

PREDICTORS OF TUBERCULOSIS RELAPSE IN PASIR PUTEH DISTRICT, KELANTAN: A CASE-CONTROL STUDY.

Hafizuddin Awang^{1,2}, Nashwa Raub¹, Ahmad Noor Ali Alias¹, Nor Asmawati Abdul Rahman¹, Zawiyah Dollah¹

¹Pasir Puteh District Health Office, 16800 Pasir Puteh, Kelantan

²Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan.

*Corresponding author: Dr Hafizuddin Awang. MD (Moscow), MPH (USM). Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan. E-mail: drhafizuddin@mail.ru

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ABSTRACT

Background: Tuberculosis relapse is one of Malaysia's public health concerns. Studying relapse of tuberculosis is a convenient way to evaluate the effectiveness of tuberculosis control programs and identify vulnerable patients. This study aimed to estimate the prevalence of tuberculosis relapse and determine its associated factors in Pasir Puteh district.

Materials and Methods: This study was a case control study between the relapsed and non-relapsed group conducted in the district of Pasir Puteh, Kelantan. All notified cases that fulfilled the inclusion and exclusion criteria from 1st January 2014 to 31st December 2018 were included in the study. Descriptive statistics, simple and multiple logistic regressions were used for data analysis.

Result: From 2014 until 2018, there were 454 tuberculosis cases registered in Pasir Puteh district. The prevalence of tuberculosis relapse cases within the five-year period was 8.4% (95%CI: 0.06, 0.11). Majority of TB relapse patients were adult group, male, had secondary level of education, and unemployed. By clinical factors, most of tuberculosis relapse patients were non-diabetic, cigarette smokers, HIV negative, had pulmonary form of tuberculosis, and had minimal lesion on chest radiographic findings. Diabetic patients and cigarette smokers were the significant factors associated with tuberculosis relapse in Pasir Puteh district with an adjusted odds ratio (AOR) of 2.98 (95%CI:1.23, 7.26; p=0.016) and 4.27 (95%CI:1.54, 11.85; p=0.005), respectively.

Conclusion: In conclusion, diabetic patients and cigarette smokers were more likely to develop tuberculosis relapse. Thus, the identified risk factors were useful for diagnosis and in planning for screening and intervention programs.

Keywords: tuberculosis, relapse, associated factors, diabetes, cigarette smoking, Malaysia.

1.0 Introduction

Tuberculosis is an infectious disease that remains a major global health problem. In 2018, an estimated 10 million people fell ill with tuberculosis worldwide affecting 5.7 million men, 3.2 million women and 1.1 million children (World Health Organization, 2019). As for Malaysia, tuberculosis remains an important public health and challenges for control in Malaysia as our nation is surrounded by 3 of the 22 countries with the world's highest tuberculosis burden (Indonesia, the Philippines and Thailand) (World Health Organization, 2016). Currently, Malaysia is classified as a country with intermediate burden of tuberculosis with notification rate of tuberculosis less than 100 cases for every 100,000 populations. In 1961, Malaysia started a National Tuberculosis Control Programme, and a tuberculosis registry was established in 1973. Over the last decade, Malaysia's National Tuberculosis Programmes (NTPs) have expanded the tuberculosis control programme with focus on early case detection among symptomatic and high-risk patients, ensuring quality laboratory services, development training module, guidelines and MyTB databases, conducting regular course and training to staffs and strengthening collaboration with other agencies. Recently, Malaysia introduced The National Strategic Plan for Tuberculosis Control (2016-2020) which is an ambitious plan to work through the goal of ending tuberculosis by 2035 (Ministry of Health, 2016).

However, the increasing number of tuberculosis poses a great challenge to control and reduce tuberculosis transmission in Malaysia as tuberculosis is attributed to various risk factors which are beyond the control of Ministry of Health alone. Risk factors for tuberculosis have been reported to include socio-economic factors (age, sex, employment and education), patient factors (such as diabetes status, smoking, HIV status), and disease factors (history of multiple disease treatment, history of receiving directly observed treatment, short-course (DOTS) and multi-drug resistant tuberculosis (MDR-TB)) (Atif, Sulaiman, Shafie, & Babar, 2015; Awang, Husain, & Abdullah, 2019b; Rafiza, Rampal, & Tahir, 2011; Thomas *et al.*, 2005).

Another serious issue in tuberculosis control in Malaysia is pertaining to tuberculosis relapse. Relapse of tuberculosis refers to the situation in which a patient becomes and remains culture-negative while receiving anti-tuberculosis drugs but develops active tuberculosis again after completion of treatment (Chang, Leung, Yew, Ho, & Tam, 2004). The reported rates of relapse after standard 6-month treatment for drug-susceptible pulmonary tuberculosis were approximately 1 to 2% at 24 months, and 3.4% over 5 years (Thomas *et al.*, 2005). Host factors such as sex (Borgdorff, Nagelkerke, Dye, & Nunn, 2000), co-morbidities (Hung, Chien, & Ou, 2015; Jiménez-Corona *et al.*, 2013) and treatment-related factors possibly interact to cause relapse (Baker *et al.*, 2011).

Tuberculosis cases in Malaysia are quite high in unfavourable outcome of retreatment including relapse. A trend of increase in the retreatment case was documented in Malaysia between 2012 until 2015; the retreatment case increased from 6.4% to 6.7%, 7.3% and 7.4% respectively. Of the 24,220 TB cases notified in 2015, about 22,427 (92.6%) were classified as new cases and 1,793 (7.4%) were retreatment case. Of the retreatment case, 1,141 (4.71%) were relapse cases, 88 (0.36%) were treatment after failure cases, 564 (2.33%) were treatment after default cases

(Ministry of Health, 2016). Hence, it is necessary to identify the risk factors and associated factors to prevent tuberculosis cases and tuberculosis relapse. Moreover, the information regarding tuberculosis relapse and its associated factors in Pasir Puteh district might be different from other places. Therefore, this study was conducted to estimate the prevalence of tuberculosis relapse and determine its associated factors in Pasir Puteh district, Kelantan, Malaysia. A better understanding of the risk factors of relapse is conducive to optimizing the current treatment and paving the way for future development.

2.0 Materials and Methods

From 1st November until 30th November 2019, we conducted a case control study between the relapsed and non-relapsed group based on retrospective record review for all cases of tuberculosis notified to Pasir Puteh District Health Office, Kelantan, Malaysia from the period of 1st January 2014 until 31st December 2018. The ratio of case to control was 1:3. Records from MyTB registry for the period of 1st January 2014 until 31st December 2018 of selected subjects were reviewed and studied data were extracted. The reference populations were all tuberculosis relapsed cases in Pasir Puteh district and the study samples were all tuberculosis cases notified to Pasir Puteh District Health Office between 1st of January 2014 to 31st of December 2018 who fulfilled study inclusion and exclusion criteria.

The inclusion criteria for case group were patients whose most recent treatment outcome was cured or completed treatment and who is subsequently diagnosed with bacteriologically positive tuberculosis by sputum smear microscopy or culture (Ministry of Health, 2012). Meanwhile, the inclusion criteria for control group were new patients in whom tuberculosis has been bacteriologically confirmed or has been diagnosed by a clinician and has no history of previous tuberculosis infection (Ministry of Health, 2012). Samples with incomplete record of 30% variables were excluded from the study.

The sample size was calculated for each variable of associated factors for tuberculosis relapse among tuberculosis patients using power and sample size calculation software (Dupont & Plummer Jr, 1990) as well to compare two independent proportions. The largest estimated sample for each group was 37 using the proportion of non-relapsed tuberculosis by the factor of diabetes (0.25) (Viswanathan *et al.*, 2012), an estimated proportion of 0.5, 5% type 1 error, 80% power and additional of 20% missing data. The ratio of case to control was 1:3. Therefore, the total sample size required was 148 samples. We employed simple random sampling for cases and controls recruitment from the total tuberculosis cases in Pasir Puteh district which fulfilled the study criteria.

Data were collected from MyTB registry (an online database for tuberculosis under the governance of Ministry of Health Malaysia) and recorded in patient's proforma. The retrieved information for independent variables included socio-demographic characteristics (age, ethnicity, gender, educational level and occupation) and clinical characteristics (diabetes mellitus status,

cigarette smoking status, human immunodeficiency virus (HIV) status, presence of Bacillus Calmette–Guérin (BCG) vaccine scar, tuberculosis categories and chest radiographic findings). The dependent variable was the tuberculosis outcome either relapsed or non-relapsed tuberculosis.

Data were analyzed by using SPSS software version 20. Descriptive statistics with mean and standard deviation (SD), frequency and percentages were calculated. Simple and multiple logistic regression analysis were used to determine factors associated with tuberculosis relapse among tuberculosis patients. All significant variables with a p-value <0.25 from univariable analysis and clinically important variables were chosen for multiple logistic regression analysis. A p-value<0.05 was considered statistically significant.

3.0 Result

From 2014 until 2018, there were 454 tuberculosis cases notified to Pasir Puteh District Health Office. Over the five years period, the prevalence of tuberculosis relapse cases was 8.4% (95%CI: 0.06, 0.11) or 38 relapse cases. The remaining 416 cases were all newly diagnosed tuberculosis cases. As for the case-control study of 148 samples, 37 tuberculosis relapse patients were randomly recruited for cases, while 111 samples were randomly selected from the remaining 416 newly diagnosed tuberculosis patients for controls. Socio-demographically, the mean (\pm SD) age for patients with tuberculosis relapse was 51.65 (\pm 18.47). Majority of tuberculosis relapse patients were adult group, male, had secondary level of education, and unemployed. Details are summarized in Table 1.

By clinical factors, majority of tuberculosis relapse patients were non-diabetic, cigarette smokers, HIV negative, had pulmonary form of tuberculosis, and had minimal lesion on chest radiographic findings. Details are shown in Table 2.

In the univariable analysis, only gender factor from the socio-demographic characteristics were selected for multivariable analysis as its p-value is less than 0.25. As for clinical factors, diabetes status, cigarette smoking status, HIV status and tuberculosis category were the significant and clinically important factors selected for multivariable analysis. Details are summarized in Table 3 and Table 4.

In the multivariable analysis using multiple logistic regression revealed diabetic patients and cigarette smokers were the significant factors associated with tuberculosis relapse in Pasir Puteh district with an adjusted odds ratio (AOR) of 2.98 (95%CI:1.23, 7.26; p=0.016) and 4.27 (95%CI:1.54, 11.85; p=0.005), respectively. Details are shown in Table 5.

Table 1: Socio-demographic characteristics of patients in accordance to their tuberculosis outcomes (n=148)

Characteristics	Frequency (%)	
	Relapsed tuberculosis (n=37)	Non-relapsed tuberculosis (n=111)
Age (years)*	51.65 (\pm 18.47)	50.87 (\pm 17.08)
Age category		
\leq 19 years old	2 (5.4)	3 (2.7)
>19 until <60 years old	23 (62.2)	71 (64.0)
\geq 60 years old	12 (32.4)	37 (33.3)
Gender		
Female	8 (21.6)	39 (35.1)
Male	29 (78.4)	72 (64.9)
Education level		
Tertiary	3 (8.1)	8 (7.2)
Secondary	22 (59.5)	60 (54.1)
Primary	5 (13.5)	27 (24.3)
None	7 (18.9)	16 (14.4)
Occupation		
Student	1 (2.7)	1 (0.9)
Professional	1 (2.7)	7 (6.3)
Agriculture/industrial	4 (10.8)	20 (18.0)
Self-employed	10 (27.0)	20 (18.0)
Unemployed	21 (56.8)	63 (56.8)

*Mean (\pm SD)

Table 2: Clinical characteristics of patients in accordance to their tuberculosis outcomes (n=148)

Characteristics	Frequency (%)	
	Relapsed tuberculosis (n=37)	Non-relapsed tuberculosis (n=111)
Diabetes status		
No	22 (59.5)	90 (81.1)
Yes	15 (40.5)	21 (18.9)
Cigarette smoking status		
No	14 (37.8)	79 (71.2)
Yes	23 (62.2)	32 (28.8)
HIV status		
Negative	30 (81.1)	100 (90.1)
Positive	7 (18.9)	11 (9.9)
BCG scar		
Present	30 (81.1)	92 (82.9)
Absent	7 (18.9)	19 (17.1)
Tuberculosis (TB) category		
Extrapulmonary TB (EPTB)	3 (8.1)	15 (13.5)
Pulmonary TB	32 (86.5)	94 (84.7)
Pulmonary with EPTB	2 (5.4)	2 (1.8)
Chest radiographic findings		
No lesion	3 (8.1)	8 (7.2)
Minimal lesion	25 (67.6)	55 (49.5)
Moderately advanced lesion	7 (18.9)	45 (40.5)
Far advanced lesion	2 (5.4)	3 (2.7)

Table 3: Socio-demographic factors associated with tuberculosis relapse in Pasir Puteh district by simple logistic regression (n=148).

Factors	β	S.E.	Wald statistics (df)	Crude OR (95% CI)	p-value
Age	0.003	0.011	0.056 (1)	1.003 (0.98, 1.02)	0.814
Age category					
≤ 19 years old				1.00	
>19 until <60 years old	-0.72	0.94	0.56 (1)	0.49 (0.08, 3.09)	0.444
≥ 60 years old	-0.72	0.97	0.55 (1)	0.49 (0.07, 3.27)	0.458
Gender					
Female				1.00	
Male	0.68	0.45	2.29 (1)	1.96 (0.82, 4.71)	0.130
Education level					
Tertiary				1.00	
Secondary	-0.02	0.72	0.001(1)	0.98 (0.24, 4.02)	0.975
Primary	-0.71	0.83	0.72 (1)	0.49 (0.10, 2.53)	0.397
None	0.15	0.82	0.04 (1)	1.17 (0.24, 5.76)	0.850
Occupation					
Student				1.00	
Professional	-1.95	1.77	1.21 (1)	0.14 (0.004, 4.61)	0.272
Agriculture/industrial	-1.61	1.52	1.13 (1)	0.20 (0.01, 3.91)	0.289
Self-employed	-0.69	1.47	0.22 (1)	0.50 (0.03, 8.85)	0.636
Unemployed	-1.10	1.44	0.59 (1)	0.33 (0.02, 5.57)	0.444

Table 4: Clinical factors associated with tuberculosis relapse in Pasir Puteh district by simple logistic regression (n=148).

Factors	β	S.E.	Wald statistics (df)	Crude OR (95% CI)	p-value
Diabetes status					
No				1.00	
Yes	1.07	0.41	6.73 (1)	2.92 (1.30, 6.57)	0.009
Cigarette smoking					
No				1.00	
Yes	1.01	0.39	6.69 (1)	2.73 (1.28, 5.86)	0.010
HIV status					
No				1.00	
Yes	0.75	0.53	2.04 (1)	2.12 (0.76, 5.95)	0.153
BCG scar					
Present				1.00	
Absent	0.12	0.49	0.06 (1)	1.13 (0.43, 2.95)	0.803
Tuberculosis (TB) category					
Extrapulmonary TB (EPTB)				1.00	
Pulmonary TB	0.53	0.67	0.64 (1)	1.70 (0.46, 6.26)	0.424
Pulmonary TB with EPTB	1.61	1.18	1.85 (1)	5.00 (0.49, 50.83)	0.174
Chest radiographic findings					
No lesion				1.00	
Minimal lesion	0.19	0.72	0.07 (1)	1.21 (0.30, 4.96)	0.789
Moderately advanced lesion	-0.88	0.79	1.24 (1)	0.42 (0.09, 1.95)	0.265
Far advanced lesion	0.58	1.14	0.26 (1)	1.78 (0.19, 16.49)	0.613

Table 5: Factors associated with tuberculosis relapse in Pasir Puteh district by multiple logistic regression (n=148).

Factors	β	S.E.	Wald statistics (df)	Adjusted OR (95% CI)	p-value
Diabetes status					
No				1.00	
Yes	1.09	0.45	5.80 (1)	2.98 (1.23, 7.26)	0.016*
Cigarette smoking					
No				1.00	
Yes	1.45	0.52	7.79 (1)	4.27 (1.54, 11.85)	0.005*
HIV status					
No				1.00	
Yes	0.91	0.63	2.05 (1)	2.48 (0.72, 8.58)	0.152
Gender					
Female				1.00	
Male	-0.23	0.60	0.15 (1)	0.79 (0.25, 2.57)	0.703
Tuberculosis (TB) category					
Extrapulmonary TB (EPTB)				1.00	
Pulmonary TB	0.31	0.71	0.19 (1)	1.37 (0.34, 5.54)	0.662
Pulmonary TB with EPTB	1.18	1.32	0.80 (1)	3.25 (0.25, 42.77)	0.370

*p-value <0.05

No multicollinearity and no interaction found.

Hosmer Lemeshow test, p-value=0.274

Classification table 75% correctly classified.

Area under Receiver Operating Characteristics (ROC) curve was 77.3%.

4.0 Discussion

The prevalence of tuberculosis relapse in Pasir Puteh district was 8.4% (95%CI: 0.06, 0.11) which is substantially higher than the prevalence of tuberculosis relapse of national level (4.71%) (Ministry of Health, 2016). For regional comparison, the prevalence of tuberculosis relapse in the Philippines, a country with high burden of tuberculosis was merely 4.7% (Vianzon, Garfin, Lagos, & Belen, 2013), which is similar with Malaysia's prevalence of tuberculosis relapse. Vietnam even showed lower prevalence of tuberculosis relapse (1.34%) (Lan *et al.*, 2003), as compared to finding in our study. Hence, it justified the need for our inferential study to be done to delineate the risk factors for tuberculosis relapse in the setting of Pasir Puteh district.

For cross-country comparison purpose, majority of tuberculosis relapse in our study occurred in adult age group, similar with finding in a Vietnamese study (Lan *et al.*, 2003). A study by Thomas *et al.* (2005) in India reported similar finding with our study in term of male gender as the larger proportion for tuberculosis relapse cases. As for level of education, our study reported higher proportion of tuberculosis relapse among patients with secondary level of education, as compared to a study conducted in India which reported patients with higher level of education were more prone to get tuberculosis relapse (Thomas *et al.*, 2005). Similar to our finding in term of employment, a study in Hong Kong also reported that majority of tuberculosis relapse patients were of unemployed individuals (53.1%) (Chang *et al.*, 2004).

For clinical factors, we found that majority of our tuberculosis relapse patients were non-diabetic, similar to finding in a Taiwanese case-control study (66%) (Lee *et al.*, 2014). Moreover, the Taiwanese study also exhibited similar finding with our study in term of cigarette smoking patients as the majority of tuberculosis relapse cases (Lee *et al.*, 2014). In contrast to our study finding, a study in San Francisco reported higher proportion of HIV positive individuals acquires tuberculosis relapse (Nahid *et al.*, 2007). As for BCG scar, there is no well-published study to show association between absence of BCG scar and tuberculosis relapse. However, as tuberculosis relapse is one of tuberculosis unfavourable outcomes, Awang, Husain, and Abdullah (2019a) reported that majority of patient with unfavourable tuberculosis outcome had BCG scar, similar to our current study finding. Meanwhile, Crampin *et al.* (2010) found that majority of tuberculosis relapse cases in Malawi were of pulmonary form of tuberculosis which was congruent to our study finding. As for chest radiographic findings, a study in Canada and the United States of America reported patients with significant changes of chest radiograph such as cavitation were the substantial contributing proportion for tuberculosis relapse (Jasmer *et al.*, 2004), in contrast to our study which reported patients with minimal lesion on chest radiograph as the main share for tuberculosis relapse.

Our multivariable analysis showed that diabetic patients were more likely to get tuberculosis relapse as compared to non-diabetic patients. This finding is congruent to many other studies worldwide reporting significant association between diabetes with tuberculosis relapse (Jiménez-Corona *et al.*, 2013; Lee *et al.*, 2014; Zhang, Xiao, & Sugawara, 2009). Previous animal studies found that diabetic hosts had higher bacterial load at infection and were more likely to have dysfunction in Th1 cell immunity and delayed responses to tuberculosis infection (Vallerskog,

Martens, & Kornfeld, 2010). A past human study also reported impaired chemotaxis of neutrophil to TB pathogens among diabetic patients (Delamaire *et al.*, 1997). All these previous studies suggested that diabetes mellitus is an important factor for tuberculosis relapse either through re-infection by new strain of tuberculosis or through reactivation of prior tuberculosis infection.

We also found a significant association between cigarette smoking with tuberculosis relapse, when other confounders were adjusted. This finding is in line with studies in the Spain, Iran and Taiwan where cigarette smokers were more likely to get tuberculosis relapse as compared to non-smokers (Millet *et al.*, 2009; Moosazadeh, Bahrapour, Nasehi, & Khanjani, 2015; Yen *et al.*, 2014). The mechanism proposed to explain this association is the neutralisation of the tumour necrosis factor α (TNF- α) in the pulmonary macrophages by substances of the tobacco, leaving the patient more susceptible to a progressive development of disease from latent tuberculosis infection. The reduction in the TNF- α in this group may be explained by the high level of iron in the bronchoalveolar macrophages of smokers. This mechanism may also be behind the development of relapse (d'Arc Lyra Batista, de Fátima Pessoa Militão de Albuquerque, de Alencar Ximenes, & Rodrigues, 2008; Yen *et al.*, 2014).

There were some limitations in this study. We did not include some other important variables in the study such as high risk behaviours (alcohol intake and illicit drug use); socio-economic backgrounds such as residential condition (overcrowding, poorly ventilated housing) and income; tuberculosis medications regime; and also nutritional status as these variables are either not available or were not completely recorded in the online registry. For future studies, it is recommended this kind of study to be done at larger setting such as state or national level to better represent the Malaysian population.

5.0 Conclusion and recommendation

In summary, tuberculosis relapse is quite prevalent in the district of Pasir Puteh as the prevalence was 8.4%, substantially higher than the national prevalence. Diabetes mellitus and cigarette smoking were the significant associated factors for tuberculosis relapse in the district of Pasir Puteh, Kelantan. As those factors can easily be screened at primary healthcare facilities, we should attempt to control the factors particularly in patients with newly diagnosed tuberculosis to prevent these patients from getting tuberculosis relapse in the future.

To reduce the risk of relapse, we recommend effective measures of smoking cessation in tuberculosis control programmes, as recommended by the World Health Organization Stop Tuberculosis Strategy. Quit Smoking Clinic should be empowered at all healthcare facilities in Malaysia to help clients to quit smoking. Besides, a comprehensive strategy and approach should be established by the Malaysian government to improve prevention, treatment, and control of diabetes as an urgent response to this growing chronic disease. It requires a well-established functioning multidisciplinary team comprising of endocrinologists, family medicine specialists,

diabetes nurse educators, dietitians, pharmacists, and others such as podiatrists are needed to provide broad ranging services in order to establish a successful diabetes care model in Malaysian healthcare facilities.

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Declaration

The authors declare that this manuscript has never been published in any other journal.

Authors contribution

Author 1: conceptualization, data analysis, manuscript drafting, editing and review.

Author 2,3,4,5: information gathering, data entry, technical and logistic supports.

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