Characteristics and Determinants of Treatment Default Among Smokers With Tuberculosis in an Industrial State of Malaysia: A Registry-based Study of the Years 2013-2017

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Abstract

Background: The increased risk of treatment default among smokers raises concern over the secondary spread within the community. This study aimed to determine the prevalence and factors associated with treatment default among TB patients who smoke.

Methods: A retrospective cohort of all registered TB patients who smoke in the state of Selangor between 2013 and 2017 via the Malaysian National MyTB database was included for analysis. TB patients who smoke were considered those with an active smoking status during the notification, while treatment default was defined as a TB patient who had interrupted treatment for 2 months or longer. There were 4 main variable domains included for analysis: sociodemographic profiles, disease profiles, treatment profiles, and comorbidities. Logistic regression analysis was used to identify determinants of treatment default among TB patients who smoke.

Results: A total of 27.6% (N=6278) of the TB patients registered in Selangor were active smokers, and 15.1% (N=813) of the TB patients who smoke experienced defaulted TB treatment. The determinants of treatment default among TB patients who smoke were patients staying in an urban area (AOR 1.47; 95% CI 1.11,1.96), median income level less than RM2160 (AOR 2.0; 95% CI 1.34,2.99), no formal education (AOR 2.12; 95% CI 1.31,3.44), previously treated cases (AOR 2.78; 95% CI 1.99,3.88), active TB case detection methods (AOR 2.05; 95% CI 1.21,3.47), treatment duration of less than 6 months (AOR 7.56; 95% CI 5.74,9.92), and patients not on DOTS during the continuation phase (AOR 27.96; 95% CI 21.1,37.1). All the significant factors gave rise to the final model of determinants, with a predictability of 92.9% (95% CI 92.0,93.7).

Conclusions: Our findings highlighted the high prevalence of treatment default among TB patients who smoke compared to the general TB population. Early risk detection that examines the two main domains of risk factors (socioeconomic factors and treatment profiles) should be provided for those who smoke in the TB population. Interventions should aim to reduce the prevalence of smoking among TB patients, together with close supervision during DOTS.

Background

TB current situation

An estimated 10 million cases of tuberculosis (TB) occurred in 2018, leading to 1.3 million deaths worldwide(1). In Malaysia, TB is the leading cause of death (mortality rates fluctuate from 4.8–6.2 cases per 100,000 population) from a single infectious disease; TB ranked above HIV/AIDS, dengue fever and malaria in the 5-year period from 2012–2016. With the current trend of the TB notification rate, it is projected that the incidence of TB will continue to increase through 2030(2). There are 11 states in the Peninsular of Malaysia and Selangor recorded the highest number of TB cases. Selangor is an industrialised state with > 90% urban population, creating more than 802,000 employment opportunities as reported in 2019(3).

TB is a mandatory national notifiable infectious disease under the Prevention and Control of Infectious Disease Act 1988. All suspected and confirmed cases of TB should be reported and notified to the nearest district health office by submission of the notification form. Data from the notification form are entered into the national TB registry by the health inspectors of the respective district health officer. The TBIS is a web-based application administered by the Ministry of Health Malaysia to record activities related to the notification, registration, investigation, and treatment of TB diseases in all states in Malaysia.

Smoking and TB remain major public health challenges globally. Tobacco smoking is responsible for 20% of the global burden of tuberculosis and will be responsible for a total of 18 million new cases and 40 million deaths in the 2010–2050 period(4). It is projected that TB incidence will increase up to 7% if we incorporate the effect of smoking compared to the effect without smoking. Numerous studies have identified smoking as a risk factor for the development of TB (5) and that it has a significant association with undesirable treatment adherence and default(6). Smoking has also been associated with more extensive lung disease and delayed sputum conversion even after 2 months of treatment in both current smokers and ex-smokers, which makes their treatment outcome worse(7). A higher prevalence of active smokers has been noted among TB patients compared to the general population in countries such as Indonesia, Africa, and India(8–10). In Malaysia, the prevalence of active smokers among TB patients was 34.0% in 2012 (11) compared to only 22.7% among the general population (NHMS, 2015).

Treatment default

In addition to smoking, defaulted TB treatment is also another threat faced by the TB control team in Malaysia. Patients with incomplete treatment for TB will become a significant economic burden on the government, with an average of RM901.63 per patient four times higher compared to the cost of completed treatment. The extra cost is normally attributed to hospital stays and patient care for complicated TB cases(12). The prevalence of treatment default varies among different countries and ranges from 2.5–44.9%(13). A very high proportion of 44.9% has been observed in rural northern Mozambique, where treatment default rates are a very serious problem(14). The prevalence of TB treatment default in Malaysia ranged from 4.0–4.8% in the years 2010–2015 among the general TB population (Ministry of Health, 2016); this number has increased to 5.6% according to the latest study(15). Studies from many other countries have shown a significant association between smoking and the tendency to default TB treatment; however, there are limited data on the prevalence of treatment default among those who smoke in the TB population. A local study in Penang found that smoking among TB patients is significantly associated with poorer treatment outcomes and increased treatment default by OR 7.17 compared to non-smokers(16). In Hong Kong, studies have concluded that smoking is the key contributor to defaulting, with a doubled risk compared to that of TB patients who never smoked(17); furthermore, a smoking habit is a good indicator for evaluating the risk of defaulting from TB treatment under DOTS(6). Similar findings have also been found in studies from Morocco and Tehran, where smokers have a double and triple increased likelihood of defaulting on their TB treatment, respectively(18, 19).

Determinants of treatment defaults

Previous studies have identified several reasons and risk factors for treatment default among TB patients, including smoking, alcohol use, comorbidities (HIV and diabetes mellitus), accessibility to a healthcare centre, socioeconomic factors (age, sex, education level, and income), and poor family support(20–22). Treatment default is also common among those who previously defaulted on TB treatment and among relapse cases; defaulting is the most common during the intensive phase of treatment(23). The evidence for a connection between smoking and treatment default, however, is inconclusive. Some studies have hypothesized that smokers with TB disease are less likely to comply with their TB treatment(24), while other studies have found that smokers have low levels of concern for their health. The behaviour of delaying seeking medical care at a more severe phase of illness and non-compliance among smokers may result in their worse prognosis (25); however, there is no solid conclusion for this hypothesis.

Despite knowing the impact of smoking and incomplete treatment among TB patients, there have been limited studies that examine these two issues. The current practice in our healthcare system is to refer all TB patients who smoke to the 'stop smoking clinic' for smoking cessation programs. However, there are no specific interventions to identify smoking populations who are at higher risk of defaulted TB treatment. This present study aimed to determine the factors associated with treatment default among TB patients who smoke in a 5-year cohort (2013–2017) of patients registered in the Selangor My-TB database.

Methods

Study setting, inclusion, and exclusion criteria.

This was a cross-sectional study that utilized data from the National MyTB database version 2.1 (TBIS) in 2013 to 2017 from the Disease Control Division, Ministry of Health. TB data from all states in Malaysia are consolidated at the national level for the surveillance database; however, in this study, we included only TB patients who smoke who were registered in the Selangor MyTB database from 2013 until 2017. The state of Selangor was selected based on its high TB incidence rate, i.e., 5,071 cases in 2018 (Malaysian MOH, 2019). Both Malaysians and non-Malaysians were included in this study. The exclusion criteria in this study included cases initially registered as TB but ultimately diagnosed as something other than TB disease, cases with missing data on treatment outcomes and cases with the outcomes not evaluated ("transferred out" to another treatment unit and whose treatment outcome is unknown) (WHO, 2013). We also excluded cases with multidrug-resistant TB (MDR-TB), as the treatment outcome definition for MDR-TB cases is different from the non-MDR-TB classification. TB treatment outcome and disease classification were defined according to the World Health Organization definition and the National TB database protocol.

Operational definition

According to the Clinical Practice Guideline for Management of Tuberculosis by Ministry of Health Malaysia and the definition and reporting framework of the WHO(26), treatment outcomes of TB can be broadly categorized into successful treatment outcomes (cured and completed treatment) and unsuccessful treatment outcomes (treatment default, treatment failure, death). In this study, the outcomes were divided into “treatment default” and “nontreatment default”. A defaulter (case) was defined as TB patients who interrupted treatment for ≥ 2 months or longer before the end of the treatment period, according to the WHO definition. Nontreatment default was defined as an outcome other than treatment default, which included being cured, completed treatment, failed treatment, and death. Being cured was defined as a negative sputum culture in the last month of treatment and on at least one previous occasion. Treatment completion was defined as completing treatment without meeting the criteria for cured or treatment failure. Treatment failure was considered as TB patients whose sputum smear or culture was positive in the fifth month or later during treatment. A patient who died before starting a treatment or during treatment was classified as a death, irrespective of the cause. The outcomes that were not included in this study included transferred-out cases or cases lost to follow-up (transfer to another country with unknown treatment outcome) and outcomes that were not evaluated (patients who were undergoing treatment and whose outcomes were not known).

Sample size calculation

The sample size was determined based on the 34.0% prevalence of smoking in the TB patient population registered in National MyTB version 2.1 in 2012(11). The sample size was calculated using Epi-Info software based on an alpha of 0.05, a power of 80%, and a design effect of 1. By adjusting to 30% of the attrition rate, in which we consider the probability of missing data, the minimum sample required in this study was 420. However, all registered TB patients who smoke in the Selangor MyTB 2.1 database from 2013–2017 were considered for the analysis, making up the total sample size of 5396.

Variable

Twenty variables related to the objective of the study were examined. The four domains of the independent variables were sociodemographic characteristics (age, sex, nationality, ethnicity, locality, education level, personal income, and occupation), disease profiles (TB category, method of TB case detection, BCG scarring, type of TB, chest X-ray status and sputum status), comorbidities (diabetes mellitus and HIV) and treatment profiles (DOTS during the intensive phase, DOTS during the continuation phase, duration of TB treatment and place of TB treatment initiated). Smoking status was specifically obtained by confirming whether the patient was an active smoker. There was no further information in terms of the duration or severity of smoking available from the database.

Data management

The data extraction flow is summarized in a flow diagram (Fig. 1). Data cleaning and processing were performed using R programming in view of the large amount of data. A total of 882 cases with exclusion criteria were excluded from the overall TB patients who smoke and were registered in the Selangor

database. Any redundant data were reviewed, and missing data were treated with data imputation. Data were kept in two backup storage in both hard and soft copies.

Confidentiality

Patient identification and information in the database remained anonymous and were kept confidential. Data will be stored for five years in a password-protected hard disk and will be destroyed after that.

Statistical analysis

Data were analysed using the SPSS statistical software package, version 23.0. The descriptive analysis of the four main independent variable domains is presented in the form of a frequency table. For continuous variables, the description is expressed as the mean ± SD, and for categorical variables, descriptions are presented as the frequency (n) and percentage (%). Simple logistic regression and multiple logistic regressions (MlogR) were performed to estimate the risk of treatment default among TB patients who smoke. Significant results with $p < 0.05$ from the univariable analysis were considered in MlogR. Multivariable analysis was performed using backward LR. A value of $p < 0.05$ from the final logistic model was considered statistically significant. Adjusted odds ratios (AORs) were used to present the results. The assumption of "linearity of logit" was checked for continuous independent variables (age). The presence of multicollinearity and interaction between the independent variables was checked.

Result

The prevalence

A total of 22785 TB patients were registered in the Selangor MyTB database from 2013–2017. Out of these 22785 TB patients, 27.6% (N = 6278) were smokers. After removing 14.0% (N = 882) of the cases from the database that met the exclusion criteria, i.e., patients with missing data on treatment outcome, 16.2% (N = 143); cases that had a changed diagnosis other than TB, 11.9% (105); duplicate cases, 29.5% (N = 260); and cases with an outcome not evaluated, 40.8% (N = 360), a total of 5396 patients were included for analysis (Fig. 1). The prevalence of treatment default among the overall TB patients in Selangor was 10.3% (95% CI 9.9,10.7) versus a default rate of 15.1% (95% CI 14.1,15.9) for TB patients who smoke in Selangor.

Characteristics of TB patients who smoke

The mean age of the TB patients who smoked was 42.36 ± 14.61 years and ranged from 8 to 96 years old. The majority were male 95.8% (N = 5,167), Malaysian citizens 89.3% (N = 4,821), lived in the urban area 82.7% (N = 4,462), and of Malay ethnicity 57.3% (N = 3,091). Most of the patients had an education level equal to at least to secondary school, worked and reported an income level of less than RM 2160 (median personal income, DOSM 2019). In terms of the disease profile, 91.8% (N = 4,955) were new TB cases, and 88.4% (N = 4.770) were pulmonary TB cases. A quarter of the TB patients who smoked had DM comorbidity 21% (N = 11,320), while 9.1% (N = 452) were reported as having HIV. TB treatment was

mostly initiated in 3,727 government hospitals (69.1%), with a treatment duration of more than 6 months at 3,523 (65.3%). DOTS was utilized by 87.7% (N = 4,733) of the patients during the intensive phase, and the percentage was reduced to 72.6% (N = 3,917) during the continuation phase (Table 1).

Table 1
Sociodemographic characteristics of the TB patients who smoke and are registered in Selangor.

Sociodemographic characteristic		N = 5369	%
Age	Mean ± SD = 42.36 ± 14.61		
	Min = 8, Max = 96		
	<=31	1445	26.8
	32–41	1308	24.2
	42–53	1387	25.7
	>=54	1256	23.3
Sex	Male	5167	95.8
	Female	229	4.2
Nationality	Malaysian	4821	89.3
	Non-Malaysian	577	10.7
Locality	Urban	4462	82.7
	Rural	934	17.3
Ethnicity	Malay	3091	57.3
	Chinese	850	15.8
	Indian	684	12.7
	Others	194	3.6
	Non-Malaysian	577	10.7
Education level	Higher education	861	16.0
	Secondary school	3466	64.2
	Primary school	494	9.2
	No education	575	10.7
Personal income	≤RM2160	4720	87.5
	>RM2160	676	12.5
Working status	Working	3331	61.7
	Not working	2065	38.3
TB anatomical location	Pulmonary TB	4770	88.4

Sociodemographic characteristic		N = 5369	%
	Extra-Pulmonary TB	626	11.6
TB case category	New case	4955	91.8
	Recurrent case	441	8.2
TB case detection	Active	185	3.4
	Passive	5211	96.6
BCG scar	Yes	4697	87.0
	No	699	13.0
X-ray status (N = 5322)	No Lesion	470	8.8
	Minimal lesion	3101	58.3
	Moderate lesion	1603	30.1
	Severe lesion	148	2.8
Sputum status (N = 5307)	Negative	1655	31.2
	Positive	3652	68.8
HIV status (N = 4962)	Negative	4510	90.9
	Positive	452	9.1
DM status	Yes	1132	21.0
	No	4264	79.0
Place of treatment initiated	Government hospital	3727	69.1
	Klinik Kesihatan	1191	22.1
	Private hospital/clinic	477	8.8
Treatment duration	Mean = 5.72 ± 3.25		
	Median = 6		
	< 6 months	1873	34.7
	≥ 6 months	3523	65.3
DOTS during the intensive phase	Yes	4733	87.7
	No	663	12.3
DOTS during the continuation phase	Yes	3917	72.6
	No	1479	27.4

Determinants of treatment defaults

Patient variables associated with treatment default were further analysed using simple and binary logistic regression, as illustrated in Table 2. After considering the effect of confounding and interactions, the variables that significantly contributed to treatment default among TB patients who smoked were those living in an urban area, AOR 1.47 (95% CI 1.10,1.96); an income level of less than RM2160, AOR 2.01 (95% CI 1.34,2.99); no education, AOR 2.12 (95% CI 1.31,3.44); previously treated TB cases, AOR 2.78 (95% CI 1.99,1.31); active TB case detection methods, AOR 2.05 (95% CI 1.21,3.48); treatment duration of less than 6 months, AOR 7.56 (95% CI 5.74,9.92); and not on DOTS during the continuation phase, AOR 27.10 (95% CI 21.09–37.06) (Table 3). HIV comorbidities were found to be significant in a univariable analysis with p-value 0.021 and crude OR 1.34 (95% CI 1.05,1.72); however, HIV comorbidity was not found to be a determinant for TB treatment default in the final logistic model, which indicated that other predictors have a stronger association with TB treatment default. All the significant factors gave rise to the final model of determinants, with a predictability of 92.9% (95% CI 92.0,93.7), which means that this model determines 92.9% of the prediction of defaulted TB treatment.

Table 2
Univariable analysis of treatment default among TB patients who smoke and are registered in Selangor.

Variables		Crude OR	95% CI		P-Value*
			Lower	Upper	
Age	≤ 31	1			
	32–41	1.17	0.96	1.42	0.118
	42–53	0.81	0.66	1.00	0.047
	≥ 53	0.58	0.46	0.73	0.001
Sex	Male	1.19	0.80	1.75	0.396
	Female	1			
Nationality	Non-Malaysian	0.60	0.46	0.80	< 0.001
	Malaysian	1			
Locality	Urban	1.28	1.04	1.57	0.023
	Rural	1			
Ethnicity	Malay	1			
	Chinese	0.48	0.37	0.62	< 0.001
	Indian	1.30	1.06	1.61	0.013
	Others	0.68	0.16	2.99	0.611
	Non-Malaysian	0.57	0.43	0.76	< 0.001
Education Level	No formal education	1.83	1.34	2.49	< 0.001
	Primary school	1.30	0.92	1.84	0.136
	Secondary school	1.73	1.34	2.49	< 0.001
	Higher education	1			
Individual Income	≤ 2160	2.21	1.65	2.95	< 0.001
	> 2160	1			
Occupation	Not Working	1.26	1.08	1.46	0.003

Variables		Crude OR	95% CI		P-Value*
	Working	1			
Site of TB	Extrapulmonary	1			
	Pulmonary	1.18	0.93	1.51	0.179
TB categories	New case	1			
	Previously treated cases	2.58	2.07	3.22	< 0.001
TB detection	Passive	1			
	Active	2.29	1.64	3.18	< 0.001
BCG status	Yes	1			
	No	0.66	0.51	0.84	0.001
X-ray status					
	No lesions	1			
	Minimal lesions	1.11	0.83	1.48	0.482
	Moderate lesions	1.40	1.04	1.89	0.027
	Severe lesions	0.99	0.57	1.72	0.964
Sputum status	Negative				
	Positive	1.31	1.11	1.55	0.002
HIV status	No	1			
	Yes	1.34	1.05	1.72	0.021
DM status	No	1			
	Yes	0.78	0.65	6.37	0.013
Place of treatment initiated	Private sector	1			
	Government Hospital	2.65	1.81	3.87	< 0.001
	Primary public clinic	3.39	2.28	5.05	< 0.001
Treatment duration	≥ 6 months	1			
	< 6 months	18.22	14.76	22.47	< 0.001

Variables		Crude OR	95% CI		P-Value*
DOTS during the intensive phase	Yes	1			
	No	4.33	3.62	5.19	< 0.001
DOTS during the continuation phase	Yes	1			
	No	30.61	24.72	37.91	< 0.001

Table 3
Determinants of treatment default among TB patients who smoke and are registered in Selangor

Variable		Crude OR	95% CI	P-value	AOR	95% CI	p-value*
Locality	Urban	1.276	1.035–1.573	0.023	1.472	1.103–1.964	0.009
	Rural	1					
Income level	≤ 2160	2.207	1.654–2.946	< 0.001	2.001	1.338–2.992	0.001
	> 2160	1					
Education Level	High Education	1					
	Secondary school	1.733	1.34–2.493	< 0.001	1.36	0.961–1.926	0.083
	Primary school	1.3	0.921–1.836	0.136	1.355	0.824–2.225	0.231
	No education	1.828	1.34–2.493	< 0.001	2.12	1.308–3.435	0.002
TB categories	New case	1					
	Previously treated cases	2.582	2.071–3.219	< 0.001	2.78	1.99–3.884	< 0.001
TB case detection	Passive	1					
	Active (screening)	2.286	1.644–3.179	< 0.001	2.047	1.206–3.473	< 0.001
Treatment duration	≥ 6 months	1					
	< 6 months	1.216	14.763–22.47	< 0.001	7.563	5.742–9.918	< 0.001
DOTS	Yes	1					

(Continuation phase)	No	30.611	24.718–37.909	< 0.001	27.961	21.098–37.058	< 0.001

*Test used: Multiple Logistic Regression Analysis (Method Backward LR; B Constant=-5.332, Model assumption are met Interaction considered in the model, No Multicollinearity)

Note: AOR = Adjusted odds ratio, CI = Confidence interval, B = Regression coefficient, Nagelkerke R^2=0.562, Hosmer and Lemeshow test = 0.189, Classification = 89.9% correct, AUC = 0.929 (95%CI: 92.0-93.7).

Overall, only 73.8% of the TB patients who smoked had favourable treatment outcomes, in which 47% were cured and 27% completed their TB treatment. Among the 26.2% of patients with unfavourable outcomes, 15.1% defaulted their treatment, 11% died, and 0.1% had failed treatment.

Discussion

In this study, we highlighted the high prevalence of smoking among TB patients in Selangor during the period 2013–2017. Almost one-third of the TB patients in this study cohort were active smokers, 27.6% (95% CI: 25.2,28.8), compared to only 22% of active smokers among the adult general population in Malaysia in 2015 (NHMS, 2015). The proportion of TB patient who smoke could be higher if we use only the adult population for this study. Previous studies conducted in Malaysia (16, 27) and other countries, such as Indonesia, Africa, and India (8–10), have reported similar findings, with a higher prevalence of smokers being found among TB patients compared to the general population. This signifies that smoking is one of the main predictors of TB infection. This current study also shows that the proportion of treatment default among TB patients who smoke is higher than that among the overall general TB patients registered in Selangor, with outcomes of 15.1% and 10.3%, respectively. Smoking behaviour among TB patients by itself has a poor prognosis for TB treatment outcomes. TB patients who smoke and who default on TB treatment will experience worse outcomes. Therefore, it is important to examine the factors associated with treatment default among TB patients who smoke to optimize their treatment adherence and assist them in quitting smoking.

Factors associated with treatment default.

Adherence to TB treatment strongly influences the outcome of patients and has an effect on the development of multidrug resistance (MDR-TB)(28). In the current study, the majority of patients who default on TB treatment had sputum samples that were smear positive when they returned for retreatment care, which indicates a high risk of transmission to others(29). Despite full supervision in the form of the directly observed therapy that is currently being delivered in our setting, the outcome was not consistently improved. Sociodemographic factors associated with treatment default among TB patients who smoke were residing in an urban area, having a low education level and a low-income level (median individual income < RM2160), all of which had significant contribution to TB treatment default. This outcome could be possible because smoking is a marker for other social and behavioural factors that

make defaulting on treatment more likely(29). A similar finding was also found in a qualitative study performed in urban Morocco, where a low income and a low level of education were barrier resources among TB patients which led to default. The reasons were due to lack of money for transportation, the need to work despite illness, and no one aiding in obtaining medication(30). This shows that socioeconomic support plays important roles in ensuring the continuation of TB treatment. Despite the full subsidization of anti-TB treatment to all TB patients, some out-of-pocket expenditures still exist, especially related transportation costs. An average of RM439.42 out-of-pocket money per patient has been estimated in order to complete a 6-month TB treatment(31). Any intervention that could reduce the cost of TB treatment will help to improve patient compliance with TB treatment.

Other studies from Hong Kong and Morocco have found that male sex and being a nonreligious person have significant associations with smoking habits and defaulting on TB treatment(6, 24). This could account for the large observed differences in the proportion of males and females in this study; however, sex was not included in the final model in this study. The influence of religious belief on the effect of patient adherence to TB treatment could not be quantified, as religious status was not available in the database.

Under the disease profiles domain, patients with a history of previously being treated for TB had an almost threefold risk of default treatment compared to new TB cases. It has been reported that previous experience with TB is a risk factor for defaulting only when there was a previous treatment default(6). This could be related to smoking habits, as studies conducted among TB patients who smoke in Hong Kong have revealed a significant association between retreatment cases among current smokers and TB patients who never smoke(17). The complex psychosocial factors of smoking may explain its association with defaults and non-adherence; however, in this study, we did not address the underlying mechanism. Additional studies from other countries, such as Sudan, Morocco, and Brazil, also found a significant association between retreatment cases and TB treatment default, with ORs ranging from 3.2 to 6.5; this indicates that patients who had been defaulting their treatment will be at higher risk of defaulting on their TB treatment again(30, 32, 33).

This study also found that TB patients who smoke and who were detected through active screening methods had a double-risk AOR of 2.047 (95% CI 1.206–3.473) for defaulted treatment compared to those who were detected through passive detection methods. This finding could be the result of the implementation of the national guideline for systematic screening for TB high-risk groups, such as TB/HIV comorbidities, inmate prisoners, diabetes patients, elderly individuals and patients in methadone replacement therapy since 2015, where the majority of these high-risk groups were significantly associated with unfavourable TB treatment outcomes (NSPTB 2016–2020). This action was intended to improve TB detection rates and to provide early TB treatment to them. Most detected TB comorbidities, for example, TBHIV and TBDM, are known to be predictors of poor TB treatment outcomes in many studies. Studies from Brazil, Kenya and Peru have found that HIV-infected patients are at higher risk of defaulted treatment than are HIV-negative patients(23, 34, 35). The outcomes are similar for diabetes mellitus (DM); clinical evidence has found DM to be a significant risk factor for poor TB treatment

outcomes, including treatment default. The literature has suggested that DM is significantly associated with the development of adverse drug reactions and delayed sputum conversion at the end of 2 months of treatment(36), which explains the high default rates among TB/DM patients in certain countries, including Kuwait and Brazil(37). In this study, TB patients who smoked and had HIV were significant in the univariable analysis but were not found to have an independent relationship to treatment default in the multiple logistic regression analysis. While TB/DM patients had no association with treatment default. The lower rates of treatment default among TB patients with comorbidities may be due to their better treatment compliance, as these patients are frequently followed up with for anti-retroviral treatment in HIV patients and chronic diabetes mellitus management(11). The increased TB detection rate and earlier TB treatment among DM patients have been improved under the National Diabetes Programme (NSPTB 2016–2020). TB/HIV collaborative activities between the National TB Control Programme and the National HIV/AIDS Control Programme have also contributed to the better surveillance, management, and treatment outcome of this group (NSPTB 2016–2020).

TB patients who smoked who received TB treatment of less than 6 months in duration had a seven times higher risk of defaulting on treatment, AOR 7.653 (95% CI 5.742–9.918) compared to those receiving treatment for 6 months or more. This result is parallel with the finding from Peru and Estonia, where the majority of patients default on treatment after the completion of the intensive phase(35) with a median duration of 124.5 days(38). In Malaysia, national TB treatment strongly recommends using patient-centred case management and utilizes the DOTS strategy when treating people with TB. DOTS supervisors could be healthcare workers, family members, NGOs, and community volunteers. Statistics have found that more patients are lost to follow-up when supervised by NGOs and volunteers than when supervised by family members and healthcare workers. The literature from other studies has showed that patients who do not adhere to their treatment and default on treatment are largely unsupervised or supervised outside the chest clinic. In Hong Kong, patient supervision by community nurses, family members and NGOs is often incomplete after a short period of time, which accounts for almost 50% of their TB patients(6). It is crucial to ensure that the selection of DOT supervisors is appropriate depending on the patients' risk of default treatment, as the determinant with the highest strength of the predictability to default treatment was patients who were not on DOTS during the continuation phase of TB treatment, with a more than twenty-fold increased risk (AOR 27.961; 95% CI 21.098–37.058). The percentage of patients on DOTS decreased from 87.7% during the intensive phase to 72.6% in the continuation phase. Many patients who do not receive DOTS will usually stop taking their medications after 2 months because they feel better or are less symptomatic(39). Other common significant factors associated with non-adherence to DOTS are poor knowledge towards TB and its treatment, the cost of transportation for DOTS at every visit and the distance of the DOTS centre from individual's home(40).

Addressing smoking issues among TB patients requires a strategic plan on its own. A study performed among TB patients who smoke in Penang showed a poor score of tobacco use knowledge and its health consequences in general among newly diagnosed patients(27). Most patients report that they are not informed about the impact of continued smoking on TB outcomes and have only received general health information and not TB-specific information(41). Evidence on the effects of smoking cessation on TB

treatment outcomes, especially on treatment default, is limited. It is also not well known whether quitting smoking during TB treatment would have an immediate impact and produce similar outcomes as those of individuals who have never smoked. However, a study performed by Wang and Shen in Hong Kong found that TB patients without smoking cessation are twice as likely to default on TB treatment than are those who achieve cessation (OR 2.03; 95% CI 0.99–4.18). This outcome is similar to a local study performed in Malaysia, which found that TB patients who receive tobacco cessation intervention during DOTS have a lower rate of treatment default than TB patients in the usual care group(42). Additionally, the literature has shown that smoking-related immunological abnormalities in TB are reversible within six weeks of smoking cessation(43). Therefore, initiating tobacco cessation intervention during DOTS will benefit TB patients in terms of their treatment outcome and improve their adherence to TB treatment. A prospective cohort in Hong Kong also found that 49.6% of smokers who quit will remain nonsmoking 5 years after the cessation intervention while receiving TB treatment(44). This finding supports the long-term effect of the TB smoking cessation intervention delivered by TB chest clinics in reducing smoking prevalence among TB patients who smoke.

Strength And Limitations

The findings from this study provide new knowledge about the characteristics and determinants of treatment default among TB patients who smoke. It also highlights the high prevalence of treatment default among TB patients who smoke for the attention of stakeholders to implement integrated intervention programmes for this specific high-risk group by addressing both TB and smoking issues. Other items of importance are the findings on the influence of social determinants among smokers on TB treatment defaults, such as education and economic status, and those on TB burden, especially in urban areas. In addition to patient characteristics, disease and treatment profiles were also identified as having significant associations with defaults. We did not find a significant association between defaults and TB comorbidities, which is similar to other studies; this outcome could be due to different clinical or preventive approaches practised by healthcare settings. The large sample size taken from the registered TB patients in the Selangor MyTB database from 2013–2017 allowed the generalizability of the study findings to the general TB population in Malaysia. However, this study has several limitations. Due to the massive data, advanced data software such as R software or STATA is required for data management and processing. The completeness of the database due to a high proportion of missing data affects the analysis for certain variables (HIV status, sputum status and X-ray status with missing values ranging from 1.3%-14.1%). There were also important missing variables from the database that could not be analysed, which limited our factor association analysis. Due to the limited information in the database in terms of smoking characteristics, we were unable to see the temporality of the associations between different smoking statuses among the patients (active smoker, ex-smoker, quit smoker) throughout TB treatment. Some TB patients might stop smoking after being diagnosed with TB; therefore, their smoking status should no longer be active. Our study also lacks details on the timely duration of patient treatment to quantify at which phases of treatment should we intensify our supervision to prevent defaults.

Recommendations

The reduction of the smoking prevalence among TB patients could be achieved through strengthening the inter-sectoral collaboration between units in the TB healthcare management system and reinforcing the communication or educational counselling quality between patients and health care providers. Integrated TB-tobacco cessation invention programs must be initiated together in TB chest clinics to cater to both issues holistically at the same time. This integrated intervention should be included in the National Strategic Plan of TB for its better implementation.

Further observational studies with primary data are highly recommended. Another area for further research is to develop prognostic scoring tools for the earlier detection of the high-risk group to default TB treatment among those who smoke in the TB population based on the determinants that have been identified from this study. Extra supervision is required for TB patients who smoke and have strong predictors of defaulting.

Conclusion

This study identified determinants for treatment defaults among TB patients who smoke and focused on patients' socioeconomic profiles, disease and treatment profiles and comorbidities. The logistic models showed that the risk of defaults could be predicted for those who reside in an urban area, have no or low levels of formal education, have a low income, are a retreatment case, are a TB case detected through active methods, are TB patients receiving treatment for less than 6 months and are not on DOTS during the continuation phase of treatment. Early risk detection for combined smoking cessation intervention and close supervision during DOTS should be provided to reduce smoking prevalence among TB patients and ultimately improve TB treatment outcomes, specifically regarding treatment default.

Abbreviations

TB: tuberculosis, DOTS: direct observation therapy short course, DM: diabetes mellitus, HIV: human immune deficiency virus, AOR: adjusted odds ratio, COR: crude odds ratio, SD: standard deviation.

Declarations

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Availability of data materials

The dataset used and analysed in this current study is available from the corresponding author on reasonable request with permission from the Disease Control Division, Ministry of Health.

Ethics approval and consent to participate

The study was approved by the Malaysia Ministry of Health Medical Research Ethics Committee (reference number NMRR-19-3860-52267) and the Research Ethics Committee (REC), UiTM. This study involved secondary data analysis; thus, no consent from respondent was required. A formal request for data utilization was made from the Disease Control Division, Ministry of Health Malaysia prior to study initiation. All registered TB cases were kept anonymous and given a unique identification numbering. There is also no conflict of interest declared in this study.

Consent for publication

Not applicable

Competing interest

The authors declare that they have no competing interests.

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Figures

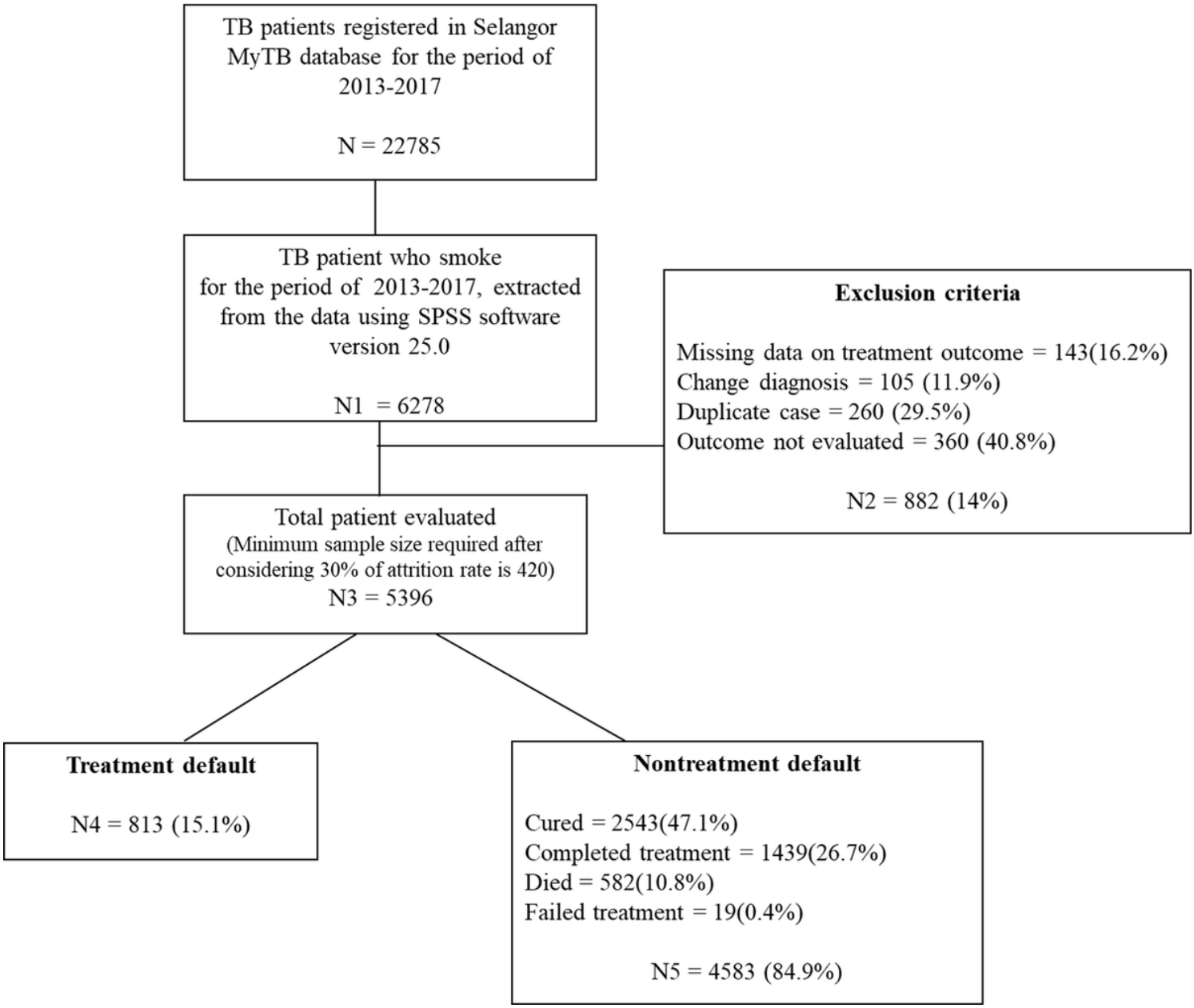

Figure 1

Flow diagram of data management flow