ORIGINAL ARTICLE

Proportions and determinants of successful tuberculosis treatment among tuberculosis patients with comorbidity registered in National Tuberculosis Registry in Negeri Sembilan from year 2018-2023

Abdul Rahman Dashuki, MPH[1,2], Aimi Nadira Mat Ruzlin, PhD[1], Mohd 'Ammar Ihsan Ahmad Zamzuri, DrPH[2], Chen Xin Wee, DrPH (Epidemiology)[1]

[1]Department of Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Selangor, Malaysia, [2]Sector of TB/Leprosy, Public Health Division, Negeri Sembilan State Health Department, Malaysia

ABSTRACT

Introduction: Tuberculosis (TB) is one of the major global health challenges and concerns. Despite the availability of effective treatment in Malaysia, it remained a consistently high notification rate of TB cases. The objective of this study was to determine the proportion of successful TB treatment outcomes and its determinants among TB with comorbidities patients in Negeri Sembilan, Malaysia.

Methods: This is a retrospective cohort study among TB with Comorbidities cases in Negeri Sembilan using multiple secondary surveillance databases: National Tuberculosis Registry (NTBR), National Aids Registry (NAR) and National Diabetic Registry (NDR). The data review was from April 2024 until June 2024. All registered TB cases with comorbidities in Negeri Sembilan from the year 2018 to 2023 were analysed to determine the determinants of successful TB treatment among TB with comorbidities patients.

Results: Out of 712 TB cases with comorbidities, 541 (76.0%) achieved a successful TB treatment outcome, and 171 (24.0%) did not. The successful TB treatment among TB with comorbidities showed predominantly among male (72.5%), Malay ethnicity (65.4%), secondary education level (60.3%), and unemployed working status (70.1%). Diabetes mellitus (DM) was the most common comorbidity (70.4%), followed by hypertension (44.8%), dyslipidaemia (36.0%), HIV (19.5%), and viral hepatitis (18.1%). Factors significantly associated with successful TB treatment were those who had a secondary education level (AOR: 2.222; 95% CI: 1.129, 4.374) and a tertiary education level (AOR: 4.474; 95% CI: 1.428-14.01), were diagnosed with TB in the government hospital (AOR: 0.053; 95% CI: 0.008-0.376), and were not done Acid-Fast Bacillus sputum in the intensive phase of treatment (AOR: 0.191; 95% CI: 0.046, 0.785), cases followed the Directly Observed Therapy at the intensive phase (AOR: 9.045; 95% CI: 4.604, 17.770), and the treatment duration was more than 6 months (AOR: 6.511; 95% CI: 3.383, 12.532).

Conclusion: The successful treatment outcome for TB with comorbidities still falls short of the target and, if not treated well, could potentially lead to prolonged disease transmission, higher mortality rates, and increased healthcare costs. Identifying the proportion of successful treatment rates and their determinants provides insight into the disease burden and helps the public health sector and medical professionals assess and take appropriate action to improve local integration and collaborative service approaches for TB patients with concurrent comorbidities.

KEYWORDS:
Tuberculosis, comorbidity, registry, Directly Observed therapy, treatment outcome

INTRODUCTION

Tuberculosis (TB) is a global health challenge and concern, with alarming rates of incidents in various parts of the world. The latest global report has revealed that in 2022, 7.5 million persons were newly diagnosed with TB, making it the world's second leading cause of death from a single infectious agent after COVID-19.[1] Patients who had both comorbidities and health-related risk factors, such as diabetes, human immunodeficiency virus (HIV), alcohol use disorders, tobacco smoking, mental disorders, malnutrition, and viral hepatitis, accounted for 4.5 million (45%) of the reported new and relapsed TB cases.[2] However, the COVID-19 pandemic has temporarily altered the pattern of TB incidence worldwide and masked the true extent of the disease.[3] The pandemic-induced disruptions in healthcare institutions have resulted in a lack of reporting, distorting data, and impeding an appropriate evaluation of the incidence of TB.[4]

Malaysia, an intermediate burden country with TB, remained a consistently high incidence notification case despite the availability of effective treatment that can complete recovery when diagnosed and treated properly. According to data from the Malaysia Ministry of Health (MOH), there was an increase in the incidence of TB cases by 17% from 2021 to 2022.[5] Negeri Sembilan is one of the states in Malaysia, having an estimated 1.2 million population that showed the highest annual increase with a 5.1% annual increase (ARR: 5.1%) from the year 2012 to 2016.[6,7]

Patients who are incomplete in their treatment for TB will impose a substantial financial burden on the government.

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Corresponding Author: Xin Wee Chen
Email: drchenxw@uitm.edu.my

The average cost per patient in this group is RM901.63 (215.49 USD), which is four times more than the cost of therapy for patients who have completed their treatment.[8] The cost of treating patient TB with comorbidities and hospital stays was 4.5 times higher than that of treating TB without comorbidities.[8]

One of the significant challenges in the current effort to control TB spread would be managing TB patients with comorbidities, in which the comorbidities worsen the effects of TB, particularly resulting in a lower success rate in treatment and a higher incidence of death. Evaluating the treatment success rate outcome is a crucial measure in the End TB Strategy 2035. It is recommended that a tuberculosis program must achieve a treatment success rate of at least 90% and a cure rate of 85% to operate effectively.[9,10]

Nevertheless, Malaysia recently reported a successful treatment rate of 79% in 2021 among TB patients who received treatment at the national level, which is far from the target.[9] Besides that, data regarding the proportion of successful treatment rates among TB patients with comorbidities is scarce in Malaysia compared to the general population. This disparity highlights a critical gap in the healthcare system's ability to address the unique challenges faced by these specific populations effectively. The treatment success gap between the general TB population and those with comorbidities results in prolonged disease transmission, higher mortality rates, and increased healthcare costs.[11]

To achieve this goal, it is important to address health-related risk factors and comorbidities such as Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS), diabetes mellitus (DM), viral hepatitis, depression, and malnutrition as components of pillar 1 of the End TB Strategy, which focuses on integrated patient-centred care and prevention, including action on TB and comorbidities.[12] This study aims to determine the proportion of successful TB treatment outcomes and its determinants among TB patients with comorbidities in Negeri Sembilan from 2018-2023.

MATERIALS AND METHODS

A retrospective cohort study involving TB patients with comorbidities in Negeri Sembilan was conducted by utilising the secondary data obtained from the Malaysian National Tuberculosis Registry (NTBR) and only TB data that was registered under the Negeri Sembilan State Health Office (Jabatan Kesihatan Negeri, Negeri Sembilan, JKNNS) surveillance registry was selected for the present study.

The NTBR is a web-based system managed by the Ministry of Health Malaysia. Its purpose is to continuously collect data and manage actions pertaining to the notification, registration, investigation, and treatment of TB cases across all states in Malaysia. The Prevention and Control of Infectious Diseases Act 1988 (Act 342) mandates the notification of all TB cases to the district health office.[13]

The NTBR in JKNNS consisted of data from seven district health offices (Seremban, Port Dickson, Kuala Pilah, Rembau, Tampin, Jempol, and Jelebu) that were responsible for monitoring the surveillance system of TB cases registered at all the health facilities in Negeri Sembilan. The sampling frame for this study consisted of all TB registered under NTBR and follow-up in health facilities in the year 2018-2023 in Negeri Sembilan.

The study included TB patients with comorbidities who met the inclusion criteria; patients who did not match these criteria were excluded. The inclusion criteria were: (i) newly diagnosed TB-comorbidities cases from 1st January 2018 until 31st December 2022; (ii) TB-comorbidities cases notified through the NTBR from January 2018 until December 2022; and (iii) TB-comorbidities aged > 18 years old. Exclusion criteria included (i) incomplete data on the independent variable, (ii) the case with incomplete data on treatment outcome (transferred to another state or defaulter), and (ii) multidrug-resistant tuberculosis.

The sample size for this study was determined using OpenEpi software version 3.01 using a single proportion formula with a 95% confidence interval (CI) and 5% absolute precision, applying an 81.49% proportion of TB treatment success among the TB-DM based on the largest sample size from a previous study performed in Malaysia.[14] The minimum sample required in this study was 279, including a 20% attrition rate. Given that the present study utilised secondary data, all cases fulfilling the inclusion criteria would be included in the analysis.

TB and HIV are mandatory notifiable diseases by law under Act 342.[13] Each respective district needs to register all TB cases that have been notified into the NTBR system. The definition stated in Malaysia's case definition of infectious disease confirmed both cases.[15] All confirmed DM patients must register at National Diabetes Registry (NDR) for surveillance and monitoring.[16]

This study used three national databases. The main data and variables were extracted from the NTBR under health facilities in Negeri Sembilan. The National AIDS Registry (NAR) and the NDR were cross-referenced as additional information to ensure comprehensive comorbidities data. The data owner performed the confirmatory process using the deterministic matching method, where three national databases were used to connect by using the unique identification number.

Twenty-three variables were extracted from the NTBR for the present analysis. The outcome variables for this study were coded as successful (yes/no). Successful TB treatment outcomes included TB patients who are (i) cured (bacteriologically confirmed TB patient who subsequently smear/culture negative during the last month of the treatment or on at least one previous occasion and was input in NTBR as 'cured'.) and ii) completed treatment (patient who completed TB treatment without meeting the criteria for cure or treatment failure was input in NTBR as 'completed treatment'.)[17]

People who finished TB treatment but did not meet the criteria for cure or treatment failure were also entered into NTBR. Unsuccessful TB treatment included (i) treatment failure (TB patient whose sputum smear or culture was

positive at 5 months or later during treatment and was input in NTBR as 'treatment failure'.), (ii) death (passes away for any reason before or during TB treatment all-cause mortality and was input in NTBR as 'died') or (iii) loss of follow-up (patient who did not initiate treatment or whose treatment was interrupted for two consecutive months or more and entered into NTBR as 'loss to follow up'). The twenty-three independent variables were categorised into three main domains. Seven variables were sociodemographic factors, twelve variables related to the TB disease profile and four variables related to the TB treatment profile.

Data Management and Analysis

Figure 1 depicted the data retrieval and extraction process which incorporated three national data sources in the form of Microsoft Excel Open XML Spreadsheet (xlsx) format. Data received from JKN Negeri Sembilan was 754. Data from NAR (n= 737) and NDR (n=126,689) had been confirmed for comorbidities with the NTBR data. The data owner performed this data linkage using the deterministic matching method, where three national databases were linked by using the unique identification number. Data cleaning was performed using the final database (n = 754). Of 754 total samples, 712 (94.4%) were found eligible for analysis after applying the inclusion and exclusion criteria. The final database (n = 712) was imported into IBM SPSS version 29.0 for further statistical analysis. The analysis used in this study included descriptive and inferential analysis. The TB treatment success rate (proportion of subjects having successful TB treatment in the present study) was calculated by using the formula as follows:

$$\text{Rate of successful TB treatment} = \frac{\text{Number of successful TB treatment among TB patient with comorbidity}}{\text{Total number of newly diagnosed TB patient with comorbidity in year 2018-2023}}$$

Estimation of the rate of successful TB treatment (95% confidence interval for the proportion interval) was calculated using the formula below:

$$95\%\ \text{Confident interval (CI)} = p \pm z^* \frac{p\,(1-p)}{n}$$

Descriptive analysis was performed to describe the characteristics of participants (sociodemographic), TB disease profile and TB treatment profile determinants. The mean (standard deviation, SD) was presented for the continuous variable. The frequency (n) and percentage (%) were presented for the categorical variables. The distribution of TB with comorbidities was presented in general and based on their treatment outcomes. The distribution was compared using descriptive and univariable analysis, such as the chi-square test for homogeneity. independent t-test and the continuity correction test.

Logistic regression analyses were performed to estimate the crude and adjusted effect of the independent variables of successful TB with comorbidities treatment. The variables were included in the multiple logistic regression model based on the statistical significance of a p-value (< 0.25). The backward LR method was used to select the variables. Subsequently, the initial model was evaluated for, interaction, linearity in the logit and multicollinearity. The Hosmer-Lemeshow goodness-of-fit test, classification table, and receiving operating characteristic (ROC) curve were used to confirm the model's fitness. The crude/adjusted odds ratio (OR), 95% CI, and their respective p-values were used to demonstrate the strength of association between all variables and the outcome measure. The statistical test was performed with a significance level of 0.05.

Ethics Approval

Two institutional review boards approved this study, which adhered to the standards outlined in the Declaration of Helsinki. The study gained ethical clearance from two institutions in May 2021: i) the Research Ethics Committee (REC) at UiTM (100 - FPR (PT.9/19) (FERC-EX-24-02)), and ii) the Medical Research Ethics Committee (MREC) of the Ministry of Health Malaysia (NMRR ID-24-00551-JKK (IIR)). The data owner secured the anonymity of participants by deleting all identifying information from the database, thereby maintaining confidentiality in this study. All data was submitted to a password-protected computer belonging to a researcher. Researchers were the sole recipients of the data. The research findings did not reveal any personal information, and the participants could not be identified.

RESULTS

A total of 712 TB patients with comorbidities were recruited, with 541 (76.0%) achieving a successful TB treatment outcome and 171 (24.0%) experiencing an unsuccessful TB treatment outcome. Table I shows the trend rate of successful TB treatment among TB patients with comorbidities, which ranged from 70.3% (62.7%–77.9%) to 79.9% (73.2%–86.6%) from 2018 to 2022. Table II shows the characteristics of TB with comorbidities, which are predominantly male (74.0%), the mean age 53 (14) years old, and Malay ethnicity (66.3%). The successful TB treatment among TB with comorbidities was predominantly found among Malaysian males aged 40 to 59 years old (50.5%), Malay ethnicity (65.4%), residing urban area (60.3%), secondary education level (60.3%), and unemployed working status (70.1%).

DM was the most common comorbidity (70.4%), followed by hypertension (44.8%), dyslipidaemia (36.0%), HIV (19.5%), and viral hepatitis (18.1%). Patients with TB and DM showed a high percentage of successful TB treatment (76.0%) compared to other comorbidities, ranging between 13.5% and 48.6%. Regarding the characteristics of the TB treatment profile, a high percentage of successful TB treatment was found in patients who were Acid-Fast Bacillus (AFB) converted in the intensive phase (84.5%) and patients who followed Directly Observed Therapy (DOT) during the intensive phase (95.0%).

Simple logistic regression analysis demonstrated that fourteen variables (i.e., education level, occupation, citizenship, TB anatomy location, sputum AFB (diagnosis), CXR upon diagnosis, health facility: TB diagnosis, AFB sputum in the intensive phase, DOTs (intensive), health facility: initiated TB treatment, treatment duration, age, gender, and ethnicity) were significantly associated with successful TB treatment at the level of significance set at p = 0.25 (Table III).

Table I: The rate of successful TB treatment trend among TB with comorbidities from 2018-2023 in Negeri Sembilan

	Rate successful treatment among TB with comorbidities from 2018-2022				
	2018	**2019**	**2020**	**2021**	**2022**
Total TB patients with comorbidities cases registered	122	179	139	134	138
Successful treatment Outcome	95	134	111	104	97
Rate of Successful Treatment (%) (95%CI)	77.9% (70.5%-85.3%)	74.9% (68.5%-81.3%)	79.9% (73.2% - 86.6%)	77.6% (70.5%-84.7%)	70.3% (62.7%-77.9%)
Cured	75	107	77	85	67
Completed treatment	20	27	34	19	30
Unsuccessful Treatment Outcome	27	45	28	30	41
Loss to follow-up	5	7	4	5	1
Treatment Failed	0	2	0	1	0
Died	22	36	24	24	40

Table II: Characteristics of TB with comorbidities in total and according to the TB treatment outcomes, 2018-2023 (n= 712)

Variables	**Total (n = 712) Mean (SD)/n (%)**	**Successful TB Treatment (n = 541) Mean (SD)/n (%)**	**Unsuccessful TB Treatment (n = 171) Mean (SD)/n (%)**	***p-value**
Socio-demographic				
Age	53 (14)	53 (13)	54 (16)	0.457[a]
18 to 39 year old	131 (18.4)	96 (17.7)	35 (20.5)	0.320[c]
40 to 59 year old	348 (48.9)	273 (50.5)	75 (43.8)	
≥ 60 year old	233 (32.7)	172 (31.8)	61 (35.7)	
Gender				
Male	527 (74.0)	392 (72.5)	135 (78.9)	0.092[c]
Female	185 (26.0)	149 (27.5)	36 (21.1)	
Ethnicity				
Malay	472 (66.3)	354 (65.4)	118 (69.0)	0.119[c]
Chinese	95 (13.3)	72 (13.3)	23 (13.5)	
Indian	114 (16.0)	95 (17.6)	19 (11.1)	
Others	31 (4.4)	20 (3.7)	11 (6.4)	
Location of residence				
Rural	287 (40.3)	215 (39.7)	72 (42.1)	0.583[c]
Urban	425 (59.7)	326 (60.3)	99 (57.9)	
Education level				
No Formal Education	120 (16.9)	74 (13.7)	46 (26.9)	< 0.001[c]
Primary Education	95 (13.3)	73 (13.5)	22 (12.9)	
Secondary Education	413 (58.0)	326 (60.3)	87 (50.9)	
Tertiary Education	84 (11.8)	68 (12.5)	16 (9.3)	
Occupation				
Unemployed	517 (72.6)	379 (70.1)	138 (80.7)	0.007[c]
Employed	195 (27.4)	162 (29.9)	33 (19.3)	
Citizenship				
Malaysian	694 (97.5)	531 (98.2)	163 (95.3)	0.076[b]
Non-Malaysian	18 (2.5)	10 (1.8)	8 (4.7)	
TB-Disease Profile				
Detection Mode				
Active	72 (10.1)	51 (9.4)	21 (12.3)	0.281[c]
Passive	640 (89.9)	490 (90.6)	150 (87.7)	
TB Anatomy Location				
Pulmonary TB	624 (87.6)	488 (90.2)	136 (79.5)	< 0.001[c]
Extrapulmonary TB	88 (12.4)	53 (9.8)	35 (20.5)	
Sputum AFB (diagnosis)				
Positive	518 (72.8)	419 (77.4)	99 (57.9)	< 0.001[c]
Negative	157 (22.1)	101 (18.7)	56 (32.7)	
Not Done	37 (5.2)	21 (3.9)	16 (9.4)	
Smoking				
Smoking	306 (43.0)	237 (43.8)	69 (40.4)	0.426[c]
Non-Smoking	406 (57.0)	304 (56.2)	102 (59.6)	
BCG Scar				
Absent	72 (10.1)	52 (9.6)	20 (11.7)	0.431[c]
Present	640 (89.9)	489 (90.4)	151 (88.3)	

Table II: Characteristics of TB with comorbidities in total and according to the TB treatment outcomes, 2018-2023 (n= 712)

Variables	Total (n = 712) Mean (SD)/n (%)	Successful TB Treatment (n = 541) Mean (SD)/n (%)	Unsuccessful TB Treatment (n = 171) Mean (SD)/n (%)	*p-value
CXR upon diagnosis				
No Lesion	82 (11.5)	61 (11.3)	21 (12.3)	0.154[c]
Minimal	337 (47.3)	258 (47.7)	79 (46.2)	
Moderate	270 (38.0)	209 (38.6)	61 (35.7)	
Advanced	23 (3.2)	13 (2.4)	10 (5.8)	
Health Facility: TB Diagnosis				
Private	28 (3.9)	26 (4.8)	2 (1.2)	< 0.001[c]
Government Clinic	222 (31.2)	212 (39.2)	10 (5.8)	
Government Hospital	462 (64.9)	303 (56.0)	159 (93.0)	
Diabetes Mellitus				
No	211 (29.6)	130 (24.0)	81 (47.4)	< 0.001[c]
Yes	501 (70.4)	411 (76.0)	90 (52.6)	
Hypertension				
No	393 (55.2)	278 (51.4)	115 (67.3)	< 0.001[c]
Yes	319 (44.8)	263 (48.6)	56 (32.7)	
Dyslipidaemia				
No	456 (64.0)	329 (60.8)	127 (74.3)	0.001[c]
Yes	256 (36.0)	212 (39.2)	44 (25.7)	
HIV				
No	573 (80.5)	468 (86.5)	105 (61.4)	< 0.001[c]
Yes	139 (19.5)	73 (13.5)	66 (38.6)	
Viral Hepatitis				
No	583 (81.9)	451 (83.4)	132 (77.2)	0.068[c]
Yes	129 (18.1)	98 (18.1)	39 (22.8)	
TB-Treatment Profile				
AFB Conversion in the Intensive Phase				
No	41 (5.8)	38 (7.0)	3 (1.8)	< 0.001[c]
Yes	503 (70.6)	457 (84.5)	46 (26.9)	
Not Done	168 (23.6)	46 (8.5)	122 (71.3)	
DOTS (intensive)				
No	134 (18.8)	27 (5.0)	107 (62.6)	< 0.001[c]
Yes	578 (81.2)	514 (95.0)	64 (37.4)	
Treatment duration	6 (3.5)	7 (1.3)	2 (1.2)	< 0.001[a]
< 6 Month	453 (63.6)	298 (55.1)	155 (90.6)	< 0.001[c]
> 6 Month	259 (36.4)	243 (44.9)	16 (9.4)	
Health Facility: Initiated TB Treatment				
Private	26 (3.6)	25 (4.6)	1 (0.6)	< 0.001[c]
Government Clinic	222 (31.2)	210 (38.8)	12 (7.0)	
Government Hospital	464 (65.2)	306 (56.6)	158 (92.4)	

Notes: AFB =Acid Fast Bacillus; BCG= Bacillus Calmette–Guérin vaccine; CXR = Chest X-ray; DOT = Directly Observed Therapy; Human Immunodefiency Virus=HIV; SD = standard deviation; [a]Independent t-test/ [b]continuity correction (Yates' correction); [c]Chi-square test for homogeneity.

Subsequently, when adjusted, those who had a secondary education level (AOR: 2.222; 95% CI: 1.129, 4.374) and a tertiary education level (AOR: 4.474; 95% CI: 1.428-14.01), were diagnosed with TB in the government hospital (AOR: 0.053; 95% CI: 0.008-0.376), and were not done AFB sputum in the intensive phase of treatment (AOR: 0.191; 95% CI: 0.046, 0.785), cases followed the DOTs at the intensive phase (AOR: 9.045; 95% CI: 4.604, 17.770), and the treatment duration was more than 6 months (AOR: 6.511; 95% CI: 3.383, 12.532) were associated with successful TB treatment (Table IV).

DISCUSSION

This study is intended to determine the success rate of TB treatment and its determinants among TB patients with comorbidities in Negeri Sembilan in 2018-2023. Our study data demonstrated that TB patients with comorbidities accounted approximately 24.0% of the reported new and relapsed TB cases and had successfully achieved TB treatment outcomes ranging between 70.3% and 79.9%.[18] This finding is significantly lower than the previous study carried out in India and Poland, which documented a success rate of 86.67% and 88% among TB cases with comorbidities.[11,19] The successful treatment rate showed slightly decrease from the year 2020 to 2022. This finding could be possible due to the disruption of TB management and treatment during the COVID-19 pandemic.[20]

Table III: Univariate Analysis of Determinant TB Successful Treatment Outcome Among TB with Comorbidity (n= 712)

Variables	B (SE)	Wald (df)	Crude OR (95% CI)	*P- value
Sociodemographic				
Age				
18 to 39 year old			1	ref.
40 to 59 year old	0.283 (0.237)	1.43 (1)	1.327 (0.835-2.11)	0.232*
>60 year old	0.028 (0.247)	0.012 (1)	1.028 (0.633-1.669)	0.911
Gender				
Male			1	ref.
Female	0.354 (0.211)	2.826 (1)	1.425 (0.943-2.155)	0.093*
Ethnicity				
Malay			1	ref.
Chinese	0.043 (0.262)	0.026 (1)	1.043 (0.624-1.744)	0.871
Indian	0.511 (0.273)	3.505 (1)	1.667 (0.976-2.845)	0.061*
Others	-0.501 (0.39)	1.648 (1)	0.606 (0.282-1.302)	0.199*
Location of residence				
Rural			1	ref.
Urban	0.098 (0.178)	0.302 (1)	1.103 (0.778-1.563)	0.583
Education level				
No Formal Education			1	ref.
Primary Education	0.724 (0.307)	5.552 (1)	2.063 (1.13-3.767)	0.018*
Secondary Education	0.846 (0.223)	14.353 (1)	2.329 (1.504-3.607)	<.001*
Tertiary Education	0.971 (0.335)	8.392 (1)	2.642 (1.369 -5.098)	0.004*
Occupation				
Unemployed			1	ref.
Employed	0.581 (0.215)	7.276 (1)	1.787 (1.172-2.726)	0.007*
Citizenship				
Non-Malaysian			1	ref.
Malaysian	0.958 (0.483)	3.938 (1)	2.606 (1.012-6.713)	0.047*
TB-Disease Profile				
Detection Mode				
Active			1	ref.
Passive	0.296 (0.276)	1.157 (1)	1.345 (0.784-2.308)	0.282
TB Anatomy Location				
Extrapulmonary TB			1	ref.
Pulmonary TB	0.863 (0.238)	13.094 (1)	2.37 (1.485-3.781)	<.001*
Sputum AFB (diagnosis)				
Not Done			1	ref.
Positive	1.171 (0.35)	11.181 (1)	3.225 (1.623-6.405)	<.001*
Negative	0.318 (0.371)	0.733 (1)	1.374 (0.664-2.845)	0.392
Smoking				
Smoking			1	ref.
Non-Smoking	-0.142 (0.178)	0.633 (1)	0.868 (0.612-1.231)	0.426
BCG Scar				
Absent			1	ref.
Present	0.22 (0.279)	0.619 (1)	1.246 (0.721-2.152)	0.431
CXR upon diagnosis				
Advanced			1	ref.
Moderate	0.969 (0.445)	4.741 (1)	2.636 (1.102-6.306)	0.029*
Minimal	0.921 (0.44)	4.386 (1)	2.512 (1.061-5.949)	0.036*
No Lesion	0.804 (0.491)	2.683 (1)	2.234 (0.854-5.848)	0.101*
Health Facility: TB Diagnosis				
Private			1	ref.
Government Clinic	0.489 (0.802)	0.372 (1)	1.631 (0.339-7.853)	0.542
Government Hospital	-1.92 (0.874)	6.727 (1)	0.147 (0.034-0.626)	0.009*
TB Treatment Profile				
AFB Conversion in the Intensive Phase				
No			1	ref.
Yes	-0.243 (0.619)	0.154 (1)	0.784 (0.233-2.64)	0.695*
Not Done	-3.514 (0.624)	31.702 (1)	0.03 (0.009-0.101)	<.001*
DOTS (intensive)				
No			1	ref.
Yes	3.46 (0.253)	187.229 (1)	31.828 (19.388-52.247)	<.001*
Treatment duration				
< 6 Month			1	ref.
> 6 Month	2.067 (0.276)	55.896 (1)	7.9 (4.595-13.58)	<.001*

Table III: Univariate Analysis of Determinant TB Successful Treatment Outcome Among TB with Comorbidity (n= 712)

Variables	B (SE)	Wald (df)	Crude OR (95% CI)	*P- value
Health Facility: Initiated TB Treatment				
Private			1	ref.
Government Clinic	-0.357 (1.062)	0.113 (1)	0.7 (0.087-5.613)	0.737
Government Hospital	-2.558 (1.024)	6.234 (1)	0.077 (0.01-0.577)	0.013*

Notes: B = unstandardised regression weight; CI = Confidence interval; df = degree of freedom; SE = Standard error; OR = odds ratio; BCG= Bacillus Calmette–Guérin vaccine; CXR = Chest X-ray; DOT = Directly Observed Therapy; AFB =Acid Fast Bacillus; *level of significance set at 0.25

Table IV: Multivariable Analysis of Determinant TB Successful Treatment Outcome Among TB with Comorbidity (n= 712)

Variables	B (SE)	Wald (df)	AOR (95% CI)	*P- value
Education level				
No Formal Education			1	ref.
Primary Education	0.916 (0.474)	3.730 (1)	2.499 (0.986-6.333)	0.053
Secondary Education	0.798 (0.346)	5.340(1)	2.222 (1.129-4.374)	0.021
Tertiary Education	1.498 (0.583)	6.614 (1)	4.474 (1.428-14.01)	0.010
Health Facility: TB Diagnosis				
Private			1	ref.
Government Clinic	-0.983 (1.064)	0.855 (1)	0.374 (0.047-3.008)	0.355
Government Hospital	-2.928 (0.999)	8.596 (1)	0.053 (0.008-0.376)	0.003
AFB Conversion in the Intensive Phase				
No			1	ref.
Yes	0.557 (0.689)	0.654 (1)	1.746 (0.453-6.734)	0.419
Not Done	-1.656 (0.721)	5.267 (1)	0.191 (0.046-0.785)	0.022
DOTS (intensive)				
No			1	ref.
Yes	2.202 (0.345)	40.846 (1)	9.045 (4.604-17.770)	<0.001
Treatment duration				
< 6 Month			1	ref.
> 6 Month	1.873 (0.334)	31.445 (1)	6.511 (3.383-12.532)	<0.001

Notes: AOR = adjusted odds ratio; B = unstandardised regression weight; CI = confidence interval; df = degree of freedom; SE = Standard error; *level of significance set at 0.05; Cox & Snell R Square:0.435; Constant = 0.831; Backward LR method was applied; No multicollinearity and no interaction; Hosmer Lemeshow test, P-value = 0.063; Classification table 90.9% correctly classified; Area under Receiver Operating Characteristics (ROC) curve = 0.92

In recent years, the treatment success rates for new tuberculosis cases in Malaysia increased steadily from 76% in 2013 to 81% in 2017 for the group of patients studied. Nevertheless, the rates remained below the target of ≥90%.[21] In Negeri Sembilan in 2021, the success rate among general TB cases was 92%, which met the recommendation target.[18] However, the success treatment rate among TB with comorbidities remains low. Therefore, these findings underscore the significance of tuberculosis in the comorbidities population, emphasizing the need for TB management and treatment to meet the success rate target.

The demographic characteristics observed in this study, such as the higher representation of middle-aged adult groups (40 - 59 years old) and males, were consistent with the prevailing global trends in tuberculosis epidemiology.[22] One study found that males are more likely to have multiple comorbidities than females due to more exposure to risk factors.[23] Furthermore, older age increases the risk associated with multiple comorbidities compared to younger age.[24] In terms of treatment outcome, males and older adults have a lower successful treatment outcome compared to females and younger adults.[25] Thus, these findings suggest a more comprehensive gender-responsive approach to addressing the dual challenge of infectious diseases and non-communicable diseases in an ageing population, particularly among patients with tuberculosis and chronic illnesses.

We also found the predominance of DM as a comorbidity compared to other diseases. A similar finding reported in Poland, where DM was the most common comorbidity (5.9%).[11] The TB treatment outcome among TB patients with DM shows a high success rate compared to other diseases. This finding is in concordance with another local study in Kelantan, which reported a high success rate for treatment among TB and DM.[14] This could shed light on the significant efforts made by the Ministry of Health to provide exceptional care and enhance the dual management of patients with co-morbidities within the existing health system. The latest Clinical Practice Guidelines (CPG) for Managing Tuberculosis recommends that all newly diagnosed with tuberculosis undergo regular screening for DM and HIV.[26]

Furthermore, TB cases with comorbidities having higher education levels were found to have higher odds of achieving successful TB treatment compared to those with low

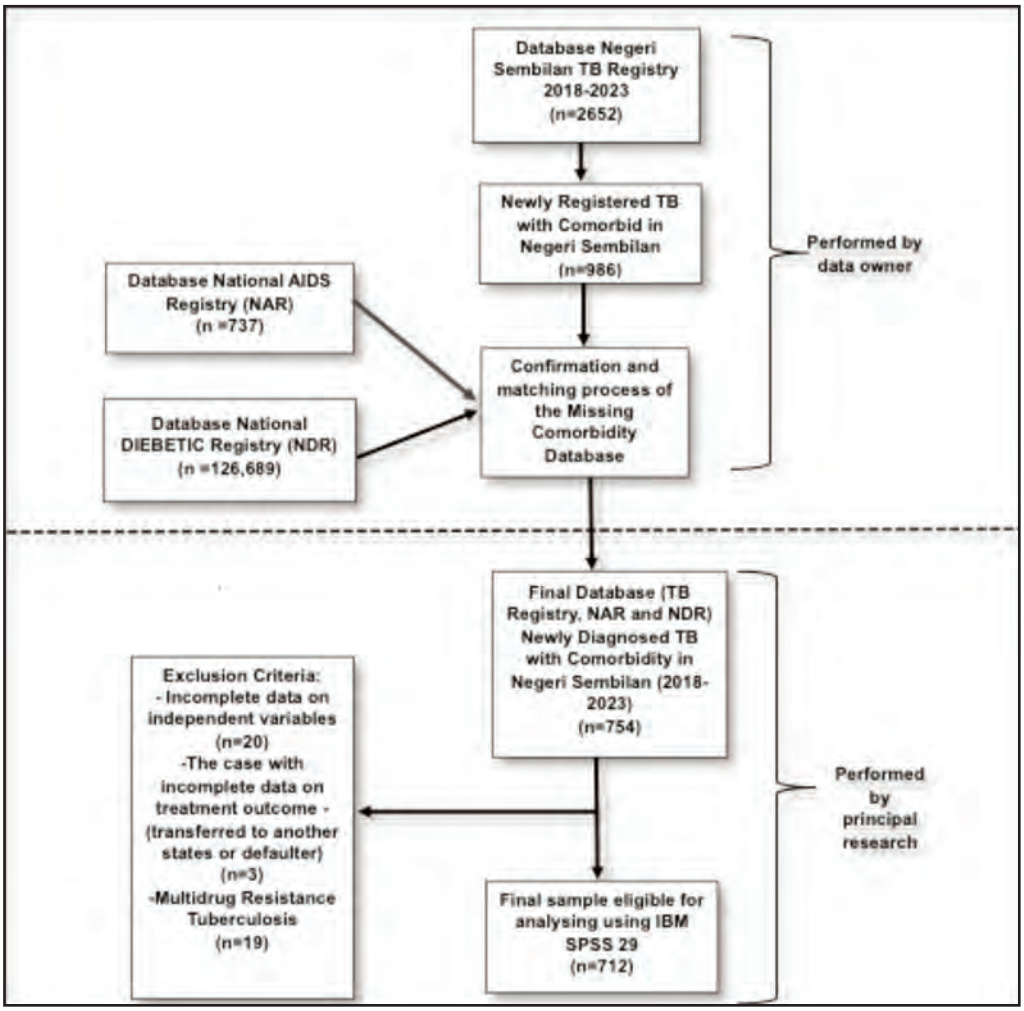

Fig. 1: Flow chart of data retrieval and extraction

education levels. Congruently, a local retrospective cohort study reported lower education levels associated with unsuccessful TB treatment outcomes.[21] These findings could be associated with health literacy and better understanding of treatment regimens. Educated patients are more likely to adhere to medication and follow the instructions, thereby improving treatment outcomes.[27]

This study also found that TB patients with comorbidities diagnosed at government hospitals were found to have lower odds 0.053 (95% CI: 0.008-0.376) of achieving successful treatment outcomes compared to private facilities. According to this finding, corresponding to another study in Lagos, Nigeria,[28] the treatment success rate among private health facilities was 78.09%, which was relatively higher compared to government health facilities. However, studies from Thailand and Vietnam showed that private health facilities were associated with poor TB treatment outcomes.[29-30] This finding may stem from the fact that patients who delay or present late for TB cases typically end up in a government hospital, potentially influencing the treatment outcome. The comorbidity, particularly HIV co-infection, can influence treatment delay.[31] Moreover, government hospitals also normally receive more patients in comparison to private hospitals, which can strain their capacity to provide individualised care.[32] Poor TB outcomes may result from overburdened healthcare systems delivering suboptimal care. Therefore, managing TB with comorbidities requires integration and collaboration between government hospitals, primary health clinics, and private health facilities. It includes strong and effective active case detection for early detection and treatment, given the effectiveness of integrating dual management between TB and DM in increasing successful TB treatment.[33]

Additionally, patients who were consistently on DOTs during the intensive phase were nine times more likely to have TB treatment success than those who were not on DOTs. Other studies strongly support this finding, demonstrating that DOTs can enhance the cure rate.[34] On the other hand, findings from a local study showed that not adhering to DOTs is one of the determinants of unsuccessful TB treatment outcomes among TB and HIV patients.[35] One possible reason is that TB patients with comorbidities perceive a greater risk of complications from tuberculosis, which may increase their motivation to adhere to their treatment regimens rigorously. Better compliance may be stimulated by the perceived severity of their condition.[36-37]

Furthermore, the other significant determinant of successful treatment was the duration of treatment more than six months. This study found that the odds of successful TB treatment were four times higher if the treatment lasted more than six months compared to less than six months. This finding is similar to a cross-sectional study conducted in Kelantan, which also found that the duration of treatment for TB patients with HIV was a significant determinant of successful treatment outcomes.[38] The prolonged therapy regimens ensure that all tuberculosis bacteria are eradicated, as they may be inactive or slow-growing. Shorter courses of antibiotics are less effective in eliminating all microorganisms from the body, increasing the likelihood of a relapse. WHO strongly recommends a six-month treatment period for all drug-susceptible TB patients, with high certainty of evidence.[39]

The retrospective cohort study design facilitates a better understanding of the determinant of successful TB treatment outcome among TB with comorbidities compared to the usual studies that focus on TB with single comorbidity as the study population.[35, 38] To the best of our knowledge, we report the latest original study assessing the determinants of successful treatment of TB with comorbidities in Negeri Sembilan. In addition, this study uses three national registry databases, which minimizes data missingness on comorbidities within the study population. The integration and merging into multi-centre registry will provide more accurate data sources and facilitates better coordination and continuity of care.[40] This study also emphasised the importance of collaborative and integrated activity in managing TB patient with comorbidities to improve the treatment outcomes.

One limitation of this study is that the analysis based on secondary surveillance data is limited by the data's completeness, such as insufficient data on other health-related factors, such as alcohol status, malnutrition and depression status.[2] Although this study demonstrates internal validity, it cannot be generalised to other states due to its single-state setting, however present findings could alert the state authorities for future policy making.

CONCLUSION

The successful treatment outcome for TB with comorbidities still falls short of the target and, if not treated well, could potentially lead to prolonged disease transmission, higher mortality rates, and increased healthcare costs. Identifying the proportion of successful treatment rates and their determinants provides insight into the disease burden. It helps the public health sector and medical professionals assess and take appropriate action to improve local integration and collaborative service approaches for TB patients with concurrent comorbidities.

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CONFLICT OF INTEREST AND FUND

None

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