistant (RR) and MDR-TB has posed significant public health challenges. Treating patients with MDR/RR *Mycobacterium tuberculosis* strains is more complex, costly, and toxic and often leads to severe social and economic repercussions compared to treatment of those with drug-sensitive strains [103]. Previous studies have identified a variety of factors associated with MDR-TB, including age, sex, immigration status, HIV/AIDS, history of incarceration, smoking, drug addiction, prior TB treatment, and unemployment [104–108].

Noormohamad Mansoori and colleagues conducted susceptibility testing using the proportion method on Lowenstein–Jensen media, gathering demographic and clinical data from the Iranian TB registry. Among 1,083 individuals diagnosed with TB, 27 (2.5%) were found to have MDR or RR TB, while 73 cases (6.7%) exhibited any form of drug resistance (ADR). Statistical analysis revealed a significant association between marital status and MDR/RR TB ($p = 0.003$). Additionally, significant associations were noted between ADR TB and both genders ($p = 0.035$) and previous TB treatment ($p = 0.02$). These findings offer critical insights into the drug resistance patterns of *Mycobacterium tuberculosis* strains and the associated risk factors in northern Iran [109].

The retrospective cross-sectional study, conducted by Evaristo Chanda, reviewed the medical records of patients diagnosed with drug-resistant tuberculosis (DR-TB) who were treated at the MDR-TB Ward of Kabwe Central Hospital between 2017 and 2021. A total of 183 patients were included in the study, with data collected from DR-TB registers. The study found that the prevalence of DR-TB among registered TB patients in Central Province was 1.4%. The majority of affected individuals were adults aged 26 to 45 years, accounting for 63.9% of cases. The analysis revealed that most patients had RR-TB (89.6%), while 9.3% had MDR-TB, 0.5% had isoniazid-resistant TB (IR-TB), and 0.5% had XDR-TB. RR-TB was present in 93.8% of new cases and 88.9% of relapse cases, while MDR-TB was found in 6.2% of new cases and 10% of relapse cases. Regarding treatment outcomes, the study found that 16.9% of patients were declared cured, 45.9% completed their treatment, 6% were lost to follow-up, and 21.3% died. Multivariate analysis identified two significant risk factors for mortality: age between 36 and 45 years (adjusted odds ratio [aOR] 0.253, 95% confidence interval [CI] [0.70–0.908], $p = 0.035$) and male gender (aOR 0.261, 95% CI [0.107–0.638], $p = 0.003$) [110].

Hyeon-Kyoung Koo and colleagues conducted a multicenter cross-sectional study on TB patients whose final treatment outcome was reported as treatment failure between 2015 and 2017. The study collected detailed data on demographics, microbiological and radiographic findings, and clinical characteristics through in-depth interviews conducted by TB nurse specialists at all Public-Private Mix (PPM) participating hospitals in South Korea. A total of 52 TB patients with treatment failure were included in the study. Conversely, Medicaid support was found to be a favorable factor for treatment success (area under the curve [AUC] = 0.79). Additionally, the presence of multidrug-resistant tuberculosis (MDR-TB) was significantly associated with the presence of cavities. Notably, 36.5% of patients in the treatment failure group had MDR-TB [118].

Collectively, these studies underscore the strong correlation between MDR-/RR-TB and treatment failure. As demonstrated by Koo et al., 36.5% of patients in the treatment failure group had MDR-TB [118], emphasizing the urgent need for more robust TB control programs. To reduce the risk of treatment failure, it is crucial to strengthen surveillance systems, improve early detection, and ensure the timely initiation of appropriate treatments for patients with MDR-/RR-TB.

12. Household Contacts

While household contacts of TB patients are known to be at heightened risk of developing the disease, there is a lack of published evidence specifically examining this high-risk group in the context of low- and middle-income countries.

In a cohort study led by Priscila F. P. S. Pinto and colleagues, individual socioeconomic data from the 100 million Brazilian cohort were linked to mortality records and TB registries. The study focused on contacts of TB patients diagnosed between January 1, 2004, and December 31, 2018. The study followed 420,854 household contacts of 137,131 TB patients. During this period, 8,953 contacts were diagnosed with TB. The incidence rate among contacts was 427.8 per 100,000 person-years at risk (95% CI 419.1–436.8), which was 16 times higher than the incidence in the general population

 doi:10.20944/preprints202412.0263.v1

(26.2 per 100,000 person-years; 95% CI 26.1–26.3). This elevated risk persisted throughout the study period. The study underscores the sustained and high risk of TB among household contacts, highlighting the critical need to expand and strengthen contact tracing and preventive treatment programs [111].

Studies from Peru and Ethiopia have similarly found that household contacts are 8 to 10 times more likely to develop TB compared to the general population [112,113].

Together, these findings reinforce the strong correlation between household contact and TB transmission, with a clear indication that household contacts represent a high-risk subpopulation. As shown in the study by Priscila F.P.S. Pinto et al. [111], the incidence rate of TB among household contacts (427.8 per 100,000 person years) is substantially higher than the general population's rate, underscoring the critical need to prioritize this group for targeted public health interventions. Expanding efforts in contact tracing, preventive therapy, and early diagnosis for household contacts is essential to controlling TB transmission and reducing the burden of disease in these high-risk communities.

13. Conclusions

Several factors can influence the success of TB treatment, including individual behaviors, sociodemographic conditions, and comorbidities. Key risk factors for poor TB treatment outcomes include a low body mass index (BMI < 24 kg/m² developing TB risk by 2,68 times), tobacco smoking (with 2/3 of TB patients being smokers), alcohol use (which is a 4.0 stronger predictor of TB treatment failure), and drug use (with nearly 20% of smokers also reporting drug use). Other demographic factors also play a role: males are 1.3 times more likely to experience treatment failure, and each additional year of age increases the risk by 1.03 times. Sociodemographic factors, such as unemployment (strongly associated with poor TB outcomes ($\chi^2 = 81.1$, $p < 0.001$) and living in urban areas (living in a town increased the risk of developing TB 3.20 times), are strongly associated with worse outcomes. Migrants face a higher risk of treatment discontinuation (4.33 times more likely), while co-infections like HIV (38.6% treatment failure in drug-susceptible TB and 65.4% in drug-resistant TB cases), diabetes (which nearly doubles TB-related mortality risk), chronic kidney disease, especially in stages 4–5 or also linked to higher treatment failure (HR: 4.719; p=0.018), and patients undergoing hemodialysis (HR: 6.13; p=0.005) face even greater challenges. The combined impact of TB and COVID-19 infection significantly increases mortality, with patients dying from both conditions at a higher rate than those succumb to either disease alone ($p<0.001$). Additionally, individuals with rheumatic diseases are 3,1 times more likely to experience poor TB outcomes. Loss to follow-up is another critical factor, increasing the likelihood of treatment failure nearly fourfold, while drug-resistant TB (including multidrug-resistant TB or MDR-TB) is present in about one-third of treatment failures. Household contacts are at 8 to 10 times higher risk of developing TB compared to the general population.

To improve treatment success, TB control programs must adopt comprehensive strategies that go beyond medication, such as patient education, counseling, psychological support, incentives, reminders, and the use of digital health technologies. These interventions can help address individual barriers to adherence, ensuring better treatment completion and improved patient outcomes.

Author Contributions: Conceptualization, Methodology, Writing—original draft: K.K., V.E.D. and E.D; Writing—review and editing: K.K., V.E.D., and E.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding".

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Furin J, Cox H, Pai M. Tuberculosis. *Lancet*. 2019;393(10181):1642–1656. doi:10.1016/S0140-6736(19)30308-3.
2. Zaman K. Tuberculosis: a global health problem. *J Heal Popul Nutr*. 2010;28(2):111.
3. Friedman LN, Dedicoat M, Davies PD. *Clinical Tuberculosis*. 6th ed. Vol. 53; 2020.

4. Allué-Guardia A, García JI, Torrelles JB. Evolution of drug-resistant mycobacterium tuberculosis strains and their adaptation to the human lung environment. *Front Microbiol*. 2021;12. doi:10.3389/fmicb.2021.612675.
5. World Health Organization. Global tuberculosis report 2020 [Internet]. World Health Organization; 2020 [cited February 17, 2022]. Available from: https://www.who.int/publications/i/item/9789240013131. Accessed May 27, 2022.
6. World Health Organization. Global tuberculosis report 2021 [Internet]. Geneva: World Health Organization; 2021 [cited February 17, 2022]. Available from: https://www.who.int/publications/i/item/9789240037021. Accessed May 27, 2022.
7. https://www.who.int/news-room/fact-sheets/detail/tuberculosis
8. World Health Organization. WHO End TB Strategy [Internet]. 2015. Available from: www.who.int/tb/post2015_strategy/en/.
9. Cox H, Nicol MP. Comment Tuberculosis eradication: renewed commitment and global investment required. Lancet Infect Dis. 2018; 18(3):228–9. https://doi.org/10.1016/S1473-3099(17)30692-8PMID: 29223584.
10. World Health Organization. Global tuberculosis report 2018. In. Geneva, Switzerland: WHO; 2018.
11. Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis. 2004;8(3):286–98.
12. Leung CC, Lam TH, Chan WM, Yew WW, Ho KS, Leung G, et al. Lower risk of tuberculosis in obesity. Arch Intern Med. 2007;167(12):1297–304. doi: 10.1001/archinte.167.12.1297.
13. Lonnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. Int J Epidemiol. 2010;39(1):149–55. doi: 10.1093/ije/dyp308.
14. Cegielski JP, Arab L, Cornoni-Huntley J. Nutritional risk factors for tuberculosis among adults in the United States, 1971–1992. American journal of epidemiology. 2012:kws007.
15. Yen YF, Hu HY, Lee YL, Ku PW, Lin IF, Chu D, et al. Obesity/overweight reduces the risk of active tuberculosis: a nationwide population-based cohort study in Taiwan. International journal of obesity (2005). 2017;41(6):971–5. Epub 2017/03/11. doi: 10.1038/ijo.2017.64.
16. Falagas ME, Kompoti M. Obesity and infection. The Lancet Infectious diseases. 2006;6(7):438–46. Epub 2006/06/23. doi: 10.1016/S1473-3099(06)70523-0.
17. Association of Body Mass Index with the Tuberculosis Infection: a Population-based Study among 17796 Adults in Rural China. Scientific Reports. 2017;7.
18. Kathamuthu G, Sridhar R, Baskaran D, Babu SJJoct, diseases om. Low body mass index has minimal impact on plasma levels of cytokines and chemokines in tuberculous lymphadenitis. 2020; 20:100163.
19. Kim S, Ye S, Ha E, Chun EJPo. Association of body mass index with incident tuberculosis in Korea.2018; 13(4):e0195104.
20. Cai N, Luo W, Ding L, Chen L, Huang Y (2024) Obesity-related indicators and tuberculosis: A Mendelian randomization study. PLoS ONE 19(4): e0297905. https://doi.org/10.1371/journal.pone.0297905.
21. Lawrence Oyewusi, Chengbo Zeng, KJ Seung, Stephanie Mpinda, Mikanda Kunda, Carole D Mitnick, Makelele Kanu, Meseret Tamirat, Joalane Makaka, Mabatloung Mofolo, Refiloe Maime, Llang Maama, Ninza Senyo, Bamidele Oguntoyinbo, Lwayi Mayombo & Molly F Franke (2024) Low body mass index as a predictor of sputum culture conversion and treatment outcomes among patients receiving treatment for multidrug-resistant tuberculosis in Lesotho, Global Health Action, 17:1, 2305930, DOI: 10.1080/16549716.2024.2305930.
22. Yerezhepov D, Gabdulkayum A, Akhmetova A et al. Pulmonary tuberculosis epidemiology and genetics in Kazakhstan. *Frontiers* 2024 Apr 19:12:1340673. doi: 10.3389/fpubh.2024.1340673. eCollection 2024.
23. Lu P, Zhang Y, Liu Q, Ding X, Kong W, Zhu L, et al. Association of BMI, diabetes, and risk of tuberculosis: a population-based prospective cohort. *Int J Infect Dis*. (2021) 109:168–73. doi: 10.1016/j.ijid.2021.06.053.
24. Koethe JR, von Reyn CF. Protein-calorie malnutrition, macronutrient supplements, and tuberculosis. Int J Tuberc Lung Dis. 2016 Jul;20(7):857-63. doi: 10.5588/ijtld.15.0936. PMID: 27287634.
25. Költringer FA, Annerstedt KS, Boccia D, Carter DJ, Rudgard WE. The social determinants of national tuberculosis incidence rates in 116 countries: a longitudinal ecological study between 2005-2015. *BMC Public Health*. (2023) 23:337. doi: 10.1186/s12889-023-15213-w.
26. Webb, G.B. The effect of the inhalation of cigarette smoke on the lungs. A clinical study. Am. Rev. Tuberc. **1918**, 2, 25–27. Available online: https://www.atsjournals.org/doi/epdf/10.1164/art.1918.2.1.25 (accessed on 5 January 2024).
27. Chan, E.D.; Keane, J.; Iseman, M.D. Should cigarette smoke exposure be a criterion to treat latent tuberculosis infection? Am. J.Respir. Crit. Care Med. **2010**, 182, 990–992. [PubMed].
28. Bay, J.G.; Patsche, C.B.; Svendsen, N.M.; Gomes, V.F.; Rudolf, F.;Wejse, C. Tobacco smoking impact on tuberculosis treatment outcome: An observational study fromWest Africa. Int. J. Infect. Dis. **2022**, 124, S50–S55.

 doi:10.20944/preprints202412.0263.v1

29. Gambhir, H.S.; Kaushik, R.M.; Kaushik, R.; Sindhwani, G. Tobacco smoking-associated risk for tuberculosis: A case-control study. Int. Health **2010**, 2, 216–222.
30. Pai, M.; Mohan, A.; Dheda, K.; Leung, C.C.; Yew,W.W.; Christopher, D.J.; Sharma, S.K. Lethal interaction: The colliding epidemics of tobacco and tuberculosis. Expert Rev. Anti Infect. Ther. **2007**, 5, 385–391.
31. Kaliner E, Bornstein S, Kabha D, Lidji M, Sheffer R, Mor Z. A retrospective cohort analysis of treatment outcomes of patients with tuberculosis who used substances in Tel Aviv, Israel. Alcohol Alcohol. 2024 Jan 17;59(2):agad073. doi: 10.1093/alcalc/agad073. PMID: 37961929.
32. Amoori N, Cheraghian B, Amini P, Alavi SM. Identification of Risk Factors Associated with Tuberculosis in Southwest Iran: A Machine Learning Method. *Med J Islam Repub Iran.* 2024 (17 Jan);38:5. https://doi.org/10.47176/mjiri.38.5.
33. Department of Microbiology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Dr. D. Y. Pati Vidyapeeth, Pimpri, Pune, Maharashtra, 411018, India. Tel.: ž91 9974770469.
34. Alavi-Naini, R.; Sharifi-Mood, B.; Metanat, M. Association between tuberculosis and smoking. Int. J. High Risk Behav. Addict. **2012**,1, 71–74. [PubMed].
35. Bishwakarma, R.; Kinney, W.H.; Honda, J.R.; Mya, J.; Strand, M.J.; Gangavelli, A.; Bai, X.; Ordway, D.J.; Iseman, M.D.; Chan,E.D. Epidemiologic link between tuberculosis and cigarette/biomass smoke exposure: Limitations despite the vast literature. Respirology **2015**, 20, 556–568. [PubMed].
36. Smith, G.S.; Van Den Eeden, S.K.; Baxter, R.; Shan, J.; Van Rie, A.; Herring, A.H.; Richardson, D.B.; Emch, M.; Gammon, M.D. Cigarette smoking and pulmonary tuberculosis in northern California. J. Epidemiol. Community Health **2015**, 69, 568–573.
37. World Health Organization. Global tuberculosis report. 2023. https:// iris.who.int/handle/10665/373828.
38. Imtiaz S, Shield KD, Roerecke M *et al.* Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. *Eur Respir J* 2017; **50**: 1700216. https://doi.org/10.1183/13993003.00216-2017.
39. Myers B, Bouton TC, Ragan EJ *et al.* Impact of alcohol consumption on tuberculosis treatment outcomes: a prospective longitudinal cohort study protocol. *BMC Infect Dis* 2018; **18**: 488. https://doi.org/10.1186/s12879-018-3396-y.
40. Volkmann T, Moonan P, Miramontes R *et al.* Tuberculosis and excess alcohol use in the United States, 1997–2012. *Int J Tuberc Lung Dis* 2015; **19**: 111–9. https://doi.org/10.5588/ijtld.14.0516.
41. Pasipanodya JG, McIlleron H, Burger A *et al.* Serum drug concentrations predictive of pulmonary tuberculosis outcomes. *J Infect Dis* 2013; **208**: 1464–73. https://doi.org/10.1093/infdis/jit352.
42. Chigutsa E, Pasipanodya JG, Visser ME *et al.* Impact of nonlinear interactions of pharmacokinetics and mics on sputum bacillary kill rates as a marker of sterilizing effect in tuberculosis. *Antimicrob Agents Chemother* 2015; **59**: 38–45. https://doi.org/10.1128/AAC.03931-14.
43. Swaminathan S, Pasipanodya JG, Ramachandran G *et al.* Drug concentration thresholds predictive of therapy failure and death in children with tuberculosis: bread crumb trails in random forests. *Clin Infect Dis* 2016; **63**: S63–74. https://doi.org/10.1093/cid/ciw471.
44. Necho M, Tsehay M, Seid M, Zenebe Y, Belete A, Gelaye H, et al. Prevalence and associated factors for alcohol use disorder among tuberculosis patients: a systematic review and meta-analysis study. Substance Abuse Treatment, Prevention, and Policy. 2021;16(1):2.
45. Bayigga, Josephine & Kakai, Ilona & Agnes, Eva & Ddungu, Ahmed & Semakula, Lynn & Nansereko, Martha & Wiltshire, Christine & Stavia, Turyahabwe & Muyanja, Stella. (2024). Alcohol use disorder among people diagnosed with Tuberculosis in a large urban case-finding project in central Uganda: prevalence, associated factors and challenges to treatment adherence. 10.21203/rs.3.rs-3981797/v1.
46. Khaitan A, Rai SK, Krishnan A, Gupta SK, Kant S, Khilnani GC. "I would rather die drinking than take the medicine": Role of alcohol use disorder in loss-to-follow-up of tuberculosis treatment in a rural area of Ballabgarh, Haryana. Indian J Community Med 2024;49:152-6.
47. Wu J, Zhang Y, Wang K, Peng P. Global, regional, and national mortality of tuberculosis attributable to alcohol and tobacco from 1990 to 2019: A modeling study based on the Global Burden of Disease study 2019. J Glob Health 2024;14:04023.
48. Aho J, Lacroix C, Bazargani M, Milot DM, Sylvestre JL, Pucella E, Trudeau N, Sicard N, Savard N, Rivest P, Soualhine H, Munoz-Bertrand M. Outbreak of tuberculosis among substance users and homeless people in Greater Montréal, Canada, 2003–2016. Can Commun Dis Rep. 2017;43(3):72-6. https://doi.org/10.14745/ccdr.v43i34a03.
49. Mbayang, Ndiaye & Diallo, Amadou & Idrissa, B. & Ba, Mouhamadou Faly & Fatoumata, Bintou & Adama, Faye. (2024). Factors associated with tuberculosis among people who inject drugs (IDUs) in Senegal in 2022. Journal of Public Health and Epidemiology. 16. 1-8. 10.5897/JPHE2023.1478.
50. Herrera Diaz, Mariana & Keynan, Yoav & López, Lucelly & Marín, Diana & Arroyave, Luisa & Arbelaez, Patricia & Vélez, Lázaro & Rueda, Zulma. (2021). Incidence and Risk Factors Associated with Latent Tuberculosis Infection and Pulmonary Tuberculosis among People Deprived of Liberty in Colombian Prisons. The American journal of tropical medicine and hygiene. 106. 10.4269/ajtmh.20-0307.

51. Coutinho SE, Lima de Braga RC, Santos AK, et al. Smoking cessation among tuberculosis patients during the coronavirus disease-2019 pandemic. *Monaldi Arch Chest Dis* doi:10.4081/monaldi.2024.2970.
52. RupaniMP. Need for implementation of national frame work for tuberculosis – alcohol (TB-alcohol) collaborative activities in India – drifting closer to TB elimination by 2025. *IndianJournalofTuberculosis*2023.https://doi.org/10.1016/j.ijtb.2023.05.019.
53. Schurz H, Salie M, Tromp G, Hoal EG, Kinnear CJ, Möller M. The X chromosome and sex-specific effects in infectious disease susceptibility. Hum Genom. 2019;13:2.
54. Hertz D, Schneider B. Sex differences in tuberculosis. Semin Immunopathol. 2019;41:225–37.
55. Hassenstein MJ, Aarabi G, Ahnert P, Becher H, Franzke C-W, Fricke J, et al. Selbst berichtete Infektionen in der NAKO Gesundheitsstudie – Einordnung in die gegenwärtige Forschungslandschaft. Bundesgesundheitsblatt - Gesundheitsforschung -Gesundheitsschutz [Internet]. 2020 [cited 2023 Jul 19];63:404–14. https://link.springer.com/article/10.1007/s00103-020-03114-x.
56. Yang W-T, Gounder CR, Akande T, De Neve J-W, McIntire KN, Chandrasekhar A, et al. Barriers and delays in tuberculosis diagnosis and treatment services: does gender matter? Tuberc Res Treat. 2014;2014: 461935.
57. Horton KC, MacPherson P, Houben RMGJ, White RG, CorbettEL. Sex differences in tuberculosis burden and notifications in low- and middle-income countries: a systematic review and meta-analysis. PLoS Med. 2016;13: e1002119.
58. Van den Hof S, Najlis CA, Bloss E, Straetemans M. A systematic review on the role of gender in tuberculosis control. TB CAP; 2010 Sep. p. 195. https://www.kncvtbc.org/uploaded/2015/09/Role_of_Gender_in_TB_Control.pdf
59. Pape, S., Karki, S.J., Heinsohn, T. *et al.* Tuberculosis case fatality is higher in male than female patients in Europe: a systematic review and meta-analysis. *Infection* **52**, 1775–1786 (2024). https://doi.org/10.1007/s15010-024-02206-z.
60. Shayan NA, Rahimi A, Stranges S and Thind A (2024) Exploring Sex Differences in Risk Factors and Quality of Life Among Tuberculosis Patients in Herat, Afghanistan: A Case- Control Study. Int J Public Health 69:1606554.doi: 10.3389/ijph.2024.1606554.
61. Oyageshio OP, Myrick JW, Saayman J, van der Westhuizen L, Al-Hindi DR, Reynolds AW, et al. (2024) Strong effect of demographic changes on Tuberculosis susceptibility in South Africa. PLOS Glob Public Health 4(7): e0002643. https://doi.org/10.1371/journal.pgph.0002643.
62. Rowley E, Mugala N. Sex-disaggregated tuberculosis data call for gender-equitable tuberculosis control. Lancet Infect Dis [Internet]. 2022 [cited 2022 Nov 30];22:155–6. https://doi.org/10.1016/S1473-3099(21)00617-4.
63. Chikovore J, Pai M, Horton KC, Daftary A, Kumwenda MK, Hart G, et al. Missing men with tuberculosis: the need to address structural influences and implement targeted and multidimensional interventions. BMJ Glob Health [Internet]. 2020;5:e002255. https://gh.bmj.com/content/5/5/e002255
64. Harris R, Millington K, Horton KC. The clock is ticking for a gender-sensitive response to End TB [Internet]. LSTM. 2021 [cited2022 Nov 30]. https://www.lstmed.ac.uk/news-events/blogs/theclock-is-ticking-for-a-gender-sensitive-response-to-end-tb.
65. P. Caraux-Paz, et al., Tuberculosis in the elderly, J. Clin. Med. (24) (2021) 10.
66. M. Uplekar, et al., WHO's new end TB strategy, Lancet 385 (9979) (2015) 1799–1801.
67. Jiang H, Chen X, Lv J, Dai B, Liu Q, Ding X, Pan J, Ding H, Lu W, Zhu L, Lu P. Prospective cohort study on tuberculosis incidence and risk factors in the elderly population of eastern China. Heliyon. 2024 Jan 19;10(3):e24507. doi: 10.1016/j.heliyon.2024.e24507. PMID: 38314308; PMCID: PMC10837496.
68. Golsha R, Mazandarani M, Sohrabi A, et al. Risk factors and treatment outcome of smear positive pulmonary tuberculosis patients: A five-year study in the North of Iran. Caspian J Intern Med 2024; 15(2): 347-353.
69. N.S. Hochberg, C.R. Horsburgh Jr., Prevention of tuberculosis in older adults in the United States: obstacles and opportunities, Clin. Infect. Dis. 56 (9) (2013) 1240–1247.
70. B. Hauer, et al., Tuberculosis in the elderly in Germany, Eur. Respir. J. 38 (2) (2011) 467–470.
71. WHO. Global Tuberculosis Report 2022 (2022). Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/globaltuberculosis-report-2022 (Accessed January 22, 2023).
72. Yasobant S, Nazli Khatib M, Syed ZQ, Gaidhane AM, Shah H, Narkhede K, et al. Health-Related Quality of Life (HRQoL) of Patients With Tuberculosis: A Review. Infect Dis Rep (2022) 14(4):509–24. doi:10.3390/idr14040055
73. Brown J, Capocci S, Smith C, Morris S, Abubakar I, Lipman M. Health Status and Quality of Life in Tuberculosis. Int J Infect Dis (2015) 32:68–75. doi:10.1016/j.ijid.2014.12.045.
74. Septiani F, Erawati M, Suhartini. Factors Affecting the Quality of Life Among Pulmonary Tuberculosis Patients: A Literature Review. Nurse Health J Keperawatan (2022) 11(1):57–69. doi:10.36720/nhjk.v11i1.351.
75. Chang B, Wu AW, Hansel NN, Diette GB. Quality of Life in Tuberculosis: A Review of the English Language Literature. Qual Life Res (2004) 13(10): 1633–42. doi:10.1007/s11136-004-0374-1.

76. Sweetland AC, Kritski A, Oquendo MA, SubletteME, Norcini Pala A, Silva LRB, et al. Addressing the Tuberculosis–Depression Syndetic to End the Tuberculosis Epidemic. Int J Tuberc Lung Dis (2017) 21(8):852–61. doi:10.5588/ijtld.16.0584.
77. Lara-Espinosa JV, Hernández-Pando R. Psychiatric Problems in Pulmonary Tuberculosis: Depression and Anxiety. J Tuberc Res (2021) 09(01):31–50.doi:10.4236/jtr.2021.91003.
78. Sa´nchez-Pe´rez HJ, Gordillo-Marroquı´n C, Va´zquez-Marcelı´n J, Martı´n-Mateo M, Go´mez-Velasco A (2024) Sociodemographic factors associated with the success or failure of antituberculosis treatment in the Chiapas Highlands, Mexico, 2019–2022. PLoS ONE 19(1): e0296924.https://doi.org/10.1371/journal.pone.0296924.
79. Oyageshio OP, Myrick JW, Saayman J, van der Westhuizen L, Al-Hindi DR, Reynolds AW, et al. (2024) Strong effect of demographic changes on Tuberculosis susceptibility in South Africa. PLOS Glob Public Health 4(7): e0002643. https://doi.org/10.1371/journal.pgph.0002643.
80. Yerezhepov D, Gabdulkayum A, Akhmetova A, Kozhamkulov U, Rakhimova S, Kairov U, Zhunussova G, Kalendar R and Akilzhanova A (2024) Pulmonary tuberculosis epidemiology and genetics in Kazakhstan. *Front. Public Health* 12:1340673. doi: 10.3389/fpubh.2024.1340673.
81. Sa´nchez-Pe´rez HJ, Dı´az-Va´zquez A, Na´jera-Ortiz JC, Balandrano S, Martı´n-Mateo M. Multidrug-resistant pulmonary tuberculosis in Los Altos, Selva and Norte regions, Chiapas, Mexico. Int J Tuberc Lung Dis. 2010; 14(1):34–9. PMID: 20003692.
82. Pe´rez-Molina A, Sa´nchez-Pe´rez HJ, Yanes-Pe´rez M, Arana-Cedeño M. Tuberculosis care in Mexico's Chiapas highlands region: A right to health analysis. Health Hum Rights. 2020; 22(1):305–16. PMID:32669809.
83. Kenya, Uganda, Zambia, and Zimbabwe TB Disability Study Group (members listed here in alphabetical order):; Adakun SA, Banda FM, Bloom A, Bochnowicz M, Chakaya J, Chansa A, Chiguvare H, Chimzizi R, Colvin C, Dongo JP, Durena A, Duri C, Edmund R, Harries AD, Kathure I, Kavenga FN, Lin Y, Luzze H, Mbithi I, Mputu M, Mubanga A, Nair D, Ngwenya M, Okotu B, Owiti P, Owuor A, Thekkur P, Timire C, Turyahabwe S, Tweyongyere E, YaDiul M, Zachariah R, Zimba K. Disability, comorbidities and risk determinants at end of TB treatment in Kenya, Uganda, Zambia and Zimbabwe. IJTLD Open. 2024 May 1;1(5):197-205. doi: 10.5588/ijtldopen.24.0082. PMID: 39022778; PMCID: PMC11249599.
84. Barreto-Duarte B, Villalva-Serra K, Miguez-Pinto JP, Araújo-Pereira M, Campos VMS, Rosier G, Nogueira BMF, Queiroz ATL, Rolla VC, Cordeiro-Santos M, Kritski AL, Martinez L, Rebeiro PF, Sterling TR, Rodrigues MM, Andrade BB. Retreatment and Anti-tuberculosis Therapy Outcomes in Brazil Between 2015 and 2022: A Nationwide Study. Open Forum Infect Dis. 2024 Jul 18;11(8):ofae416. doi: 10.1093/ofid/ofae416. PMID: 39100532; PMCID: PMC11297487.
85. DF diabetes atlas reports [homepage on the Internet]. International Diabetes Federation, 2024. Available from: https://diabetesatlas.org/. Accessed February 29, 2024.
86. World Health Organization. *Framework for Collaborative Action on Tuberculosis and Comorbidities*. Licence: CC BY-NC-SA 3.0 IGO. Geneva: World Health Organization;2022.4.
87. Noubiap JJ, Nansseu JR, Nyaga UF, et al. Global prevalence of diabetes in active tuberculosis: a systematic review and meta-analysis of data from 2·3 million patients with tuberculosis. *Lancet Glob Health*. 2019;7(4):e448–e460. doi:10.1016/S2214-109X(18)30487-X.
88. Wu Q, Liu Y, Ma YB, Liu K, Chen SH. Incidence and prevalence of pulmonary tuberculosis among patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Ann Med*. 2022;54(1):1657–1666. doi:10.1080/07853890.2022.20853187.
89. Huangfu P, Ugarte-Gil C, Golub J, Pearson F, Critchley J. The effects of diabetes on tuberculosis treatment outcomes: an updated systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2019;23(7):783–796. doi:10.5588/ijtld.18.04338.
90. Gautam S, Shrestha N, Mahato S, Nguyen TPA, Mishra SR, Berg-Beckhoff G. Diabetes among tuberculosis patients and its impact on tuberculosis treatment in South Asia: a systematic review and meta-analysis. *Sci Rep*. 2021;11(1):2113. doi:10.1038/s41598-021-81057-29.
91. Li J, Zhao Y, Jiang Y, Zhang Y, Zhang P, Shen L, Chen Z. Prevalence and Risk Factors of Diabetes in Patients with Active Pulmonary Tuberculosis: A Cross-Sectional Study in Two Financially Affluent China Cities. Diabetes Metab Syndr Obes. 2024 Mar 2;17:1105-1114. doi: 10.2147/DMSO.S450507. PMID: 38450415; PMCID: PMC10916512.
92. Shi H, Yuan Y, Li X, Li YF, Fan L, Yang XM. Analysis of the influencing factors and clinical related characteristics of pulmonary tuberculosis in patients with type 2 diabetes mellitus. World J Diabetes. 2024 Feb 15;15(2):196-208. doi: 10.4239/wjd.v15.i2.196. PMID: 38464376; PMCID: PMC10921156.
93. Armstrong LR, Kammerer JS, Haddad MB. Diabetes mellitus among adults with tuberculosis in the USA, 2010-2017. *BMJ Open DiabetesRes Care* 2020; **8** [PMID: 32641300 DOI: 10.1136/bmjdrc-2020-001275].
94. Mundra A, Deshmukh PR, Dawale A. Magnitude and determinants of adverse treatment outcomes among tuberculosis patients registered under revised national tuberculosis control program in a tuberculosis unit, Wardha, Central India: A record-based cohort study. J Epidemiol Glob Health 2017;7:111-8.

95. Kant S, Singh A, Parmeshwaran G, Haldar P, Malhotra S, Kaur R. Delay in initiation of treatment after diagnosis of pulmonary tuberculosis in primary health care setting: Eight-year cohort analysis from district Faridabad, Haryana, North India. Rural Remote Health 2017;17:1-8. doi: 10.22605/RRH4158.
96. Ahmad S, Velhal G. Study of treatment interruption of new sputum smear positive TB cases under DOTS strategy. Int J Med Sci Public Health 2014;3:977-81.
97. Mittal C, Gupta S. Noncompliance to DOTS: How it can be decreased. Indian J Community Med 2011;36:27-30.
98. Krishnan A, Kapoor SK. Involvement of private practitioners in tuberculosis control in Ballabgarh, Northern India. Int J Tuberc Lung Dis 2006;10:264-9.
99. Khaitan A, Rai SK, Krishnan A, Gupta SK, Kant S, Khilnani GC. "I would rather die drinking than take the medicine": Role of alcohol use disorder in loss-to-follow-up of tuberculosis treatment in a rural area of Ballabgarh, Haryana. Indian J Community Med 2024;49:152-6.
100. Barreto-Duarte B, Villalva-Serra K, Miguez-Pinto JP, Araújo-Pereira M, Campos VMS, Rosier G, Nogueira BMF, Queiroz ATL, Rolla VC, Cordeiro-Santos M, Kritski AL, Martinez L, Rebeiro PF, Sterling TR, Rodrigues MM, Andrade BB. Retreatment and Anti-tuberculosis Therapy Outcomes in Brazil Between 2015 and 2022: A Nationwide Study. Open Forum Infect Dis. 2024 Jul 18;11(8):ofae416. doi: 10.1093/ofid/ofae416. PMID: 39100532; PMCID: PMC11297487.
101. Braga S, Vieira M, Barbosa P, Ramos JP, Duarte R. Tuberculosis screening in the European migrant population: a scoping review of current practices. Breathe (Sheff). 2024 Mar;20(1):230357. doi: 10.1183/20734735.0357-2023. Epub 2024 May 14. PMID: 38746905; PMCID: PMC11091716.
102. Chen EC, Owaisi R, Goldschmidt L, Maimets IK, Daftary A. Patient perceptions of video directly observed therapy for tuberculosis: a systematic review. J Clin Tuberc Other Mycobact Dis. 2023 Nov 30;35:100406. doi: 10.1016/j.jctube.2023.100406. PMID: 38380432; PMCID: PMC10877938.
103. World Health Organization. WHO consolidated guidelines on drug- resistant tuberculosis treatment. Geneva: World Health Organization; 2019.
104. Ali A, Hasan Z, Jafri S, et al. *Mycobacterium tuberculosis* Central Asian Strain (CAS) lineage strains in Pakistan reveal lower diversity of MIRU loci than other strains. Int J Mycobacteriol. 2014;3(2):108–16.
105. Demile B, Zenebu A, Shewaye H, et al. Risk factors associated with multidrug-resistant tuberculosis (MDR-TB) in a tertiary armed force referral and teaching hospital, Ethiopia. BMC Infect Dis. 2018;18(1): 249.
106. Jimma W, Ghazisaeedi M, Shahmoradi L, et al. Prevalence of and risk factors for multidrug-resistant tuberculosis in Iran and its neighbor- ing countries: systematic review and meta-analysis. Rev Soc Bras Med Trop. 2017;50(3):287–95.
107. Pradipta IS, Forsman LD, Bruchfeld J, et al. Risk factors of multidrug- resistant tuberculosis: a global systematic review and meta-analysis. J Infect. 2018;77(6):469–78.
108. Saifullah A, Mallhi TH. Evaluation of risk factors associated with the development of MDR- and XDR-TB in a tertiary care hospital: a retro- spective cohort study. PeerJ. 2021;9:e10826.
109. Mansoori N, Pahlavanzadeh B, Atarjalali M. Risk factors associated with multidrug-resistant tuberculosis in areas with a moderate tuberculosis burden. Int Health. 2024 Jun 14:ihae039. doi: 10.1093/inthealth/ihae039. Epub ahead of print. PMID: 38873833.
110. Chanda E. The clinical profile and outcomes of drug resistant tuberculosis in Central Province of Zambia. BMC Infect Dis. 2024 Apr 1;24(1):364. doi: 10.1186/s12879-024-09238-8. PMID: 38556907; PMCID: PMC10983631.
111. Pinto PFPS, Teixeira CSS, Ichihara MY, Rasella D, Nery JS, Sena SOL, Brickley EB, Barreto ML, Sanchez MN, Pescarini JM. Incidence and risk factors of tuberculosis among 420 854 household contacts of patients with tuberculosis in the 100 Million Brazilian Cohort (2004-18): a cohort study. Lancet Infect Dis. 2024 Jan;24(1):46-56. doi: 10.1016/S1473-3099(23)00371-7. Epub 2023 Aug 14. PMID: 37591301; PMCID: PMC10733584.
112. Otero L, Shah L, Verdonck K, et al. A prospective longitudinal study of tuberculosis among household contacts of smear-positive tuberculosis cases in Lima, Peru. *BMC Infect Dis* 2016; **16:** 259.
113. Yassin MA, Yirdaw KD, Datiko DG, Cuevas LE, Yassin MA. Yield of household contact investigation of patients with pulmonary tuberculosis in southern Ethiopia. *BMC Public Health* 2020; **20:** 737.
114. Feldman, C.; Theron, A.J.; Cholo, M.C.; Anderson, R. Cigarette Smoking as a Risk Factor for Tuberculosis in Adults: Epidemiology and Aspects of Disease Pathogenesis. *Pathogens* **2024**, *13*, 151. https://doi.org/10.3390/pathogens13020151.
115. AlOsaimi HM, Alshammari MK, Almijlad GK, Alotaibi NM, Alqahtani DA, Alshamrani MM, Shutur TA, Alhazmi MF, Hurubi MA, ALShammari KS, Alzahrani KM, Aldaghriri HM, Alshammari AA, Alatawi OS, Alharbi RA. Prevalence, Clinical Characteristics and Determinants of Unsuccessful Treatment Outcomes Among Pulmonary Tuberculosis Patients: A 5-Year Registry-Based Retrospective Cohort Study. Patient Relat Outcome Meas. 2024 May 23;15:187-198. doi: 10.2147/PROM.S463396. PMID: 38803383; PMCID: PMC11129759.

116. Matulyte E, Davidaviciene E, Kancauskiene Z, Diktanas S, Kausas A, Velyvyte D, et al. (2023) The socio-demographic, clinical characteristics and outcomes of tuberculosis among HIV infected adults in Lithuania: A thirteenyear analysis. PLoS ONE 18(3): e0282046. https://doi.org/10.1371/journal.pone.0282046.
117. Nowiński A, Wesołowski S and Korzeniewska-Koseła M (2023) The impact of comorbidities on tuberculosis treatment outcomes in Poland: a national cohort study. *Front. Public Health* 11:1253615.doi: 10.3389/fpubh.2023.1253615.
118. Koo, HK., Min, J., Kim, H.W. *et al.* Prediction of treatment failure and compliance in patients with tuberculosis. *BMC Infect Dis* **20**, 622 (2020). https://doi.org/10.1186/s12879-020-05350-7.
119. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet*. 2013;382:260–272. doi:10.1016/S0140- 6736(13)60687-X2.
120. Romanowski K, Baumann B, Basham CA, Ahmad Khan F, Fox GJ, Johnston JC. Long-term all-cause mortality in people treated for tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2019;19:1129–1137. doi:10.1016/S1473-3099(19)30309-36.
121. Bardenheier BH, Pavkov ME, Winston CA, et al. Prevalence of tuberculosis disease among adult us-bound refugees with chronic kidney disease. *J Immigr Minor Health*. 2019;21:1275–1281. doi:10.1007/s10903-018-00852-88.
122. Cheng KC, Liao KF, Lin CL, Liu CS, Lai SW. Chronic kidney disease correlates with increased risk of pulmonary tuberculosis before initiating renal replacement therapy: a cohort study in Taiwan. *Medicine*. 2018;97:39–45.9.
123. Xiao J, Ge J, Zhang D, Lin X, Wang X, Peng L, Chen L. Clinical Characteristics and Outcomes in Chronic Kidney Disease Patients with Tuberculosis in China: A Retrospective Cohort Study. Int J Gen Med. 2022 Aug 19;15:6661-6669. doi: 10.2147/IJGM.S367090. PMID: 36016982; PMCID: PMC9398214.
124. Pradhan RR, Sigdel MR. Prevalence, Clinical Presentation, and Outcome of Tuberculosis in Patients with Chronic Kidney Disease at a Tertiary Care Hospital in Nepal. Int J Nephrol. 2020 Nov 1;2020:7401541. doi: 10.1155/2020/7401541. PMID: 33204531; PMCID: PMC7652626.
125. Ong CWM, Migliori GB, Raviglione M, et al. Epidemic and pandemic viral infections: impact on tuberculosis and the lung. Eur Respir J 2020; 56: 2001727.
126. Boulle A, Davies MA, Hussey H, et al. Risk factors for coronavirus disease 2019 (COVID-19) death in a population cohort study from the Western Cape province, South Africa. Clin Infect Dis 2021; 73: E2005–E2015.
127. Sy KTL, Haw NJL, Uy J. Previous and active tuberculosis increases risk of death and prolongs recovery in patients with COVID-19. Infect Dis 2020; 52: 902–907.
128. Global Tuberculosis Network and TB/COVID-19 Global Study Group. Long-term outcomes of the global tuberculosis and COVID-19 co-infection cohort. Eur Respir J 2023; 62: 2300925[DOI: 10.1183/13993003.00925-2023].
129. Nalunjogi J, Mucching-Toscano S, Sibomana JP, Centis R, D'Ambrosio L, Alffenaar JW, Denholm J, Blanc FX, Borisov S, Danila E, Duarte R, García-García JM, Goletti D, Ong CWM, Rendon A, Thomas TA, Tiberi S, van den Boom M, Sotgiu G, Migliori GB; Global Tuberculosis Network. Impact of COVID-19 on diagnosis of tuberculosis, multidrug-resistant tuberculosis, and on mortality in 11 countries in Europe, Northern America, and Australia. A Global Tuberculosis Network study. Int J Infect Dis. 2023 May;130 Suppl 1:S25-S29. doi: 10.1016/j.ijid.2023.02.025. Epub 2023 Mar 8. PMID: 36893943; PMCID: PMC9991328.
130. Marie, I.; Hachulla, E.; Chérin, P.; Hellot, M.F.; Herson, S.; Levesque, H.; Hatron, P.Y. Opportunistic infection in polymyositis and dermatomyositis. Arthritis Rheum. **2005**, 53, 155–165.
131. Minozzi, S.; Bonovas, S.; Lytras, T.; Pecoraro, V.; González-Lorenzo, M.; Bastiampillai, A.J.; Gabrielli, E.M.;Lonati, A.C.; Moja, L.; Cinquini, M.; et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: A systematic review and meta-analysis. Expert Opin. Drug Saf.**2016**, 15, 11–34.
132. Bouza, E.; Moya, J.G.; Muñoz, P. Infections in systemic lupus erythematosus and rheumatoid arthritis. Infect. Dis. Clin. N. Am. **2001**, 15, 335–361.
133. Carmona, L.; Hernández-García, C.; Vadillo, C.; Pato, E.; Balsa, A.; González-Alvaro, I.; Belmonte, M.A.; Tena, X.; Sanmartí, R.; EMECAR Study Group. Increased risk of tuberculosis in patients with rheumatoid arthritis. J. Rheumatol. **2003**, 30, 1436–1439.
134. Arkema, E.V.; Jonsson, J.; Baecklund, E.; Bruchfeld, J.; Feltelius, N.; Askling, J.; ARTIS Study Group. Are patients with Rheumatoid arthritis still at an increased risk of tuberculosis and what is the role of biological treatments? Ann. Rheum. Dis. **2015**, 74, 1212–1217. [PubMed].
135. Askling, J.; Fored, C.M.; Brandt, L.; Baecklund, E.; Bertilsson, L.; Cöster, L.; Geborek, P.; Jacobsson, L.T.; Lindblad, S.; Lysholm, J.; et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum. **2005**, 52, 1986–1992. [PubMed].
136. Wolfe, F.; Michaud, K.; Anderson, J.; Urbansky, K. Tuberculosis infection in patients with rheumatoid arthritis and the e_ect of infliximab therapy. Arthritis Rheum. **2004**, 50, 372–379. [PubMed].

 doi:10.20944/preprints202412.0263.v1

137. Miltinienė, D.; Deresevičienė, G.; Nakčerienė, B.; Davidavičienė, V.E.; Danila, E.; Butrimienė, I.; Dadonienė, J. Incidence of Tuberculosis in Inflammatory Rheumatic Diseases: Results from a Lithuanian Retrospective Cohort Study. *Medicina* **2020**, *56*, 392. https://doi.org/10.3390/medicina56080392.
138. Yamada T, Nakajima A, Inoue E, *et al* Increased risk of tuberculosis in patients with rheumatoid arthritis in Japan *Annals of the Rheumatic Diseases* 2006;**65:**1661-1663.