TRENDS AND FACTORS ASSOCIATED WITH TUBERCULOSIS-RELATED MORTALITY DURING THE INTENSIVE PHASE OF ANTI-TUBERCULOSIS TREATMENT IN JOHOR FROM 2013 TO 2022

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by

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LIST OF SYMBOLS

=	Equal to
<	Less than
%	Percent
*	Asterisk
:	Colon
\	Backslash
>	Greater than
≤	Less than or equal to
≥	Greater than or equal to
±	Plus-minus
β	Regression coefficient
n	Sample size
p	p-value (probability value in statistical tests)
P_0	Probability of factor in TB patients who are still alive after IP
P_1	Estimated probability of factors in TB patients who died during IP

LIST OF ABBREVIATIONS

AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
AOR	Adjusted odds ratio
ARDS	Acute Respiratory Distress Syndrome
ART	Antiretroviral therapy
BAL	Bronchoalveolar lavage
BCG	Bacillus Calmette–Guérin
CD4	Clusters of differentiation 4
CI	Confidence interval
CXR	Chest radiography
DOTS	Directly Observed Treatment, Short-course
EMB	Ethambutol
EPTB	Extra pulmonary tuberculosis
FDC	Fixed-dose combination
HR	Hazard ratio
HIV	Human immunodeficiency virus
IP	Intensive phase
INH	Isoniazid
LAM	Lipoarabinomannan
MTB	Mycobacterium tuberculosis
MDR	Multidrug-resistant
MyTB	Malaysian Tuberculosis Information System
MOH	Ministry of Health

OR	Odd ratio
PLHIV	Person living with HIV
PTB	Pulmonary tuberculosis
PYR	Pyrazinamide
ROC	Receiving operating characteristics
RIF	Rifampicin
SEA	Southeast asia
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
TBM	Tuberculous meningitis
WHO	World Health Organization

ABSTRAK

TREND DAN FAKTOR YANG BERKAITAN DENGAN KEMATIAN BERKAITAN TUBERKULOSIS SEMASA FASA INTENSIF RAWATAN ANTI-TUBERKULOSIS DI JOHOR DARI 2013 HINGGA 2022

Latar Belakang: Tuberkulosis (TB) kekal sebagai cabaran utama kesihatan global. Di Malaysia, data TB terkini menunjukkan penyimpangan ketara dari sasaran yang ditetapkan oleh Strategi End TB, dengan peningkatan 28% dalam kematian TB pada tahun 2022 berbanding 2021. Walaupun usaha kawalan TB yang meluas, negeri Johor telah menyaksikan kadar kematian yang berubah-ubah semasa fasa intensif (IP) rawatan anti-TB, yang menekankan keperluan untuk analisis mendalam mengenai faktor yang berkaitan.

Objektif: Kajian ini bertujuan untuk menerangkan kadar dan trend kematian berkaitan TB serta faktor-faktor yang berkaitan semasa IP rawatan anti-TB di Johor dari 2013 hingga 2022.

Metodologi: Kajian kes-kawalan telah dijalankan dari Januari 2024 hingga akhir Mei 2024 menggunakan data sekunder daripada sistem MyTB. Kadar kematian berkaitan TB dan jumlah kes TB dikira berdasarkan data yang diekstrak daripada sistem MyTB tanpa menggunakan kaedah persampelan. Kes (n=372) terdiri daripada pesakit TB yang meninggal dunia akibat TB semasa IP, manakala kumpulan kawalan (n=1671) dipilih secara rawak daripada kes TB yang selamat semasa IP. Statistik deskriptif dan regresi logistik digunakan untuk analisis data menggunakan SPSS versi 29.

Keputusan: Kadar kematian berkaitan TB semasa ~~fasa intensif (IP)~~IP di Johor dari 2013 hingga 2022 berkisar antara 0.8% hingga 3.6%, dengan kadar tertinggi pada 2022. Daripada 2,043 peserta, purata umur kes ialah 49.2 tahun manakala kawalan ialah 42.5 tahun. Kebanyakan peserta adalah lelaki (76.3%), rakyat Malaysia (89.5%), dari kawasan bandar (65.1%), HIV-negatif (81.5%), menerima vaksinasi BCG (86.8%), kes TB baharu (92.2%), mempunyai AFB positif dalam sputum (79.3%), memulakan rawatan di hospital kerajaan (88.4%), dan tidak mematuhi DOTS (80.1%). Faktor risiko bebas yang signifikan untuk kematian berkaitan TB semasa IP adalah berusia lebih 65 tahun (AOR: 10.14; 95% CI: 1.27, 80.7; p=0.029), tinggal di kawasan bandar (AOR: 0.55; 95% CI: 0.35, 0.86; p=0.008), HIV-positif (AOR: 2.95; 95% CI: 1.53, 5.69; p=0.001), AFB positif (AOR: 2.42; 95% CI: 1.43, 4.10; p=0.001), lesi yang jauh pada radiograf dada (AOR: 14.53; 95% CI: 7.12, 29.64; p<0.001), memulakan rawatan di hospital kerajaan (AOR: 5.73; 95% CI: 2.07, 15.86; p<0.001), dan pematuhan kepada DOTS (AOR: 0.009; 95% CI: 0.006, 0.015; p<0.001).

Kesimpulan: Kajian ini menyoroti trend yang berubah-ubah dalam kematian berkaitan TB semasa IP, dengan kemuncak yang ketara pada 2022. Strategi kesihatan awam harus memberi tumpuan kepada pengesanan awal, penjagaan bersepadu TB-HIV, dan pematuhan ketat kepada DOTS, terutamanya bagi populasi berisiko tinggi. Sejajar dengan Strategi End TB Kebangsaan, penemuan ini penting untuk membimbing intervensi dan dasar masa depan yang bertujuan mengurangkan kadar kematian TB dan meningkatkan hasil rawatan di Johor dan kawasan serupa.

Kata Kunci: Kematian berkaitan Tuberkulosis, fasa intensif, faktor berkaitan, kadar, trend, Malaysia

ABSTRACT[d1]

TRENDS AND FACTORS ASSOCIATED WITH TUBERCULOSIS-RELATED MORTALITY DURING INTENSIVE PHASE OF ANTI-TUBERCULOSIS TREATMENT IN JOHOR FROM 2013 TO 2022

Background: Tuberculosis (TB) remains a major global health challenge. In Malaysia, recent TB data reveal a significant deviation from the targets set by the End TB Strategy, with a 28% increase in TB fatalities in 2022 compared to 2021. Despite extensive TB control efforts, Johor state has witnessed fluctuating mortality rates during the intensive phase (IP) of anti-TB treatment, underscoring the need for an in-depth analysis of associated factors.

Objective: This study aimed to describe the proportion and trends of TB-related mortality and its associated factors during the IP of anti-TB treatment in Johor from 2013 to 2022.

Methods: A case-control study was conducted in January 2024 until the end of May 2024 using secondary data from the MyTB system. The proportion of TB-related mortality and total of TB cases were calculated based on the data extracted from MyTB system with no sampling method applied, A case (n=372) consists of a TB patient who dies due to TB during the IP and the ~~the~~ control group (n=1671) was randomly selected from TB cases who survived during the IP. Descriptive statistics and logistic regressions were employed for data analysis using SPSS version 29.

Results: The proportion of TB-related deaths during the ~~intensive phase (IP)~~IP in Johor from 2013 to 2022 ranged between 0.8% and 3.6%, with 2022 having the highest rate. Of the 2,043 participants, the average age was 49.2 years for cases and 42.5 years for controls. Most were male (76.3%), Malaysian (89.5%), from urban areas (65.1%), HIV-negative (81.5%), had received BCG vaccination (86.8%), were new TB cases (92.2%), had positive sputum AFB (79.3%), were initially treated at government hospitals (88.4%), and did not adhere to DOTS (80.1%). The significant independent risk factors for TB-related mortality during IP were being older than 65 years (AOR: 10.14; 95% CI: 1.27, 80.7; p=0.029), living in an urban area (AOR: 0.55; 95% CI: 0.35, 0.86; p=0.008), HIV-positive (AOR: 2.95; 95% CI: 1.53, 5.69; p=0.001), AFB positive (AOR: 2.42; 95% CI: 1.43, 4.10); p=0.001), far-advanced lesions on chest radiograph (AOR: 14.53; 95% CI: 7.12, 29.64; p<0.001), initiating treatment at a government hospital (AOR: 5.73; 95% CI: 2.07, 15.86; p<0.001), and adherence to DOTS (AOR: 0.009; 95% CI: 0.006, 0.015; p<0.001).[d2][NN3]

Conclusion: This study highlights fluctuating trends in TB-related mortality during the IP, with a notable peak in 2022. Public health strategies should focus on early detection, integrated TB-HIV care, and strict adherence to DOTS, particularly for high-risk populations. In line with the National TB End Strategy, these findings are crucial for guiding future interventions and policies aimed at reducing TB mortality rates and improving treatment outcomes in Johor and similar settings.

Keywords: Tuberculosis-related mortality, intensive phase, associated factors, proportion, trends, Malaysia

CHAPTER 1

INTRODUCTION[d4][NN5]

1.1 Overview of tuberculosis

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* (MTB). It primarily affects the lungs but can also spread to other organs, including the intestines, meninges, bones, joints, lymph nodes, and skin, resulting in extrapulmonary TB (EPTB) (Agyeman and Ofori-Asenso, 2017). The disease is transmitted through airborne particles, which makes it highly communicable (Basalingappa *et al.*, 2021). Diagnosis is crucial and involves a combination of clinical, radiographic, microbiological, and histopathologic assessments. Sputum specimens and nucleic acid amplification tests are essential for detecting active TB (Hasan *et al.*, 2019). Treatment typically adheres to the DOTS strategy. This involves an initial two-month regimen of isoniazid (INH), rifampicin (RIF), pyrazinamide (PYR) and either ethambutol (EMB) or streptomycin followed by an additional four months of INH and RIF (Ankrah, 2020). Preventive measures, such as vaccination and addressing social determinants like overcrowding and malnutrition, are essential for effective TB management (Sia and Wieland, 2011).

1.2 Tuberculosis treatment

The TB treatment is divided into two main phases, which is the intensive phase (IP) and the maintenance phase, each with distinct objectives and regimens. The IP aims to

rapidly reduce the bacterial load and prevent the development of drug resistance (Akhtar *et al.*, 2023). It typically involves a combination of four drugs which is INH, RIF, PYR, and EMB administered daily for the first two months of anti-TB treatment (MOH, 2021b).

The IP incorporates a standard anti-TB regimen endorsed by the World Health Organization (WHO) which consists of a fixed-dose combination (FDC) of drugs mentioned above. Among these, INH exhibits the most substantial bactericidal activity, RIF is noted for its sterilizing capabilities, and EMB acts as a bacteriostatic agent. This combination is crucial in preventing the emergence of resistant strains of TB bacilli (MOH, 2021b). Additionally, this phase is also crucial for achieving sputum smear conversion, which is a key indicator of treatment efficacy (Crabtree-Ramirez *et al.*, 2022). IP also is designed to rapidly reduce the bacterial load, achieving a significant decrease in TB bacilli in the patient's body (Maitre *et al.*, 2022). However, this TB drug regimens can lead to the haematological effects which can affect red and white blood cells, platelets and the coagulation system, thereby requiring continuous monitoring (Maitre *et al.*, 2022).

Despite the importance of the IP in reducing the bacterial load, it is also marked by the highest rate of TB-related deaths during anti-TB treatment. This is evident in a study conducted in Northwest Ethiopia, where over 56.7% of TB patient fatalities occurred during this period, highlighting a critical period of vulnerability (Birlie *et al.*, 2015). Similarly, research in Lishui City, China, found that most TB patients died during the IP, with advanced age, extensive lung lesions, and low sputum negative conversion rates identified as significant risk factors for adverse outcomes, including death (Guo *et al.*, 2023a). Other risk factors contributing to early mortality among TB

patients include human immunodeficiency virus (HIV) positivity, low body weight, and retreatment cases (Molie et al., 2019).

Following the IP, the maintenance phase lasts for four months and involves fewer drugs, typically INH and RIF. The maintenance phase of TB treatment aims to consolidate the gains achieved during the IP, ensuring the complete eradication of the MTB bacteria to prevent relapse and the development of drug resistance. This phase typically involves a continuation of antibiotic therapy, often with a reduced frequency of administration, such as twice-weekly regimens, which have been shown to be as effective and safe as daily therapy when supervised properly (Williams *et al.*, 2008). By this stage, the bacterial load is significantly reduced, thus lowering the risk of developing drug resistance and adverse drug reactions (Gashu *et al.*, 2021).

The IP of TB treatment poses numerous critical challenges, affecting both patient outcomes and healthcare infrastructures. A key concern is the elevated mortality rate, especially among those with multidrug-resistant TB (MDR-TB) (Akhtar *et al.*, 2023). Factors like older age, diabetes, smoking, and being underweight significantly increase the risk of death in these patients (Birlie *et al.*, 2015). Non-adherence to treatment, driven by financial difficulties, job loss, and insufficient nutritional support, complicates the treatment process further, as observed in India (Batra and Parwar, 2022).

Despite the significance of early mortality during TB treatment, research specifically addressing fatalities within the first two months remains scarce (Rodrigo *et al.*, 2016). The IP is particularly pivotal due to its association with the highest incidence of TB mortality, emphasizing the urgent need for targeted interventions and

enhanced monitoring during this crucial phase to mitigate disproportionately high mortality rates (Min *et al.*, 2019).

1.3 Tuberculosis mortality during intensive phase

TB is a death-preventable infectious disease yet it remains a significant global health concern, with high mortality rates in certain regions. In 2022, TB was reported as the world's second leading cause of death from a single infectious agent, following COVID-19 particularly in low- and middle-income countries (WHO, 2023). TB also caused almost twice as many deaths as HIV/AIDS and the mortality rate from TB is particularly high in cases where the disease is left untreated, with an approximate death rate of about 50% (Lelisho *et al.*, 2022).

Globally, TB mortality rates have shown a 19% reduction from 2015 to 2022, but the rate of decrease varies significantly by region and demographic factor (WHO, 2023). For instance, in 2015, TB caused approximately 1.3 million deaths globally, with a significant decline observed from 2005 to 2015 (Kyu *et al.*, 2018). However, the highest TB mortality rates were observed in Southeast Asia (SEA) and Africa, which together accounted for more than 70% of global TB deaths (Dodd *et al.*, 2017).

In 2020, SEA accounted for more than half of global TB deaths, with a mortality rate of 41 per 100,000 population, more than double the global rate of approximately 19 per 100,000. While in Malaysia, TB data revealed a troubling scenario, with key indicators significantly deviating from the targets set by the End TB Strategy for 2020. With a population of 34 million, Malaysia saw an 80% increase in TB deaths in 2022 compared to 2015. In 2022, Malaysia recorded a troubling increase

in TB mortality. The number of TB deaths reached 3,160, equating to one death every three hours. This represents a significant rise from the 2,460 deaths reported in 2021, marking a 28% increase. This significant rise contrasts sharply with the goal of reducing TB mortality by 35% compared to 2015 levels (WHO, 2023).

Several factors contribute to TB mortality, including sociodemographic, lifestyle, clinical, comorbid, disease characteristics and treatment factors. Advanced age is a significant predictor, with older patients showing higher mortality rates (Xie *et al.*, 2020; Tian *et al.*, 2022). Male sex is also associated with an increased risk (Hameed *et al.*, 2019). Comorbidities such as HIV/AIDS, diabetes mellitus, and chronic liver disease significantly elevate the risk of death in TB patients (Gaifer, 2017). Undernutrition and low body mass index are critical factors, with malnutrition exacerbating the risk (Akhtar *et al.*, 2023). Additionally, smoking and alcohol abuse further contribute to higher mortality rates (Wessels *et al.*, 2019). Clinical factors such as recurrent TB, drug resistance, and delayed treatment initiation are significant predictors of TB mortality (Smitha and Prabhakar, 2022). Lastly, the presence of a positive sputum acid-fast bacilli (AFB) at the first follow-up and delayed visits (≥14 days) are also linked to increased mortality risk (Kumawat *et al.*, 2023).

It is important to differentiate between TB mortality and TB-related mortality during IP. TB mortality includes all deaths from TB while TB-related mortality specifically results from TB infection (Jeong *et al.*, 2023). Similarly, in Denmark, TB-related mortality was defined as deaths where TB significantly contributed, with many deaths occurring soon after diagnosis due to factors like septic shock (Lee-Rodriguez *et al.*, 2020)

Studies on TB-related mortality during the IP remain scarce globally and locally due to diverse and multifactorial factors. This diversity makes it challenging to isolate specific variables (Wang *et al.*, 2021; Singh *et al.*, 2023a). Additionally, TB patients requiring ICU admission represent a small fraction of total TB cases, with estimates ranging from 1% to 25%, making it a less frequent focus of research (Akhtar *et al.*, 2023). The complexity of TB cases in the ICU, often involving acute respiratory failure, septic shock, and multi-organ dysfunction, further complicates the study of mortality predictors (Anton *et al.*, 2021; Wang *et al.*, 2021). The high prevalence of comorbidities such as diabetes, HIV, and malnutrition among TB patients adds layers of complexity to studying mortality during the IP (Muthu *et al.*, 2018; Tatar *et al.*, 2018). Furthermore, delays in TB diagnosis and treatment initiation, particularly in ICU settings, are associated with higher mortality, yet these delays are challenging to document and analyze systematically (Molie *et al.*, 2019; Chaudhry and Tyagi, 2021). Lastly, the high burden of TB in certain regions and the focus on broader public health measures rather than intensive care outcomes may divert attention from this specific area of study.

Collectively, these factors contribute to the limited research on TB-related mortality during the IP of treatment. This gap in research highlights the need for more focused studies on TB mortality during the IP particularly considering the complex interplay of clinical and sociodemographic factors that influence outcomes.

1.4 Problem statement and study rationale

TB remains a significant global health concern, particularly in low- and middle-income countries. Despite global efforts to reduce TB mortality, recent data suggest a troubling

reversal in progress. In Malaysia, the TB mortality rate has shown an alarming increase, rising from 4-5 per 100,000 individuals between 2008 and 2017 to approximately 6 per 100,000 in 2021 (UNESCAP, 2023). Furthermore, the Ministry of Health (MOH) reports a 36.8% increase in TB deaths from 1,696 cases in 2015 to 2,320 cases in 2022 (MOH, 2021a). Finding in Sabah also revealed approximately 1,343 (74.9%) of TB mortality occurred during the IP of TB treatment, and out of this, 592 (44.1%) is due to TB-related mortality, underscoring significant challenges in clinical interventions and management during this phase (Avoi and Liaw, 2021).

Numerous studies have explored factors contributing to TB mortality at various stages of treatment, but there is still a notable scarcity of research focusing specifically on TB-related mortality during the IP (Avoi and Liaw, 2021). This gap is particularly concerning given the high mortality rates observed during this phase. Understanding the trends and factors contributing to TB-related mortality during the IP is crucial for improving patient outcomes and achieving global health targets.

This study is necessitated by the critical need to address TB-related mortality during the IP of TB treatment. The insights derived from this research are expected to guide the Johor State Health Department and the MOH in enhancing standards of care and developing effective TB management strategies. These improvements are essential for meeting both national and global health targets, particularly those outlined in the United Nations End TB Strategy and the Sustainable Development Goals (SDGs).

Identifying the factors contributing to TB mortality during the IP will enable healthcare providers to implement targeted interventions, improving patient outcomes and significantly reducing mortality rates. Early identification of high-risk patients can

lead to more personalized treatment plans and timely interventions, enhancing patient survival rates. The findings of this study will inform healthcare providers and policymakers, facilitating more efficient allocation of resources and improved treatment protocols. Enhanced training for healthcare professionals based on the study's insights will improve the overall quality of TB care, particularly during the critical IP.

Improved management of TB during the IP will contribute to reduced transmission rates, benefiting public health and enhancing the quality of life for TB patients and their families. Increased public awareness and community engagement in TB prevention and treatment efforts will further support these outcomes. Reducing TB mortality and improving treatment outcomes will result in significant cost savings for the healthcare system and the broader economy. Decreased healthcare costs associated with TB treatment and reduced burden on healthcare resources will enhance the overall economic productivity of the population.

This study also aligns with the United Nations End TB Strategy, which aims to end the global TB epidemic and reduce TB mortality by 95% by 2030 (WHO 2015b). The insights gained from this study will contribute to national and global efforts to achieve these targets, ensuring healthier lives and promoting well-being for all at all ages. This research directly supports SDG 3.3, which aims to end the global TB epidemic. By identifying and addressing the factors contributing to TB-related mortality during the IP, this study will help achieve the SDG targets, promoting health and well-being on a global scale. Failure to conduct this study will result in continued high mortality rates during the IP, ineffective treatment protocols, and missed opportunities for crucial policy interventions.

1.5 Research questions

1. What is the proportion and trends of TB-related death during the intensive phase of anti-TB treatment in Johor, Malaysia?
2. What are the risk factors of TB-related mortality during the intensive phase of anti-TB treatment in Johor, Malaysia?

1.6 Research objectives

1.6.1 General objective

To study the proportion and risk factors of TB-related mortality during the intensive phase of anti-TB treatment in Johor between 2013 to 2022.

1.6.2 Specific objectives

1. To describe the proportion and trend of TB-related mortality during the intensive phase of anti-TB treatment in Johor from 2013 to 2022.
2. To determine factors associated with TB-related mortality during the intensive phase of anti-TB treatment in Johor from 2013 to 2022.

1.7 Hypothesis

There are associations between sociodemographic, lifestyle, clinical, comorbid, disease and drug regime factors and TB-related mortality during the intensive phase of anti-TB treatment in Johor.

CHAPTER 2

LITERATURE REVIEW

Literature was searched using journal search engines, mainly PubMed, Scopus, Science Direct, and Google Scholar. Recent literature was selected using keywords such as TB mortality, TB-related mortality, intensive phase, anti-TB treatment, and associated factors. Several searching strategies were applied using Boolean operators like “AND,” “OR,” and “NOT.”

2.1 Tuberculosis burden

TB continues to pose a significant global health burden, with an estimated 10 million people contracting the disease and 1.2 million dying from it annually. It is the leading cause of death from a single infectious agent, surpassing even HIV (Peloquin and Davies, 2021). Despite a 45% decline in global TB mortality from 1990 to 2013, the disease still resulted in 1.5 million deaths in 2014, exceeding the 1.2 million deaths caused by HIV that same year (WHO, 2015).

Even with the general decline in TB incidence and mortality over the past few decades, the disease remains a major public health challenge. In 2019, the age-standardized incidence, disability-adjusted life years and death rates for HIV-negative TB were significant, with higher burdens observed in low socio-demographic regions (Xue *et al.*, 2022). SEA and Africa, in particular, bear the highest TB burden, with these regions accounting for the majority of TB cases and deaths (Ding *et al.*, 2022).

In the SEA region, including countries such as India, Indonesia, and Thailand, over 45% of global TB cases and more than half of all TB-related deaths were reported in 2021 (Bhatia *et al.*, 2023). Factors such as rapid urbanization, high population density, and rising diabetes rates, which increase susceptibility to TB, drive the high TB burden in this region. Efforts to combat TB include expanding high-quality TB services, integrating social protection measures, and enhancing public-private partnerships to improve case detection and treatment outcomes.

Meanwhile in Malaysia, TB remains a significant public health challenge, with an estimated incidence rate of 81 cases per 100,000 people per year and a mortality rate of 4.9 per 100,000 population (Qamruddin *et al.*, 2023). A considerable proportion of fatalities among individuals with TB occur during the IP of anti-TB treatment. However, there is still a limited body of research specifically examining the mortality rate during the IP of TB treatment (Jonnalagada *et al.*, 2011).

2.2 Trends of TB mortality according to anti-TB treatment

TB-related mortality during the IP of anti-TB treatment was observed, with many TB-related deaths occurring within the first month, highlighting the need for early targeted interventions (Avoi and Liaw, 2021). The proportion of TB mortality varies between the types of TB mortality (TB-related or non TB-related), anti-TB treatment phase, study location and setting. A study conducted in Manjung, Perak, and Terengganu recorded the proportion between 0.14% - 0.16% (Awang *et al.*, 2022; Qamruddin *et al.*, 2023). However, a study conducted in Sabah and South Korea reported the proportion of TB-related mortality during the IP between 0.30% - 0.33% (Min *et al.*, 2019; Avoi and Liaw, 2021). A population-based prospective cohort study conducted

in Spain examined a cohort of 5,182 patients between January 1, 2006, and December 31, 2013, found out, 180 (3.5%) died during their treatment period. Among these 180 deaths, 87 (48.3%) occurred during the IP of TB treatment, which is the initial two months of therapy and the case fatality rate during the IP was calculated to be 1.7% (Rodrigo *et al.*, 2016).

A retrospective cohort study in Denmark, which included all patients notified with TB from January 1, 2009, to December 31, 2014, found that TB-related deaths in Denmark decreased significantly from 6.7% to 3.2% during this period. This indicates an improvement in TB management and treatment outcomes. However, the majority of TB-related deaths occurred soon after diagnosis, with 49% of these deaths happening within one month of starting anti-TB treatment (Holden *et al.*, 2020).

The global decline in TB incidence is progressing slowly, making it difficult to achieve the SDG to end the TB epidemic by 2030. Accelerated efforts in diagnosis, treatment, and prevention are crucial, particularly in high-burden countries (Chen *et al.*, 2022).

2.3 Factors associated with TB mortality during anti-TB treatment

Previous research has extensively identified numerous factors linked to TB mortality during the IP of anti-TB treatment. However, there is a lack of published articles specifically studying the determinants of TB-related mortality. Based on the limited number of studies available, the identified factors can be classified into four main categories: sociodemographic factors; lifestyle factors; clinical and comorbid diseases; and treatment characteristics.

2.3.1 Sociodemographic

The associated factors of TB mortality vary between countries and regions as they differ from the sociodemographic and behavioural status of that population. However, some similarities and differences can be detected throughout the literature review.

a) **Patients' age**

Age more than 50 years old is among the associated factors of TB-related mortality during the IP of anti-TB treatment. A local retrospective study in Sabah by Avoi and Liaw (2021) found that, age more than 65 years old have a significant factor for TB-related death with 44.1% of TB-related mortality occurs during the IP (AOR: 3.18; 95% CI: 1.70, 5.94).

A retrospective study in Spain that involved patients diagnosed with TB between January 1, 2006, and December 31, 2013, across 61 Spanish hospitals reported that the probability of being more than 50 years old increases the risk factor of TB-related mortality during the IP (HR: 67.4; 95% CI:9.37, 485.0) (Rodrigo *et al.*, 2016). Another retrospective study reported in South Korea that included a total of 760 patients between January 2013 and December 2015 found 74 patients died during anti-TB treatment and out of it, 36 patients died during IP. Additionally, they found aged more than 70 years old, with a median age of 78 years, are at higher risk for TB-related death, especially during the early IP of anti-TB treatment (Lee *et al.*, 2017).

A similar finding emerged from a retrospective study conducted in Japan among 246 TB patients aged 18 and above. This study revealed that patients aged 75 years and older had a significantly higher risk of dying during TB treatment compared

to younger patients, with 38.5% of older patients dying during treatment versus 6.2% of younger patients (HR: 10.09; 95% CI: 1.31, 77.5) (Hase *et al.*, 2021).

b) **Gender**

Studies in Korea revealed that males were more at risk for TB-related death during TB treatment (Chung *et al.*, 2021). This finding is consistent with the results reported by Avoi and Liaw (2021), which indicated that males are more prone to TB-related death (AOR: 1.01; 95% CI: 0.68, 1.50). Between the years 2015 and 2017, it was observed that male patients accounted for a substantial 68.0% of the total TB-related mortality cases in South Korea, highlighting a notable gender gap in TB mortality rates (Min *et al.*, 2019). Similar findings were observed in Iran, where it was found that males have a higher risk of TB mortality compared to females (AOR: 1.34; 95% CI: 1.23, 1.45) (Fallahzadeh *et al.*, 2023).

c) **Ethnicity**

Ethnicity plays a significant role in TB mortality, with various studies highlighting disparities among different racial and ethnic groups. Research indicates that genetic factors associated with TB susceptibility and resistance vary among ethnic groups, suggesting that unique environmental and selective pressures have shaped these genetic predispositions worldwide.

In the United States, TB-related mortality rates from 1990 through 2006 were higher among racial/ethnic minorities, including Hispanic, Asian, Black, and Native American populations (Jung *et al.*, 2010). A local study conducted in Terengganu showed Malay has a significant number of TB mortality (AOR: 2.48; 95% CI: 0.57,

10.76) (Awang *et al.*, 2022). However, most of the studies conducted in Malaysia are not focused on ethnicity as the independent cause of TB-related death during IP (Ho *et al.*, 2023).

d) **Place of residence**

More cases living in rural areas showed a higher number of TB-related deaths compared to cases residing in urban areas. This statement was supported by the findings of Avoi and Liaw (2021), where cases from rural areas had a higher number of TB-related deaths. Another study by Chung *et al.* (2021) also recorded that TB death was more common among people living in non-metropolitan areas. However, a study conducted in Thailand by Khunthason *et al.* (2020) showed no significant association between living in urban areas and TB-related mortality compared to those living in rural areas (AOR: 1.62; 95% CI: 0.88, 2.99). On the other hand, another finding indicated that urban residents diagnosed with TB exhibited a stronger correlation with unsuccessful treatment outcomes, implying that residing in urban areas may present obstacles to the successful completion of TB treatment (AOR: 1.21; 95% CI: 1.17, 1.26; $p<0.001$) (Tok *et al.*, 2020).

e) **Education status**

TB patients with no formal education were linked to all causes of TB death, as well as TB-related death (Chung *et al.*, 2021). Another similar study found that those with no formal education contributed the higher TB mortality (AOR: 2.04; 95% CI: 1.89, 2.20) compared to primary educational status (AOR: 1.81; 95% CI:1.67, 1.95) and secondary educational status (AOR: 1.67; 95% CI:1.56, 1.79) (Tok *et al.*, 2020).

However, a study in Western Uganda found contrasting results. Their study found that TB patients who were not educated were 9.01 times more likely to get cured compared to educated patients. This higher cure rate among uneducated patients might be due to less stigma and better adherence to treatment protocols, as educated individuals may face more stigma in formal employment settings, leading to poorer adherence (Nabimanya *et al.*, 2022).

f) **Employment status**

A study conducted in Spain by Rodrigo *et al.* (2016) found that actively employed individuals had a higher number of TB-related deaths during the IP of anti-TB treatment (AOR: 2.40; 95% CI: 1.11, 5.14). However, a study conducted in the USA by Hannah *et al.* (2017) found that retired individuals had a higher number of TB-related deaths (AOR: 1.98; 95% CI: 1.52, 2.57). Additionally, a similar study found that unemployed individuals were associated with higher TB mortality (AOR: 1.43; 95% CI: 1.36, 1.49) (Chung *et al.*, 2021). Similarly, a study conducted by Dewan *et al.* (2004), found that unemployment status showed a 4.9 times higher risk of death during TB treatment.

g) **Marital status**

A study conducted in Argentina by Zerbini *et al.* (2017) revealed a notably higher incidence of TB-related deaths among married individuals. The research indicated that married people face an elevated risk compared to their single counterparts, primarily due to the increased likelihood of transmission from a spouse with active TB. In contrast, a study conducted in Korea showed a higher number of TB deaths among

single individuals compared to those who are married (AOR: 1.35; 95% CI: 1.31, 1.39) (Chung *et al.,* 2021). Opposite findings were observed in Cameroon, where being single had no significant association with early mortality during the IP of anti-TB treatment (Bigna *et al.,* 2015).

h) **Nationality**

TB deaths are higher among non-Malaysian citizens. This can be seen in a study conducted in Malaysia by Tok *et al.* (2020), which found that non-Malaysians are significantly associated with unfavourable outcomes (TB death) (AOR: 2.94; 95% CI: 2.77, 3.12; p<0.001). Another study in Sabah by Avoi and Liaw (2021) found that non-citizens contributed to TB-related deaths during the IP as most cases presented with more advanced disease (AOR: 2.32; 95% CI: 1.44, 3.72 However, this finding contrasts with results reported in Spain, the USA, and Argentina, where citizens had a higher number of TB-related deaths compared to non-citizens (Rodrigo *et al.,* 2016; Hannah *et al.*, 2017; Zerbini *et al.*, 2017).

Another study done in Manjung, Perak, showed non-Malaysians were significant risk factors for all causes of TB mortality during anti-TB treatment (AOR: 5.18; 95% CI: 2.04, 13.14; p<0.001). This finding is also supported by a registry-based cohort study in Malaysia, which found that non-Malaysians were significantly associated with unsuccessful TB outcomes (AOR: 2.94; 95% CI:2.77, 3.12) (Tok *et al.*, 2020).

i) **Income status**

People with unstable or low income might struggle to complete their TB treatment because they cannot afford the cost of transportation to health facilities or nutritious food or may lose income during their illness, which can lead to higher rates of death from TB. A study by Avoi and Liaw (2021) found that having no steady income were significantly associated with TB-related death during the IP compared to those with regular and fixed income (AOR: 1.63; 95% CI: 1.28, 2.07).

2.3.2 Lifestyle, clinical and comorbid

a) Smoking

Smoking contributed to the highest number of TB-related mortality regardless of the phase of anti-TB treatment. The study reported by Tok *et al.* (2020) found that smoking was significant in association with TB mortality (AOR: 1.08; 95% CI: 1.04, 1.13). Another study conducted in Denmark by Holden *et al.* (2020) shows tobacco is the factor associated with TB-related mortality (HR: 2.22; 95% CI: 1.32, 3.75). Additionally, a study by Yaghi *et al.* (2022) also found that smoking was a statistically significant risk factor for TB mortality (HR: 1.72; 95% CI: 1.08, 2.75). However, study in Terengganu conducted by Awang *et al.* (2022) found that smoking is not a significant variable for TB mortality (AOR: 1.30, CI: 0.88, 1.92)

b) BCG vaccination

The absence of a BCG scar is one of the reported factors associated with unfavourable TB outcomes, including TB mortality. A study in Malaysia by Tok *et al.* (2020) found

that the absence of a BCG scar was an associated factor for TB death (AOR:1.21; 95% CI: 1.15, 1.27).

However, study conducted in Manjung, Perak, by Qamruddin *et al.* (2023) and in Terengganu by Awang *et al.* (2022) showed that the absence of a BCG vaccination had no significant association with TB mortality (AOR: 0.61; 95% CI: 0.36, 1.03). (AOR: 1.37; 95% CI: 0.65, 2.89) respectively.

c) Alcoholics

Alcoholics were found to be a non-significant risk factor for TB-related mortality in certain studies. A study conducted in Sarawak by Bigna *et al.* (2015), found that alcohol was not a significant risk factor for TB-related death (AOR: 5.75; 95% CI: 0.83, 19.74). A local study in Sabah by Avoi and Liaw (2021) reported similar findings (AOR: 1.29; 95% CI: 0.79, 2.10). However, a study in Denmark by Holden *et al.* (2020), found that alcohol abuse is a significant risk factor for TB-related death (HR: 3.57; 95% CI: 1.92, 6.63).

d) Diabetes

Underlying diabetes is not a significant risk factor in TB-related mortality. Jeong *et al.* (2023) found that cases with underlying diabetes were not associated with TB-related mortality. Study in Ethiopia also reported no association between TB mortality during the IP of anti-TB treatment and the diabetes status of the patients (Workneh *et al.*, 2016). Similar findings were observed in Sabah, where diabetes mellitus was not a significant risk factor for TB death (AOR: 0.76; 95% CI: 0.36, 1.62) (Avoi and Liaw, 2021). Additionally, a local study conducted in Manjung, Perak, also found that

diabetes mellitus was not a significant risk factor for TB mortality, with a p-value of 0.978 (Qamruddin *et al.*, 2023).

e) HIV status

HIV positivity is still the leading cause of TB mortality, making HIV testing essential for every TB case. However, a study conducted in the USA by Hannah *et al.* (2017) found that most TB-related mortality during anti-TB treatment was higher among TB cases where an HIV test was not done (AOR: 4.77; 95% CI: 3.96, 5.76). Rodrigo *et al.* (2016), recorded that HIV-positive status was a significant risk factor for the probability of TB death during the IP (HR: 3.38; 95% CI: 1.73, 6.64). Additionally, a study in Tanzania by Bukundi *et al.* (2021) also supports that HIV-positive status was the significant risk factor for TB death (HR: 2.5; 95% CI: 2.26, 2.79). A local study in Sabah also found that HIV-positive status has a strong association with TB death (AOR: 3.66; 95% CI: 1.80, 7.43) (Avoi and Liaw, 2021).

2.3.3 TB disease characteristics

a) TB category

Most studies show that TB cases categorized as new have a higher number of TB-related mortalities. A study by Oruc *et al.* (2022) showed that new TB cases contributed more to TB-related deaths (HR: 2.0; 95% CI: 1.28, 15.26). However, a study conducted in Spain by Rodrigo *et al.* (2016) found that new TB cases were not associated with TB death during the IP (HR: 1.28; 95% CI: 0.52, 3.17).

In contrast, a study conducted in Sabah by Avoi and Liaw (2021) found that TB retreatment cases had a positive association with TB-related death (AOR: 1.59; 95% CI: 1.08, 2.36). This finding is supported by research in South Africa by Heunis *et al.* (2017), where TB retreatment cases were a significant risk factor for TB death (AOR: 1.32; 95% CI: 1.21, 1.42).

b) TB anatomical site

Pulmonary involvement in TB disease is associated with a higher number of TB-related mortalities. A study conducted in Turkey by Oruc *et al.* (2022) found that pulmonary TB was a common risk factor for TB-related death (HR: 2.91; 95% CI:1.00, 8.50). Another study by Holden *et al.* (2020) also identified pulmonary TB as an associated factor for TB-related mortality.

c) Initial AFB status

For every TB case, it is mandatory to take a sputum test to classify the case as PTB smear-positive or PTB smear-negative. TB-related mortality was found to be significant among PTB smear-positive cases compared to PTB smear-negative cases. This is supported by a study conducted in Spain by Rodrigo *et al.* (2016), which found that pulmonary TB smear-positive cases were strongly associated with TB-related mortality during the IP. Another study conducted in Sabah by Avoi and Liaw (2021) also found that TB-related mortality was higher among the PTB smear-positive.

d) Type of TB case detection

The detection of TB cases can be either active, through screening, or passive, through patients who present with symptoms at a health clinic. TB-related mortality during the IP was found to be higher among TB patients who were passively detected. This was demonstrated in a study conducted in Sabah, where passive case detection was associated with TB-related mortality (AOR: 1.57; 95% CI: 1.02, 2.40) (Avoi and Liaw, 2021).

e) Chest X-ray finding

Chest radiograph (CXR) results of far more advanced findings contributed to a higher risk of TB-related mortality. A study conducted in USA by Hannah *et al.* (2017) found that an abnormal CXR was associated with TB-related mortality outcomes and (AOR: 1.68; 95% CI: 1.29, 2.18). Another study found that bilateral lung involvement was also a significant factor associated with TB-related mortality ($p<0.001$) (Jeong *et al.*, 2023).

f) TB Miliary

TB miliary, also known as disseminated TB, is a potentially life-threatening type of TB that occurs when a large number of bacteria travel through the bloodstream and spread throughout the body. A study conducted in Sabah found that TB-related mortality was significantly higher in TB meningitis patients ($p<0.001$) (Avoi and Liaw, 2021).

g) TB meningitis

TB meningitis is a type of extra-pulmonary TB due to the seeding of the meninges with the bacilli of *Mycobacterium tuberculosis*. It is characterized by inflammation of the membranes (meninges) around the brain or spinal cord (Haiga, 2022). A study by Avoi and Liaw (2021) found that TB meningitis was significantly associated with TB-related mortality ($p<0.001$).

h) Multidrug-resistant TB

Multidrug-resistant TB (MDR-TB) is caused by an organism that is resistant to at least isoniazid and rifampin, the two most potent TB drugs (Prasad *et al.*, 2014). A study conducted in the USA from 2009 to 2013 by Hannah *et al.* (2017) found that MDR-TB were a significant risk factor for TB-related mortality (AOR: 3.42; 95% CI: 1.95, 5.99). However, a study by Rodrigo *et al.* (2016) in Spain showed that drug resistance was not a significant factor for TB death during the IP (HR: 1.38; 95% CI: 0.66, 2.85).

2.3.4 TB treatment

a) **Drug regime**

A study conducted in Spain by Rodrigo *et al.* (2016) found that the use of three loose drug regimens was a significant risk factor for TB death during the IP. These regimens typically involve combinations of first-line anti-TB drugs, which are essential for effective therapy and the prevention of drug resistance. While this regimen is effective, its lengthy duration often leads to issues with non-adherence and treatment failure (Soedarsono, 2021). Another study also found that the use of loose tablets during the

IP was associated with TB-related death (AOR: 2.15; 95% CI: 1.71, 2.68) (Avoi and Liaw, 2021).

b) **Adherence to DOTS**

TB cases that adhere to or comply with Directly Observed Therapy-Short Course (DOTS) showed reduced odds of dying (AOR: 0.006, 95% CI: 0.003, 0.013) (Avoi and Liaw, 2021). Conversely, TB patients with poor treatment adherence were reported to be a significant factor in TB-related death (AOR: 3.73; 95% CI: 1.92, 7.33) (Zerbini *et al.*, 2017). Another study in Spain found that difficulty in patient comprehension of treatment contributed to TB death during the IP (HR: 3.76; 95% CI: 1.72, 8.22) (Rodrigo *et al.*, 2016).

c) **Treatment centre**

A study conducted in Manjung, Perak, found that TB cases treated at government hospitals had a higher number of TB deaths, as most of the cases presented with advanced or complicated TB (AOR: 6.78; 95% CI: 3.04, 15.09) (Qamruddin *et al.*, 2023). Another study conducted in Spain by Rodrigo *et al.* (2016) found a similar finding, where cases treated at government hospitals had an increased odds ratio of TB death (AOR: 4.27; 95% CI: 1.71, 10.7).