Unsuccessful treatment outcome and associated factors among smear-positive pulmonary tuberculosis patients in Kepong district, Kuala Lumpur, Malaysia

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Abstract

Purpose – The purpose of this study was to assess tuberculosis (TB) treatment outcomes among new smear-positive pulmonary tuberculosis (PTB) patients and identify the risk factors of unsuccessful treatment outcomes in Kepong district, Kuala Lumpur, Malaysia.

Design/methodology/approach – A retrospective cohort study was conducted using registry-based data from the Tuberculosis Information System (TBIS) between 2014 and 2018. Simple random sampling was used to select 734 males and 380 females from the TBIS registry. Smear-positive PTB patient's sociodemographic, clinical and behavioral characteristics were extracted and analyzed. Logistic regression was used to find the possible independent risk factors for unsuccessful treatment outcomes.

Findings – The treatment success rate was 77.20% ($n = 860$) which was still below the target set by the WHO (>90%). In total, 254 patients showed an unsuccessful treatment outcome: 106 died, 99 defaulted, 47 not evaluated and 2 showed treatment failure. Unsuccessful treatment outcome was significantly associated with older age, male gender, non-citizen, unemployment and being HIV positive.

Originality/value – The study focuses on all these contributing factors of unsuccessful treatment outcome for a better risk assessment and stratification of TB patients and identify effective surveillance and management strategies to strengthen the control programs of tuberculosis in Kepong district.

Keywords Smear positive pulmonary tuberculosis, Treatment outcome, Unsuccessful treatment, Malaysia

Paper type Research paper

Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. Based on the World Health Organization (WHO) report, there was an increasing trend of estimated new TB cases from 2014 (9.6 million people) to 2018 (10 million people) [1]. In 2018, 1.5 million people died from TB [1].

In Malaysia, the estimated incidence rate of TB was at 92 cases per 100,000 population in 2018 [1]. Over the years, the recording and reporting system of TB cases in Malaysia was strengthened by introducing the Tuberculosis Information System (TBIS). In 2014-2018,

Wilayah Persekutuan Kuala Lumpur (WPKL) was one of the top 5 states with the highest number of TB cases [2].

In 2015, the WHO launched the End TB Strategy. One of the critical indicators of the End TB Strategy at the global and national level is the treatment success rate. The TB treatment's recommended target success rate for all countries is >90% [1]. In 2018, the successful treatment outcome's global rate was 85%, which was in increasing trend compared to 2017 (82%) [1]. Even though Malaysia is not included in the 30 high-burden countries, the treatment outcome rate still does not reach the WHO's standard. In 2017, the TB treatment success rate for Malaysia was 81% [1].

There were plenty of studies conducted locally and in other countries that aimed to identify the associated factors with the different outcomes of the TB success rate treatment among TB patients. However, the results were differed according to the setting and study population. All these studies not only focused on the demographic characteristic but also on clinical and behavioral aspect. All the risk factors based on each characteristic will provide better information on disease control management.

There are various findings based on the previous studies regarding TB treatment. This has urged researchers to perform more studies on this topic. It is important to provide information and feedback about the national TB control program. In Malaysia, the studies on TB treatment outcome differ in terms of study location, population and time. This has resulted in the variability of findings. The improvement in the national TB database (TBIS) helps the researcher to obtain complete and informative data. A comprehensive national strategic plan for TB can only be achieved by understanding the disease epidemiology and trends of a specific locality.

The study aims to provide the updated findings on the TB treatment outcome and associated risk factors by looking at the recent cohorts of TB patients registered in the Kepong district from 2014 until the year 2018. This study focuses on the risk factors associated with the unsuccessful treatment outcome among smear-positive TB patients.

Methodology

Study design. A retrospective cohort study was conducted among smear-positive PTB patients registered in the TBIS registry in Kepong district, Kuala Lumpur, from 2012 to 2018. PTB patients' diagnosis was based on the clinical manifestation, sputum smear, culture results and radiological findings on chest X-ray. Once diagnosed, the patient's information, sociodemographic factors, medical history and treatment progress were recorded by the respective healthcare professionals into the registry database.

Data were collected from the TBIS registry database. Only new cases of smear-positive PTB were selected for analysis. The exclusion criteria were drug-resistant PTB cases and those with incomplete data. The treatment outcome, sociodemographic factors and clinical and behavior characteristics were included for analysis.

Sample size. The sample size of the study was 1,114 samples. The sample size estimation was done based on a previous study [3]. The required sample size was calculated using the power and sample size program (PS2) based on the double proportion formula.

Variable selection and measurement. The dependent variable was the TB treatment outcome. It was conducted based on one-year surveillance and defined based on the Clinical Practice Guideline for Management by the Ministry of Health, Malaysia [2], and the WHO [1]. The operational definitions of TB treatment outcome by the WHO was used in this study, which were:

(1) Cured (a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment, becomes smear- or culture-negative in the last month of the treatment, and at least one previous occasion).

(2) Treatment completed (a patient who has completed TB treatment, but without the evidence of negative bacteriology result in the last month of the treatment and at least one previous occasion was negative).

(3) Treatment failed (a patient with sputum smear or culture positive at least 5 months or later) and died (a patient who died for any reason during TB treatment).

(4) Defaulter (a patient whose TB treatment was interrupted for two consecutive months or more after registration).

(5) Not evaluated (a patient who has been referred or transferred out to another treatment unit, and whose treatment outcome was unknown).

The TB treatment outcomes were categorized into successful outcomes (cured and completed treatment) and unsuccessful outcomes (death, treatment failed, defaulter and not evaluated).

The independent variables were selected based on the following available information and complete data in the TBIS registry: sociodemographic (age, gender, citizenship, race, educational level, employment status and type of work, either healthcare or non-healthcare worker), clinical (BCG scar, diabetes status, HIV status, CXR findings and DOTs supervisor) and behavioral characteristics (smoking). For the citizenship variable, non-citizens were those who were mainly immigrants from other countries.

Statistical analysis. Data analysis was carried out using Statistical Package Social Science (SPSS software version 25). Descriptive analysis was performed to summarize the study population's characteristics (sociodemographic, clinical and behavior). Pearson chi-square test was used to determine the association between the TB treatment outcome and the risk factors. The independent variables (sociodemographic, clinical and behavioral characteristics) were compared between the successful and unsuccessful groups to assess the potential predictor variables of unsuccessful treatment outcome using univariate and multivariate logistic regression. In the univariate analysis, independent variables with a p-value < 0.20 were included in the multivariate logistic regression (stepwise backward selection method). The variables with p-value < 0.05 in the final multiple logistic regression model were the significance of potential predictors. Hosmer–Lemeshow test and overall classification percentage were used to assess the fit of the model.

Ethical consideration. This study was approved by National Medical Research Registry (NMRR-20-784-54265, http://www.nih.gov.my/mrec, May 20, 2020) and the Ethics Committee of Universiti Kebangsaan Malaysia (FR 20-052, sepukm@ukm.edu.my, July 13, 2020).

Results

Table 1 presents the findings from the descriptive analysis of patient's characteristics. In this study, the total sample included 1,114 patients. The majority (77.20%) showed a successful treatment outcome (Table 2), while 22.8% showed unsuccessful treatment outcome – 41.73% patient died, which was the largest group among those with an unsuccessful outcome followed by defaulters (38.97%), not evaluated (18.50%) and treatment failure (0.80%). The mean (SD) age for the total sample was 42.84 (16.579). Most of the patients were male (65.9%) where 80.5% were Malaysian nationals.

The bivariate analysis was performed using the chi-square to determine the relationship of the independent variables to the dependent variable (Table 3). The independent variables that showed a significant relationship to the treatment outcome were gender ($X^2 = 28.26$, $p < 0.001$), citizenship ($X^2 = 30.291$, $p < 0.001$), race ($X^2 = 13.051$, $p < 0.001$), education status ($X^2 = 10.844$, $p = 0.001$), smoking ($X^2 = 4.308$, $p = 0.038$), BCG scar ($X^2 = 8.004$, $p = 0.005$), HIV status ($X^2 = 4.746$, $p = 0.029$) and DOTS ($X^2 = 122.348$, $p < 0.001$). Meanwhile, diabetes,

| Variable | | (Total $n = 1114$) | |
		n	$\%$
Age	*Mean/SD	42.84	SD 16.579
Age group	0–20 years old	90	8.1
	21–40 years old	429	38.5
	41–60 years old	418	37.5
	61 years old and above	177	15.9
Gender	Male	734	65.9
	Female	380	34.1
Citizenship	Citizen	897	80.5
	Non-citizen	217	19.5
Race	Malay	451	40.5
	Non-Malay	663	59.5
Education status	No education	218	19.6
	Education	896	80.4
Employment	Employed	597	53.6
	Non-employed	517	46.4
Healthcare worker	Yes	11	1.0
	No	1103	99.0
Diabetes	Yes	252	22.6
	No	862	77.4
HIV status	Positive	34	3.1
	Negative	1080	96.9
CXR findings	No lesion	61	5.5
	Lesion	1053	94.5
DOTS	Yes	1079	96.9
	No	35	3.1
BCG scar	Present	1000	89.8
	Absent	114	10.2
Smoking	Yes	374	33.6
	No	740	66.4

Note(s): HIV: human immunodeficiency virus, CXR: chest X-ray, DOTS: direct observed short-course therapy, BCG: bacillus Calmette-Guerin

Table 1.
Descriptive statistics of patient characteristics (sociodemographic, clinical and behavior)

Treatment outcome		N	$\%$	Total (%)
Successful	Cured	841	75.49	77.20
	Completed treatment	19	1.71	
Unsuccessful	Treatment failure	2	0.18	22.80
	Died	106	9.52	
	Defaulter	99	8.89	
	Transferred out/Missing	47	4.21	
	Total	1114	100	100

Table 2.
Treatment outcome among smear positive TB patients in Kepong district (according to WHO standard criteria)

employment, healthcare worker and CXR findings did not show a significant relationship to the treatment outcome.

The simple logistic regression (Table 4) that showed a significant association with unsuccessful treatment included the following criteria: male (OR 2.466, 95% CI: 1.762, 3.452), non-citizen (OR 2.426 95% CI: 1.759-3.347), non-Malay (OR 1.728, 95% CI: 1.282, 2.330), no education (OR 1.730, 95% CI: 1.245, 2.404), HIV positive (OR 2.155 95% CI: 1.063-4.368), absent BCG scar (OR 1.815, 95% CI: 1.195, 2.755) and smoker (OR 1.359, 95% CI: 1.017, 1.816).

| | TB treatment outcome (total $n = 1114$) | | | | | |
| | Unsuccessful | | Successful | | | |
Risk factors	n	%	n	%	x^2 value	p-value
Gender						
Male	203	27.7	531	72.3	28.826	0.000
Female	51	13.4	329	86.6		
Citizenship						
Citizen	174	19.4	723	80.6	30.291	0.000
Non-citizen	80	36.9	137	63.1		
Race						
Malay	78	17.3	373	82.7	13.051	0.000
Non-Malay	176	26.5	487	73.5		
Educational status						
No education	68	31.2	150	68.8	10.844	0.001
Education	186	20.8	710	79.2		
Employment						
Employed	126	21.1	471	78.9	2.100	0.147
Non-employed	128	24.8	389	75.2		
Healthcare worker						
Yes	0	0.0	11	100.0	2.103	0.070
No	254	23.0	849	77.0		
Diabetes						
Yes	54	21.4	198	78.6	0.348	0.555
No	200	23.2	662	76.8		
HIV status						
Positive	13	38.2	21	61.8	4.746	0.029
Negative	241	22.3	839	77.7		
CXR findings						
No lesion	14	23.0	47	77.0	0.001	0.977
Lesion	240	22.8	813	77.2		
DOTS						
Yes	219	20.3	860	79.7	122.348	0.000
No	35	100	0	0.0		
BCG scar						
Present	216	21.6	784	78.4	8.004	0.005
Absent	38	33.3	76	66.7		
Smoking						
Yes	99	26.5	275	73.5	4.308	0.038
No	155	20.9	585	79.1		

Note(s): HIV: human immunodeficiency virus, CXR: chest X-ray, DOTS: direct observed short-course therapy, BCG: bacillus Calmette-Guerin; *level of significance $p < 0.05$

Table 3.
Bivariate analysis (chi-square) between risk factors to the treatment outcome among smear-positive tuberculosis patients in Kepong district

Multiple logistic regression (Table 5) was done to control confounding variables. Male gender (OR 2.561, 95% CI: 1.765, 3.715), non-citizen (OR 3.458, 95% CI: 2.020, 5.920) and HIV positive (OR 2.251, 95% CI: 1.087, 4.662) were significantly associated to unsuccessful treatment outcome.

This model fit was based on a non-significant Hosmer–Lemeshow test ($p = 0.175$), with an overall 77.4% from the classification table.

Variables	B	S.E.	Wald	df	Sig	Exp(B)	95% C.I.for EXP(B)	
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Age (years)	0.008	0.004	3.182	1	0.074	1.008	0.999	1.016
Gender (male vs female)	0.903	0.172	27.662	1	0.000	2.466	1.76	3.452
Citizenship (non-citizen vs citizen)	0.886	0.164	29.176	1	0.000	2.426	1.759	3.347
Education (no versus yes)	0.548	0.168	10.680	1	0.001	1.730	1.245	2.404
Race (non-Malays vs Malay)	0.547	0.152	12.881	1	0.000	1.728	1.282	2.330
Diabetes (yes vs no)	−0.102	0.173	0.348	1	0.555	0.903	0.643	1.268
Smoking (yes vs no)	0.307	0.148	4.291	1	0.038	1.359	1.017	1.816
BCG scar (absent vs present)	0.596	0.213	7.827	1	0.005	1.815	1.195	2.755
Employment (unemployed vs employed)	−0.207	0.143	2.097	1	0.148	0.813	0.614	1.076
Healthcare worker (no versus yes)	19.996	12118.648	0.000	1	0.999	483311060.201	0.000	
CXR finding (lesion vs no lesion)	−0.009	0.313	0.001	1	0.977	0.991	0.536	1.831
HIV status (positive versus negative)	0.768	0.360	4.539	1	0.033	2.155	1.063	4.368
DOTS (no versus yes)	22.571	6793.852	0.000	1	0.997	6343873812.109	0.000	

Note(s): HIV: human immunodeficiency virus, CXR: chest X-ray, DOTS: direct observed short course; therapy, BCG: bacillus Calmette-Guerin; *level of significance $p < 0.25$

Table 4.
Simple logistic regression analysis of risk factors and TB treatment outcome among smear-positive TB patients in Kepong district

Variables	B	S.E.	Wald	df	Sig	Exp (B)	95% C.I.for EXP (B)	
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Age (years)	0.012	0.005	5.439	1	0.020	1.012	1.002	1.022
Gender (male vs female)	0.940	0.190	24.514	1	0.000	2.561	1.765	3.715
Citizenship (non-citizen vs citizen)	1.241	0.274	20.455	1	0.000	3.458	2.020	5.920
Education (no versus yes)	−0.141	0.233	0.364	1	0.546	0.869	0.550	1.372
Race (non-Malay vs Malay)	0.055	0.179	0.094	1	0.759	1.056	0.744	1.501
Smoking (yes vs no)	0.109	0.164	0.438	1	0.508	1.115	0.808	1.538
BCG scar (absent vs present)	−0.014	0.257	0.003	1	0.956	0.986	0.595	1.632
Employment (unemployed vs employed)	0.448	0.158	8.044	1	0.005	1.566	1.149	2.135
HIV status (positive versus negative)	0.812	0.371	4.776	1	0.029	2.251	1.087	4.662

Note(s): HIV: human immunodeficiency virus, BCG: bacillus Calmette-Guerin; *level of significance $p < 0.05$

Table 5.
Multiple logistic regression analysis of risk factors and TB treatment outcome among smear-positive TB patients in Kepong district

Discussion

The treatment success rate for the Kepong district was 72%. This percentage of success rate was below the WHO's target, which is >90% [1]. Compared to the previous local studies, this result was similar with a success rate of 67.26% [4] and 78.5% [5]. A local study showed a success rate more than the target, 93% [3]. A study from China showed a higher success rate compared to the WHO target [6]. Lower treatment success rates were seen in a study done in

Morocco (53.6%) [7], Eastern Ethiopia (81%) [8] and India (81%) [9]. These comparisons showed that TB control in the Kepong district is not good and needs to be improved.

It is very important to study factors associated with the treatment outcome, especially risk factors for the unsuccessful treatment. Although TB is treatable, this disease still becomes a significant threat to other countries such as Malaysia.

The major contributors to unsuccessful treatment outcomes were death (9.52%), followed by defaulting (8.89%), not evaluated (4.21%) and finally treatment failure (0.18%). These findings were similar to previous studies [4, 10]. Other studies in Ethiopia showed that the defaulter group was the highest percentage in the unsuccessful treatment outcome [11]. It was also similar to a study done in Morocco [7]. Therefore, specific measures such as early identification of defaulter need to improve compliance with the treatment, prevent loss of follow-up and reduce the mortality rates.

A better understanding of factors associated with unsuccessful treatment outcomes is essential to plan effective interventions and strategies for reducing morbidity and mortality from TB infections. In this study, based on the final multiple logistic regression, the factors significantly associated with unsuccessful treatment outcomes are older age, male gender, non-citizen, unemployment and HIV positive.

Older people with TB were associated with a high mortality rate in previous studies [6, 11]. In this study, older age was significant with unsuccessful treatment outcomes. Older people related to age-related comorbidities (malnutrition, diabetes and cancer) with physiological and biological changes may weaken the immune response, thus increasing the risk of unsuccessful treatment among this age group. Male gender is significantly associated with unsuccessful treatment outcomes in this study. This finding is similar to a study done in Northwest Ethiopia [12]. A possible explanation for this finding might be because the men are involved in unhealthy behaviors such as smoking and drinking alcohol. Meanwhile, another study showed that women were significant associated with an unsuccessful outcome [13, 14]. Another study that showed no significant association of gender was a study done in Northern Ethiopia [15].

For the citizenship factor, this study showed that non-citizen was significantly associated with unsuccessful treatment outcomes. The result of this study was similar to the one done in Busan [10]. Other local study showed that local citizen was at a higher risk for unsuccessful treatment outcome [5]. In Malaysia, there was an influx of immigrants into this country looking for a job. This event may increase the risk of TB transmission, and due to low social income and education, they were at a high risk of default if diagnosed with the disease.

Several studies showed that PTB patients with HIV positive were strongly associated with unsuccessful treatment outcome. This study also showed a similar finding. A study in Kelantan showed that HIV was strongly associated with unsuccessful treatment outcome [3]. Other studies also showed a similar finding [16–18]. HIV tends to weaken the immune system. Thus, latent TB infection can quickly progress to TB disease. Therefore, all PTB patients are required to perform HIV screening to determine patient risk for poor outcomes and close monitoring.

Awareness of the importance of complying with the treatment course is vital for successful treatment. Low education level was significantly associated with unsuccessful treatment outcomes in several studies [5, 19]. Low socioeconomic factors such as unemployed are also associated with poor outcomes. The unemployed patients were at high risk for defaulting and not complying with medication, which resulted in with unsuccessful treatment outcomes [15]. A possible justification for this finding might be that most of the time was used for seeking a job. There was no time to seek healthcare and because of this, they ended up with default in treatment. This study showed unemployed had a significant association with unsuccessful treatment outcomes. The treatment facility needs to focus on these groups to ensure good results in their treatment course.

The healthcare workers are at high risk of getting TB, especially those who are dealing with TB patients. The healthcare workers were not significantly associated with the treatment outcome. There are only eleven healthcare workers (1%) from the total study sample diagnosed with smear-positive PTB. All of them had a successful treatment outcome. This could be due to the awareness among healthcare workers about the importance of complying to medication. They also did not face much trouble seeking any help regarding their treatment, as they could refer to a lot of doctors and health personnel. However, a study done in Japan showed that a nurse was associated with unsuccessful treatment outcomes [20]. One of the possible reasons could be the healthcare workers were taking their diseases lightly and thus ending up with poor outcomes.

A study showed that diabetes patients with PTB have a higher risk of unsuccessful treatment outcomes [21]. In this study, the diabetes factor was not significantly associated with treatment outcome. A similar study showed that diabetes was not significantly associated with the unsuccessful treatment outcome [4, 22]. Since this study only focuses on new smear-positive PTB cases, it may contribute to this result. Diabetes was associated with a severe type of TB and may end up with mortality [1]. Therefore, comprehensive care and control of TB and diabetes are vital due to the increasing trend of diabetes worldwide, including in Malaysia.

Most PTB patients had abnormalities on their CXR findings. In this study, CXR findings showed no association with the unsuccessful treatment outcome. Several studies found that PTB patients with abnormal CXR would end up with more severe complications and poor outcomes [4–6]. Patients with severe findings in their CXR must be treated as soon as possible to prevent more complications.

Most of the samples in this study had their BCG scar. BCG vaccination is essential to prevent the severe complication of TB [1]. The absence of BCG scar was found in non-citizens. It showed the BCG vaccination program was effective among the citizens. Some studies showed the absence of BCG scar was associated with unsuccessful treatment outcomes [5]. In this study, BCG scar was not a significant predictor for unsuccessful treatment outcomes.

One effective way to ensure PTB patients adhere to their medication is by assigning another person to monitor them. This method is called directly observed treatment short-course (DOTS). It will help the patient to comply with the medication with continuous monitoring. The DOTS also can prevent the risk of a patient defaulting or missing. The National TB Program in Malaysia has already implemented DOTS for TB patients since 2002, and this showed better results in monitoring the patients [2]. This study did not show a significant association of DOTS to unsuccessful treatment outcomes. The percentage of poor outcomes was higher than the non-DOTS group in this study. Other studies showed a significant association between non-DOTS and unsuccessful treatment outcomes [5]. The health facility must ensure the patients follow DOTs until completing their treatment.

Smoking also plays an important factor in determining the treatment outcome. In this study, smoking was not significantly associated with unsuccessful treatment outcomes. This study focused on positive smear cases only instead of all types of TB. However, several studies showed that smoking could be the predictor for unsuccessful treatment outcomes [5, 23, 24]. Thus, all PTB patients who were smoking need to attend counseling sessions for smoking cessation.

Limitation of this study
Firstly, only smear-positive pulmonary TB patients were assessed, so the study cannot represent all TB cases in Kepong district, Kuala Lumpur. Secondly, there was limited information available from the surveillance database (TBIS registry). Other important risk factors such as malnutrition and risk behavior (alcohol and drug abuse) were not readily

available. It is recommended that future studies may consider other data resources such as patients' files in the clinics and use questionnaires to obtain all the valuable information. Besides that, future studies can focus more on the race category. The current study focuses on Malay and non-Malay only, which does not represent the multiracial population in Malaysia. This may affect the result of this study.

Conclusion

This study showed that older age, male, non-citizen, unemployment and being HIV positive were significantly associated with unsuccessful treatment outcomes. The proportion of patients in a successful outcome category could be improved by closely monitoring the patients' clinical improvement with identified risk factors. Similarly, more aggressive follow-up of treatment defaulters could also improve the TB treatment success rate. A further study focusing on the risk factors of defaulter might be beneficial. The clinicians may encourage non-citizens to complete their treatment in Malaysia. Perhaps, this measure could improve the treatment success rate.

Conflict of Interest: None

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