PROPORTION AND FACTORS ASSOCIATED WITH UNFAVORABLE OUTCOMES AMONG PULMONARY TUBERCULOSIS PATIENTS IN KELANTAN: 10 YEARS PERSPECTIVE

DR MOHD KHAIRI SAFWAN BIN JOHARI

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By

DR MOHD KHAIRI SAFWAN BIN JOHARI

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LIST OF ABBREVIATIONS

ACF	Active case findings
AFB	Acid fast bacilli
COVID-19	Coronavirus disease of 2019
CXR	Chest X-ray
DOTs	Direct Observation Therapy, short course
DST	Drug susceptibility test
HIV	Human Immunodeficient Virus
JEPeM-USM	Human Research Ethics Committee of Universiti Sains Malaysia
JKNK	Jabatan Kesihatan Negeri Kelantan
LTFU	Lost to follow up
MDR-TB	Multi drug resistant tuberculosis
Mtb	Mycobacterium Tuberculosis
NMRR	National Medical Research Register
NTBR	National Tuberculosis Registry
PCF	Passive case finding
PTB	Pulmonary Tuberculosis
RR-TB	Rifampicin-resistant Tuberculosis
TB	Tuberculosis
USM	Universiti Sains Malaysia
XDR-TB	Extensively drug-resistant

LIST OF SYMBOLS

<	Less than
>	More than
%	Percentage
P	Proportion
d	Different
Z_a	Z score associated with level of significant alpha
n	Number of samples
P_0	The proportion of participant with exposure to factor without outcome
P_1	The proportion of participant with exposure to factor with the outcome
m	The ratio of independent variables
α	Alpha

PERATUSAN DAN FAKTOR YANG BERKAITAN KETIDAKSEMPURNAAN HASIL RAWATAN DALAM KALANGAN PESAKIT PTB DI KELANTAN: PERSPEKTIF 10 TAHUN

ABSTRAK

Latar Belakang: Tuberkulosis (TB) adalah salah satu isu kesihatan dan penyebab kematian paling tinggi di seluruh dunia. Walaupun terdapat banyak usaha untuk mengawal tuberkulosis, ketidaksempurnaan hasil rawatan masih menjadi masalah.

Objektif: Menentukan peratusan hasil yang tidak baik dan faktor faktor yang berkaitan dengan pesakit PTB di Kelantan dari tahun 2013 hingga 2022.

Metodologi: Kajian kohort retrospektif telah dijalankan dengan data sekunder daripada daftar Tuberkulosis Kebangsaan (NTBR) di Kelantan. Kajian ini melibatkan 1,260 pesakit PTB yang dipilih secara rawak. Data mengenai ciri-ciri sosiodemografi, komorbiditi, dan ciri klinikal telah dianalisis menggunakan statistik deskriptif, serta analisis regresi logistik univariat dan multivariat.

Keputusan: 20.8% pesakit PTB mempunyai ketidaksempurnaan hasil rawatan. Status HIV positif (OR disesuaikan 5.69, 95% CI: 3.78-8.57, p<0.001), pesakit kerintangan anti-tibi (MDR-TB) (OR disesuaikan 5.69, 95% CI: 2.40-13.52, p<0.001), dan pengawasan DOTs oleh ahli keluarga (OR disesuaikan 5.02, 95% CI: 1.73-14.59, p=0.003). Semuanya dikaitkan dengan ketidaksempurnaan hasil rawatan.

Kesimpulan: Keputusan ini menunjukkan bahawa terdapat banyak masalah besar dalam menguruskan tuberkulosis, terutamanya di kalangan pesakit HIV positif dan MDR-tuberkulosis. Ia juga menunjukkan betapa pentingnya pengawasan profesional dalam DOT. Hasil ini adalah penting untuk membangunkan intervensi sasaran yang akan meningkatkan hasil rawatan TB di Kelantan.

Kata Kunci: TB paru-paru, ketidaksempurnaan hasil rawatan, Kelantan

PROPORTION AND FACTORS ASSOCIATED WITH UNFAVORABLE OUTCOMES AMONG PTB PATIENTS IN KELANTAN: 10 YEARS PERSPECTIVE

ABSTRACT

Background: Tuberculosis (TB) is a major global health concern and a leading cause of death worldwide. Despite significant efforts to control TB, unfavorable treatment outcomes remain a challenge.

Objective: To determine the proportion of unfavorable outcomes and identify factors associated among PTB patients in Kelantan from 2013 to 2022.

Methodology: A retrospective cohort study design was employed, utilizing secondary data from the National Tuberculosis Registry (NTBR) in Kelantan. The study included 1,260 PTB patients selected through simple random sampling. Data on sociodemographic characteristics, comorbidities, and clinical features were analysed using descriptive statistics, and univariable, and multivariable logistic regression analyses.

Results: The proportion of unfavorable outcomes among PTB patients was 20.8%. Key factors associated with unfavorable outcomes included positive HIV status (Adjusted OR 5.69, 95% CI: 3.78-8.57, p<0.001), multidrug-resistant TB (MDR-TB) status (Adjusted OR 5.69, 95% CI: 2.40-13.52, p<0.001), and DOTs supervision by family members (Adjusted OR 5.02, 95% CI: 1.73-14.59, p=0.003).

Conclusion: The findings highlight significant challenges in managing PTB, particularly among HIV-positive and MDR-TB patients and underscore the importance of professional supervision in DOTs. These insights are crucial for developing targeted interventions to improve PTB treatment outcomes in Kelantan.

Keywords: Pulmonary tuberculosis, unfavorable outcomes, Kelantan

CHAPTER 1

INTRODUCTION

Tuberculosis (TB) is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide. The bacillus Mycobacterium tuberculosis (Mtb), which causes tuberculosis, is spread through the air by sick individuals. About a quarter of the global population is estimated to have been infected with TB but most people will not go on to develop TB disease and some will clear the infection. Adults account for over 90% of all tuberculosis cases each year, with men outnumbering women. The disease primarily affects the lungs, pulmonary tuberculosis (PTB), but can sometimes affect other organ, extra-pulmonary tuberculosis(WHO, 2022).

1.1 Background of the study

In 2022, the global situation regarding TB reflected both recovery and ongoing challenges. After a decline in TB diagnoses during the initial years of the COVID-19 pandemic, there was a significant increase in 2022 with 7.5 million people newly diagnosed with TB, marking the highest annual total since the World Health Organization (WHO) began its monitoring efforts in 1995. This surge is attributed partly to a backlog of undiagnosed cases from previous years when health services were disrupted by the pandemic. TB remained the world's second deadliest infectious disease after COVID-19 in 2022, causing an estimated 1.30 million deaths. This represents a decrease from the 1.4 million deaths in each of the years 2020 and 2021, but it underscores the persistent threat posed by TB. The pandemic is estimated to have

resulted in almost half a million excess TB deaths from 2020 to 2022 due to delayed diagnoses and interrupted treatment. The overall TB incidence rate was 133 cases per 100,000 people in 2022, showing a modest reduction of 8.7% from 2015, which is well below the WHO target of a 50% reduction by 2025. Regionally, Africa and Europe showed better progress compared to global averages, with some countries achieving significant reductions in TB cases. The global burden of TB remains concentrated in a few high-burden countries. Thirty countries accounted for 87% of all TB cases, with eight countries (India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh, and the Democratic Republic of the Congo) accounting for two-thirds of the global total. Multidrug-resistant TB (MDR-TB) continues to be a major challenge, with only about 43% of those needing treatment receiving it in 2022.

Despite improvements in diagnosis rates post-pandemic, the global targets for TB treatment and prevention from 2018 to 2022 were not met. Only 34 million people were treated for TB, falling short of the 40 million targets. Financial and economic barriers remain significant, with approximately 50% of TB patients facing catastrophic costs related to treatment. This highlights the need for better healthcare access and more robust social protection measures(WHO, 2023).

In Malaysia, 23 644 cases of TB were notified in 2020, 91.7% of them new cases and 58.0% smear positive PTB. Adult patients with active PTB typically present with a history of productive cough, haemoptysis, loss of appetite, unexplained weight loss, fever, night sweats and fatigue. However, typical symptoms may be absent in the immunocompromised or elderly patients. When reviewing a patient with suspected TB, taking a full history and conducting a complete clinical examination is a must,

followed by performing a chest radiograph (CXR) and sputum smear microscopy. In a centre where radiography facilities are not available, diagnosis of PTB can be made based on clinical findings and positive sputum smear results. Over the last decade, significant progress has been achieved in treatment outcomes of TB cases. The cure rate of pulmonary smear positive TB cases increased from 67% in 2009 to 77.0% in 2015. The full cohort analysis of the 2014 cohort of new AFB- positive cases are the following: favorable outcome is 78.1% and unfavorable outcomes was divided into loss to follow-up: 4.9%, failure: 0.2%, death: 9%, not evaluated: 7.5%. All patients with clinically diagnosed or bacteriologically confirmed TB must be notified under the Prevention and Control of Infectious Diseases Act, 1988 (Act 342) to the District Health Office. TB notification is mandatory within seven days of diagnosis and failure to notify is compoundable (MOH, 2021).

Malaysia aims to end TB by 2035, showing our dedication to improving the nation's health. The goal for TB control here is to lessen the disease's impact by making sure everyone has access to quick, quality diagnosis and treatment for all types of TB. Through the combined efforts of healthcare professionals, policy makers, and the community, we are committed to advancing in TB control, improving the health of our citizens, and moving Malaysia closer to this important public health goal(MOH, 2016).

There are studies done to identify the associated factors that can influence the treatment outcomes for tuberculosis treatment elsewhere. Among associated factors that were highlighted in the literature were socio-demographic characteristics, comorbidities such as diabetes and HIV, chest radiograph findings, history of previous

TB treatment sputum cultures and drug susceptibility testing for Mycobacteria, multi-drug resistance status, as well as smoking status(Ronaidi et al., 2011).

1.2 Problem statement

Sustainable Development Goal (SDG) Target 3.3 aims to end the epidemics of AIDS, TB, malaria, and neglected tropical diseases by 2030, as well as combat hepatitis, water-borne diseases, and other communicable diseases (WHO, 2022b).

The End TB Strategy outlines ambitious goals: achieving an 80% reduction in TB incidence by 2030, a 90% reduction in TB deaths by 2030, and ensuring that no TB-affected households face catastrophic costs (WHO, 2022b).

This study aims to address a critical knowledge gap regarding the factors associated with unfavorable outcomes in PTB patients in Kelantan over a ten-year period. Previous research in Malaysia has primarily focused on specific populations and has been hospital-oriented, underscoring the need for a study that includes the general population, especially PTB patients, who are more contagious compared to those with extrapulmonary tuberculosis.

1.3 Study rationale

TB remains a significant public health challenge globally, particularly in regions like Kelantan, where socio-economic factors, healthcare access, and healthcare infrastructure can heavily influence treatment outcomes. Despite global advancements in TB control, Malaysia continues to face challenges, especially in Kelantan, where rural settings, low socio-economic status, and limited healthcare resources create

barriers to successful TB management. Current research often lacks a comprehensive focus on Kelantan's population over an extended period, leaving gaps in understanding the socio-demographic factors contributing to unfavorable TB outcomes. Addressing this gap is crucial, as local and regional studies can provide more accurate data to tailor interventions that reflect the specific health challenges of the population.

The findings will guide local and national public health policymakers in designing targeted strategies for TB control, not only improving outcomes in Kelantan but also offering insights that can be applied to other regions with similar socio-economic profiles. Ultimately, this research will contribute to global TB control objectives by providing context-specific solutions to reduce TB-related morbidity and mortality in underserved populations.

1.4 Research questions

1. What is the proportion of unfavorable outcomes among pulmonary tuberculosis patients in Kelantan over 10 years?
2. What are the factors associated with unfavorable outcomes among pulmonary tuberculosis patients in Kelantan over 10 years?

1.5 Objectives

1.5.1 General objective

To determine the proportion and factors associated with unfavorable outcomes among pulmonary tuberculosis patients in Kelantan over 10 years.

1.5.2 Specific objectives

1. To determine the proportion of unfavorable outcomes among pulmonary tuberculosis patients in Kelantan over 10 years.
2. To determine factors associated with unfavorable outcomes among pulmonary tuberculosis patients in Kelantan over 10 years.

1.6 Research Hypothesis

There is no association between factors (sociodemographic factors, comorbidity, and clinical characteristics) and unfavorable outcomes among PTB patients in Kelantan.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

The literature review was conducted by using multiple search engines available freely on the web, such as PubMed and Science Direct. Besides that, the university-subscribed database is also being utilized as a medium to look for literature. The entire literature search was filtered to only published between 2011 to 2023. Numerous searching strategies were applied, such as a combination of terms with the use of Boolean operators (AND, OR NOT). List of keywords applied during search treatment outcome, unfavorable, pulmonary tuberculosis, Kelantan, factors associated and 10 years.

2.1.1 Transmission of TB

TB is caused by the organism Mycobacterium Tuberculosis (Mtb). There are also nontuberculous mycobacteria which can cause diseases that mimicking TB, often complicating the diagnosis with same symptoms. These organisms, including types like Mycobacterium avium-complex, typically do not transmit from person to person but they can interfere with laboratory tests designed to diagnose TB.

The transmission of TB occurs through airborne particles. When an individual with active, infectious TB coughs, sneezes, speaks, or sings, tiny droplet nuclei containing Mtb are released into the air. These droplets, ranging from 1 to 5 microns in diameter,

can linger in the air for hours depending on environmental conditions. When another individual inhales these contaminated droplets, they may become infected.

2.1.2 Risk factors of contracting TB

2.1.2(a) Bacteria

Mtb faces unique challenges in control and eradication, due to its complex biological characteristics. A key characteristic of Mtb is its ability to enter and remain in a non replicating latent form within host cells, usually for prolonged periods without causin g active illness. This ability not only complicates TB detection and treatment, but also increases the chance of reactivation, particularly when the host's immune system is compromised. Mtb's thick, waxy cell wall complicated treatment efforts by restricting drug penetration and interaction with target areas inside the bacteria, giving it intrinsic resistance to several medicines. This cell wall also plays a role in evading host immune defences, making the infection highly persistent once established (Gordon & Parish, 2018).

Furthermore, Mtb demonstrates a notable capacity for genetic mutation, which enhances its capability to build resistance to the standard anti-TB regimen that is used for TB treatment. This is compounded by the usual long tuberculosis treatment protocols, which can result in poor patient compliance and consequently, the development of drug-resistant tuberculosis strains, such as multi drug resistant (MDR) TB and extensively drug-resistant (XDR) TB. The ability to adapt metabolically is essential for its survival within macrophages, where nutrition availability is limited. In

addition, Mtb generates a range of immunomodulatory substances that might influence the immunological responses of the host, so aiding the formation and continuation of the infection. The chemicals, which are components of the bacteria's complex cell wall and secreted proteins, engage with immune cells of the host to regulate and frequently inhibit effective immunological reactions. This enables the bacterium to evade eradication. Overall, these characteristics not only make Mtb an unique infectious microorganism but also emphasize the urgent requirement for ongoing investigation into novel treatment approaches, enhanced diagnostic methods, and improved effectiveness of existing vaccines with the aim to eradicate the global TB epidemic (Smith et al, 2012).

2.1.2(b) Host

People with weakened immune systems, such as those with HIV/AIDS, diabetes mellitus, or chronic kidney disease, are far more likely to have TB. The vulnerability arises mostly from the compromised cellular immunity that is vital to combating TB infections, particularly the decrease in CD4+ T cell levels found in individuals with HIV/AIDS.

Moreover, genetic factors are crucial in determining the susceptibility to TB. Variations in genes responsible for immunological responses, particularly cytokine production, can predispose certain individuals to develop active TB when exposed to Mtb.

Nutritional deficiencies, especially in vitamin D, significantly worsen this risk. Vitamin D is needed for good immunological function, and its shortage can hamper the macrophages' capacity to eradicate TB efficiently (Kumari et al., 2014).

2.1.2(c) Environment

Socioeconomic and behavioural factors such as poor living conditions, characterized by overcrowding and poor ventilation, alongside harmful behaviours like smoking and alcohol consumption, also contribute to higher TB susceptibility. These conditions are prevalent among migrants and lower socioeconomic groups, presenting additional challenges in controlling TB within these populations. Addressing these factors through targeted public health interventions is crucial for effective TB control, especially in populations that are exposed to environmental conditions which promote the disease transmission (Hayward et al., 2018).

2.1.3 Case definition

In TB case definitions, there are two main categories: bacteriologically confirmed and clinically diagnosed TB. A bacteriologically confirmed TB case involves a patient from whom a biological specimen has tested positive through smear microscopy, culture, or a WHO-recommended rapid diagnostic (WRD) such as Xpert MTB/RIF. These cases are required to be reported, regardless of whether the treatment for TB has started. On the other hand, a clinically diagnosed TB case is identified when a patient does not meet the criteria for bacteriological confirmation but is diagnosed with active TB based on a clinician's assessment and subsequent decision to administer complete

TB treatment regimen. This category often includes cases diagnosed based on lesion seen in X-ray imaging or suggestive histology, as well as extrapulmonary TB cases that lack laboratory confirmation. If clinically diagnosed cases are later found to be bacteriologically positive, whether before or after the initiation of treatment, they should be reclassified as bacteriologically confirmed TB.

Further, TB cases are stratified by the anatomical site of the disease, previous treatment history, drug resistance, and HIV status. For example, of anatomical classification, PTB includes any TB case, whether bacteriologically confirmed or clinically diagnosed, that affects the lung parenchyma or the tracheobronchial tree. Miliary TB is categorized under PTB owing to the presence of lesions in the lungs. On the other hand, extrapulmonary TB means that TB infections in anatomical sites other than the lungs, such as the pleura, lymph nodes, abdomen, or genitourinary tract and others.

The classification based on the history of previous TB treatment categorizes patients into new or previously treated. New patients have either never received TB treatment or have taken anti-TB medication for less than one month. Previously treated patients have undergone TB treatment for a month or more and are further divided based on the outcome of their most recent treatment course, into categories such as relapse, treatment after failure, treatment after loss to follow-up, and other previously treated patients whose treatment outcomes are either unknown or undocumented.

In terms of HIV status, a TB patient can be classified as HIV-positive, HIV-negative, or with unknown HIV status based on results from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care. Any

reclassification is based on subsequent findings, especially if an initially HIV-negative patient later tests positive for HIV.

Drug resistance classification is vital for determining the appropriate TB treatment regimen and involves categories based on the drug susceptibility testing (DST) of clinical isolates. These categories include monoresistance, polydrug resistance, multidrug resistance, extensive drug resistance, and rifampicin resistance. Each category specifies the type and extent of resistance, guiding treatment options and public health interventions to manage and curb the spread of resistant TB strains effectively.

This detailed classification system is essential for the effective management and treatment of TB, ensuring that each patient receives the most appropriate and effective therapeutic interventions based on their specific diagnosis and the characteristics of their TB infection.

2.1.4 Case detection

Active case detection is the proactive search for tuberculosis cases within the population, with a particular focus on high-risk groups. This approach involves systematic screening and proactive measures to identify individuals who have symptoms of tuberculosis or are more susceptible to get the disease. Effective techniques for actively detecting cases consist of using Chest X-ray (CXR) to identify lung abnormalities and performing Sputum for Acid-Fast Bacilli tests to detect Mtb in sputum samples. Active case detection is a systematic method that has the potential to

identify a greater number of cases, particularly among those who may not actively seek medical attention despite having symptoms.

Passive case detection, in contrast, depends on persons actively seeking medical care of their own will upon experiencing symptoms of TB. This approach is less aggressive and depends on the patient's initiative to seek medical care at a healthcare facility. Passive case detection depends on symptoms as the basis for identification, where patients usually seek medical attention when they present symptoms such as a prolonged cough, weight loss, fever, or night sweats. Successful implementation of this approach requires efficient distribution of knowledge among patients and active involvement of individuals to ensure their awareness of tuberculosis symptoms and immediate treatment. However, it is susceptible to limitations, as it may fail to consider situations in asymptomatic individuals or those who delay seeking medical attention due to poor knowledge or inadequate access to healthcare services.

However, passive case detection depends on individuals actively seeking medical care of their own will when they exhibit symptoms of TB such as a persistent cough, weight loss, fever, or night sweats. This approach is more passive and relies on the patient's proactive decision to seek medical attention. This highlights the limitations of incorrect diagnosis among asymptomatic patients or individuals who may not seek medical care due to inadequate awareness or poor access to healthcare services (Mohd Hassan et al., 2022).

2.1.5 Screening

The process of screening for active TB includes identifying common symptoms such as a history of productive cough, haemoptysis, lack of appetite, unexplained weight loss, fever, night sweats, and fatigue. Immunocompromised or elderly patients may not exhibit these symptoms, which can complicate diagnosing the disease. A thorough physical examination is crucial when evaluating people who are suspected of having tuberculosis.

A CXR is performed to detect radiographic abnormalities, usually found in the apical and posterior segments of the upper lobe or the superior segments of the lower lobe. Radiographic findings are crucial for identifying suspected TB infections, especially in cases when the clinical signs are unclear.

Laboratory investigations involve collecting at least two sputum specimens for microscopic analysis, with a preference for early morning specimens to increase the chances of obtaining accurate results. It is necessary to send sputum samples for mycobacterial culture to verify the existence of Mtb and rule out drug-resistant tuberculosis. Moreover, the Xpert Ultra test is employed to identify TB and rifampicin resistance, especially in cases where smear-negative PTB is suspected. It is recommended to perform routine screening for HIV and diabetes mellitus in all patients suspected of having TB. The use of dual screening ensures a thorough management of concurrent illnesses that may affect the treatment and results of TB (MOH, 2021b).

2.2 Unfavorable outcomes among PTB patients

Unfavourable treatment outcomes in TB are determined by criteria that show a lack of success with achieving successful treatment. An example of a potential outcome is mortality, in which the patient succumbs to death while undergoing treatment for tuberculosis.

Another unfavourable outcome is being lost to follow up. Discontinuation of treatment refers to the situation where a patient cease attending treatment sessions or follow-up appointments, leading to an incomplete course of therapy.

Treatment failure is the third unfavourable outcomes. This condition is defined by the patient's TB not showing sufficient response to the specified treatment plan, resulting in a chronic or worsening infection. The occurrence of treatment failure highlights the difficulties in managing tuberculosis, especially in cases where drug-resistant strains are involved (Foster et al., 2022).

In Malaysia, among those who had unfavorable treatment outcomes, total of 19.3%, a breakdown reveals that 10.2% died, 5.3% were lost to follow-up, 3.6 not evaluated, and the rest did not respond to treatment (Tok et al., 2020). Meanwhile, in Uzbekistan, unfavorable outcomes were noted in 20 % of the cases, with the remaining 80% achieving favorable responses to treatment (Gadoev et al., 2021).

2.3 Factors associated with unfavorable outcomes among PTB patient in Kelantan

2.3.1 Age

Age has been proven to be an important factor associated with unfavourable results in patients with PTB. Age and treatment results are correlated, as several studies have revealed, indicating that older patients typically have poorer treatment outcomes than younger patients (Mukhtar et al, 2018) did a study in Pakistan that revealed greater unfavorable outcomes for PTB patients between the ages of 35 and 54 and 55 and older than for the younger age group of 15 to 34. According to this study, differences in outcomes can be explained by physiological changes brought on by ageing, underlying medical disorders, and the potential for a delayed diagnosis or initiation of treatment.

Results of TB treatment for those 15 years of age and older were investigated at Chawama Level One Hospital in Lusaka, Zambia. According to the study, the likelihood of older patients receiving a successful treatment was substantially decreased. As compared to individuals between the ages of 15 and 24, those 65 and older had a 72.4% lower chance of treatment success (OR (95% CI): 0.276 (0.086–0.881), p =.030). This trend continued even after adjusting for other variables, indicating a long-term association between advanced age and poor treatment outcomes (adjusted odds ratio (95% confidence interval): 0.271 (0.083–0.882), p =.030). The study underlines the need of specific interventions to improve treatment outcomes in the elderly population, who may face unique challenges including concurrent medical illnesses and a decreased immune response, both of which could make tuberculosis treatment more challenging, (Chilyabanyama et al, 2024).

2.3.2 Gender

It was found during the study of a retrospective cohort that males showed more susce ptibility to unfavorable treatment outcomes compared to females.

Furthermore, 13.4% of females and 27.7% of men exhibited unfavorable outcome in relationship with the patients (Arsad & Ismail, 2022). This can be explained by men are more prone to risky activities, such as drinking alcohol and smoking, which may significantly compromise their commitment to treatment and hence result in unfavorable outcomes of TB treatment. Additionally, there might be some inherent biological differences that might compromise the male to more severe forms of tuberculosis or challenges that come along with treatment.

Another study was done in Denmark, male gender turned out to be an independent risk factor associated with unfavorable treatment outcomes. In multivariate logistic regression analysis, the male sex predisposed one to 2.56 times more odds of experiencing unfavorable outcomes compared to females. This association reached statistical significance, with a confidence interval (CI) of 1.19–3.63, which was a strong finding in the study population. These findings are of significant value in calling for the need to implement targeted interventions to reduce these risk factors in male patients to improve outcomes of treatment (Holden et al., 2019).

2.3.3 Nationality

Nationality played an important role when it came to unfavorable outcomes of treatment in PTB patients in Malaysia. With the data from national TB surveillance databases of the 97,505 TB cases reported between 2014 and 2017, it was found that non-Malaysians carry a significantly higher odd of failing treatment outcomes compared to Malaysians, with the risk being almost three times unfavorable treatment outcomes among non-Malaysian TB patients as compared to Malaysian TB patients (AOR 2.94; 95% CI 2.77, 3.12). There are multiples factors, including access to health care, socioeconomic status, and a continuum of care. Most non-Malaysian TB patients are migrant workers who are deported at the point of notification and diagnosis. This probably disrupts their treatment and follow-up. Most of the cases that fall under the unfavorable outcomes have not been assessed and mostly belong to the non-Malaysian population, indicating the difficulty in terms of treatment continuity of this group. Cross-border collaboration must be robust to ensure that all foreign TB patients have been given full and continuous treatment irrespective of their nationality (Tok et al., 2020).

2.3.4 Race

The study showed the factor of an unfavorable outcomes was higher among patients of ethnicity categorization "Others" than among Malay patients. In particular, the hazard ratio for the unfavorable treatment outcome among the "Others" categorization was equal to 3.056, stating the risk for them was over three times incurring unfavorable treatment outcomes than the Malay patients. Additionally, those who belonged to Indian ethnicity had a HR of 1.991 but were not statistically significantly at the 0.05

level (p=0.084). These comparisons with some other Malaysian studies highlight the fact that the Malay patients had worse treatment outcomes (Kirandeep et al., 2022).

2.3.5 Districts

The geographic distribution of the patients which is, district of residence—is also one of the factors that could affect TB treatment outcome. A study of TB patients in Kelantan reported that the rate of treatment success was highly variable among various districts of the state. Overall treatment success for Kelantan was reported to be 57.1%, with the rest, 42.9 % being unsuccessful, including cases of treatment failure, death, and default. The result of the study could imply a high degree of heterogeneity of treatment outcome by districts. Examples of these are the districts of Jeli and Kuala Krai, which showed a higher rate of failures compared to other districts. Specifically, the current study found that patients in Jeli (55.6% unfavorable) and Kuala Krai (55.3% unfavorable) were associated with less favorable odds than patients in other districts, such as Kota Bharu (40.9% unfavorable) and Bachok (36.4% unfavorable).

These disparities could be explained by various factors that are district-specific, like a disparity in the level of accessibility and quality of health care, socioeconomic status, infrastructure and resources availability. More treatment default is seen in districts with nonavailability of health facilities which, in turn, leads to death, since after a discovery of disease, treatment cannot be started immediately. Also, the disparities in the socioeconomic factors across districts may affect adherence to a treatment regimen of patients, with levels of high poverty in some districts highly likely to relate to high treatment default. Infrastructure differences, such as the transportation network and

the distribution of health facilities, also play a role. With poor infrastructure that is in areas where timely and regular treatment cannot be administered, then it is most unlikely that treatment will be given appropriately (Romaino et al., 2022).

2.3.6 Residency

The study from Pakistan concluded there was a significant difference in the treatment outcome of tuberculosis between rural and urban residents. Rural residence was significantly related to the increased likelihood of an unfavorable outcome of treatment among patients with PTB. Factors significantly associated with an unfavorable outcome of treatment with PTB in rural areas, as determined by multivariate logistic regression, were close to double the odds for patients in rural areas with an adjusted OR of 1.98 (95% CI = 1.14–3.47). These include factors such as access to health services, limited access to health care services, delayed diagnosis, and the commencement of treatment, which is more common in rural settings.

Such findings have extensive implications for TB control programs, particularly within developing countries like Pakistan, where a relatively large proportion of the population still resides within rural areas (Mukhtar et al., 2018).

2.3.7 Education

Educational status emerged as one of the significant predictor variables for unfavorable outcomes of TB in a single study carried out in Southern Ethiopia. More precisely, there was an association of attending tertiary educational levels with decreased possibility of occurrence of unfavorable treatment outcomes. A significant,

69% reduction in the risk of unfavorable treatment outcome compared with those attending primary education. An increased level of education probably boosts health literacy and improves understanding and, therefore, adherence to a treatment protocol (Bogale et al., 2021).

2.3.8 Occupation

Occupation is one of the strong predictors in treatment outcomes of PTB patients, where the unemployed were found to have higher chances of unfavorable outcomes. Similar findings were demonstrated by different studies conducted in Malaysia, where the probability of defaulting and failing the treatment was higher in the unemployed, since they often have associated financial constraints, a lack of social support, and non-regular access to health facilities for treatment. Furthermore, being employed in the informal sector carries higher odds of unfavorable outcomes, probably due to irregular income and lack of health benefits, leading to low adherence to treatment regimen and low general health status (Arsad et al., 2022).

In Uganda, informal workers and non-schooled or working children had statistically increased probabilities of unfavorable outcomes. This may be due to economic instability and the inability to afford good health care. Other factors up the risk: inadequate food, migratory life, and lack of social protection. These are occupationally related disparities that can be solved only by an integrated approach, considering the socio-economic enablers of conditional cash transfers and schemes of social protection to assist patients along the whole treatment journey (Nidoi et al., 2021).

2.3.9 Income

A study in Georgia showed that there is a direct association between a low household income level and the outcome of treatment against tuberculosis; the chances of a poor treatment result dramatically increase with a significantly increased household income level. Those in the lowest-income tertile had an adj. OR for poor outcomes of 6.18 compared with the highest-income tertile; the middle-income tertile had an adj. OR of 4.28 (Djibuti et al., 2014).

2.3.10 HIV status

Co-infection with HIV has been significantly found to be related to higher rates of unfavorable outcomes (11.8% vs. 6.4%) by increasing the mortality and reducing the cure (Romaino et al., 2022). This is because of the immunosuppressive property of HIV, which further compromises the situation with TB by accelerating its course and severity. In Kelantan, Malaysia, it was indicated that TB/HIV co-infected patients, the unfavorable outcomes was higher, at 42.9% (Romaino et al., 2022). Another Ethiopian study also revealed that the outcome of TB treatment was less satisfactory with HIV co-infection as compared to patients without HIV infection, where generally the unfavorable outcome among TB patients co-infected with HIV was 11.8% while in non-HIV-infected patients, it was 6.4 % (Ali et al., 2016).

2.3.11 Smoking

Smoking has also been an important factor in unfavorable outcomes for TB treatment. In India, high prevalence, and its effect in patients with newly diagnosed pulmonary TB have been observed. The study reported that smoking among these patients was associated with extensive lung disease, higher rates of lung cavitation, and positivity

for sputum smear and culture at the baseline. After two months of treatment, the proportion of current smokers and ex-smokers with both positive sputum smears and cultures remained significantly higher. The same group also showed higher default rates, treatment failure, and relapse rates when compared with the non-smokers (Mahishale et al., 2015).Another systematic review shown that estimated that 23% more unfavorable outcomes could be expected for smokers, along with 55% more delayed smear or culture conversion compared with non-smokers (Wang et al., 2020). In a multicentre retrospective study in Malaysia, the prevalence of smoking among TB patients was 46.2%, with a higher prevalence in males and urban residents a smokers had lower treatment success and a higher percentage of death, default, and interruption of treatment. An important finding is that smoking significantly negatively affects the treatment success of TB, and therefore, smoking-cessation interventions could be a very good strategy in reducing failures of treatment and resistance (Khan et al., 2020).

2.3.12 Case detection

Active case findings (ACF) for TB are aimed at discovering cases that remain undiagnosed, thereby increasing treatment success rates. However, a study on the treatment outcomes of TB patients detected through ACF in Haridwar district, Uttarakhand, shows many difficulties in this pathway. The treatment outcome for the ACF-detected TB patients in the Haridwar district of Uttarakhand revealed that there was an initial high loss to follow-up (22%) among the patients. Reasons for this high loss to follow-up are logistic barriers, de-motivation of patients because they assume that their symptoms are not severe, and lack of a perceived need for care. These barriers do not allow the patients to commence or complete treatment, which results in

unsuccessful outcomes. The treatment outcome was available for 1,115 patients; loss to follow up (LTFU) was responsible for 18% of patients with unsuccessful outcomes, but death has also been a crucial factor. Furthermore, socio-economic challenges, especially a migratory population in Haridwar, further make it difficult for ACF patients to have continued follow-up and adherence to treatment protocols (Singh et al., 2020). Passive case detection for tuberculosis involves diagnosing individuals when they seek care at health facilities after experiencing symptoms, such as a persistent cough. This method relies on the patient initiating the health-seeking behaviour, which often results in delayed diagnosis and treatment (Saunders et al., 2019).

2.3.13 BCG scars

Unfavorable outcomes were associated significantly with the absence of a Bacille Calmette-Guerin (BCG) scar in a registry-based, cohort study in Malaysia. Patients without a BCG scar, a surrogate indicator for prior BCG vaccination, had higher odds of unsuccessful treatment, which in turn was associated with mortality during the study period (2014–2017). Specifically, the odds of unsuccessful treatment were 1.21 times among those with no BCG scar compared to those with a BCG scar. The study says having a BCG scar is protective in ensuring favorable TB treatment outcomes. The present findings advocate for more importance to be given to the BCG vaccination in TB strategies, followed by the need to continue vaccination activities, so that successful treatment rates for TB patients can be increased (Tok et al., 2020).