ORIGINAL ARTICLE

Factors Associated With Unsuccessful Treatment Outcome Among New Pulmonary Tuberculosis Patients in Malaysia: A Retrospective Cohort Study

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ABSTRACT

Introduction: Achieving the World Health Organization's (WHO) target treatment success rate for new tuberculosis (TB) cases remains a challenge despite the TB End strategy and ongoing control efforts. Unsuccessful treatment outcomes heighten the risk of disease transmission and the emergence of drug resistance. This research aims to identify the patterns of TB treatment outcomes and explore the determinants of unsuccessful treatment among newly diagnosed pulmonary tuberculosis (PTB) patients in Malaysia. **Materials and methods:** A retrospective cohort study analysed 39,117 new pulmonary TB cases from the National Tuberculosis Database (TBIS) between January 2018 and January 2022. Multiple logistic regression determined factors associated with unsuccessful outcomes, using significance at p-value < 0.05. **Results:** Among the patients, 84.9% reported successful treatment, while 15.1% had unsuccessful outcomes, attributed to death (59.1%), loss to follow-up (23.2%), and not evaluated (15.0%). Factors such as age over 40 years old, male sex, Indian ethnicity, no formal education, urban residency, unemployment, smoking, HIV status, absence of BCG scar, positive sputum smear, severe initial chest x-ray results, no DOT supervision, and passive case detection significantly increased the risk of unsuccessful treatment. **Conclusion:** The study highlights specific sociodemographic and clinical factors linked to unsuccessful TB treatment outcomes, suggesting the need for targeted interventions in TB control programs and risk assessment strategies.
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INTRODUCTION

Tuberculosis (TB), caused by the bacterium Mycobacterium tuberculosis, is the foremost cause of mortality linked to a singular infectious agent. The majority of TB cases are pulmonary TB (85.0%), and the remaining 15.0% are extrapulmonary TB. The disease affected 10.6 million people worldwide and was responsible for 1.6 million deaths in the year 2021 (1). According to the World Health Organisation (WHO), worldwide incidence and mortality rates of tuberculosis (TB) have increased since 2015 by 8.4% and 46.0%, respectively. Despite efforts taken to engage all sectors to address socio-economic and cultural change for TB elimination, TB still remains a major disease burden in many nations, particularly in developing countries such as Indonesia, Philippines, Bangladesh, Vietnam and India (1, 2).

In 2015, WHO introduced the End TB Strategy as part of the Sustainable Development Goals (SDG), to combat the TB epidemic with the ultimate goal of "End of Tuberculosis in 2035"(3). Essentials update of implementing this strategy in 2022 set a target to achieve 90.0% treatment success rate, 90.0% reduction number

of TB deaths and 80.0% reduction in the TB incidence rate (3, 4).

Assessing tuberculosis treatment results is vital for gauging the success of TB management programs. Besides, if TB patients are not treated, the mortality rate will be high (1). Unsuccessful TB treatment outcomes can be defined as TB cases that are failed treatment, die during the treatment period, loss to follow-up, transferred out or disappear, as well as those that are not evaluated (5). Defaulted patients or a loss to follow-up will need to re-start a new treatment cycle, which will lead to an extended treatment period and increased risk for TB drug resistance (6, 7). Plus, patients who fail treatment are at risk of spreading the disease in the community (8). As a result, this increases the health burden on the country.
The diagnosis and management of tuberculosis pose ongoing challenges to Malaysia's healthcare system. In 2021 alone, the incidence of tuberculosis increased to 97 cases per 100,000 population from 72 cases per 100,000 population in 2015 and the number of deaths increased to 2,560 from 1,696 in 2015 (1). The country's struggle with high death rates and treatment success rates not meeting the WHO's End TB strategy targets places Malaysia in the category of countries with a moderate TB burden (9). Based on the WHO 2020 report, the global success rate for treating new TB cases was 86.0% (10), whereas Malaysia's success rate for new TB cases stood at 76.0%, below both global and national benchmarks (11).

Based on the highlights of previous research, several studies have focused on examining the outcomes of tuberculosis treatment in specific subpopulations. For example, among aboriginal people, healthcare workers with positive TB smear results, TB patients with comorbid conditions and specific regions within Malaysia (12-16). Few factors were identified from each study including age, gender, citizenship, socioeconomic background (financial constraint/poverty that affects access to education), location of residence, smoking and clinical factors which include Human Immunodeficiency Virus (HIV) status, presence of comorbid such as Diabetes Mellitus (DM), previous lung diseases and Directly Observed Treatment (DOT) status (6, 8, 12, 14, 17-19).
To improve disease management and control efforts, it is essential to determine TB trends and treatment outcomes in healthcare facilities. This can be done through routine monitoring of the treatment's performance and understanding the underlying causes. This study utilizes recent cohorts of TB patients in Malaysia, spanning from 2018 to 2021, to analyse the latest patterns in TB treatment outcomes and identify factors leading to unsuccessful treatment in new cases of pulmonary TB.

MATERIALS AND METHODS

Study design

This study retrospectively analyzed a cohort over four years, spanning from January 2018 to January 2022, utilizing data obtained from the MyTB national surveillance database.

Database and study setting

The national MyTB database is owned by the Disease Control Division, which is under the purview of the Ministry of Health. Tuberculosis (TB) is recognized as a communicable disease that requires reporting, as mandated by the Prevention and Control of Infectious Disease Act (Act 342), which necessitates its notification. The reporting of TB cases is facilitated by the employment of the tuberculosis information system form, notably form TBIS 10A-1, which is then recorded in the state's MyTB database. All TB cases that were notified and reported in the TBIS adhere to a standardised recording and reporting procedure applicable to both the public and private healthcare sectors.

In Malaysia, the confirmation of TB diagnosis is achieved through the laboratory analysis for the isolation of Mycobacterium tuberculosis, utilizing either acid-fast bacilli (AFB) detection in sputum smears or through culture methods (20). The guidelines for TB management advocate for a treatment regimen lasting six months with isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z) for individuals with TB that is susceptible to drugs, including both pulmonary and extrapulmonary cases. This involves administering all four medications during the initial two months, followed by a continuation with H and R for the final four months (20, 21).

Study population and sampling

The study included all newly diagnosed PTB patients registered in TBIS within the designated study timeframe that met the specific inclusion and exclusion criteria. New PTB cases are patients who either not previously diagnosed with TB or those who had been under treatment for less than four weeks (5, 22). The inclusion criteria were age more than 18 years old, cases registered in the national TBIS between 1st January 2018 until 1st January 2022 and patients with outcomes determined within 1 year of treatment initiation. This study excludes patients whose diagnosis changed throughout treatment, who are still in treatment and patients with multi-drug-resistant tuberculosis (MDR-TB). Cases with MDR-TB were not included due to different treatment outcomes and drug regimen requirements (22).

The sample size was estimated using the OpenEpi calculator version 3, based on odd ratio (r =1.36) data from a domestic study (16) with alpha of 0.05 and power of 80%, the maximum sample size calculated was 7344. However, in this study, all registered new PTB patients who fulfilled the criteria were included in analysis (n= 39,117).

Outcome variables

The primary dependent variable was the outcome of PTB treatment, divided into two categories: successful (a combination of cured cases and those who completed treatment) and unsuccessful treatment (comprising deaths, loss to follow-up, treatment failure, and cases not evaluated). Each outcome category follows standard definitions from the WHO Reporting framework for tuberculosis, also used in the Malaysia Clinical Practice Guidelines for TB management (20, 22).

Cured patients are those with bacteriological confirmation of TB at the start who then show negative smear or culture results in the final treatment month and on at least one more occasion. Patients who completed treatment showed no signs of failure but lacked evidence of negative sputum smear or culture in the final month and on another occasion, possibly due to not undergoing tests or unavailable results. Both cured and completed treatment for six months belonged to successful treatment outcomes categories. Treatment failure is identified in patients with positive sputum smear or culture at the fifth month or later of treatment. Death cases refer to patients dying for any reason before or during the treatment. Loss to follow-up includes patients who either did not initiate treatment or whose treatment was interrupted for two or more consecutive months. Not evaluated cases are those not assigned a treatment outcome, including patients transferred out to another unit or when the treatment outcome remains unknown to the reporting unit (5). This outcome category was used when a patient's final TB treatment result was missing, often due to incomplete transfer of information between reporting units (health facilities across state or country). This occurs when patients were diagnosed TB at Hospital in state 'A', then he/she moved to different state and transferred his/her treatment to Hospital B. If Hospital A reports the case to the national TB registry, but does not have information on his final treatment outcome from Hospital B, this case will be classified as "not evaluated" in the treatment outcome data from Hospital A.

Independent variables

This study analyzed sociodemographic variables such as age, gender, ethnicity, nationality, residential location, employment status, and education level. Regarding clinical attributes, the research focused on smoking habits, diabetes mellitus (DM) condition, HIV status, the presence of a Bacille Calmette-Guerin (BCG) vaccination scar, chest radiography (CXR) findings at diagnosis, initial sputum smear results, the approach of case detection, the implementation of directly observed treatment (DOT), and the supervision of DOT.

Data analysis

The analysis was conducted using IBM SPSS software, version 25.0. The study summarized the sociodemographic details and clinical aspects of TB patients, including their treatment results. Categorical data were presented through frequencies and percentages, while means and standard deviations were used for continuous variables that followed a normal distribution. The dataset underwent a cleaning process to remove any duplication, missing values, inconsistencies, and outliers.

To investigate the relationship between the sociodemographic and clinical characteristics of TB patients and the outcomes of their treatment (specifically focusing on unsuccessful treatment outcomes), simple binary logistic regression (SLR) was employed. Further, to adjust for potential confounding factors, a multivariable analysis was performed using multiple logistic regression (MLR), yielding adjusted odds ratios (aORs) with 95% confidence intervals (CIs). The threshold for statistical significance was established at $p < 0.05$.

Variables for the final model were identified using the Backward LR method. The presence of multicollinearity and interaction between the independent variables was checked. The interaction was considered in the final model. The model demonstrates good model fit, as indicated by a Hosmer and Lemeshow test (p=0.109) with an overall classification table accuracy of 84.9%. We assessed multicollinearity among the variables to ensure the reliability of the binary logistic regression model. The Variance Inflation Factor (VIF) values ranged from 1.014 to 1.396, all well below the commonly accepted threshold of 10, while tolerance values ranged from 0.716 to 0.986, all exceeding the threshold of 0.1. These results confirm that multicollinearity was not a concern in the final model.

Ethical Clearance

Identifying information about the patients (such as names, addresses, or any other personal details) was not disclosed in the study. Additionally, the results of this study will be presented in aggregate form, ensuring that no individual's identity is specifically mentioned. The study received ethical approval from the Medical Research and Ethics Committee (MREC) of Malaysia's Ministry of Health [NMRR ID-23-00651-7CA (IIR)] and Universiti Kebangsaan Malaysia ethics committee [UKM PPI/11/8/JEP-2023-242].

RESULTS

Over the last four years, from January 1st, 2018 to January 31st, 2022, 73,767 new PTB cases were

recorded in the national TB registry. Of these, 39,117 cases were included for analysis after excluding cases with missing values, MDR-TB cases and patients with changed diagnoses. The average age of these patients was reported to be 47.4 (SD 17.18) years. Based on Table I, the majority of the participants were male (67.2%), of Malay ethnicity (48.9%), Malaysian citizens (99.9%), and residents living in urban areas (52.3%). The distribution of new PTB cases varies among states in Malaysia; with Sarawak (18.4%), Sabah (14.8%), and Selangor (12.4%) reporting the highest percentages. Additionally, a significant portion of the patients had attained formal education (88.8%) and were employed (49.7%).

Table I: Sociodemographic and socioeconomic characteristics of new pulmonary tuberculosis patients in Malaysia (total patients, n=39,117)

Sociodemographic characteristics		n (%)
Age group (years)	18 - 39	14,125 (36.1)
	40 - 59	14,285 (36.5)
	≥60	10,707 (27.4)
Gender	Male	26,301(67.2)
	Female	12,816 (32.8)
Race	Malay	19,122 (48.9)
	Pribumi Sabah/Sarawak	10,234 (26.2)
	Chinese	6,904 (17.6)
	Indian	1,978 (5.1)
	Others	879 (2.2)
Nationality	Malaysian	39,103 (99.9)
	Non-Malaysian	14 (0.1)
Location of residence	Urban	20,452 (52.3)
	Rural	18,665 (47.7)
State	Sarawak	7,214 (18.4)
	Sabah	5,775 (14.8)
	Selangor	4,846 (12.4)
	Johor	3,653 (9.3)
	Wilayah Persekutuan	2,799 (7.2)
	Kedah	2,781 (7.1)
	Perak	2,764 (7.1)
	Pulau Pinang	2,699 (6.9)
	Kelantan	1,996 (5.1)
	Pahang	1,502 (3.8)
	Negeri Sembilan	1,078 (2.8)
	Terengganu	1,017 (2.6)
	Melaka	578 (1.5)
	Wilayah Persekutuan Labuan	161 (0.4)
Socioeconomic characteristic		
Employment	Employed	19,450 (49.7)
	Unemployed	19,667 (50.3)
Formal education	Yes	34,746 (88.8)
	No	4,371 (11.2)

Table II demonstrates that the majority of the patients had a BCG scar (92.6%), did not smoke (64.2%), were non-diabetic (75.0%), and were HIV-negative (96.0%). Upon diagnosis, most of the patients were smear-negative (59.9%) and had no or minimal lesions on CXR (55.8%). In terms of patients' management, most of the patients received treatment under Direct Observation Therapy (DOT) (99.7%) and were supervised by healthcare workers (69.2%). Most of the cases were detected through passive case detection (91.4%). Passive case detection refers to the detection of TB cases in people who seek care, usually with symptoms, from health providers or community health workers. This differs from active case detection which involves healthcare proactively screening populations for asymptomatic and symptomatic cases outside of routine health services.

Table II: Clinical characteristics of new pulmonary tuberculosis patients in Malaysia (n=39,117).

Clinical characteristics	n (%)
Smoking status	
No	25,131 (64.2)
Yes	13,986 (35.8)
Diabetes Mellitus	
No	29,337 (75.0)
Yes	9,780 (25.0)
HIV status	
Negative	37,558 (96.0)
Positive	1,559 (4.0)
BCG scar	
Present	36,238 (92.6)
Absent	2,879 (7.4)
Sputum smear upon diagnosis	
Negative	23,450 (59.9)
Positive	15,667 (40.1)
Chest x-ray upon diagnosis	
No/minimal lesion	21,832 (55.8)
Moderately advanced	15,430 (39.4)
Far advanced	1,855 (4.7)
DOTS status	
Yes	38,987 (99.7)
No	130 (0.3)
DOTS supervision	
Healthcare worker	27,079 (69.2)
Non- Healthcare worker	11,908 (30.4)
No supervision	130 (0.3)
Case detection	
Active or Screening	3,351 (8.6)
Passive	35,766 (91.4)
Treatment outcome	
Successful (n=33,200, 84.9%)	
Cured	23,557 (60.2)
Completed treatment	9,643 (24.7)
Unsuccessful (n=5,917, 15.1%)	
Treatment failed	154 (2.6)
Loss to follow-up	1,374 (23.2)
Died	3,499 (59.1)
Not evaluated	890 (15.0)

Notes: BCG=Bacillus Calmette-Guerin; DOTS=Directly Observed Therapy.

Over the last four years, 33,200 patients achieved a successful outcome (84.9%) while 5,917 patients experienced unsuccessful outcomes, representing 15.1%. Among the unsuccessful outcomes, the largest proportion was due to deaths (59.1%), with loss to follow-up (23.2%) and cases that were not evaluated

(15.0%) following behind. Number of new PTB cases reported in TB database showed significant decline in 2020 (14.2% reduction compare to year 2018). While the successful treatment rate was plateau for these 4 years period ranging from 84.3% to 85.4% and 14.6% to 15.7% for the unsuccessful treatment rate (Table III).

Table III: Trend of new PTB cases and treatment outcome rate from 2018 until 2021 (n=39,117)

Year	2018	2019	2020	2021
Total case	10,675	10,801	9,163	8,478
Completed treatment	2,493	2,637	2,343	2,170
Cured	6,508	6,582	5,478	4,989
Died	940	863	851	845
Failed	43	51	32	28
Loss to follow-up	471	399	276	228
Not evaluated	220	269	183	218
Successful treatment rate[a]	84.3%	85.4%	85.4%	84.3%
Unsuccessful treatment rate[b]	15.7%	14.6%	14.6%	15.7%

[a]Rate of successful treatment (sum of completed and cured case per total case)
[b]Rate of unsuccessful treatment (sum of died failed, loss to follow-up, and not evaluated per total case)

Simple logistic regression analysis showed that variables age, gender, race, education, residence site, employment status, smoking status, DM, HIV, BCG scar, sputum and CXR upon diagnosis, DOT supervision and case detection method were linked with TB treatment results (Table IV). After controlling for additional covariates using binary logistic regression, the factors that contributed to unsuccessful TB treatment results were identified. Table V provides the final model. Among the variables, age >60 years old (aOR: 2.22, 95% CI: 2.04-2.41), males (aOR: 1.46, 95% CI: 1.35–1.57), Indians (aOR: 1.56, 95% CI: 1.38–1.75), no formal education (aOR: 1.47, 95% CI: 1.34–1.61), urban residence (aOR: 1.31, 95% CI: 1.23–1.40), unemployed (aOR: 1.59, 95% CI: 1.49–1.69), smoking (aOR: 1.22, 95% CI: 1.15–1.31), HIV positive (aOR: 3.48, 95% CI: 3.09–3.90), positive sputum smear upon diagnosis (aOR: 1.38, 95% CI: 1.30–1.46), moderately advanced (aOR: 1.16, 95% CI: 1.09–1.23) and far advanced CXR upon diagnosis (aOR: 1.77, 95% CI: 1.57–1.99), no DOT supervision (aOR: 5.44 95% CI: 3.79–7.80), and passive case detection (aOR: 1.24, 95% CI: 1.117–1.39) were discovered to be the factors with higher odds of unsuccessful TB treatment outcome.

Table IV: Simple logistic regression analysis for factors associated with treatment outcome.

Variables	Unsuccessful, n (%)	Successful, n (%)	Unadjusted OR	95% CI	*p*-value
Age group (years)					
18 - 39	1,507 (10.7)	12,618 (89.3)	1		
40 - 59	2,052 (14.4)	12,233 (85.6)	1.40	1.31, 1.51	<0.001*
≥60	2,358 (22.0)	8,349 (78.0)	2.37	2.20, 2.54	<0.001*
Gender					
Female	1,466 (11.4)	11,350 (88.6)	1		
Male	4,451 (16.9)	21,850 (83.1)	1.58	1.48, 1.68	<0.001*
Race					
Malay	3,039 (15.9)	16,083 (84.1)	1		
Chinese	1,113 (16.1)	5,791 (83.9)	1.02	0.94, 1.09	0.657
Indian	479 (24.2)	1,499 (75.8)	1.69	1.52, 1.89	<0.001*
Others	117 (13.3)	762 (86.7)	0.81	0.67, 0.99	0.040*
Pribumi Sabah/Sarawak	1,169 (11.4)	9,065 (88.6)	0.68	0.64, 0.73	<0.001*
Formal education					
Yes	5,005 (14.4)	29,741 (85.6)	1		
No	912 (20.9)	3,459 (79.1)	1.57	1.45, 1.70	<0.001*
Residence site					
Rural	2,563 (13.7)	17,098 (83.6)	1		
Urban	3,354 (16.4)	16,102 (86.3)	1.23	1.17, 1.31	<0.001*
Employment status					
Employed	2,257 (11.6)	17,193 (88.4)	1		
Unemployed	3,660 (18.6)	16,007 (81.4)	1.74	1.65, 1.84	<0.001
Smoking status					
No	3,463 (13.8)	21,668 (86.2)	1		
Yes	2,454 (17.5)	11,532 (82.5)	1.33	1.26, 1.41	<0.001*
DM					
No	4,298 (14.7)	25,039 (85.3)	1		
Yes	1,169 (16.6)	8,161 (83.4)	1.16	1.09, 1.23	<0.001*

CONTINUE

Table IV: Simple logistic regression analysis for factors associated with treatment outcome. (CONT.)

Variables	Unsuccessful, n (%)	Successful, n (%)	Unadjusted OR	95% CI	*p*-value
HIV status					
Negative	5,381 (14.3)	32,177 (85.7)	1		
Positive	536 (34.4)	1,023 (65.6)	3.13	2.81, 3.49	<0.001*
BCG scar					
Present	5,328 (14.7)	30,910 (85.3)	1		
Absent	589 (20.5)	2,290 (79.5)	1.49	1.36, 1.64	<0.001
Sputum smear upon diagnosis					
Negative	3,117 (13.3)	20,333 (86.7)	1		
Positive	2,800 (17.9)	12,867 (82.1)	1.42	1.34, 1.50	<0.001*
Chest X-ray upon diagnosis					
No/minimal lesion	2,964 (13.6)	18,868 (86.4)	1		
Moderately advanced	2,519 (16.3)	12,911 (83.7)	1.24	1.17, 1.32	<0.001*
Far advanced	434 (23.4)	1,421 (76.6)	1.94	1.73, 2.18	<0.001*
DOT supervision					
Healthcare worker	4,525 (16.7)	22,554 (83.3)	1		
Non-healthcare worker	1,329 (11.2)	10,579 (88.8)	0.63	0.59, 0.67	<0.001*
No supervision	63 (48.5)	67 (51.5)	4.69	3.32, 6.62	<0.001*
Case detection					
Active or Screening	411 (12.3)	2,940 (87.7)	1		
Passive	5,506(15.4)	30,260 (84.6)	1.30	1.17, 1.45	<0.001*

*$p < 0.05$; OR, odds ratio; CI, confidence interval.

Table V: Determinants of treatment outcome among new pulmonary tuberculosis patients in Malaysia.

Variables	Unsuccessful n (%)	Successful n (%)	cOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value[a]
Age group (years)						
18 - 39	1,507 (10.7)	12,618 (89.3)	1		1	
40 - 59	2,052 (14.4)	12,233 (85.6)	1.40 (1.31, 1.51)	<0.001	1.34 (1.24, 1.45)	<0.001
≥60	2,358 (22.0)	8,349 (78.0)	2.37 (2.20, 2.54)	<0.001	2.22 (2.04, 2.41)	<0.001
Gender						
Female	1,466 (11.4)	11,350 (88.6)	1		1	
Male	4,451 (16.9)	21,850 (83.1)	1.58 (1.48, 1.68)	<0.001	1.46 (1.35, 1.57)	<0.001
Race						
Malay	3,039 (15.9)	16,083 (84.1)	1		1	
Chinese	1,113 (16.1)	5,791 (83.9)	1.02 (0.94, 1.09)	0.657	0.79 (0.73, 0.86)	<0.001
Indian	479 (24.2)	1,499 (75.8)	1.69 (1.52, 1.89)	<0.001	1.56 (1.38, 1.75)	<0.001
Others	117 (13.3)	762 (86.7)	0.81 (0.67, 0.99)	0.040	0.81 (0.65, 0.99)	0.044
Pribumi Sabah/Sarawak	1,169 (11.4)	9,065 (88.6)	0.68 (0.64, 0.73)	<0.001	0.78 (0.72, 0.85)	<0.001
Formal education						
Yes	5,005 (14.4)	29,741 (85.6)	1		1	
No	912 (20.9)	3,459 (79.1)	1.57 (1.45, 1.70)	<0.001	1.47 (1.34, 1.61)	<0.001
Residence site						
Rural	2,563 (13.7)	17,098 (83.6)	1		1	
Urban	3,354 (16.4)	16,102 (86.3)	1.23 (1.17, 1.31)	<0.001	1.31 (1.23, 1.40)	<0.001
Employment status						
Employed	2,257 (11.6)	17,193 (88.4)	1		1	
Unemployed	3,660 (18.6)	16,007 (81.4)	1.74 (1.65, 1.84)	<0.001	1.59 (1.49, 1.69)	<0.001
Smoking status						
No	3,463 (13.8)	21,668 (86.2)	1		1	
Yes	2,454 (17.5)	11,532 (82.5)	1.33 (1.26, 1.41)	<0.001	1.22 (1.15, 1.31)	<0.001
DM						
No	4,298 (14.7)	25,039 (85.3)	1		1	
Yes	1,169 (16.6)	8,161 (83.4)	1.16 (1.09, 1.23)	<0.001	0.93 (0.87, 0.99)	0.045
HIV status						
Negative	5,381 (14.3)	32,177 (85.7)	1		1	
Positive	536 (34.4)	1,023 (65.6)	3.13 (2.81, 3.49)	<0.001	3.48 (3.09, 3.90)	<0.001

CONTINUE

Table V: Determinants of treatment outcome among new pulmonary tuberculosis patients in Malaysia. (CONT.)

Variables	Unsuccessful n (%)	Successful n (%)	cOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value[a]
BCG scar						
Present	5,328 (14.7)	30,910 (85.3)	1		1	
Absent	589 (20.5)	2,290 (79.5)	1.49 (1.36, 1.64)	<0.001	1.20 (1.08, 1.33)	0.001
Sputum smear upon diagnosis						
Negative	3,117 (13.3)	20,333 (86.7)	1		1	
Positive	2,800 (17.9)	12,867 (82.1)	1.42 (1.34, 1.50)	<0.001	1.38 (1.30. 1.46)	<0.001
Chest x-ray upon diagnosis						
No/minimal lesion	2,964 (13.6)	18,868 (86.4)	1		1	
Moderately advanced	2,519 (16.3)	12,911 (83.7)	1.24 (1.17, 1.32)	<0.001	1.16 (1.09, 1.23)	<0.001
Far advanced	434 (23.4)	1,421 (76.6)	1.94 (1.73, 2.18)	<0.001	1.77 (1.57, 1.99)	<0.001
DOT supervision						
Healthcare worker	4,525 (16.7)	22,554 (83.3)	1		1	
Non-healthcare worker	1,329 (11.2)	10,579 (88.8)	0.63 (0.59, 0.67)	<0.001	0.70 (0.65, 0.75)	<0.001
No supervision	63 (48.5)	67 (51.5)	4.69 (3.32, 6.62)	<0.001	5.44 (3.79, 7.80)	<0.001
Case detection						
Active or Screening	411 (12.3)	2,940 (87.7)	1		1	
Passive	5,506(15.4)	30,260 (84.6)	1.30 (1.17, 1.45)	<0.001	1.24 (1.11, 1.39)	<0.001
Interaction						
Sputum*BCG						
Negative*BCG present					1	0.020
Negative*BCG absent	-	-	-	-	1.28 (1.12, 1.47)	<0.001
Positive*BCG absent					1.09 (0.93, 1.27)	0.313
Positive*BCG present					1.40 (1.32, 1.50)	<0.001
Sputum*X-ray						
Negative*No/minimal lesion					1	<0.001
Negative*Moderately advanced					1.06 (0.98, 1.15)	0.167
Negative*Far advanced	-	-	-	-	1.35 (1.13, 1.61)	0.001
Positive*No/minimal lesion					1.22 (1.12, 1.32)	<0.001
Positive*Moderately advanced					1.31 (1.20, 1.43)	<0.001
Positive *Far advanced					2.34 (1.99, 2.76)	<0.001

OR= odds ratio; aOR= adjusted odds ratio; CI= confidence interval; cOR=crude/unadjusted odds ratio. Significant p-value <0.05.
[a]Adjusted for age, gender, race, education, residence site, employment status, smoking status, DM, HIV, BCG scar, sputum upon diagnosis CXR upon diagnosis, DOT supervision and case detection. Backward LR Multiple Logistic Regression model was applied. Multicollinearity was checked and not found. Hosmer-Lemeshow test (p=0.109), the model of this study noted to be fit and classified as good model with a score of 84.9%, and no outlier noted.

There was also a significant interaction observed between sputum status and BCG vaccination (p=0.020) toward the likelihood of unsuccessful treatment outcomes. From analysis to assess the interaction between sputum and BCG among new PTB patients, it shows that among patients without BCG scar with negative sputum had increased likelihood of an unsuccessful treatment outcome (aOR = 1.28, 95% CI: 1.12–1.47, p < 0.001). While among patients without BCG scar with positive sputum did not show a significant association. Interestingly, patients with BCG scar and positive sputum also had significantly higher odds of unsuccessful outcome (aOR = 1.40, 95% CI: 1.32–1.50, p < 0.001).
The interaction between sputum status and chest X-ray findings was also significant. Among patients with negative sputum and with moderately advanced lesions, the odds of an unsuccessful outcome were elevated but not significant (aOR = 1.06, 95% CI: 0.98–1.15, p = 0.167). However, among those with far-advanced lesions (aOR = 1.35, 95% CI: 1.13–1.61, p = 0.001), the odds of unsuccessful treatment were significantly increased. Positive sputum patients with advanced chest X-ray lesions also demonstrated significantly higher odds of unsuccessful outcome (aOR = 2.34, 95% CI: 1.99–2.76, p < 0.001).

DISCUSSION

This study reported an 84.9% treatment success rate surpassing a prior local study's 80.7% yet falling short of the WHO's target of over 90% (3). The rate of unsuccessful treatment was also lower than that observed in a registry-based cohort study of all registered TB patients in Malaysia from 2014 to 2017 (18).

The successful treatment rate for these four years was plateau, and the number of new PTB cases registered showed a significant decline since 2020, as Malaysia was hit by the Covid-19 outbreak and due to the implementation of the Movement Control Order in March 2020 (23). Even though the pandemic occurred, the successful treatment rate in 2020 (85.4%) was slightly better than in 2018 (84.3%). The outcome of this study suggests that Malaysia has been successful in upholding the standard of treatment and care, even in the face of several disruptions caused by the pandemic.
The reduction in newly reported cases of tuberculosis implies a rise in undiagnosed and untreated tuberculosis patients in the community. This findings coincide with the data reported in the WHO Global Tuberculosis Report for the year 2022 (1). The pandemic led to delayed

treatment seeking and reduced healthcare utilisation due to fear of contracting Covid-19, especially among patients who have mild symptoms of TB (24). Moreover, TB patients encountered restricted access to diagnostics and treatments due to Covid-19-induced strains on health systems (25).

Findings in this study showed that older patients over 60 years of age and males were at higher odds of unsuccessful treatment. These findings were consistent with other local and international studies in developing countries (8, 12, 16, 18, 26, 27). Older people are two times more likely to die from tuberculosis, with high death rates among those over 40 years. Besides, chronic disease worsens with age and weakens immune systems, which contribute to treatment failure. Also, older patients may have unusual symptoms, which cause delays in detection and treatment, contributing to a rise in tuberculosis-related morbidity and mortality. In addition, the treatment process for the elderly is complicated by a higher risk of negative reactions to medication (26). These include risk of adverse drug reactions (ADRs) such hepatitis, gastrointestinal upset, skin rash, and joint pain (28). Factors increasing ADR risk include polypharmacy, age-related physiological changes, and comorbidities (29). Studies have identified old age as an independent risk factor for PZA-related toxicity, which can manifest as severe liver injury or other systemic reactions.

Males were more likely to fail treatment because of their unhealthy behaviours such as smoking and alcohol consumption (16). These habits significantly impair the body's ability to combat TB and reduce treatment efficacy. Smoking damages the immune system, specifically weakening CD4+ and CD8+ T cells crucial for fighting TB, while nicotine interferes with the immune response to Mycobacterium tuberculosis (30). Smokers often experience delayed conversion to negative smear or culture, indicating persistent infection and increased risk of recurrent TB. Alcohol use similarly raises the risk of TB recurrence, with studies showing enhanced IFN-α production leading to increased macrophage death in TB-infected subjects. The combined effect of smoking and alcohol use accounts for a substantial proportion of recurrent TB cases, collectively compromising the body's defenses and the effectiveness of TB medications (31).

Our findings also reveal that individuals living in urban settings face a greater risk of treatment failure compared to their rural counterparts, a fact corroborated by studies from Ethiopia and Brazil (26, 32). Despite urban areas being more advanced in aspects such as education, life expectancy, and income, significant disparities in living standards exist, leading to a higher incidence of patients discontinuing treatment in urban settings (32). Moreover, urban areas are characterized by the presence of substantial pockets of poverty and persistent periphery regions. It is important to acknowledge that this information will aid stakeholders in implementing targeted measures to identify prospective possibilities and geographical regions for prioritizing tuberculosis control and preventive efforts.

Previous research has consistently demonstrated that low education or no formal education and being unemployed are significant determinants of unsuccessful treatment outcomes (16, 18, 33). Similarly, we observed that patients with no formal education were more likely to experience unsuccessful treatment compared to those who had received formal education. Patients with low socioeconomic status are at greater risk of treatment failure due to their typically poor knowledge and behaviour regarding the disease (14). These lead to underutilization of health services and delay in seeking diagnosis as they usually have misconceptions about TB and discrimination against TB patients (34). Therefore, improvement of community social aspects is important to be addressed by our government to ensure everyone has adequate social capacity for health access. Meanwhile, unemployed patients were twice as likely to get unsuccessful treatment compare to employed patients. This was likely because they spent most of the time seeking a job, faced difficulties attending the follow-up, and missed their medications. Subsequently, they will eventually abandon treatment (16).

Research from a meta-analysis indicated that smokers, especially in middle-income countries, have a substantially increased risk of experiencing unfavourable treatment outcomes (35). The research also highlighted a correlation between smoking and treatment results, with smokers showing a greater likelihood of failing to achieve successful treatment outcomes compared to non-smokers. The study further identified a higher incidence of treatment discontinuation among smokers. The previous multi-centre study also found that tobacco consumption is associated with poor adherence to medical treatments and increased mortality rates (35, 35). Non-adherence can be reduced by good communication between patients and health providers, as well as counselling. Besides, it is imperative to prioritise the implementation of smoking cessation awareness programmes or campaigns among tuberculosis patients. This measure is crucial to mitigate the progression of the disease towards severe symptoms or complications, as well as to decrease mortality rates.

HIV-positive status was also found to have higher odds of unsuccessful treatment outcomes. These were consistent with several other studies (16, 18, 19, 37). The coexistence of TB and HIV presents a unique and complex challenge in healthcare. One of the primary reasons for this is that HIV patients with TB often exhibit ambiguous or atypical TB symptoms, which can be easily mistaken for other illnesses or conditions. This diagnostic ambiguity can lead to delays in accurately diagnosing

TB and initiating appropriate treatment, which in turn negatively impacts treatment outcomes. Furthermore, the coexistence of TB and HIV in individuals can lead to compromised immunity, thereby heightening their susceptibility to severe TB manifestations and treatment-related complications.

In response to this challenge, Malaysia has taken proactive measures by implementing a nationwide guideline for the systematic screening of individuals at high risk for tuberculosis, including people living with HIV (PL-HIV), since 2015 (11). This guideline aims to ensure that PL-HIV are regularly screened for TB, allowing for early detection and prompt treatment initiation. This not only improves the chances of successful TB treatment outcomes but also helps in preventing the spread of TB within the community and among PL-HIV, who are particularly vulnerable. This integrated approach to TB and HIV management ultimately leads to improved health outcomes for affected individuals.

Sputum smear microscopy is a diagnostic technique used to identify acid-fast bacilli (AFB), essential for monitoring and managing TB cases (20). AFB-positive sputum indicates pulmonary tuberculosis represents the transmissible form of TB, significantly contributing to the spread of the disease. This indicates a high mycobacterial load present in the sputum (5000–10,000 AFB/mL) (20). High bacterial loads can lead to persistent symptoms, increased transmission risk, and a greater likelihood of treatment failure (38). This study also revealed that individuals with positive sputum smears had a twofold increase in the likelihood of experiencing unsuccessful treatment outcomes, aligning with results from research conducted in northwest Ethiopia (26). Hence, it is imperative to conduct a comprehensive evaluation of patients' sputum specimens to improve treatment effectiveness and enable proper monitoring and intervention.

Since 1984, DOT implementation in the national TB control programme has improved patient monitoring. By assigning another individual to monitor TB patients, constant monitoring increases medication adherence (11). Findings from this study showed that without supervision, patients were five times more likely to fail treatment. Similar to other studies that showed no supervision is linked to poor treatment outcomes (14). MOH has created a flowchart to trace defaulted patients (5). However, this effort required collaboration with the community and other agencies to ensure patient compliance (16, 39). It is necessary to expand educational efforts regarding the significance of treatment adherence and the completion of tuberculosis treatment to individuals affected by tuberculosis as well as the wider community.

BCG vaccination was part of the national immunisation programme and was effective among citizens (16). The present research observed that all citizens (100%) had BCG vaccination scars, whereas none of the non-citizens did. There was a significant relationship between not having BCG scars and the outcomes of treatment. This finding is consistent with a previous local study that found BCG scars have significant determinants for unsuccessful treatment outcomes (18). Considering Malaysia's appeal to migrant workers from neighbouring nations with high rates of tuberculosis, including Indonesia, Myanmar, and the Philippines, it is essential to screen all immigrants for infectious diseases before they are employed. This screening aims to discover those at the beginning stages of sickness to prevent the spread of the disease in the community.

The study also highlights the interaction between sputum status, BCG vaccination and chest x-ray in predicting TB treatment outcomes. Significant interaction between sputum positive and BCG status suggests that even among vaccinated individuals, the presence of active infection increases the risk of unsuccessful treatment. This could reflect the underlying variation of immune system variation or differences in vaccine efficacy (40). In Malaysia, where TB transmission is high, sputum-positive patients not only contribute to continued transmission but also risk more severe disease progression and hence poor treatment outcomes (26). Therefore, this interaction indicates the importance of both sputum status and BCG vaccination in TB management.

Additionally, observed interaction between sputum status and chest x-ray emphasizes that regardless of sputum status, patients with far advanced lesions had significantly higher risk of unsuccessful outcomes. These findings were similar with with previous study (6). The degree of lung involvement, as seen on chest X-rays, serves as an indicator for disease severity, extensive lung damage, and poorer treatment responses. These findings reinforce the need for early screening and intervention, and close monitoring to enable alteration of treatment protocols for patients with advance chest x-ray findings. Many studies found a correlation between DM and unsuccessful treatment outcomes (12, 13, 17, 18, 41). However, in our study patients with DM shows a 7% reduced likelihood for unsuccessful outcomes. This was probably due to proportional differences between those with and without DM as this study only included newly diagnosed pulmonary TB patients which most of whom did not have diabetes. Besides, diabetes is also linked to severe tuberculosis (13). Due to the rising prevalence in Malaysia, comprehensive TB and diabetes care are essential, and patients need to be advised regularly about their diabetic control to prevent further complications.

Significant improvements have been observed in Malaysia's tuberculosis (TB) control plan since the introduction of the End TB Strategy in 2015. The latest National Strategic Plan for TB Control 2016–2020 has highlighted a few strategies that, in line

with the Sustainable Development Goals (SDG) and End TB Strategy, include enhancing case detection, strengthening laboratory networks, and ensuring uninterrupted treatment supply (11). Nevertheless, the persistent problem of eradicating the tuberculosis (TB) epidemic is attributed to the dynamic sociodemographic makeup of the population. Effectively tackling the social determinants of individual health, which play a critical role in the fight against tuberculosis, requires the implementation of a comprehensive and integrated approach that involves the collaboration of several sectors.

In comparison with other countries, China stands out as one of the countries bearing a significant tuberculosis burden that has achieved the WHO End-TB strategy goal (a treatment success rate exceeding 90%) since the year 2000 (10). Among the elements that contribute to this is the targeted approach to high-prevalence areas and vulnerable populations (poor and ethnic minorities), the highest level of government support, and the multichannel of financial resources allocated towards implementing comprehensive tuberculosis screening programmes (42). They also expanded the "Directly Observed Treatment, Short-course" (DOTS) method, guaranteeing cost-free healthcare services and complete six-month therapy for individuals diagnosed with tuberculosis. They also introduced performance-based financial rewards for physicians and healthcare workers who identify and refer patients with tuberculosis (43).
The study has revealed the key factors behind the failure of tuberculosis treatment outcomes, which could guide important stakeholders, especially public health physicians, the Ministry of Health, and the government, towards improving tuberculosis treatment outcomes in Malaysia. It is vital to continuously invest in a health system that can meet the needs of underprivileged populations and withstand the challenges posed by infectious diseases, focusing on improving case detection, lab testing accessibility, and staffing. Besides, it is crucial to build collaborative initiatives between governmental bodies and local communities to foster networking possibilities among community members and local authorities. The use of a collaborative strategy is crucial in enabling the community to effectively monitor and address the transmission of tuberculosis within their own geographic area.

Also, this is especially important to ensure the preparedness of our health system for pandemic events that may affect our health service capacity. Besides, it's also important to keep educating, advocating for, and empowering communities, as well as influencing policymakers to ensure that tuberculosis and Covid-19 remain a priority on the international stage due to their similar symptoms, modes of transmission, and substantial burden on healthcare systems (43,44).

Limitation

The retrospective nature of this study and its reliance on secondary data sources introduce certain limitations. Our ability to examine specific variables is limited, such as socioeconomic status (as measured by income level), other comorbid conditions, nutritional status, risky behaviours, and proximity to treatment services. Furthermore, 40.0% of the missing data on income and antiretroviral therapy was omitted from the analysis. Hence, future research should aim to overcome these limitations by ensuring comprehensive data collection at the diagnosis stage and during data transfer. This study focuses exclusively on new cases of pulmonary tuberculosis, suggesting that its findings may not extend to every tuberculosis type found in Malaysia. Nevertheless, the strength of this study is in its sample, which represents the demographic composition of the Malaysian population. This suggests that findings could inform the tuberculosis control efforts throughout Malaysia, offering critical insights for evaluating the national tuberculosis control program.

CONCLUSION

In Malaysia, the rate of treatment success has stayed under the World Health Organization's established target. According to this research, various factors are responsible for the lack of success in treatment outcomes. These factors include being over the age of 40, being male, belonging to the Indian population, lacking formal education, residing in urban areas, being unemployed, engaging in smoking habits, testing positive for HIV, not BCG vaccinated, having a positive sputum smear and advanced lesion on chest X-ray at the time of diagnosis, not receiving directly observed therapy (DOT) supervision, and being detected through passive case detection. Importantly, the interaction findings between sputum status, BCG vaccination, and chest X-ray severity highlight the complex interactions of these variables. Positive-sputum individuals with BCG scar or advanced chest X-ray lesions are at a higher risk of treatment failure, despite their immunisation status. These findings highlight the need for a targeted approach that prioritises early detection, intensified treatment for high-risk groups, and improved monitoring strategies to improve treatment success rates and bring Malaysia closer to achieving the World Health Organization's tuberculosis control goals. The aforementioned findings can aid stakeholders in implementing a targeted approach informed by the identified risk factors that exhibit a greater likelihood of leading to an unfavourable treatment outcome.

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REFERENCES

1. World Health Organization. Global tuberculosis report [Internet]. Geneva: World Health Organization; 2022 [cited 2023 June 20]. Available from:https://www.iom.int/sites/g/files/tmzbdl486/files/documents/2023-03/Global-TB-Report-2022.pdf
2. Lye KH, Kadir MNA, Noordin NM, Teh SY. Tuberculosis elimination in Malaysia by 2035: Linkages and implications to SDGs. International Journal of Social Science and Humanity. 2019;9(4):126-32. doi: 10.18178/ijssh.2019.9.4.1003
3. World Health Organization. The End TB Strategy [Internet]. Geneva: World Health Organization; 2015 [cited 2023 June 22]. Available from: https://www.who.int/publications/i/item/WHO-HTM-TB-2015.19.
4. World Health Organization. Implementing the End TB Strategy: The Essentials 2022 Update [Internet]. Geneva: World Health Organization; 2022 [cited 2023 June 4]. Available from: https://www.who.int/docs/default-source/documents/tuberculosis/end-tb-essential3923df7f247e420f953605a7a624febe.pdf?sfvrsn=e1ba6289_1.
5. Bahagian Kawalan Penyakit. Manual sistem maklumat Tibi kebangsaan (semakan 2018). Putrajaya: Bahagian Kawalan Penyakit Kementerian Kesihatan Malaysia; 2019.
6. Wen Y, Zhang Z, Li X, Xia D, Ma J, Dong Y, et al. Treatment outcomes and factors affecting unsuccessful outcome among new pulmonary smear positive and negative tuberculosis patients in Anqing, China: a retrospective study. BMC Infectious Diseases. 2018;18(1):104. doi: 10.1186/s12879-018-3019-7
7. Fun WH. Health and economic impact of tuberculosis management in Malaysia [Internet]. Monash: Monash University; 2017 [cited 2023 May 20]. Available from https://doi.org/10.4225/03/58af9338dbdc0
8. Araia ZZ, Kibreab F, Kibrom AA, Mebrahtu AH, Girmatsion MG, Teklehiwet YW, et al. Determinants of unsuccessful tuberculosis treatment outcome in Northern Red Sea region, Eritrea. PLOS ONE. 2022;17(8):1-13. doi: 10.1371/journal.pone.0273069
9. World Health Organisation. Summary of tuberculosis data [Internet]. 2022. [cited June 21]. Available from: https:// worldhealthorg .shinyapps.io/TBrief/? _inputs_&sidebar Collapsed= true&entity _ type=%22 country%22& iso2 =%22M Y%22& sidebarItem Expande d=null.
10. The World Bank Data. Tuberculosis treatment success rate (% of new cases) [Internet]. 2023 [cited July 5]. Available from: https://data.worldbank.org/indicator/SH.TBS.CURE.ZS.
11. Ministry of Health. National stragtegic plan for tuberculosis control (2016-2020) [Internet]. Putrajaya: Disease Control Division (TB/ Leprosy Sector), Ministry of Health; 2016 [cited 2022 April 23].
12. Zulkipli ZA, Mohd Salleh MAH, Ahmed MN. Pulmonary tuberculosis: treatment outcomes and factors associated with poor treatment outcome in Pahang, Malaysia. IIUM Medical Journal Malaysia. 2018;17(1). doi: 10.31436/imjm.v17i1.899.
13. Shariff NM, Safian N. Diabetes mellitus and its influence on sputum smear positivity at the 2nd month of treatment among pulmonary tuberculosis patients in Kuala Lumpur, Malaysia: A case control study. International Journal of Mycobacteriology. 2015;4(4):323-9. doi: 10.1016/j.ijmyco.2015.09.003.
14. Selimin DS, Ismail A, Ahmad N, Ismail R, Mohd Azman NF, Azman A. Tuberculosis treatment outcome in patients with TB-HIV coinfection in Kuala Lumpur, Malaysia. Journal of Tropical Medicine. 2021;2021:10. doi: 10.1155/2021/9923378
15. Ibrahim MN, Husain NRN, Daud A, Chinnayah T. Epidemiology and risk factors of delayed sputum smear conversion in Malaysian aborigines with smear-positive pulmonary tuberculosis. International Journal of Environmental Research and Public Health. 2022;19. doi: https://doi.org/10.3390/ijerph19042365
16. Arsad FS, Ismail NH. Unsuccessful treatment outcome and associated factors among smear-positive pulmonary tuberculosis patients in Kepong district, Kuala Lumpur, Malaysia. Journal of Health Research. 2022;36(3):484-93. doi: 10.1108/JHR-10-2020-0478
17. Mahato RK, Laohasiriwong W, Koju R. The role of Diabetes mellitus comorbidity on tuberculosis treatment outcomes in Nepal: A prospective cohort study. Southeastern European Journal of Public Health. 2022;2:1-13. doi: 10.11576/seejph-5329
18. Tok PSK, Liew SM, Wong LP, Razali A, Loganathan T, Chinna K, et al. Determinants of unsuccessful treatment outcomes and mortality among tuberculosis patients in Malaysia: A registry-based cohort study. PLoS ONE. 2022;15(4). doi: https://doi.org/10.1371/journal.pone.0231986
19. Debash H, Nega J, Bisetegn H, Tesfaw G, Feleke DG, Ebrahim H, et al. Tuberculosis treatment outcomes and its predictors among tuberculosis patients registered at Tefera Hailu Memorial General Hospital, Sekota Town, Northeast Ethiopia: A seven-year retrospective study. Canadian Journal

of Infectious Diseases and Medical Microbiology. 2023;2023:9. doi: 10.1155/2023/4212312
20. Ministry of Health. Clinical practice guideline management of tuberculosis [Internet]. Putrajaya, Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2021 [cited 2022 August 18]. Available from https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Respiratory/CPG-_Management_of_Tuberculosis_(4th_Edition).pdf
21. World Health Organization. Global tuberculosis report [Internet]. Geneva: World Health Organization; 2021 [cited 2023 June 20]. Available from: https://www.who.int/publications/digital/global-tuberculosis-report-2021/
22. World Health Organization. Definitions and reporting framework for tuberculosis. Geneva: World Health Organization; 2013 [cited 2022 October 23]. Available from: https://www.who.int/publications/i/item/9789241505345.
23. Hashim JH, Adman MA, Hashim Z, Mohd Radi MF, Kwan SC. Covid-19 Epidemic in Malaysia: Epidemic progression, challenges, and response. Front Public Health. 2021;9:1-9. doi: 10.3389/fpubh.2021.560592.
24. Feyisa JW, Kitila KM, Lemu JC, Hunde MD, Hunde AD. Healthcare-seeking delay during Covid-19 pandemic among tuberculosis patients in Ilubabor zone health facilities, south-west Ethiopia. SAGE Open Med. 2022;10:1-10. doi: 10.1177/20503121221142469.
25. Tom W, Luis C, Peter M. Tackling two pandemics: A plea on World Tuberculosis Day. Lancet Respiratory Medicine 2020;8(6):536-8. doi: https://doi.org/10.1016/S2213-2600(20)30151-X
26. Melese A, Zeleke B. Factors associated with poor treatment outcome of tuberculosis in Debre Tabor, northwest Ethiopia. BMC Res Notes. 2018;11(1):25. doi: 10.1186/s13104-018-3129-8.
27. Abebe G, Bonsa Z, Kebede W. Treatment outcomes and associated factors in tuberculosis patients at Jimma University Medical Center: A 5-year retrospective study. International Journal of Mycobacteriology. 2022;8(1):35-41. doi: 10.4103/ijmy.ijmy_177_18.
28. Lin HS, Cheng CW, Lin MS, Chou YL, Chang PJ, Lin JC, Ye JJ. The clinical outcomes of oldest old patients with tuberculosis treated by regimens containing rifampicin, isoniazid, and pyrazinamide. Clinical Interventions in Aging. 2016; 11, 299–306. doi:10.2147/CIA.S95411
29. Teo AKJ, Morishita F, Islam T, Viney K, Ong CWM, Kato S, et al. Tuberculosis in older adults: challenges and best practices in the Western Pacific Region. The Lancet Regional Health Western Pacific 2023;36:100770. doi: https://doi.org/10.1016/j.lanwpc.2023.100770
30. Lampalo M, Jukić I, Bingulac-Popović J, Stanić HS, Barišić B, Popović-Grle S. The Role of Cigarette Smoking and Alcohol Consumption in Pulmonary Tuberculosis Development and Recurrence. Acta Clin Croat. 2019;58(4):590-594. doi: 10.20471/acc.2019.58.04.04.
31. Thomas BE, Thiruvengadam K, S R, Kadam D, Ovung S, Sivakumar S, Bala Yogendra Shivakumar SV, Paradkar M, Gupte N, Suryavanshi N, Dolla CK, Gupte AN, Kohli R, Pradhan N, Sivaramakrishnan GN, Gaikwad S, Kagal A, Dhanasekaran K, Deluca A, Golub JE, Mave V, Chandrasekaran P, Gupta A; CTRIUMPH-RePORT India Study. Smoking, alcohol use disorder and tuberculosis treatment outcomes: A dual co-morbidity burden that cannot be ignored. PLoS One. 2019;14(7):e0220507. doi: 10.1371/journal.pone.0220507.
32. Lima S, de Araujo K, Nunes MAP, Nunes C. Early identification of individuals at risk for loss to follow-up of tuberculosis treatment: A generalised hierarchical analysis. Heliyon. 2021;7(4):e06788. doi: 10.1016/j.heliyon.2021.e06788.
33. Suliman Q, Lim PY, Md. Said S, Tan K-A, Mohd. Zulkefli NA. Risk factors for early TB treatment interruption among newly diagnosed patients in Malaysia. Scientific Reports. 2022;12(1):745. doi: 10.1038/s41598-021-04742-2.
34. Matakanye H, Tshitangano TG, Mabunda JT, Maluleke TX. Knowledge, Beliefs, and Perceptions of TB and Its Treatment amongst TB Patients in the Limpopo Province, South Africa. Int J Environ Res Public Health. 2021 Oct 2;18(19):10404. doi: 10.3390/ijerph181910404.
35. Burusie A, Enquesilassie F, Addissie A, Dessalegn B, Lamaro T. Effect of smoking on tuberculosis treatment outcomes: A systematic review and meta-analysis. PLoS One. 2020;15(9):e0239333. doi: 10.1371/journal.pone.0239333
36. Khan AH, Sulaiman SAS, Hassali MA, Khan KU, Ming LC, Mateen O, et al. Effect of smoking on treatment outcome among tuberculosis patients in Malaysia; a multicenter study. BMC Public Health. 2020;20(1):854. doi: 10.1186/s12889-020-08856-6.
37. Teferi MY, El-Khatib Z, Boltena MT, Andualem AT, Asamoah BO, Biru M, et al. Tuberculosis treatment outcome and predictors in Africa: A systematic review and meta-analysis. International Journal of Environmental Research and Public Health. 2021;18(20):10678. doi:10.3390/ijerph182010678.
38. Kassa GM, Merid MW, Muluneh AG, Fentie DT. Sputum smear grading and associated factors among bacteriologically confirmed pulmonary drug-resistant tuberculosis patients in Ethiopia. BMC Infect Dis. 2021;21(1):238. doi: 10.1186/s12879-021-05933-y.
39. Kementerian Kesihatan Malaysia. Clinical practice guideline management of tuberculosis. Putrajaya: Malaysian Health Technology Assessment Section (MaHTAS); 2021.

40. Pereira Dos Santos PC, Messina NL, Dias De Oliveira R, Vieira Da Silva P, Puga MAM et al. Effect of BCG vaccination against Mycobacterium tuberculosis infection in adult Brazilian health-care workers: a nested clinical trial. The Lancet Infectious Diseases. 2024; 24(6):594–601. https://doi.org/10.1016/S1473-3099(23)00818-6
41. Huangfu P, Ugarte-Gil C, Golub J, Pearson F, Critchley J. The effects of diabetes on tuberculosis treatment outcomes: An updated systematic review and meta-analysis. Int J Tuberc Lung Dis. 2019;23(7):783-96. doi: 10.5588/ijtld.18.0433.
42. Zhang H, Liu X, Xu C, Hu D, Li X, Li T, et al. Guiding tuberculosis control through the Healthy China Initiative 2019-2030. China CDC Wkly. 2020;2:948-50.Doi: 10.46234/ccdcw2020.236.
43. The World Bank . China: Tuberculosis Control Project [Internet]. 2010. Available from: https://www.worldbank.org/en/news/feature/2010/09/24/china-tuberculosis-control-project0
44. Togun T, Kampmann B, Stoker NG, Lipman M. Anticipating the impact of the Covid-19 pandemic on TB patients and TB control programmes. Annals of Clinical Microbiology and Antimicrobials. 2020;19(1):21. doi: 10.1186/s12941-020-00363-1.