Review

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Tuberculosis treatment failure: What are the risk factors? A comprehensive literature review

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ABSTRACT

Tuberculosis (TB), induced by *Mycobacterium tuberculosis*, is 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, and COVID-19 are associated with increased rates of treatment failure. Supplementary challenges, including loss to follow-up and drug-resistant TB, elevate the probability of treatment failure. This review's findings intend to furnish essential insights for policymakers, healthcare professionals, and TB control programs, 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.

Key words: tuberculosis management; tuberculosis risk factors; tuberculosis treatment outcome.

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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) indicates that in 2023, TB likely reclaimed its position as the leading cause of death from a single infectious agent after being surpassed by COVID-19 for three years. TB now results in nearly double the fatalities caused by HIV/AIDS. Each year, over 10 million individuals are diagnosed with TB, and this figure has been steadily rising since 2021 [5]. 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) [6]. 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 [7]. Strengthening health systems is vital for enhancing the early detection of TB and improving the overall quality of care, diagnosis, and treatment [8].

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 [9].

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

We believe this review's findings will offer valuable insights for policymakers, healthcare providers, and TB control programs, enabling them to refine strategies and interventions. Ultimately, this research aims to improve TB management's effectiveness globally, focusing on ensuring better treatment outcomes in regions where they are needed most.

Malnutrition

Low body mass index (BMI) is a well-established risk factor for the development of TB [10]. 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 [11-14]. 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 [15]. For instance, one study found that a BMI above 28 kg/m² was independently associated with reduced susceptibility to TB in rural China [16]. 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 [12]. 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 [17,18].

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 [19]. The study by Cai et al. suggests that central adiposity may be a risk factor for TB, potentially through mechanisms involving chronic low-grade inflammation, insulin resistance,

and altered cytokine profiles. Visceral adipose tissue is metabolically active and can impair immune function by promoting a pro-inflammatory milieu that paradoxically weakens the host's ability to control TB infection.

In another observational study involving 264 patients, Oyewusi et al. [20] 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 indicated that improving BMI could 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 [20].

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 [21].

Malnutrition or a low BMI plays a significant role in TB outcomes [22]. Educating TB patients on the importance of proper and adequate nutrition for successful treatment outcomes is crucial. If needed, provide nutritional and social support.

Tobacco smoking

The relationship between cigarette smoking and TB has been a topic of ongoing debate since at least 1918 [23]. A 2010 editorial [24] 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 attributed mainly to various confounding factors [25,26]. Given the substantial evidence linking smoking to TB, it is recommended that TB control programs incorporate tobacco control as a preventative strategy [27].

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 *M. 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 [23].

Kaliner et al. [28] 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. In Israel, an average of 250–400 TB patients were diagnosed annually over the past decade, with the majority being migrants from TB-endemic countries. The prevalence of TB is particularly high among populations at elevated risk of infection, such as individuals who use substances. The Tel Aviv district, the country's main metropolis, has the highest number of individuals who use substances. 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 [28].

Tobacco smoking has a significant impact on TB treatment outcomes. In Kaliner et al.'s study, nearly 70% of patients who were smokers were confirmed treatment failure [28]. 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 [28, 29, 30]. Tobacco-smoking patients seldom succeed in quitting without structured support or intervention, underscoring the need for targeted smoking cessation programs tailored to this population. Moreover, tobacco use is frequently associated with multiple comorbidities; therefore, effective smoking cessation not only improves overall health but also contributes to reducing the risk and burden of these coexisting conditions. It is essential to educate patients about the negative impact of smoking on treatment outcomes and to encourage and support them in quitting.

Alcohol use

Heavy alcohol consumption is a well-known risk factor for both the development of TB and negative treatment outcomes [31]. 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). Furthermore, reducing alcohol consumption could potentially prevent up to 17% of new TB cases and 15% of TB-related deaths [32]. 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 [33, 34]. 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 [35, 36, 37]. Finally, both alcohol use disorder (AUD) and TB are marked by social marginalization and stigma. Their coexistence further exacerbates individuals' disadvantages, making it more difficult to seek and maintain care [38].

The study conducted by Bayigga J. et al. [39] 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. Out of the 325 individuals with TB examined, 62 (18.7%) were identified as having AUD, with a predominant majority being male (82.3%). This analysis revealed that being male (adjusted prevalence ratio [aPR] 2.32) and residing in an urban area (aOR 1.79) 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 [39].

Khaitan A. et al. [40] 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 [40].

In a global observational study by Jinyi W. et al. [41], 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 in 1990 to 2.54 in 2019. Significant declines were observed in Andean Latin America (average annual percent change [AAPC] = –7.59), East Asia (AAPC = –7.32) and Central Latin America (AAPC = –7.31). 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 suggested that by 2035, the age-standardized mortality rate for TB linked to alcohol intake would be 1.29 per 100,000 individuals [41].

Alcohol use significantly affects TB treatment outcomes. Kaliner et al. [28] 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 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) [28].

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 [28].

Drug 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 [42].

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 [43]. In 2021, over 296 million people reported using at least one drug, reflecting a 23% increase since 2011. According to projections from the UNODC [44], 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 [45].

Sandra E. 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 reported several barriers to smoking cessation, including anxiety/depression (47.4%), seeing others smoke (38.5%), drug use (19.2%) [46].

Given the poorer treatment outcomes observed in TB patients who use substances, collaborative efforts are essential to address these challenges in the effort to eliminate TB. Establishing joint initiatives focused on TB and drug use is recommended to enhance treatment success [47].

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 [48]. 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 [49]. 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 [48].

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 [50]. 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 [51, 52, 53].

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. The analysis revealed a pooled male-to-female TB fatality risk ratio of 1.4. Notably, higher male TB fatality rates were observed in studies with greater levels of homelessness (coefficient 3.18) and a lower proportion of migrants (coefficient -0.24). These findings suggest that TB case fatality rates for males in Europe are 30–50% higher than those for females [50]. Many countries implement TB screening protocols for migrants, enabling earlier diagnosis and timely linkage to care—often before symptoms become severe. Migrant populations tend to be younger and healthier due to selection effects, which may contribute to lower TB fatality rates. Additionally, migrants are often better integrated into formal healthcare systems through asylum procedures, public health initiatives. Stronger familial and community networks, particularly among women, further promote treatment adherence. In contrast, homelessness disproportionately affects men and is associated with delayed diagnosis, poor treatment access, and multiple co-occurring vulnerabilities, all of which elevate TB mortality. Together, these patterns highlight how structural and social determinants influence sex-specific disparities in TB outcomes across different population groups.

In a study conducted in Afghanistan by Shayan N. et al., 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 [53].

Similarly, in an observational study in South Africa, Oshiomah P. et al. [55] 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) [55].

Hind M. AlOsaimi and colleagues conducted a registry-based retrospective cohort study at King Fahad Medical City in Riyadh, Saudi Arabia, using data from the National Tuberculosis Registry to assess treatment outcomes in 427 patients with pulmonary tuberculosis (PTB) between January 1, 2018, and December 31, 2023. 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 aOR of 1.3 [56].

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. Given these findings, future research should prioritize the examination of sex- and gender-related factors that affect TB mortality and fatality.

Age factor

The highest incidence of TB cases is observed in individuals aged 25 to 54 years. However, the epidemic predominantly impacts older adults in the Eastern Mediterranean, Southeast Asia, and Western Pacific regions, as defined by the WHO. In these areas, TB notification rates increase consistently with age, peaking in individuals aged 65 and older [57].

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 [58].

In Iran, Golsha R. et al. [59] 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. The study highlights that age is a significant risk factor for active TB and its treatment outcomes [59].

B. Hauer et al. analyzed national TB notification data from Germany between 2002 and 2006, compiling a pooled 5-year dataset divided into two age groups: younger adults (15–59 years) and the elderly (aged ≥60 years). 31,459 TB cases in individuals aged 15 years and older were identified. The treatment failure rate was significantly higher in the elderly (33.0%) compared to younger adults (14.2%) (OR 0.34), with the rate progressively increasing with age, reaching 63.2% in patients aged ≥90 years. The study highlighted key epidemiological features of TB in the elderly, including lower treatment success and higher mortality rates [60].

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 [61] and 11.2 cases per 100,000 in Germany [60].

These studies collectively highlight the significant role of age in influencing TB outcomes. 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.

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 [62]. The impact of TB on patients' quality of life is intricate and multifaceted, encompassing physical, psychological, and social well-being [63, 64]. Physical manifestations, including chronic coughing, fever, and weight loss, may result in considerable deterioration of physical functioning and general health [65]. Moreover, the psychological and social consequences of TB—including stigma, discrimination, and social isolation—further detract from patients' quality of life [66]. 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 [67, 68]. 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 [63].

In a retrospective study 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 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%) than 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 [69].

In another study, Braga S. 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. Out of the 1,109 papers screened, 34 studies met the inclusion criteria, encompassing 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), a lower rate of treatment completion (RR=0.313), and a higher rate of loss to follow-up (RR=4.331). 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 [70].

These studies collectively highlight the significant role of factors such as urban living, unemployment, and migrant status in influencing TB outcomes. Oshiomah et al. [55] found that residing in a town significantly increased the risk of developing TB, with an odds ratio of 3.20. Migrants, particularly in Europe, are also at higher risk of losing follow-up and discontinuing treatment, with an RR of 4.33, as reported by Cotugno Sergio [70]. 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 ($\chi^2 = 81.1$, $p < 0.001$) [70].

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 [72, 73].

Co-morbidity

Human immunodeficiency virus

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 [42].

The study conducted by Adakun et al. explored the feasibility of assessing and referring to adults who 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 [74].

The study conducted by Barreto-Duarte aimed to investigate factors associated with unfavorable outcomes in anti-tuberculosis treatment (ATT) among patients undergoing retreatment in Brazil. This observational study included 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 [75].

Similarly, Matulyte E. et al. [76] 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. TB is a significant public health issue in Lithuania, which is one of the 18 high-priority TB countries in the European region. Since 2015, it has been the most common AIDS-indicative disease, with the highest proportion of cases in the EU/EEA. The study included 345 cases involving 311 patients (239 new and 106 previously treated cases). 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 [76].

Nasir Tayib Nur and colleagues conducted a retrospective, unmatched case-control study at public health facilities, recruiting 264 participants (53 cases

and 211 controls) to investigate TB treatment failure in Ethiopia. Between 2017 and 2020, the national prevalence of tuberculosis treatment failure ranged from 7.5% to 26%. The prevalence varied by region, with Southeast Ethiopia reporting 8.8%, central Ethiopia 14.5%, and Western Ethiopia 17.5%. A total of 264 records (53 cases and 211 controls) were included from tuberculosis registers. The study identified that the odds of tuberculosis treatment failure were 4.78 times higher among HIV-positive patients compared to HIV-negative patients [77].

These studies collectively reinforce the critical role of HIV in influencing TB treatment outcomes. 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.

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 [78, 42]. The WHO emphasizes the importance of collaborative efforts to address both TB and DM as essential components of the End TB strategy [79]. A systematic review found that nearly 15% of TB patients also had diabetes, with a notably higher prevalence of comorbidity in countries with a high TB burden [80, 81].

As a major risk factor for TB, diabetes impacts disease control and treatment effectiveness at multiple levels. Numerous have highlighted the unfavorable outcomes of TB in patients with diabetes, underscoring the critical need for integrated approaches in managing these interconnected health issues [82, 83].

In one systematic review Huangfu P. and colleagues updated previous analyses and examine the heterogeneity across studies. 104 publications were included, with 64 studies involving 56,122 individuals with TB-DM and 243,035 individuals with TB, all reporting mortality data. Some outcomes revealed significant heterogeneity between studies, which could not be entirely explained, though confounding factors and country income levels contributed to some variations. The analysis showed that TB-DM patients had higher odds of death (OR 1.88) and relapse (OR 1.64) compared to those with TB alone. Limited evidence suggested that TB-DM patients had nearly double the risk of developing MDR-TB (OR 1.98). The study highlights that diabetes mellitus is associated with an increased risk of poor TB treatment outcomes, particularly mortality, and may elevate the risk of developing primary MDR-TB [82].

In another study, Sanju Gautam and colleagues conducted a systematic review and meta-analysis to assess the burden of diabetes among TB patients and its impact on TB treatment outcomes in South Asia, which includes Afghanistan, Bangladesh, Bhutan, Maldives, Nepal, India, Pakistan, and Sri Lanka between 1980, and 2020. Out of the 74 studies included, 65 focused on the prevalence of diabetes among TB patients, and 9 evaluated the impact of diabetes on TB treatment outcomes. The studies included 47 from India, 10 from Pakistan, 4 from Nepal, and 2 from Bangladesh and Sri Lanka. The pooled prevalence of diabetes in TB patients was 21%, with prevalence ranging from 11% in Bangladesh to 24% in Sri Lanka. When compared to non-diabetic TB patients, those with both TB and diabetes had higher odds of mortality (OR 1.7) and treatment failure (OR 1.7), but no significant association with MDR-TB (OR 1.0). This study highlights the significant burden of diabetes among TB patients in South Asia and indicates that TB-diabetes patients face an increased risk of treatment failure and mortality compared to those with TB alone [83].

Nowiński and colleagues analyzed 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 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 OR of 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 [84].

Together, these studies highlight the critical role of diabetes in influencing TB treatment outcomes.

Chronic kidney disease

Chronic kidney disease (CKD) is a major global health concern, affecting approximately 8–16% of the population worldwide [85]. 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 [86]. Previous research has indicated that individuals with CKD, particularly those undergoing hemodialysis (HD), experience a higher rate of TB compared to the general population [87, 88].

Xiao 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 TB patients' clinical characteristics and treatment outcomes with and without CKD, analyzing mortality-related factors. Among the 167 patients, 66.7% of those on hemodialysis (HD), 41.1% of pre-dialysis (pre-HD) patients, and 32.0% 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), hypoalbuminemia (HR: 2.879), CKD stage 4–5 (HR: 4.719), and HD treatment (HR: 6.13) 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 [89].

In a similar study by Pradhan et al. in Nepal, TB prevalence, clinical features, and outcomes in patients with CKD were evaluated. In Nepal, CKD is a significant public health concern, with a prevalence of approximately 10.6% in urban areas. In 2014, Nepal registered a total of 37,025 cases of TB. The overall treatment success rate for drug-susceptible TB was 91%, with a 1.1% failure rate, a 2% default rate, and a 3.3% mortality rate. 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 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 [90].

Taken together, these studies underscore the critical impact of CKD on TB treatment outcomes. These findings highlight the urgent need for integrated management strategies addressing CKD and TB co-infection. Such approaches are essential to improve treatment success and mitigate the dual burden of these diseases.

COVID–19

Globally, TB has likely regained its status as the leading cause of death from a single infectious agent, following three years during which COVID-19 temporarily took the top spot [6]. 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 [91]. 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 [92, 93].

Nicolas Casco 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 recovered, died, or ended the cohort period. 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 [94].

Similarly, Nalunjogi et al. conducted a study comparing the number of new or recurrent TB diagnoses, drug-resistant TB (DR-TB) incidence, and TB-related deaths in 2020 versus 2019 across 11 countries in Europe, North America, and Australia. The results revealed a decrease in the number of TB cases (new diagnoses and recurrences) reported in 2020 compared to 2019, except in 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 [95].

COVID-19, like other viral infections, impairs the host immune response to *Mycobacterium tuberculosis*. An effective and robust immune system is essential for the successful treatment of TB. Immunosuppression, particularly in the context of recurrent COVID-19 infections—as reported in some patients—represents a significant predisposing factor for unfavorable TB treatment outcomes. Together, these studies highlight the significant impact of COVID-19 on TB treatment outcomes.

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 [96-100].

Khaitan and colleagues conducted a study in the Ballabgarh block of Haryana, India, involving TB patients who had been LTFU and staff from the National TB Elimination Program (NTEP). The research aimed to explore stakeholder perspectives on the factors contributing to LTFU, focusing on alcohol use. Almost all key informants, along with many patient participants, believed that alcohol consumption was a significant factor in 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 [40].

Similarly, 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. Additionally, LTFU was the primary risk factor for subsequent loss to follow-up (OR, 4.93). 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 [75].

The 2020 revised guidelines categorize TB treatment outcomes as either successful or unsuccessful, with the latter including LTFU patients. This classification underscores a significant challenge: physicians often struggle to ensure 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 [100].

Together, these studies underscore the critical role of LTFU in determining TB treatment outcomes.

Drug-resistance *Mycobacterium tuberculosis*

The rising prevalence of rifampicin-resistant (RR) and MDR-TB has posed significant public health challenges. Treating patients with MDR/RR *M. 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 [102]. 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 [103-107].

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 ($p = 0.003$). Among TB patients, those who were single, divorced, or widowed were more likely to develop MDR or RR TB than those who were married. Several factors contribute to this issue. First, socioeconomic status plays a crucial role, as unmarried, divorced, or widowed individuals may face limited access to healthcare and adequate living conditions, increasing their risk of drug-resistant TB. Second, behavioral factors are significant; risky behaviors such as living in overcrowded situations or inconsistent TB treatment adherence can contribute to the development of drug-resistant strains. Third, social support is important. Married individuals often benefit from stronger support networks, which help them stick to treatment, whereas unmarried individuals may lack this support, leading to potential interruptions in care. Finally, psychological factors are relevant as the emotional challenges of being unmarried or divorced can raise stress and anxiety levels, weakening the immune system and heightening susceptibility to drug-resistant TB. Additionally, significant associations were noted between ADR TB and previous TB treatment. These findings offer critical insights into the drug resistance patterns of *M. tuberculosis* strains and the associated risk factors in Northern Iran [108].

The retrospective cross-sectional study conducted by 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, Zambia. In Zambia, the burden of DR-TB is not well understood due to limited routine surveillance data despite the country being ranked among the top 30 nations with the highest burden of both TB and DR-TB. The prevalence of MDR-TB was reported at 1.8% in 2001. However, the proportion of MDR-TB cases has increased significantly, rising from 0.3% in new cases and 8.1% in previously treated cases in 2014 to 2.8% in new cases and 18% in previously treated cases by 2018. A total of 183 patients were included in the study. Most 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%), 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 (aOR 0.253) and male gender (aOR 0.261) [109].

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 in South Korea. A total of 52 TB patients with treatment failure were included in the study. The presence of MDR-TB was significantly associated with the presence of cavities. Notably, 36.5% of patients in the treatment failure group had MDR-TB [110].

Collectively, these studies underscore the strong correlation between MDR-/RR-TB and treatment failure.

Directly-observed treatment

Directly Observed Treatment (DOT) refers to the process where a healthcare team personally supervises and administers medication to patients to ensure they follow their TB treatment regimen. Carrying out DOT requires healthcare professionals, transportation, time, and the ability to be physically present at the patient's location. However, fulfilling all these requirements can be challenging, especially given the many TB patients who would benefit from such monitoring.

In a study by Dashuki and colleagues, a retrospective cohort analysis was performed on TB cases with comorbidities in Malaysia. Among the 712 TB cases with comorbidities, 76% achieved a successful TB treatment outcome, while 24.0% did not. Out of the patients with unsuccessful TB treatment outcomes, 37.4% had followed DOT during the intensive phase, while 62.6% did not receive DOT [111].

However, implementing DOT presents significant challenges for patients and healthcare providers, primarily due to limited financial and human resources. Growing evidence indicates that emerging digital adherence technologies, such as video directly observed therapy (VDOT), offer promising alternatives to traditional methods. In a study by J.N. Sekandi, a 2-arm, parallel-group, open-label randomized trial was conducted in Kampala, Uganda. The VDOT group received a smartphone with an app for monitoring, while the UCDOT group followed the routine practices established by the Uganda National TB Program. The results showed that VDOT users were significantly more likely to achieve ≥80% adherence to their prescribed doses than UCDOT users (adjusted risk ratio 8.4). The most common reasons for failure to submit medication intake videos included having an uncharged phone battery, forgetting to record the videos during intake, and losing the smartphone [112].

The key benefits of VDOT likely lie in its time efficiency, resource savings, and patient convenience. A similar study conducted in Brazil by dos Santos and colleagues reports that only 9.7% of patients discontinued their VDOT follow-up due to abandonment. In comparison, the cure/treatment completion rate was 57.5%. Regarding adherence to the prescribed treatment period for TB, 67% of patients completed more than 66% of their treatment. The findings indicated that patients and healthcare professionals well accepted the system. The study suggests that VDOT could be a promising tool to complement traditional TB DOT, expanding its reach to improve adherence and reduce abandonment rates [113].

N. T. Nur and colleagues conducted a retrospective, unmatched case-control study at public health facilities, recruiting 264 participants to examine TB treatment failure in Ethiopia. The study included a total of 264 records from TB registers. The odds of TB treatment failure were 3.94 times higher among patients who did not receive DOTS compared to those who received DOTS [77].

These studies suggest that while DOT faces significant challenges, VDOT offers a viable and well-received alternative that could help improve treatment adherence and outcomes for TB patients.

Conclusions

Several factors can influence the success of TB treatment, including individual behaviors, sociodemographic conditions, and comorbidities (Table 1). These risk factors require tailored management strategies: patients with a low BMI should receive nutrition support, while those who smoke tobacco or use alcohol need psychological assistance. Individuals with alcohol or drug use should undergo inpatient TB treatment for the entire duration of therapy. Men, older adults, those living in urban areas, migrants, and patients with comorbidities should receive directly observed treatment. Unemployed individuals require psychological and social support. Additionally, patients at risk of loss to follow-up or those at risk of developing drug-resistant TB should also receive inpatient treatment for the full duration of their TB therapy.

Key risk factors for poor TB treatment outcomes include a low body mass index (BMI < 24 kg/m^2 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

Table 1. Several factors that can influence the success of tuberculosis (TB) treatment and areas.

Risk factors	Potential intervention measure
Low body mass index (BMI < 24 kg/m²)	Nutritional support
Tobacco smoking	Psychological support
Alcohol use	Psychological support, inpatient TB treatment for the entire duration of TB therapy
Drug use	Inpatient TB treatment for the entire duration of TB therapy
Males	Directly observing treatment
Older age	Directly observing treatment
Unemployment	Psychological and social support
Living in urban areas	Directly observing treatment
Migrants	Directly observing treatment
Co-morbidities like HIV, diabetes, chronic kidney disease, COVID-19 infection	Directly observing treatment, treating co-morbidities
Risk of loss to follow-up	Inpatient TB treatment for the entire duration of TB therapy
Drug-resistant TB	Inpatient TB treatment for the entire duration of TB therapy

treatment failure, and particularly, the increasing rate of TB treatment failure among individuals aged 65 and older. 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 more significant 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 who succumb to either disease alone (p<0.001). Loss to follow-up is another critical factor, increasing the likelihood of treatment failure nearly fourfold. At the same time, drug-resistant TB (including multidrug-resistant TB or MDR-TB) is present in about one-third of treatment failures. However, VDOT users had significantly better adherence (≥80%, OD 8.4) than those who followed routine DOT practices.

All the risk factors for TB treatment failure discussed in this article are closely interlinked. The greater the number of risk factors a patient has, the higher the risk of treatment failure. Those with a lower BMI, male gender, migrant status, urban residency, and additional behaviors such as smoking, alcohol, and drug use are at a higher risk. Comorbidities like diabetes, renal failure, and HIV further increase the likelihood of poor outcomes. Therefore, patients with multiple risk factors should be closely monitored and managed with personalized care plans.

The success of TB treatment is significantly influenced by a range of sociodemographic and clinical risk factors. Evidence indicates that male gender, smoking, alcohol use, unemployment, low educational level, and comorbidities such as HIV, chronic kidney disease, and COVID-19 are associated with poorer treatment outcomes. These factors often coexist and may interact synergistically, compounding their negative impact on treatment efficacy. Therefore, comprehensive patient assessment and targeted interventions for individuals with multiple risk factors are essential to improve treatment success rates and reduce the burden of TB.

TB control programs must adopt comprehensive strategies beyond medication, such as patient education, counseling, psychological support, incentives, reminders, and digital health technologies to improve

treatment success. These interventions can help address individual barriers to adherence, ensuring better treatment completion and improved patient outcomes.

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