

REVIEW ARTICLE

Non-success in pulmonary tuberculosis treatment: A narrative review of key contributing factors

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Abstract

Medical factors and non-medical factors account for a high number of difficulties in treating tuberculosis. This study aims to comprehensively examine the factors that contribute to failure in tuberculosis treatment. We searched for relevant articles in various databases, such as PubMed, ScienceDirect, ProQuest, Research Gate and Google Scholar. The summary of the results from several of these articles are that advanced age, the presence of comorbidities such as diabetes mellitus and HIV, low vitamin C, low body mass index, and non-adherence to treatment are the key factors for failure in pulmonary tuberculosis treatment. The role of health workers in the medical field and support from the patient's family are important to provide support to patients with tuberculosis to increase their compliance with treatment. (*Afr J Reprod Health 2024; 28 [10s]: 421-429*).

Keywords: Advanced age, comorbidities, vitamin C, BMI, non-adherence, tuberculosis

Résumé

Les facteurs médicaux et non médicaux expliquent un grand nombre de difficultés dans le traitement de la tuberculose. Cette étude vise à examiner de manière approfondie les facteurs qui contribuent à l'échec du traitement de la tuberculose. Nous avons recherché des articles pertinents dans diverses bases de données, telles que PubMed, ScienceDirect, ProQuest, Research Gate et Google Scholar. Le résumé des résultats de plusieurs de ces articles montre que l'âge avancé, la présence de comorbidités telles que le diabète sucré et le VIH, un faible taux de vitamine C, un faible indice de masse corporelle et la non-observance du traitement sont les facteurs clés d'échec dans la tuberculose pulmonaire. traitement. Le rôle des agents de santé dans le domaine médical et le soutien de la famille du patient sont importants pour apporter un soutien aux patients atteints de tuberculose afin d'accroître leur observance du traitement. (*Afr J Reprod Health 2024; 28 [10s]: 421-429*).

Mots-clés: Âge avancé, comorbidités, vitamine C, IMC, non-observance, tuberculose

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. According to the latest data from the World Health Organization (WHO), 10 million people worldwide were expected to suffer from tuberculosis in 2020. These include 5.6 million men, 3.3 million women, and 1.1 million children. In the same year, 1.5 million people died from TB, including 214,000 people who were co-infected with HIV¹. The high incidence rate and the difficulty in preventing the disease are attributable to medical (comorbidities, micronutrient intake, etc.) as well as

non-medical factors (low knowledge, lack of family support, non-compliance with taking medication), which all lead to failure in tuberculosis treatment. Moreover, individuals afflicted with tuberculosis may experience an unsafe health environment and diminished public hygiene². The pulmonary tuberculosis epidemic occurs most often in elderly people and is progressive, increasing the incidence rate with increasing age^{3,4}. The presence of comorbidities⁵ like HIV⁶, diabetes mellitus, and malignancy⁷ are often associated with the failure to cure pulmonary tuberculosis⁸. Recognizing comorbidities in patients with TB is important to

ensure early diagnosis and improve co-management. Worldwide, individuals with poor nutritional status suffer from tuberculosis more than those with better nutrition⁹. Poor nutrition is considered one of the factors that increases the risk of pulmonary tuberculosis¹⁰. Poor nutritional status can reduce the immune system so that the disease can easily enter and infect the body. Poor nutrition can also affect the healing process from the disease¹¹. Poor nutrition will generally cause a decrease in BMI. A low BMI has a greater risk of failure to cure pulmonary tuberculosis¹². Evidence suggests that BMI < 16 kg/m² is associated with an increased number of lung cavities and zones affected in pulmonary tuberculosis patients¹³.

Dietary micronutrient intake is important for human health^{14,15}. The multitude of effects that vitamin C has on human health can be attributed to its antioxidant properties and its role as a cofactor for various biosynthetic enzymes¹⁶. Overall, the significance of vitamin C in maintaining optimal immunity is widely recognized¹⁷.

Treatment compliance in tuberculosis patients is a complex behavioral problem and has many aspects that need to be better understood¹⁸. The success in curing tuberculosis depends greatly on the extent to which TB patients comply with taking prescribed medications¹⁹. Therefore, this article aims to provide an update and clarification regarding factors that contribute to treatment failure which include. We specifically investigated the role of advanced age, comorbid diseases, low intake of vitamin C, body mass index (BMI), and non-compliance with prescribed medications as causative factors in reducing the effectiveness of treatment of tuberculosis.

Methods

This was a narrative review that employed a comprehensive strategy by searching for articles in research journal databases, using the Internet, and reviewing articles. Database searches via PubMed, ScienceDirect, ProQuest, Research Gate and Google Scholar. Five articles were created to analyze each article's topic, objectives, methods used, sample size, and applicability of findings. Writing a

Literature Narrative Review follows 2 steps proposed by Green *et al*²⁰, including: Preparation and General Guidelines. Steps are outlined as follows:

Stage 1: Preparation

The preparation stage consists of (1) Topic selection: The topic of this narrative review was 'what causes pulmonary tuberculosis treatment failure'. (2) Initial Search: literature search from several databases such as; PubMed, ScienceDirect, ProQuest, Research Gate and Google Scholar. The keywords used were failure, pulmonary, treatment and tuberculosis. (3) Objective: The objective of this study was to determine the key factors in pulmonary tuberculosis treatment failure.

Stage 2: General guidelines

There are no rigid guidelines for what should or should not be included. We synthesise the literature by integrating the findings obtained from the note-taking or table-making process. This is necessary for readers who are less familiar with the topic presented, so as to describe a clear, relevant, and easy-to-read synthesis. There is no registration for narrative reviews.

Results

The five selected articles (Table.1) had appropriate topics, namely factors related to the causes of failure in the treatment of pulmonary tuberculosis. In terms of research objectives, one article²¹ aimed to assess the determining factors for the success of TB treatment in DOTS patients in the city of Jimma, southwest Ethiopia, while another article²² investigated the impact of comorbidities on healing outcomes and mortality rates in TB patients in Poland. Another article²³ investigated the relationship between dietary micronutrient intake with pulmonary tuberculosis cure outcomes, while the fourth article²⁴ investigate the impact of diabetes and low body mass index (BMI) on tuberculosis (TB) treatment outcomes in a South Indian, The final article²⁵ aimed to understand how non-adherence

Table 1: Narrative review articles

No	Researcher, year, and title	Research objectives	Methods	Sample	Result
1	Teka, 2023, Determinants of Unsuccessful TB Treatment Outcomes Among Patients on Directly Observed Treatment Short Course in Jimma Town Health Facilities, Southwest Ethiopia: A Case-Control Study ²¹	To assess the determinants of unsuccessful TB treatment outcomes among patients with directly observed treatment, short-course (DOTS) in Jimma town, southwest Ethiopia	Unmatched case-control study.	590 participants (118 cases with unsuccessful treatment and 472 successful treatment)	Significant determinants of unsuccessful TB treatment outcomes included age > 35 years, lack of contact person, HIV positive status, and malnutrition
2	Nowiński A <i>et al</i> , 2023, The impact of comorbidities on tuberculosis treatment outcomes in Poland: a national cohort study ²²	To analyze the impact of comorbidities on TB treatment outcomes in Poland	Multinomial regression analysis of registry data.	19,217 records from the TB registry	Presence of comorbidities (e.g., diabetes, HIV, alcoholism) was associated with lower treatment success rates and higher mortality.
3	Xiong K <i>et al</i> , 2020, Association of Dietary Micronutrient Intake with Pulmonary Tuberculosis Treatment Failure Rate: ACohort Study ²³	The purpose of the study was to investigate the association between dietary micronutrient intake and the treatment outcome of pulmonary tuberculosis (PTB). Specifically, it aimed to determine if low intake of certain micronutrients, such as vitamin C and zinc (Zn), is associated with a higher failure rate of PTB treatment.	The study was a prospective cohort study	The study included 1834 participants who met the inclusion criteria, which were being diagnosed with pulmonary tuberculosis, aged over 18, and provided informed consent	Low intake of vitamin C (adjusted OR (95% CI): 1.80 (1.07, 3.04), Ptrend = 0.02) and Zn (adjusted OR (95% CI): 2.52 (1.25, 5.08), Ptrend = 0.02) was associated with a higher treatment failure rate.
4	Kornfeld <i>et al</i> , 2020, Impact of Diabetes and Low Body Mass Index on Tuberculosis Treatment Outcomes ²⁴	To investigate the impact of diabetes and low body mass index (BMI) on tuberculosis (TB) treatment outcomes in a South Indian cohort	Prospective cohort study	The cohort consisted of 389 participants, including 256 individuals with diabetes and 133 with normal glucose tolerance	Low BMI was significantly associated with adverse TB treatment outcomes, including higher rates of treatment failure and death.

5	Chimeh, R. A <i>et al</i> , 2020, Clinical and economic impact of medication non-adherence in drug-susceptible tuberculosis: a systematic review ²⁵	The study aimed to understand how non-adherence affects clinical outcomes such as death and treatment failure, as well as the economic burden associated with non-adherence.	Systematic review following the PRISMA guidelines	The review included 14 studies meeting the inclusion criteria. These studies were conducted in various countries and included both retrospective and prospective cohort studies, as well as case-control studies. Population sizes ranged from 83 to 2416 patients, with varying age groups and a higher proportion of males in most studies	Non-adherence was associated with a higher risk of treatment failure.
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affects clinical outcomes such as death and treatment failure, as well as the economic burden associated with non-adherence.

The analysis method used can be explained as follows: of the five articles, two articles used a prospective cohort study; one article used unmatched case-control design; one article used multinomial regression analysis of registry data ; and one article systematic review following the PRISMA guidelines .

The sample size in the four articles that used data from reports collected during the research period and one article uses mixed data, primary data in the form of questionnaires and medical records. Two article used a sample size of more than 10,000; one article used a sample size of more than 1000; while the remaining 2 articles used less than 1000 sample sizes. The results of the analysis of the five selected articles are as follows. The first article focuses on the determinants of success of tuberculosis treatment in patients following short, directly observed treatment at a health facility in Jimma City, Southwestern Ethiopia²¹. Advanced age, HIV positive, lack of people to contact, and malnutrition were the key determining factors identified for the success of TB treatment. Those aged over 34.7 years were 2 times more likely to have an unsuccessful treatment outcome than those aged ≤ 34.7 years.

The second article focuses on the impact of comorbidities on tuberculosis treatment outcomes in Poland. Comorbidities were associated with a lower healing success rate and a higher mortality rate. Comorbidities such as diabetes, alcoholism, substance addiction, immunosuppressive therapy, cancer, and tobacco use increase the risk of failure to cure tuberculosis. The findings in this article are that diabetes, alcoholism, immunosuppressive therapy, and cancer are associated with lower cure success rates and higher mortality in TB patients in Poland²².

The third article focuses on the relationship between micronutrient intake and the rate of failure to cure pulmonary tuberculosis. Low intake of micronutrients such as vitamin C and zinc is associated with higher rates of treatment failure in TB patients. Food intake is an important factor in regulating the nutritional status of tuberculosis patients and may ultimately affect the outcome of tuberculosis cure. Low vitamin C and zinc intakes are associated with higher rates of cure failure in patients with tuberculosis. Supplementing with vitamin C and zinc may help treat tuberculosis. The lowest percentiles of vitamin C and zinc intake were associated with increased rates of tuberculosis cure failure, whereas the lowest and middle percentiles of magnesium intake were associated with a lower risk of cure failure²³.

The fourth article focuses on the impact of diabetes and low body mass index on tuberculosis recovery outcomes. Low body mass index (BMI) and diabetes are independently associated with increased risk of tuberculosis and adverse outcomes²⁴. Paradoxically, uncontrolled diabetes has a protective effect in patients with low BMI and pulmonary tuberculosis, resulting in sputum conversion and cure rates approaching those in normal-BMI-high-BMI diabetics and non-diabetics.

The fifth article focuses on how non-adherence affects clinical outcomes such as death and treatment failure, as well as the economic burden associated with non-adherence²⁵. Non-adherence to tuberculosis treatment is significantly associated with tuberculosis patients relapsing or relapsing. A high recurrence rate indicates unsuccessful treatment²⁶. Five articles focus on factors that can lead to failure during tuberculosis treatment. Failure to treat tuberculosis can lead to an increased risk of disease, drug resistance, transmission, and death²⁷.

Discussion

Tuberculosis, caused by the *Mycobacterium tuberculosis* complex bacteria, is one of the oldest diseases known to affect humans and is a leading cause of death worldwide²⁸. The disease remains the leading cause of infection-related deaths worldwide, with poverty being the leading associated predisposing factor. Clinically, TB manifests as "latent" TB and active TB, with each disease treated differently²⁹. Many factors can cause failure in curing pulmonary tuberculosis. Therefore, it is necessary to take steps or identify the risk factors that are associated with failure to recover, which is an important component in maximizing the effectiveness of TB control programs³⁰.

The elderly population continues to increase worldwide. Most tuberculosis patients are over 50 years old, with higher rates of case fatality and failure in patients over 65 years old³¹. Pulmonary tuberculosis occurs most frequently in the elderly due to endogenous reactivation of the infection³². Advanced age is often a causal factor in treatment failure, this can be caused by; (1) The immune

system declines so that as we get older, the immune system tends to weaken. A body that is unable to fight infection effectively can cause difficulties in dealing with tuberculosis bacteria, (2) difficulty in undergoing treatment. Tuberculosis treatment regimens generally require discipline and persistence in taking medication regularly over a fairly long period. In old age, patients may experience difficulty in adhering to treatment schedules due to various factors, such as memory impairment, and limited mobility. So the death rate for elderly tuberculosis patients is much higher than for young patients³³. Atypical clinical manifestations in old age can cause delays in diagnosis and treatment, resulting in high morbidity and mortality rates. The clinical approach to tuberculosis in elderly patients is complicated by various factors, necessitating a high index of suspicion for tuberculosis in this population³⁴.

Comorbidities contribute to TB deaths across all ages, with two-thirds of deaths occurring within two months of TB registration. Therefore, they can be a factor in treatment failure, as diabetes increases the risk of treatment failure, death, and relapse in TB patients³⁵. The presence of comorbidities, such as diabetes, HIV, alcoholism, drug addiction, immunosuppressive therapy, and cancer, is associated with lower cure success rates and higher mortality among TB patients²². For this reason, doctors must monitor side effects and response to antituberculosis therapy in patients with comorbidities³⁶. Comorbidities can increase the risk of severe infections, affect tissue healing, and affect drug metabolism.

Micronutrients are closely related to pulmonary tuberculosis (PTB). Micronutrient support may reduce chronic inflammation and improve sputum smear or culture conversion to contribute to anti-TB cure³⁷. Micronutrients, one of which is vitamin C, play an important role in curing pulmonary tuberculosis. Low intake of vitamin C has been reported to be associated with a higher incidence of TB failing to cure³⁸. Giving high doses of vitamin C (15 g/day) orally to seriously ill tuberculosis patients every day for 6 to 8 months increases appetite and physical activity without negative effects³⁹.

Individuals with pulmonary tuberculosis tend to fall into the underweight category⁴⁰. Individuals with low BMI tend to have a higher risk of treatment failure for TB. Poor nutritional status, often reflected in low BMI, can weaken the immune system and hinder the body's ability to fight TB infection. Additionally, low BMI can also affect the absorption of TB medication in the body, which in turn can reduce the effectiveness of treatment. The significant association between TB and BMI is only observed in cases of pulmonary TB, not extra-pulmonary TB⁴¹. Individuals suffering from tuberculosis with a Body Mass Index (BMI) below 18.5 are independently predicted to experience mortality within 8 weeks, thus greatly increasing the potential for treatment failure⁴². Attaining a favorable body mass index requires maintaining regular physical activity and following a balanced, nutritious diet consistently.

Adherence to TB medication is critical for successful treatment outcomes, controlling spread and preventing the development of drug resistance in TB⁴³. Main reasons for non-compliance with TB treatment, food support, reminders and encouragement; busy work commitments; being away from home; perceived and experienced stigma and discrimination; beliefs, e.g. about health/treatment; perceived risks; other than anti-TB drugs, financial constraints in obtaining adequate food and medical expenses; poor relationships between healthcare providers and patients, such as communication gaps, lack of respect for patients, poor quality of healthcare, and insufficient patient satisfaction; Health Information/ Education, drug exposure, persistence of symptoms after initiation of treatment⁴⁴. Reasons for patient non-compliance with tuberculosis treatment include; already feeling better, no longer showing symptoms or getting better, in the recovery period, afraid of the side effects of the drug⁴⁵. Attaining a favorable body mass index requires maintaining regular physical activity and following a balanced, nutritious diet consistently. This involves a holistic approach that includes patient education, social support, understanding and managing drug side effects and addressing economic or psychological factors that

may influence adherence. The medical team also has an important role in monitoring and supporting patients so that they can follow the treatment plan correctly.

Based on the articles reviewed, the reasons behind the ineffectiveness of pulmonary tuberculosis treatment encompass various factors, such as older age, concurrent health conditions, inadequate vitamin C intake, body mass index (BMI), and lack of adherence to treatment protocols. Hence, addressing these factors is crucial in mitigating treatment failure.

The findings highlight the importance of health worker roles and family support in improving treatment adherence, which can inform public health policies and interventions to enhance TB treatment success rates. As a narrative review, the study may be subject to selection bias, as it relies on the authors' discretion in choosing which studies to include, potentially overlooking some relevant studies.

Conclusion

The studies included in this review show that advanced age, the presence of comorbid diseases, low vitamin C, low body mass index (BMI), and non-adherence to treatment are factors that can cause pulmonary tuberculosis treatment failure. Therefore, the role of health workers in the medical field and support from the patient's family is very important to provide support to TB patients in increasing compliance with treatment.

Contribution of authors

Hasrah Junaidi: conceptualized and designed the study,
 Iskandar Arfan: collected and analyzed the data,
 Annis Catur Adi: reviewed empirical studies,
 Prehatin Trirahayu Ningrum: designed the methodology,
 Hasrah Junaidi, and Iskandar Arfan: wrote the introduction and edited the paper.

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