PULMONARY TUBERCULOSIS AND TOBACCO SMOKING: FACTORS ASSOCIATED WITH ITS MORTALITY IN TERENGGANU FROM 2012 UNTIL 2016

By
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF SYMBOLS AND ABBREVIATION

AFB	acid-fast bacilli
aOR	Adjusted odd ratio
BCG	Bacillus Calmette-Guerin
CI	Confidence interval
DM	Diabetes mellitus
DOTS	Directly Observed Treatment, Short-course
HIV	Human Immunodeficiency Virus
LR	Likelihood Ratio
MDG	Millennium Development Goal
MOH	Ministry of Health
PTB	Pulmonary tuberculosis
ROC	Receiver Operating Characteristics
SDG	Sustainable Development Goal
TB	Tuberculosis
TBIS	Tuberculosis Information System
WHO	World Health Organization
=	equal to
<	less than
%	percent
*	asterix

ABSTRAK

TB PULMONARI DAN MEROKOK: FAKTOR-FAKTOR PENYUMBANG KEPADA KEMATIAN DI TERENGGANU DARI 2012 HINGGA 2016

Latar belakang: Tuberculosis (TB) adalah antara masalah utama di dalam sektor kesihatan awam. Kadar insiden kes TB telah menurun dengan kadar yang perlahan secara global. Namun, di Terengganu, kadar insiden kes TB telah meningkat dari tahun 2009 hingga ke tahun 2012 dan tidak menunjukkan penurunan sehingga tahun 2016. Di Malaysia, bilangan perokok telah menurun berdasarkan Kajian Morbiditi dan Kesihatan Kebangsaan 2006 dan 2011. Namun, masih kurang kajian yang telah dilakukan untuk mengkaji faktor-faktor kematian perokok dalam2w kalangan pesakit TB pulmonari.

Objektif: Kajian ini bertujuan untuk mengenalpasti kadar kematian dan faktor-faktor yang berkaitan dengan kematian dalam kalangan perokok dan pesakit TB pulmonari di Terengganu dalam tahun 2012 hingga 2016.

Metodologi: Kajian kes kontrol ini telah dijalankan pada bulan April 2018 dengan menggunakan data sekunder dari Sistem Maklumat TB (*MyTB*) dan dari borang TBIS10A1. Peratusan kematian pesakit TB pulmonari yang merokok dikira berdasarkan data yang diperoleh dari Sistem MyTB secara menyeluruh. Persampelan secara rawak menggunakan komputer telah digunakan untuk mendapatkan 185 kes dan 740 kontrol dari bilangan tersebut. Kes adalah pesakit TB pulmonari yang merokok yang telah meninggal semasa menjalani rawatan TB. Kontrol adalah pesakit

TB pulmonari yang telah sembuh atau sempurna rawatan. Analisa deskriptif, regresi logisitic mudah dan berganda digunakan untuk menganalisa data menggunakan SPSS versi 24.

Keputusan: Kadar kematian pesakit TB pulmonari yang merokok adalah antara 14.8% dan 23.4%. Daripada 925 kes, purata umur pesakit adalah 48.6 tahun bagi kes dan 45.8 tahun bagi kontrol. Majoriti pesakit adalah lelaki, berketurunan Melayu, tinggal di luar bandar, mempunyai tahap pendidikan pada Tingkatan 4 dan ke atas, tidak mempunyai pendapatan bulanan yang tetap, tidak mempunyai penyakit diabetes, mendapat imunisasi BCG, dikesan secara pasif, didiagnosa sebagai TB pulmonari sapuan kahak positif dan adalah kes baru TB. Hampir separuh bilangan kes adalah HIV positif dan majoriti daripada kontrol adalah HIV negatif. Lebih separuh bilangan kes mempunyai keputusan x-ray dada yang separa teruk manakala lebih separuh kontrol mempunyai keputusan minimal. Usia *(aOR=1.04; 95% CI: 1.03, 1.05; p<0.001)* dan HIV positif *(aOR=9.51; 95% CI: 6.08, 14.88; p<0.001)* adalah faktor yang menyumbang kepada kematian TB pulmonari yang merokok. Manakala, penghidap diabetes *(aOR=0.58; 95% CI:0.35, 0.94; p=0.028)* dan yang berpendapatan lebih RM 940 *(aOR=0.38; 95% CI: 0.20, 0.73; p=0.003)* mempunyai kebarangkalian yang lebih rendah untuk kematian.

Kesimpulan: Kadar peratusan perokok dalam kalangan pesakit TB pulmonari menurun dalam kadar yang perlahan dari tahun 2012 hingga tahun 2016. Pesakit yang mempunyai faktor yang menyumbang kepada kematian tinggi pesakit TB pulmonari yang merokok perlu diberi perhatian di dalam program kawalan TB kebangsaan bagi mengurangkan kadar kematian.

KATA KUNCI: tuberkulosis, kematian, merokok, umur, diabetis melitus, HIV positif, pendapatan bulanan.

ABSTRACT

PULMONARY TUBERCULOSIS AND TOBACCO SMOKING: FACTORS ASSOCIATED WITH ITS MORTALITY IN TERENGGANU FROM 2012 UNTIL 2016

Background: Tuberculosis (TB) is a major public health problem. The incidence of TB cases is reducing at a slower rate than expected as well as the TB death rate worldwide. However, the incidence of TB cases in Terengganu had increased from the year of 2009 until 2012 and had been fluctuating until 2016. The number of tobacco smoker in Malaysia had reduced accordingly. Little studies have been done to analyse tobacco smoker with pulmonary tuberculosis (PTB) patients as the subjects to determine the factors for its mortality.

Objective: The aim of this study was to determine the proportion of mortality and the associated factor with mortality among PTB patients who smoke tobacco in Terengganu from 2012 until 2016.

Methodology: A case-control study was conducted in April 2018 using a secondary data from MyTB System and from TBIS10A1 forms. The proportion of mortality among PTB and tobacco smoker were calculated based on the data extracted from MyTB System with no sampling method applied. Simple random sampling using a computer software was applied to select 185 cases and 740 controls. A case is the PTB patient who smokes tobacco smoking who had died during the TB treatment. A control is the PTB patient who smokes tobacco and was cured or completed TB treatment.

Descriptive analysis, simple and multiple logistic regression were used for analysis using SPSS version 24.

Result: The proportion of mortality among PTB and tobacco smoking patients were between 14.8% and 23.4%. From the 925 selected respondents, the mean age for the case was 48.6 years (14.87) and the mean age for control was 45.8 years (15.32). Majority of the respondents are male, Malays, from a rural area, have the educational status of Form 4 and above, had no fixed monthly income, non-diabetic, received BCG immunisation, detected passively, diagnosed as PTB smear positive and were new cases. Almost half of the cases were HIV positive and the majority of the controls were HIV negative. More than half of the cases had chest x-ray results of moderately advanced while more than half of the controls had chest x-rays results of minimal. Age (aOR=1.04; 95% CI: 1.03, 1.05; $p<0.001$) and HIV positive (aOR=9.51; 95% CI: 6.08, 14.88; $p<0.001$) were the factors contributing to mortality among PTB and tobacco smoking patients. Meanwhile, diabetic patient (aOR=0.58; 95% CI: 0.35, 0.94; $p=0.028$) and having monthly income of more than RM 930 (aOR=0.38; 95% CI: 0.20, 0.73; $p=0.003$) had less risk for mortality.

Conclusion: The proportion of mortality among PTB patients who smoke tobacco is reducing slowly from 2012 until 2016. Factors associated with mortality among PTB patients who smoke tobacco should be focus more in the national TB control programme in order to reduce the mortality risk.

KEY WORDS: tuberculosis, mortality, smoking, age, diabetes mellitus, HIV positive, monthly income.

CHAPTER 1

INTRODUCTION

1.1 Background

Tuberculosis (TB) is an infectious disease that is caused by *Mycobacterium tuberculosis*. It remains as one of the public health issue globally. A patient is considered as a TB patient once the laboratory investigations showed bacteriologically confirmed for TB or is diagnosed as a TB patient by a physician (World Health Organization, 2004). Commonly, a patient who has active TB disease will present with symptoms of having prolonged cough more than two weeks, haemoptysis, and any chest symptoms such as chest pain and shortness of breath (World Health Organization, 2011). TB may infect any organs in the body but mostly will infect the lung resulting in pulmonary TB (PTB) (World Health Organization, 2018).

Once diagnosed with TB, the patient will have to undergo treatment under Directly Observed Treatment, Short-course (DOTS) strategy. DOTS strategy was introduced by Dr Karel Styblo for TB patients in Tanzania. In fact, a lot of patients had been benefited from the strategy all around the world after it was introduced in the 1970s. Using the five key components of DOTS strategy, the cure rate for TB patients has improved and increased. Other than that, the success of DOTS strategy has reduced the number of TB death especially in low-developing countries (World Health Organization, 1999).

In the 1990s, there has been a rising of TB cases worldwide. In the countries located in European Region and Regions of the Americas, the transmission of TB in the middle and high-income countries has been due to the increased immigration activity throughout the world. The high prevalence of Human Immunodeficiency Virus (HIV) cases in low developing countries contributes to the transmission of TB cases among the population. TB and smoking have also been responsible for the increase transmission of TB infection to other people on the population confounded by poverty, overcrowding and alcohol usage, causing a high incidence of TB cases world widely (van Zyl Smit *et al.*, 2010). This increases the risk for TB mortality among the population.

The increasing trend of TB cases in the 1990s has prompted for an effective control programme. In order to reduce the number of TB incidence in the world, Stop TB Strategy has been introduced in 1995. Stop TB Strategy has set a goal of detecting at least 70% of a patient diagnosed with PTB smear positive by 2005 to then reduce the number of TB cases by 50% compared to the number of TB cases by 1995 (World Health Organization, 2006).

Thus, the world had achieved the target of Millennium Development Goal (MDG) 6 which is to combat HIV and Acquired Immunodeficiency Syndrome, malaria and other diseases. The number of TB cases has reduced by years since 2014 after the introduction of expanded DOTS strategy but it reduces slower than targeted (World Health Organization, 2014b). In 2016, there are still about 10.4 million people were diagnosed with TB. TB has also been one of the top 10 causes of death worldwide. The reclining of TB incidence each year is only by two percent each year while the

aim of reducing the rate that we aim is about four to five percents for each year (World Health Organization, 2017b).

With the introduction of Sustainable Development Goal (SDG) in 2015 following MDG, the number of TB incidence has been monitored periodically. The progression of the achievements has been reported for people to know that the action is been ongoing and will be continuously aiming to control TB infection (United Nation, 2017). Each of the countries will have to report back to the United Nation regarding the achievement of infectious disease control mainly of TB and HIV infection.

Hence, to ensure that the control of TB infection has been continuing aggressively to stop the transmission of TB in the world, SDG has set a target of reduced number of TB death by 90% in 2030. In 2015, "The End TB Strategy" has been introduced which aim to further reduce the number of TB death by 95% in 2035 (World Health Organization, 2015).

1.2 Global TB burden

Since United Nation has set a goal of reduction for TB cases globally to be achieved via MDG in 2015, the incidence of TB cases has decreased from estimated 13.7 million people to 10.6 million people in 2016 (World Health Organization, 2009; World Health Organization, 2017a). The TB infection has spread to almost all around the world. The World Health Organization (WHO) African Region are affected the most by the diseases with an estimated incidence rate of 343 per 100 000 population in 2005 (Dye and Borgdorff, 2008).

Before 2005, the incidence rate of TB cases in the African Region has been increased due to the increasing number of HIV infected people living in the countries. TB infection is easily spread through people who have low immunity due to HIV infection giving rise to the prevalence of TB cases in the region. As TB has been considered as one of the major public health issues that should be controlled, improvements to the screening method and case detection have been conducted, thus giving rise to the number of incidence cases, especially in the African Region. As well as in African region, before 2005, there is also increasing trend of TB cases in Eastern Europe region (Dye and Borgdorff, 2008). This may be due to increasing immigration activity of people coming from high TB burden disease (World Health Organization, 2017a).

However, in 2016, there has been a shift of trend in TB cases worldwide. Predominantly, WHO South-East Asia region has the highest number of incident cases followed by WHO African region, WHO Western Pacific Region, WHO Eastern Mediterranean Region, WHO European Region and WHO Region of the Americas. Globally, the average rate of declining was 1.4% with WHO European Region has the fastest rate of declining number of TB cases (World Health Organization, 2017a).

A similar trend has also been described by Murray *et al.* (2014). The incidence for TB cases has been constantly increasing before 2005 and then started to reduce slowly until 2013. The prevalence of TB cases has been reducing since the year of 2000 until 2013. The trend portrayed that the target that is set by the Stop TB Strategy was achieved even though it is in a slower rate than expected (World Health Organization, 2006). Since TB has been recognized as one of the major public health issues, the control programme has been constantly aimed at reducing the mortality as to in-line with the MDG and now with SDG (World Health Organization, 2017b). Murray *et al.*

(2014) also described that the African Region and Southern Asia has the highest incidence and prevalence of TB cases compared to other regions.

1.3 TB burden in Malaysia

Malaysia is one of the countries situated in South-East Asia. In 1958, Malaysia which previously known as Malaya has joined the WHO Western Pacific Region. Since joining the WHO, Malaysia has actively improved its health services in order to achieve the target set by WHO such as MDGs and now towards achieving the target that already being outlined by SDG.

Despite the reducing in the trend of TB cases portrayed by the WHO Western Pacific Region, the number of TB cases in Malaysia has been increasing gradually since the year 2004 (Terengganu State Health Department, 2018). During this year, Ministry of Health (MOH), Malaysia has intensified active case finding in order to detect all possible TB cases in our country, so that we can treat them earlier before they get any complications from the disease.

In 2014, there is around 24,711 number of new cases diagnosed with TB (Ministry of Health Malaysia, 2015b). In 2015, TB remains the highest mortality rate among all the communicable diseases occurred (Ministry of Health Malaysia, 2016). The annual death rate for TB has been reducing from 1990 until 2013 with the latest reducing rate of 2.48 (95% Confidence Interval (CI): -4.41, -1.15) (Murray *et al.*, 2014).

Murray *et al.* (2014) also described that Malaysia has the moderate burden of TB disease where the incidence of TB cases is 65 to 116 cases per 100,000 population. Meanwhile, the death rate for TB cases was also high in South Africa countries and some countries in Asia. Malaysia is grouped as a country with moderate TB death rate which is 6.9 to 18 death per 100,000 population (Murray *et al.*, 2014).

1.4 TB burden in Terengganu

Terengganu is one of the states situated in East coast area of Peninsular Malaysia. It covers around 12,959 kilometres square, bounded by Kelantan in north and northwest, Pahang in the south and South China Sea in the east. The number of population in Terengganu is approximately 1.18 million people in 2016 (Department of Statistics Malaysia, 2018b).

The number of all TB cases in Terengganu has been increasing from 2004 until 2009. However, since 2009 until now, the number of all TB cases has been fluctuating. The average number of all TB cases was 720 patients per year. The same goes for the number of PTB smear positive in Terengganu, the number of patients fluctuates since 2008 until now (Terengganu State Health Department, 2016).

In 2013, Terengganu has the second highest death rate of TB patients in Peninsular Malaysia after Perlis (Ministry of Health Malaysia, 2013; Ministry of Health Malaysia, 2014; Ministry of Health Malaysia, 2015b; Ministry of Health Malaysia, 2016; Ministry of Health Malaysia, 2017) even though Terengganu is not the state with the highest TB incidence compared to Sabah, Labuan and Kuala Lumpur. The death rate for Terengganu in 2013 was 7.01 per 100,000 population following after Perlis with

8.29 per 100,000 population. From 2012 until now, the death rate of TB cases in Terengganu has been fluctuating almost with the similar trend with its incidence of TB cases.

1.5 Smoking and Tuberculosis

Previously, the relationship between tobacco smoking and TB was not clearly known. A lot of studies has been conducted to see the effect of tobacco smoking on TB infection since then. One study reported that tobacco smoking reduces the immunological response of the body to prevent TB infection. At the same time, tobacco smoking may also disrupt the ciliary function of the lung tissue, thus these resulting in high risk for people who smoke tobacco to have TB infection (van Zyl Smit *et al.*, 2010).

Tobacco smoking has been highly associated with TB infection (Slama *et al.*, 2007; van Zyl Smit *et al.*, 2010). About 0.8 million of TB cases has been contributed by tobacco smoking worldwide (World Health Organization, 2017a). There is a reduction in a number of tobacco smoker in the Malaysian population. The prevalence for current tobacco smoker based on Global Adult Tobacco Survey 2011 is 23.1% while the prevalence found in National Health and Morbidity Survey 2015 is 22.8% (Ministry of Health Malaysia, 2015c; World Health Organization, 2012). The prevalence of TB patient who ever smoked is higher compared to non-smoker group with 54.22% (Awaisu *et al.*, 2010). Based on 13 studies done, the risk of getting TB disease for tobacco smoker is 2.33 (adjusted for age and sex) (Bates *et al.*, 2007).

It was estimated that there will be 101 million deaths due to TB occurred by 2050 if nothing has been done to reduce the prevalence of smoking. The model also suggests that there will be a delay of 35 years in order to achieve the SDG target (Basu *et al.*, 2011). Tobacco smoking is associated with prolonging the duration of treatment with an adjusted odd ratio (aOR) of 2.43 (95% CI 1.18 to 5.03) (Atif *et al.*, 2014a). Tobacco smoking reduces the rate of successful treatment in a TB patient even after controlling the other factors such as baseline characteristics, comorbidities, the extent of lung disease, lung cavitation and bacteriology (Leung *et al.*, 2004).

1.6 Rationale of the study

The number of tobacco smoker is decreasing in Malaysia but the prevalence of PTB patients who smoke tobacco simultaneously is increasing in our population and showed no sign of reducing (Ministry of Health Malaysia, 2013; Ministry of Health Malaysia, 2014; Ministry of Health Malaysia, 2015b; Ministry of Health Malaysia, 2016; Ministry of Health Malaysia, 2017). Therefore, there is a need to study for the PTB patient who smokes tobacco as the subject. However, no study was found to determine mortality rate in and the risk factor for mortality among PTB patients who smokes tobacco, especially in Terengganu.

Even though limited study had been conducted in determining the prevalence of tobacco smoker among PTB patients especially in Malaysia, none of the studies had focused on the trend of PTB patients who smoke tobacco over a duration of time (Atif *et al.*, 2014b; Liew *et al.*, 2015). Analysing the trend of prevalence for PTB patients who smoke tobacco is important because it reflects the current intervention plan that was done for them to encourage and help them to quit smoking. Therefore, we can

review back and revise a new strategy to deliver health education for them. It also helps the government to focus more on the specific group when delivering the messages.

Since 2014, MOH Malaysia had started to strengthen assessing tobacco smokers among TB patients when they come for DOTS every day for anti-TB treatment. Ideally, we would want to intervene with all smokers who had been diagnosed with TB and encourage to change their lifestyle to no smoking. This is in conjunction with a number of studies that had mentioned how smoking affected treatment outcome and may increase the risk for mortality among TB patients (Bates *et al.*, 2007). However, because of the high number of TB patients attended the session, the healthcare provider may want to focus more on patients with specific factors which may contribute more to poor treatment outcome. Thus, targeting this group of patients may increase the chance for successful treatment, thus reducing the mortality rate among TB patients much higher and much faster according to the target set by SDG (United Nation, 2017).

1.7 Research Questions

We have been asking two questions regarding tobacco smoking behaviour, TB patients and mortality.

i. What is the proportion of mortality among PTB patients who smokes tobacco in Terengganu between the years 2012 and 2016?
ii. What are the associated factors for mortality among PTB patients who smokes tobacco in Terengganu between the years 2012 and 2016?

1.8 Hypothesis

As the first research question is regarding the prevalence of mortality among PTB patients who smoke tobacco in Terengganu, no hypothesis can be deducted for the questions. For the second research objective, the hypothesis is age, gender, ethnicity, place of living, diabetes mellitus (DM) status, HIV status, immunisation status, category of TB and type of PTB smear are associated with mortality among PTB patients who smokes tobacco in Terengganu between 2012 and 2016.

1.9 Objectives

1.9.1. General objective

The general objective of this study was to determine the mortality rate and factors associated with mortality among PTB patients who smokes tobacco in Terengganu between 2012 and 2016.

1.9.2 Specific objectives

There were two specific objectives for this study answering both the research questions that has been asked previously.

i. To determine the proportion of mortality among PTB patients who smoke tobacco in Terengganu between 2012 and 2016.
ii. To determine the risk factors associated with mortality among PTB patients who smoke tobacco in Terengganu between 2012 and 2016.

CHAPTER 2

LITERATURE REVIEW

2.1 The proportion of PTB patients who smoke tobacco

The reported proportion of overall tobacco smoker among TB patients which included current smoker and ex-smoker in Kuala Lumpur Federal Territory and Penang was 54.2% in 2010 (Awaisu *et al.*, 2010). More specific report regarding the proportion of TB and tobacco smoking among patients treated in *Hospital Pulau Pinang*, *Hospital Universiti Sains Malaysia* and University Malaya Medical Centre was 39.0% (Syed Suleiman *et al.*, 2012). Furthermore, Atif *et al.* (2014a) reported that 52.1% of TB patients were tobacco smoker in *Hospital Pulau Pinang*. These reports highlighted the high proportion of TB and tobacco smoking patients in Malaysian population.

The high prevalence of PTB patients who smoke tobacco could be due to the high number of male TB patients in the population. Based on National Health and Morbidity Survey 2015, 43.0% of current smoker were among male while only 1.4% of female population were smoker (Ministry of Health, 2015). Therefore, with the majority of male patients were diagnosed with TB, we would expect that the prevalence of tobacco smoker will be high.

2.2 The proportion of mortality among tobacco smoker and TB

Few studies and reports claimed a closed relationship between TB patients who smokes tobacco and mortality rate. The current report claimed the mortality rate in TB patient who smokes was 11.8% in 2015 in Malaysia (Liew *et al.*, 2015). The mortality rate of tobacco smoker and diagnosed with TB in Iran was slightly high as compared to Malaysia which was 16.8% (Alavi-Naini *et al.*, 2013). A different study highlighted the lower tendency for favourable outcome among PTB patients who smoke tobacco with an odd ratio of 0.8 (95% CI: 0.36, 1.79) (Dujaili *et al.*, 2015).

Atif *et al.* (2014b) had reported that smoking is highly associated with poor treatment outcome for TB due to its impact on the overall quality of life after diagnosed with TB disease. Smoking had been described to be able to reduce patient's immunity thus resulting in an unfavourable outcome. Furthermore, smoker, especially among male TB patients was more likely to be non-compliance with TB medication, therefore, will more likely be resulting in TB death among tobacco smokers (Lavigne *et al.*, 2006).

2.3 Associated factors for TB mortality

As for the associated factors of TB mortality, limited study had been found to report on the associated factors for mortality among PTB patients who smoke tobacco. In contrast with that, a lot of other studies had been conducted to determine the factors associated with TB mortality comparing between tobacco smoker and non-tobacco smoker. Few studies had actually reported the associated factors for mortality among PTB patients who smoke tobacco as reported by Lin *et al*. (2014) and Reed *et al*. (2013).

However, Lin *et al*. (2014) only reported the association of age and gender with TB-related mortality and non-TB-related mortality while Reed *et al.* (2013) only determine the association between the number of cigarettes smoked per day among diabetic smoker who died and alive. No other study was found to determine the association of different factors with mortality among PTB patients who smoke tobacco.

2.3.1 Age

Older age was considered a factor for increased mortality among TB patients with concurrent DM. A study in Taiwan reported the mean age for mortality related to TB disease was 75 years old (Lin *et al*., 2014). Furthermore, Syed Suleiman *et al*. (2012) had described that elderly with TB and DM had a greater risk for mortality with an aOR of 12.3 compared to a patient with TB or DM alone. For each increasing of 1 year of age, the risk for mortality is 1.03 (95% CI: 1.01, 1,06; p=0.036) (Atif *et al*., 2014a).

2.3.2 Gender

Both studies in Malaysia and in Penang showed that male TB patients had a higher risk of mortality compared to female. The crude odd ratio for TB mortality among male was 1.68 and the aOR was 1.22 as described by Liew *et al*. (2015). Another study claimed gender was not significantly associated with mortality as the aOR for TB mortality among male in Penang was 1.79 (95% CI: 0.64, 4.98; p=0.268) but was significantly associated with unfavourable outcomes (aOR=2.15, 95% CI: 1.20, 3.87; p=0.10) (Atif *et al*., 2014a). In South Korean, male was also found to be significantly higher hazard ratio compare to female with hazard ratio of 1.58 (95% CI:

1.27, 1.97) in male and hazard ratio of 1.55 (95% CI: 1.00, 2.41) in female after adjusting to age and age-squared (Jee *et al.*, 2009). Liew *et al.* (2015) had described that the reason why male had higher mortality rate compared to female was because of the compliancy to anti-TB treatment was less in male compared to female.

2.3.3 Ethnicity

Ethnicity also played a role in determining the favourable or the unfavourable outcome in TB patients. Different ethnic was reported to have a significant relationship with TB mortality.

Ismail and Bulgiba (2013b) carried out a study among TB patients in Institute of Respiratory Medicine, Malaysia and found that Malay has the higher risk of mortality with adjusted hazard ratio of 4.48 (95% CI: 1.73, 11.64; p=0.002) among TB/HIV patient compared to another ethnicity besides Chinese and Indian. Their findings in line with a study conducted by Liew *et al.* (2015) which showed non-Malay ethnicity (Chinese, Indigenous West Malaysia, Indigenous Sabah and others) were significantly less associated with mortality with the lower aOR for mortality ranged from 0.72 to 0.97 (p-value ranging from <0.001 to 0.012). A similar study of determining the factors for unsuccessful outcome among patients with TB/HIV also reported the percentage of the population studied who have unsuccessful outcome are the highest among Malay and Indian patients (Ismail and Bulgiba, 2013a).

This reflects back to the National TB Programme that has been established in Malaysia. Lower risk for mortality among indigenous people in Malaysia has been linked to the successful of TB programme in the area where a greater coverage for

DOTS has been seen among the indigenous TB patients. Furthermore, they have less co-morbidities compared to Malay people which reduces the risk of dying among the indigenous patient (Liew *et al.*, 2015).

However, based on a study reported by Dooley *et al.* (2009), there was no association between TB treatment outcome for death between the ethnicity of the Asian, Black or White population in 2005. Another study from United States of America reported that the risk for TB death was significantly higher among non-citizen population compared to United States citizen (Rodwell *et al.*, 2008).

2.3.4 Place of living

There are very limited studies measured the relationship between an urban or rural area with TB mortality. In Malaysia, rural has higher risk of mortality with crude odd ratio of 1.26 (95% CI: 1.15, 1.38; $p<0.001$) and aOR of 1.25 (95% CI: 1.08, 1.44; $p=0.002$) (Liew *et al*., 2015). From a study reported in 2016, overcrowding area and a lower socioeconomic region that could be refer to the rural area were associated with increased incidence of TB cases (Krieger *et al*., 2016), thus may also lead to increased risk for mortality among the population. Contradict to Liew *et al*. (2015) and Krieger *et al*. (2016), Kliiman and Altraja (2009) reported that urban was significantly associated with poorer TB treatment outcome among multi-drug resistance and extensive-drug resistance among Estonia population. This could be due to a lot of other factors such as work that may interfere with the accessibility for the patient to take their TB medication as required.

2.3.5 Diabetes Mellitus

Many studies found TB patient with DM as their co-morbid had a higher risk of mortality. A recent study that was conducted in patient who has TB and DM showed high mortality rate as compared to patient with TB alone with the crude odd ratio of 1.34 (95% CI: 1.19, 1.50; $p<0.001$) but the aOR was 1.02 (95% CI: 0.85, 1.19; $p=0.942$) (Liew *et al*., 2015). Another published study in 2014 reported that DM was not significantly associated with mortality (aOR=2.02, 95% CI: 0.97, 4.18; $p=0.060$) but was significantly associated with prolonged TB treatment (aOR=6.80, 95% CI: 2.98, 15.51, $p<0.001$) in Penang (Atif *et al.*, 2014a). Reed *et al.* (2013) reported based on a study conducted in the Republic of Korea that the adjusted hazard ratio for TB/DM patient who smoked more than one pack per day was 4.25 (95% CI: 1.06, 17.08; $p=0.004$).

Patient with DM is said to be more compliance to anti-TB treatment especially when they had been compliance with the diabetic treatment that they had been receiving before the diagnosis of TB, thus diabetic patient were more adhered to medication and reduces the risk for mortality (Liew *et al.*, 2015). However, Atif *et al.* (2014a) reported that due to the effect of diabetes to the immune system of TB patients, patient will more likely to have prolonged TB treatment compared to non-diabetic patient.

2.3.6 HIV status

HIV is already known to weaken immune status and worsened the disease progression in TB patient. It was reported as significantly associated with mortality among TB patients in Malaysia with the aOR for mortality of patient with TB and HIV

co-infection was 8.76 (95% CI: 7.24, 10.58; $p<0.001$) (Liew *et al*., 2015). However, in San Francisco, Nahid *et al*. (2011) reported the adjusted hazard ratio for TB and HIV co-infection patient was 2.57 (95% CI: 1.17, 5.64; $p=0.02$), much less as compared to Malaysia. A similar finding was reported based on a study in Estonia where TB patient with HIV positive has higher mortality rate compared to HIV negative patient (aOR=10.16, 95% CI: 1.17, 88.84; $p=0.04$) (Kliiman and Altraja, 2009).

2.3.7 BCG immunisation status

All new born babies are given Bacillus Calmette–Guérin (BCG) vaccination globally including in Malaysia. The role of immunisation for TB has been questionable nowadays. However, patient without BCG scar had been reported to have higher risk for TB mortality with crude odd ratio of 1.14 (95% CI: 1.02, 1.26; $p=0.016$) and the aOR of 1.13 (95% CI: 0.94, 1.35; $p=0.185$) (Liew *et al*., 2015). Aaby *et al.* (2011) reported based on a study in six districts in Guinea Bassau, the mortality rate for infant received BCG vaccination was not significantly reduced, but the actual number of mortality was reduced as the BCG vaccination may help to boost infant's immunity throughout neonatal period. Based on a systematic review done by Mangtani *et al*. (2013), BCG vaccination given after birth has significant protection against TB disease during childhood, thus may reduce the risk for mortality among those who were vaccinated.

2.3.8 Category of TB: New/Retreatment

Each time patient is diagnosed with TB, he or she will be categorized accordingly whether the patient is a new case of TB or a retreated patient. In Malaysia, a patient who had TB previously had a higher risk for mortality with a crude odd ratio of 1.48 (95% CI: 1.26, 1.74; $p<0.001$) but with the aOR of 1.02 (95% CI: 0.81, 1.30; $p=0.850$) (Liew *et al*., 2015). This result is similar with a study done in Iran where a patient who had TB previously had the higher tendency for mortality compared to a patient who was newly diagnosed with TB with an aOR of 6.8 (95% CI: 2.22, 21.3; $p=0.017$) (Alavi-Naini *et al.*, 2013). This could be due to the fact that the patient had been given treatment before and was more likely to develop drug resistance to anti-TB treatment, thus may lead to unfavourable treatment outcome among TB patients (Kliiman and Altraja, 2009).

However, a study done in Hong Kong found that the risk for mortality was higher in newly diagnosed patient compared to retreatment TB patient with odd ratio of 2.61 (95% CI: 1.80, 3.80; $p<0.001$) in newly diagnosed TB patient compared to 2.48 (95% CI: 1.04, 5.89; $p=0.04$) in retreated TB patient (Leung *et al.*, 2004).

2.3.9 Type of PTB smear: Positive/Negative

PTB patient can be diagnosed with PTB smear positive or PTB smear negative. A different type of smear was reported to have different impact on mortality rate. A study conducted in Malaysia showed PTB smear positive patients were higher risk for mortality with a crude odd ratio of 1.33 (95% CI: 1.20, 1.47; $p<0.001$) as compared to those smear negative (Liew *et al*., 2015). In South Africa, TB/HIV patient with sputum

smear positive noted to have less risk for mortality with a crude hazard ratio of 0.73 (95% CI: 0.63, 0.84; $p<0.001$) (Pepper *et al*., 2015). Meanwhile, contradicts with the previous study, a study conducted in Iran reported TB patient with sputum smear positive showed the much higher risk of mortality with an aOR of 13.4 (95% CI: 6.8, 33.6; $p=0.002$) (Alavi-Naini *et al.*, 2013).

2.4 Conceptual framework

Figure 2.1 illustrates factors that may associate with mortality as one of the treatment outcomes for PTB patients who smoke tobacco. The highlighted factors are written in bold and marked with asterisk (*) were not included in this study. All PTB patients who are tobacco smoker will be marked with smoking status as "Yes". Along the course of completing the treatment for TB, age, gender, ethnicity, place of living, educational status, monthly income, marital status, DM status, HIV status, number of presenting symptoms, sputum AFB reading, chest x-ray, MDR-TB status, case detection, case category, type of PTB, immunisation status, places of treatment and whether DOTS was been given by a healthcare provider are associated with the success of the treatment or can also interpret as a lot of factors might be contributed to the patient to die during the course of treatment for TB.

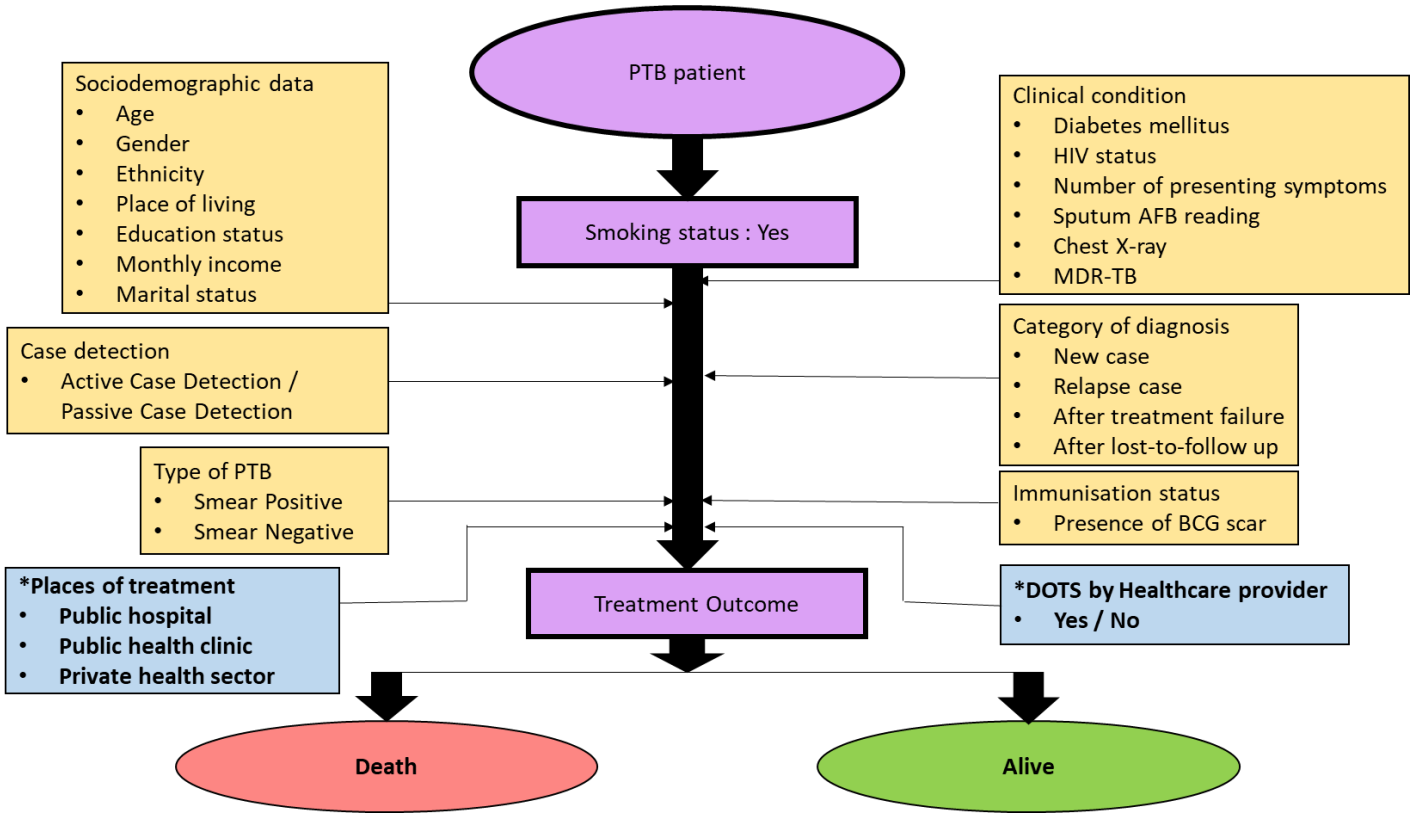

Figure 2.1: The conceptual framework explaining the factors associated with mortality among PTB patients who smoke tobacco

CHAPTER 3

METHODOLOGY

3.1 Research design

For objective 1, a retrospective cohort study was conducted to determine the prevalence of PTB patients who smokes tobacco died in Terengganu from the year 2012 to 2016. A case-control study was conducted in order to answer the second objective.

3.2 The study area, time & duration

The study area was in Terengganu which is one of the states in Malaysia. It is situated in East coast area of Peninsular Malaysia covering around 12,959 kilometres square. At its north, it is bounded by Kelantan and at its south, it is covered by Pahang. The South China Sea is located in the east. There are eight districts in Terengganu which are Kuala Terengganu as the capital city of Terengganu, Kuala Nerus, Marang, Hulu Terengganu, Besut, Setiu, Dungun and Kemaman.

The number of population in Terengganu is approximately 1.18 million people in 2016 increasing to 1.21 million people in 2017. The number of male population is higher compared to female which is 620,000 of male and 590,000 of female in 2017 (Department of Statistics Malaysia, 2018b). In 2016, the crude death rate among

Terengganu population is 5.8 per 1,000 population (Department of Statistics Malaysia, 2018c).

About 60% of the Terengganu people aged below 30 years old with the age group of 20 to 24 years old had the highest number of population in 2017. In terms of ethnicity, 94.4% of its population are Malays. There are only 2.4% of the Chinese population in Terengganu, 0.2% Indians and 0.3% is other Malaysian ethnicity. Only 2.8% of the population in Terengganu is non-citizen (Department of Statistics Malaysia, 2018a).

The duration of the study was between 8th of April 2018 after ethical approval for National Medical Research Register and Universiti Sains Malaysia Research Ethics Committee (Human) were obtained until 30th of April 2018 with a total of three weeks.

Figure 3.1: Map showing the location of Terengganu in Peninsular Malaysia (smaller box on the upper right) and the districts in Terengganu

3.3 Reference population

The reference population for this study was patient who were diagnosed as PTB and smokes tobacco. Thus, the result of this study can be inferred to this reference population that present in Terengganu.

3.4 Source population

The source population for this study was patients who were diagnosed as PTB patient and smokes tobacco registered in the TB Information System (TBIS) in Terengganu in 2012 until 2016. Those patients who were registered in TBIS from the year 2012 to 2016 were chosen in order to ensure patients had completed their course of TB treatment. Thus, the treatment outcome of all TB patients already completed and stated in the TBIS.

3.5 Sampling frame

For selection of a case, the cases were PTB patients who smoke tobacco, died and registered in Terengganu in the MyTB System in the year 2012 until 2016, fulfilled the inclusion criteria, and had already ruled out the exclusion criteria.

For selection of a control, the controls were PTB patients who smoke tobacco registered in Terengganu in the MyTB System in the year 2012 until 2016, alive at the end of TB treatment, fulfilled the inclusion criteria, and had already ruled out the exclusion criteria.

3.6 Data criteria

For case, the inclusion criteria were patients registered as PTB and reported as tobacco smoker with the treatment outcome of died. The exclusion criterion for the case was being non-Malaysian.