DEVELOPMENT AND EFFECTIVENESS OF TUBERCULOSIS RISK SCORE FOR SMOKERS IN TUBERCULOSIS SCREENING UPTAKE AND DETECTION

DR TENGKU NOOR FARHANA BINTI TENGKU KHALID

Dissertation submitted in partial fulfilment of the requirements for the degree of Doctor of Public Health (Epidemiology)

MARCH 2022

ACKNOWLEDGEMENT

Bismillahirrahmanirrahim.

In the name of Allah, the Most Gracious, the Most Merciful. Alhamdulillah, I have completed my thesis write-up for my study titled ‘Development and Effectiveness of Tuberculosis Risk Score Among Smokers in Tuberculosis Screening and Uptake’. These past two years have been very hectic for my friends and me as we have been tested with the pandemic of COVID-19 since March 2020. All the proposed plans had been delayed. However, we still managed to complete this study and the write-up within the allocated period.

First and foremost, I would like to convey my appreciation to my main supervisor, Prof Madya Dr Wan Mohd Zahiruddin bin Wan Mohammad for always giving me support and helping me complete this study. Since my first year in DrPH studies, he has been my academic supervisor and research supervisor. Without his help, I might not be able to come out with the study proposal. Furthermore, he had been supervising my write-up until the last minute. Thank you so much, Prof Zahir.

I would like to thank my co-supervisor, Prof Madya Dr Nik Rosmawati binti Nik Husain and my co-researcher, Dr Razan binti Abd Samat. It might be difficult for me to conduct my study without their support, especially in community and health clinic settings. They also helped me to provide the TB experts involved in this study. Thank you so much, Prof Nik Ros and Dr Razan.

Not to forget, my friends also known as my comrades in DrPH. We have been together ever since we enrolled ourselves for MPH study in 2017. A lot of happy memories were created when we were together. I hope our friendship will continue even after we complete our studies in USM and are posted anywhere in Malaysia.

Last but not least, to my husband, Dr Ahmad Shamil bin Semanat, and my children, Ahmad Ilham, Ahmad Ikram and Alia Insyirah, no words can describe how much I appreciate your thoughtfulness and patience with me throughout my studies at USM. We have been apart a few times to give me space for my examinations and COVID-19, but you always show me your love and support for whatever I do. I love you so much.

Finally, I am grateful to whoever is reading my thesis. I hope you can appreciate the effort I have put into completing this study. With that, thank you and enjoy your reading.

TABLE OF CONTENTS

ACKNOWLEDGEMENT ii
TABLE OF CONTENTS iv
LIST OF TABLES vi
LIST OF FIGURES vii
LIST OF APPENDICES viii
LIST OF ABBREVIATIONS ix
LIST OF SYMBOLS x
ABSTRAK xi
ABSTRACT xiv
CHAPTER 1 1
INTRODUCTION 1
1.1 Background 1
1.2 Global burden of TB 1
1.3 The burden of TB disease in Malaysia 2
1.4 Low TB case detection in Malaysia 4
1.5 Type of TB screening method 4
1.6 Current TB screening programme in Malaysia 6
1.7 Problem statement 12
1.8 Study rationale 13
1.9 Research questions 14
1.10 Objectives 15
1.11 Hypothesis 16
CHAPTER 2 18
LITERATURE REVIEW 18
2.1 TB and smokers 18
2.2 Predictors for TB disease 19
2.3 Current screening programme 27
2.4 Predictive modelling for risk score 32
2.5 Conceptual framework 35
CHAPTER 3 39

METHODOLOGY 39
3.1 Overview 39
3.2 Phase 1: Factor associated with TB disease among smoker in Bachok, Kelantan 39
3.3 Phase 2: Development and validation of TB Risk Score for Smokers (TBRSS) 51
3.4 Phase 3: The effectiveness of TBRSS in TB screening uptake and detection 59
3.5 Summary of the study flowchart 71
3.6 Ethical considerations 73
CHAPTER 4 76
RESULT 76
4.1 Phase 1 76
4.2 Phase 2 85
4.3 Phase 3 95
CHAPTER 5 103
DISCUSSION 103
5.1 Characteristics of the smoker population 103
5.2 Predictors of TB disease 104
5.3 Development and validation of TBRSS 108
5.4 Effectiveness of TBRSS 116
5.5 Strengths and limitations 120
CHAPTER 6 125
CONCLUSION 125
6.1 Future studies 126
REFERENCES 128
APPENDICES 140

LIST OF TABLES

Table 3.1: The estimated sample size needed for Phase 1 study according to each factor 44
Table 3.2: The sample size calculation for objective 7 63
Table 3.3: The formula used for analysis in objective 5 68
Table 4.1: Clinical characteristics of participants in Bachok, Kelantan for Phase 1 (n = 159) 79
Table 4.2: The predictors for TB disease among smokers in Bachok, Kelantan (n = 159) 81
Table 4.3: To determine the score for each of the variables 86
Table 4.4: The characteristic of experts for content validation of TBRSS (n=8) 92
Table 4.5: The factor-content validation index (F-CVI) for each factor and scale-level content validity index, averaging method (S-CVI/Ave) of the respondents (n=8) 92
Table 4.6: The characteristic of experts for face validation of TBRSS (n=20) 94
Table 4.7: The face validity index (FVI) for each factor (n=20) 94
Table 4.8: The characteristics of participants in the Phase 3 study (n=156) 96
Table 4.9: The number of participants with different risks of TB disease and their TB status 98

LIST OF FIGURES

Figure 1.1: The number of TB cases reported and incidence rate in Malaysia 2012-2019 3
Figure 1.2: Achievement of high-risk group TB screening, Malaysia in 2015 7
Figure 1.3: Investigations for Contact Tracing in Adults 9
Figure 2.1: The conceptual framework for risk factors for population to have TB disease. 36
Figure 2.2: The conceptual framework on how the smoker undergo for TB screening and diagnostic test for TB 38
Figure 3.1: Maps of Bachok district and Kelantan state 42
Figure 3.2: The study flowchart for Phase 1 50
Figure 3.3: The study flowchart for Phase 2 59
Figure 3.4: The formula for diagnostic study 61
Figure 3.5: The single proportion formula 62
Figure 3.6: The study flowchart for Phase 3 70
Figure 3.7: Summary of the study flowchart for this study 72
Figure 4.1: The Receiver Operating Characteristics (ROC) curve for the final multiple logistic regression analysis model 84
Figure 4.2: The sensitivity-specificity curve to determine the cut-off point for TBRSS 87
Figure 4.3: The derived risk score based on multiple logistic regression analysis 88
Figure 4.4: The algorithm to determine the risk for TB disease using decision tree classification 90
Figure 4.5: The percentage of participants attending health clinics for diagnostic tests after being screened with TBRSS according to different duration in days (n = 156) 100
Figure 4.6: The number of patients screened for TB disease before and after intervention according to weeks. 102

LIST OF APPENDICES

Appendix	Document
A	Proforma checklist for Phase 1
B	Proforma checklist for Phase 2a
C	Proforma checklist for Phase 2b
D	The developed and validated Tuberculosis Risk Score for Smoker (TBRSS) form (Malay version)
E	Patient Information Sheet and Consent Form (Malay & English version) for Phase 1
F	Patient Information Sheet and Consent Form (Malay & English version) for Phase 2a
G	Patient Information Sheet and Consent Form (Malay & English version) for Phase 2b
H	Patient Information Sheet and Consent Form (Malay & English version) for Phase 3
I	Ethical approval letter from Human Research Ethics Committee (JEPeM) USM
J	Ethical approval letter from National Medical Research Register (NMRR) / Medical Research & Ethics Committee (MREC), MOH Malaysia
K	Example of TBIS101A file
L	TBIS102A record
M	TBIS10A-1 form
N	TBIS10A-3 form

LIST OF ABBREVIATIONS

AFB	Acid Fast-Bacilli
AUC	area under the curve
BCG	*bacille Calmette-Guerin*
BMI	body mass index
CCRC	cure and care rehabilitation centre
CXR	chest X-ray
COPD	chronic obstructive pulmonary disease
F-CVI	factor-level content validity index
FVI	face validity index
HCW	health care worker
HIV	human immunodeficiency virus
HR	hazard ratio
IGRA	Interferon Gamma Release Assay
JKNK	Kelantan State Health Department
KBM	Quit Smoking Clinic
MOH	Ministry of Health
NPV	negative predictive value
OR	odds ratio
PPV	positive predictive value
S-CVI/Ave	scale-level content validity index, averaging method
SD	standard deviation
SDG	Sustainable Development Goal
SPSS	Statistical Package for Social Studies
TB	tuberculosis
TBIS	Tuberculosis Information System
TBRSS	Tuberculosis Risk Score for Smokers
TST	Tuberculin skin test
USM	Universiti Sains Malaysia
WHO	World Health Organization

LIST OF SYMBOLS

<	less than
>	more than
=	equal to
X	times
α	alpha
β	beta
%	percentage
:	ratio

ABSTRAK

PEMBENTUKAN DAN KEBERKESANAN PEMARKAHAN RISIKO PENYAKIT TUBERKULOSIS DI KALANGAN PEROKOK DALAM MENINGKATKAN SARINGAN DAN PENGESANAN KES TUBERKULOSIS

Latarbelakang: Tuberkulosis (TB) merupakan salah satu penyakit berjangkit yang utama di dunia. Perokok adalah berisiko tinggi untuk penyakit TB. Masih banyak kes TB yang belum ditemui, terutamanya di kalangan perokok.

Objektif: Untuk menentukan faktor-faktor yang menyumbang kepada penyakit TB di kalangan perokok, merangka, mengesahkan dan menilai keberkesanan Pemarkahan Risiko Penyakit Tuberkulosis di Kalangan Perokok (TBRSS) di Bachok, Kelantan.

Kaedah: Kajian ini mengandungi tiga fasa. Kajian kes-kontrol melibatkan 159 orang pesakit TB dan bukan pesakit TB. Status perokok mereka, sama ada perokok aktif, bekas perokok atau perokok pasif diketahui dan mereka berumur 18 tahun dan ke atas. Pesakit-pesakit ditemubual menggunakan proforma (45 item). Regresi logistik mudah dan berganda telah digunapakai untuk menganalisa data-data tersebut. Semasa di fasa 2, permarkahan risiko dirangka berdasarkan regresi logistic berganda dan klasifikasi pokok keputusan. Kajian validasi kandungan melibatkan lapan pakar TB. Nilai-nilai indeks pengesahan-kandungan factor (F-CVI) dan indeks purata kepada indeks pengesahan kandungan pada level skala (S-CVI/Ave) diperolehi. Dua puluh petugas kesihatan di klinik-klinik kesihatan dipilih untuk kajian pengesahan

pemuka dan nilai-nilai indeks pengesahan pemuka (FVI) diperolehi. Kajian kuasi-ekperimen melibatkan 156 orang peserta berumur 18 tahun dan ke atas yang mana status perokok mereka diketahui dan mereka disaring menggunakan TBRSS. Pecahan pesakit yang menjalani saringan dan ujian diagnosa pada hari yang berbeza dicatat. Bilangan perokok yang disaring dengan TB sebelum dan selepas TBRSS diimplementasi dicatat. Perbezaan antara garisan regresi dan nilai R^2 diperolehi berdasarkan analisa siri-siri masa tergendala.

Keputusan: Dalam kajian fasa 1, kebanyakan pesakit adalah lelaki dan mempunyai median umur lebih 40 tahun. Pesakit-pesakit terdiri daripada pecahan bilangan perokok aktif, bekas perokok dan perokok pasif yang berbeza-beza. Hampir semua pesakit tidak pernah mendapat penyakit TB sebelum ini. Lebih daripada separuh pesakit mempunyai batuk dan berkahak, tidak berpeluh malam, tiada sakit dada dan tiada batuk berdarah. Median tempoh masa untuk symptom TB ialah 30 hari untuk kes dan tujuh hari untuk kontrol. Empat pembolehubah didapati berkaitan secara signifika dengan penyakit TB: status perokok, berpeluh malam, kurang berat badan secara signifika dan tempoh masa symptom TB. Dari itu, dua pemarkahan risiko dirangka. Pakar-pakar memberi nilai-nilai F-CVI dan S-CVI/Ave 0.83 dan ke atas, manakala petugas kesihatan memberi nilai-nilai FVI 0.88 dan ke atas. Pakar-pakar TB memilih pemarkahan risiko berdasarkan regresi logistic berganda sebagai TBRSS. Di fasa 3, ketepatan TBRSS adalah 20.5% dengan nilai sensitiviti 80.0% dan nilai kekhususan 18.5%. Nilai jangkaan positif adalah 3.1% dan nilai jangkaan negative adalah 96.6%. Kebanyakan peserta (87.2%) menjalani ujian diagnosa pada hari yang sama dengan saringan. Garisan regresi menjadi bertambah baik dengan nilai R^2 berubah dari 0.064 kepada 0.160 selepas intervensi.

Konklusi: TBRSS adalah kaedah saringan TB yang baru dirangka dan telah divalidasi. Ia berkesan meningkatkan bilangan saringan TB dalam populasi perokok. Masih banyak kajian diperlukan untuk terus menilai kegunaan TBRSS.

Kata kunci: Tuberkulosis, kaedah saringan, keberkesanan, rangka, validasi

ABSTRACT

DEVELOPMENT AND EFFECTIVENESS OF TUBERCULOSIS RISK SCORE FOR SMOKERS IN TUBERCULOSIS SCREENING UPTAKE AND DETECTION

Background: Tuberculosis (TB) remained one of the major infectious diseases worldwide. Smokers are considered as high-risk for TB disease. Many TB cases are still undetected, especially among the smoker population.

Objective: To determine the factors associated with TB diseases among the smoker population, developing, validating, and evaluating the effectiveness of the Tuberculosis Risk Score for Smoker (TBRSS) in Bachok, Kelantan.

Method: This study consists of three phases. The case-control study in phase 1 consists of 159 patients comparing patients with TB and those without the disease. Their smoking status was either active, ex- or passive smokers aged 18 years and above. The patients were interviewed using proforma (45 items). Simple and multiple logistic regressions were applied to analyse the data. In Phase 2, the risk score was derived from multiple logistic regression or decision tree classification analysis. The content validation study involved eight TB experts. Values were obtained for factor content-validity index (F-CVI) and scale-level content validity index, averaging index (S-CVI/Ave). Twenty healthcare workers (HCWs) in health clinics were selected for the face validation study and face validity index (FVI) values were obtained. The quasi-experimental study in phase 3 involved 156

participants 18 years and above known for their smoking status screened with TBRSS. The proportion of patients who underwent screening and diagnostic tests at different dates was noted. The number of smokers screened before and after implementing the TBRSS was noted. The difference between the regression line and R^2 before and after were obtained based on interrupted time series analysis.

Results: In the Phase 1 study, most participants are male with a median age of more than 40 years. The patients consisted of a mixed number of active, ex- and passive smokers. Almost all patients never had TB before. More than half of the patients had cough with sputum, did not have night sweat, no chest pain and no haemoptysis. The median duration of TB symptoms is 30 days for the cases and seven days for the controls. Four variables were significantly associated with TB disease: smoking status, presence of night sweat, significant weight loss and duration of TB symptoms. From that, two risk scores developed. The experts gave the F-CVI and S-CVI/Ave values of 0.83 and above, and the HCWs gave the FVI values of equal or more than 0.88. The TB experts chose the risk score derived from multiple logistic regression as the TBRSS. In the Phase 3 study, the accuracy of the TBRSS is 20.5%, with a sensitivity value of 80.0% and specificity value of 18.5%. The positive predictive value is 3.1% and the negative predictive value is 96.6%. Most participants (87.2%) had their diagnostic tests done on the same day with screening. The regression line improved with the R^2 value changing from 0.064 to 0.160 during the intervention

Conclusion: The TBRSS is a validated newly developed TB screening tool. It effectively increases the number of TB screenings among the smoker population. More studies need to be conducted to evaluate the usefulness of the TBRSS further.

Keywords: Tuberculosis, screening tool, effectiveness, development, validation

CHAPTER 1

INTRODUCTION

1.1 Background

Tuberculosis (TB) has remained one of the significant public health issues globally. In 2017, about 10 million people were diagnosed with TB worldwide. The number of TB incidence is declining each year, but the rate of decline was slower than expected. The World Health Organization (WHO) had set an expectation of four to five percent of declining rate each year, but the report of declining rate was only two percent each year (WHO, 2018). Because the rate of TB incidence is crucial, it has been monitored by the Sustainable Development Goal (SDG) under SDG 3: Good Health and Well Being. SDG has set the goal of ending the epidemic of TB diseases by 2030 (United Nation, 2016). To achieve the target set by SDG, the WHO had implemented the End TB Strategy, where the target was set to reduce the number of TB incidence by 90% in 2035 (WHO, 2015).

1.2 Global burden of TB

The majority of TB incidence cases were high in the Southern Africa region, South Asia region and the Southeast Asia region. About 90% of the cases were adults. Out of all the TB cases worldwide, two-third of the TB cases were in these eight countries: 27% were in India, about nine percent from Indonesia, less than 10% were

in the Philippines, TB cases in Pakistan were about five percent, Nigeria accounted nearly for four percent while Bangladesh and South Africa had four percent and three percent of TB cases respectively. The WHO European region and WHO region of America only had about six percent cases out of all TB cases globally (WHO, 2018).

1.3 The burden of TB disease in Malaysia

In Malaysia, the number of TB incidence is still high. The trend of TB incidence rate in Malaysia increased from 2012 until 2019 (Ministry of Health (MOH) Malaysia, 2013, 2014, 2015a, 2016a, 2017, 2018, 2019, 2020). This increasing trend (Figure 1.1) had alerted the health authorities to improve the current national TB prevention and control program into a better program to counter this issue. Kelantan, one of the states located on the east coast of Peninsular Malaysia, is among the top five states with the highest incidence rate among states in Peninsular Malaysia (MOH Malaysia, 2019).

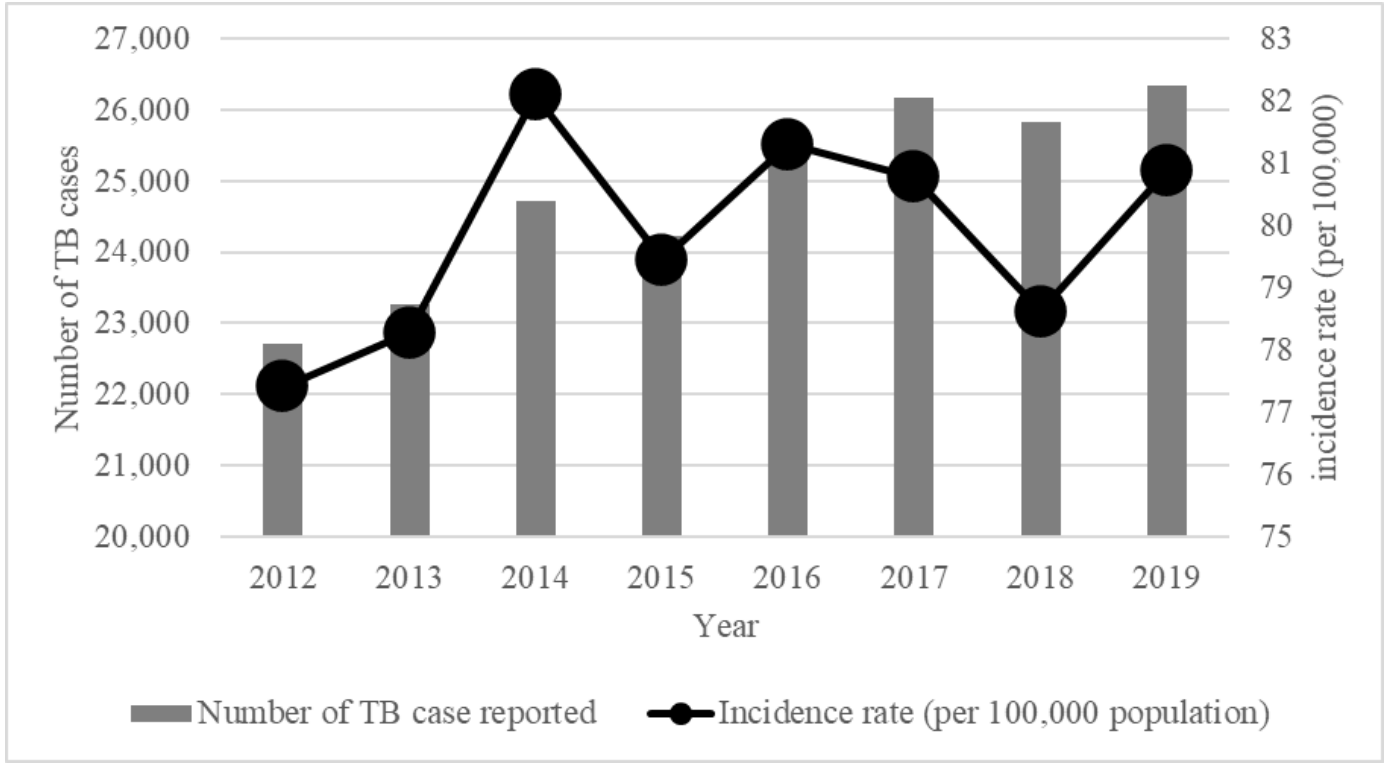


Figure 1.1: The number of TB cases reported and incidence rate in Malaysia 2012-2019 (MOH Malaysia, 2013, 2014, 2015a, 2016a, 2017, 2018, 2019, 2020)

1.4 Low TB case detection in Malaysia

Even though many programs have been implemented to detect TB cases, many remain undetected. The WHO reported that approximately 3.6 million TB cases were not detected worldwide (WHO, 2015). The MOH also reported in 2016 that about 6000 cases of TB disease were still not found and diagnosed as TB cases (MOH Malaysia, 2016b). Therefore, as a response to this problem, the WHO had advocated a systematic screening of TB cases in the community as one of the strategies to combat TB disease. By implementing this screening method, we can also reduce the complications that the TB cases might encounter and minimize TB transmission by shortening the duration of TB infectiousness within the community (WHO, 2013b).

1.5 Type of TB screening method

The WHO has introduced two methods of screening for active TB disease. Both methods have advantages and disadvantages. Therefore, health authorities need to weigh the benefits and risks of these methods before screening population.

One of the methods is by using symptomatic screening. Using this screening method, the health care worker (HCW) will interview the person for any symptoms suggestive of TB diseases such as cough, fever, chest pain, unexplained weight loss, night sweats, or haemoptysis. The duration of each symptom will also be asked during the interview (WHO, 2013).

Chest X-ray (CXR) is widely used as one of the screening methods for TB disease. The WHO recommends that this method be used as the second test to screen a patient for active TB disease. It requires a patient to go to the radiology centre to get an X-ray for his upper thorax region. The images of the CXR can be printed using film or copied into a compact disc. From these images, we can detect any abnormalities present in the lung that might indicate the presence of TB disease (MOH Malaysia *et al.*, 2012; WHO, 2013).

Other than screening for active TB disease, tuberculin skin test (TST) and Interferon Gamma Release Assay (IGRA) test have also been used as screening methods. However, these tests can only detect patients with TB infection but cannot differentiate those with TB disease. Mantoux test is one of the commonly used TST in Malaysia. It is done by injecting 1 millilitre (ml) of the tuberculin unit into the lower arm's skin, either left or right arm. After 48 hours to 72 hours, the reaction is recorded based on the diameter of the induration, which is the palpable, hardened area of the skin surrounding the injection site. In routine practice, more than 10mm diameter is recorded as TST positive (MOH Malaysia *et al.*, 2012).

The IGRA test is one of the newest screening methods that has been implemented worldwide. The IGRA test is done by testing the person's blood for a TB infection. Instead of injecting the protein derivative of TB in the skin, each person needs to give 2ml of intravenous blood to the HCW before the blood needs to be centrifuged and used by the machine for testing (MOH Malaysia *et al.*, 2012). The effectiveness of the IGRA test in detecting latent TB infection among the population was compared to the standard Mantoux test. It was found that the specificity and the predictive values are better in the IGRA test than the Mantoux test (Diel *et al.*, 2011).

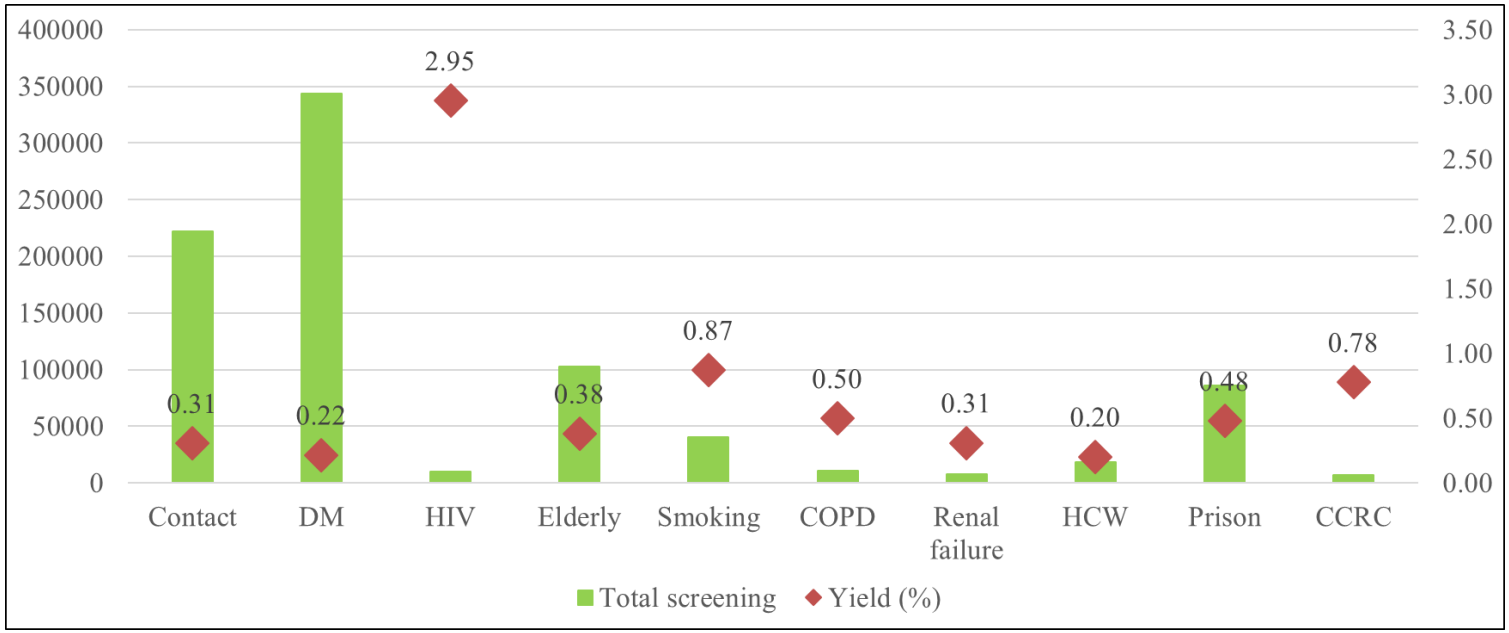
1.6 Current TB screening programme in Malaysia

To increase TB detection among the Malaysian population, a few screening programmes have been implemented since 2013. Some of the screening programmes had produced a good positive yield for TB disease among the population that had been screened. The screening programmes targeted people who are at high risk to get TB disease.

The TB contacts, diabetic patients, elderly and smokers are usually done at the health clinics and primary care centres. The patients living with human immunodeficiency virus (HIV), patients with COPD and patients with renal failure were conducted during their appointments with the specialist clinics. The HCWs usually were screened before they started their job in the new health facilities. The prisoner and those admitted to the cure and care rehabilitation centre (CCRC) was screened when they were registered to the centres (MOH Malaysia, 2016a, 2016b). The community volunteers and the non-government organization were encouraged to refer suspected TB patients to the health clinics for TB diagnostic tests through their community programs (MOH Malaysia, 2016a).

In 2015, nearly 850,000 people had been screened using symptomatic screening and CXR for TB disease (Figure 1.2). Out of these number, 0.36% of them was diagnosed as TB cases (MOH Malaysia, 2016b). Figure 1.2 shows that the percentage of yield for TB disease among smokers is the second highest after patients with HIV positive, higher than the percentage yield of TB disease among patients with DM. However, the number of people screened for TB disease is lower than a DM patient. Therefore, a higher yield percentage can be expected if the

number of smokers screened for TB disease increases.

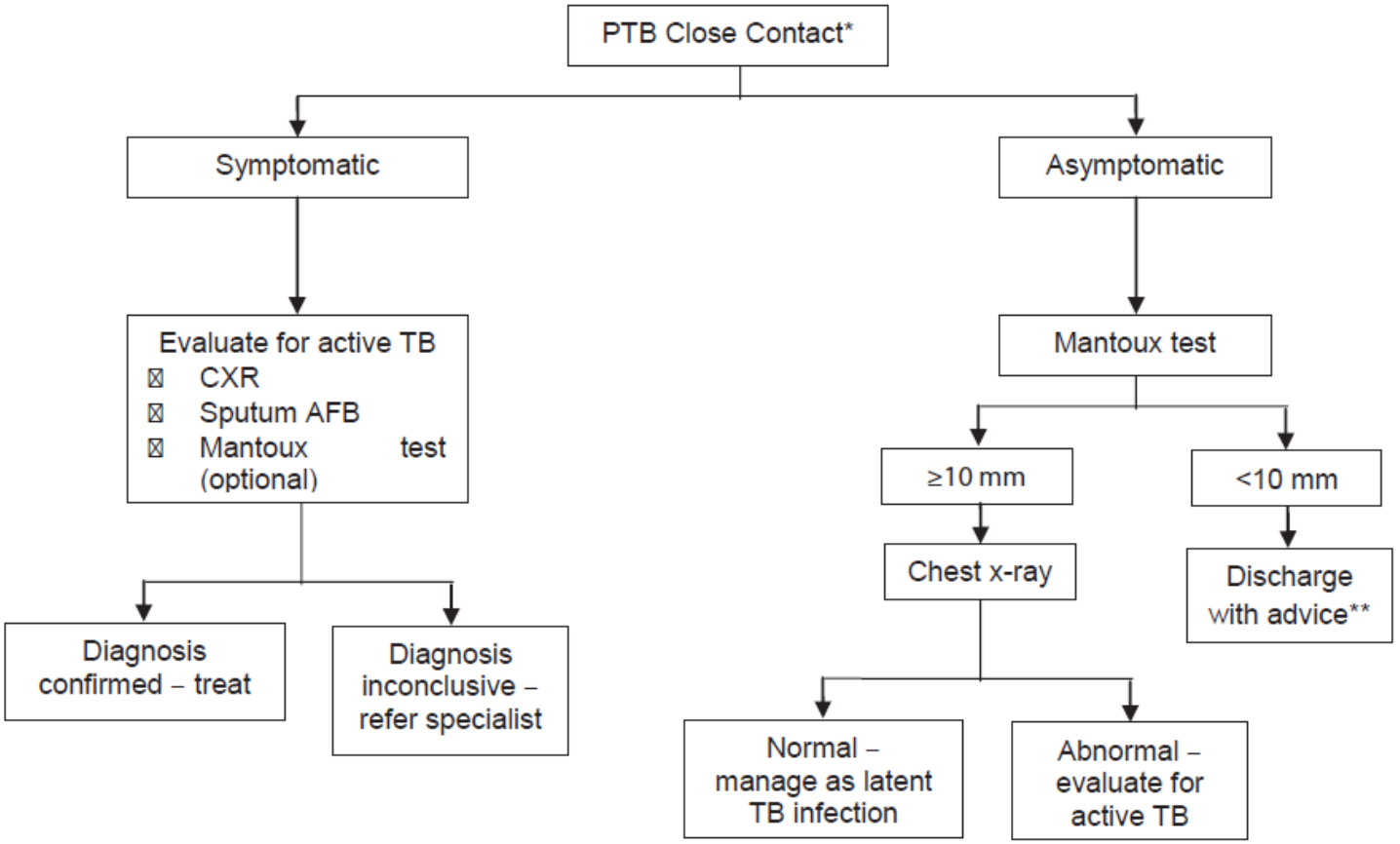


CCRC = cure and care rehabilitation centre; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HCW = healthcare worker; HIV = human immunodeficiency

Figure 1.2: Achievement of high-risk group TB screening, Malaysia in 2015 (MOH Malaysia, 2016b)

1.6.1 Contact screening

Based on the current TB screening program in Malaysia, for each TB index cases, at least 10 relatives or friends need to be identified as contacts to the TB cases. These contacts can be either close contact or social contact. The identification of the contacts is based on the history given by the index cases. The investigations that need to be done for TB contacts are listed in Figure 1.3 (MOH Malaysia *et al.*, 2012). Each of the contacts is required to be followed up at least four times: within two weeks after the contact had been identified (month 0); after three months since the first visit (month 3); after six months since the second visit (month 9); and after 12 months since the third visit (month 21) (MOH, 2016b). Contacts will undergo symptomatic screening during all the visits, Mantoux test during the first visit and CXR during the first and fourth visit.



AFB = acid-fast bacilli; CXR = chest X-ray; PTB = pulmonary TB

Figure 1.3: Investigations for Contact Tracing in Adults (MOH Malaysia *et al.*, 2012)

1.6.2 High-risk group (Other than smoker)

The patients at high risk for TB disease will have to be screened for TB disease. According to the MOH Malaysia *et al.*, (2012), diabetic patients, HIV patients, COPD patients and patients with renal failure are usually screened at least once a year for symptoms of TB disease during their appointment. These patients are also required to have their CXR done at least once every two years. This guideline required those suspected of having TB diseases based on these two screening methods to provide their sputum for AFB test (MOH Malaysia, 2014b, 2016c).

Evidence has shown that being elderly may increase the risk of TB disease (Lin *et al.*, 2009). Thus, those living in the institution for the elderly will be asked to be screened for TB disease at least once a year and every two years for CXR. Usually, the medical team from nearby health clinics will go to the elderly centre to screen the people living there. If CXR is required, the older people will be transported to the nearest health centre with an X-ray machine (MOH Malaysia, 2016c).

HCW is also grouped as high risk for TB disease due to the possibility of high engagement with the TB patient during their services. Thus, the MOH had come out with a guideline for the workers to be screened before and during their services which involve symptomatic screening, CXR and TST, and IGRA test if required (MOH Malaysia, 2014b).

As being prisoner and CCRC occupants increase the risk of having TB disease, a guideline has been developed to cater to both populations and how to screen them for TB disease during their times in prison and CCRC. The primary method of screening

is using symptomatic screening, followed by CXR. The TST was used to differentiate prisoner and CCRC occupants with TB infection, thus considering Isoniazid Prophylaxis Therapy to prevent TB disease (MOH Malaysia and Ministry of Home Affairs Malaysia, 2017).

1.6.3 High-risk group (Smoker)

Globally, the number of smokers kept on increasing each ear. It has reached 1.1 billion smokers worldwide in 2019, mainly active smokers. The seriousness of this issue has been reported where smoking has accounted for 7.69 million death throughout the globe (Reitsma et al., 2021). That is why the WHO had included smokers as part of the high-risk group of TB. Some countries do accept this decision to include smokers in the group. Meanwhile, others such as the Centers for Disease Control and Prevention, Atlanta still did not considered smokers as people who are more susceptible to TB disease despite the association shown in many studies (Centers for Disease Control and Prevention, 2016b; MOH Malaysia, 2016b; WHO, 2021). The WHO also reported that 0.73 million new TB cases were attributable to smoking.

In Malaysia, the only specific TB screening programme targeting smoker is among Quit Smoking Clinic (KBM) attendees. The screening is done during their appointment with the clinic. Medical doctors in charge of the clinic are trained to conduct symptomatic screening and ensure the attendees did CXR at least once every two years. Accordingly, additional screening methods will be required, such as sputum for AFB or TST (MOH Malaysia, 2016c).

However, screening only the attendees of KBM is biased and under-represented. National Health and Morbidity Survey 2015 showed that only about 10% of smokers had visited healthcare providers within 12 months (MOH Malaysia, 2015b). Sadly, in Kelantan, less than 0.1% of smokers registered for KBM (Kelantan State Health Department (JKNK), 2019), indicating that most smokers in Kelantan are not screened for TB disease.

There is a limited study done on screening among smokers. Therefore, the best method for TB screening among smokers cannot be evaluated based on studies.

1.7 Problem statement

The current screening programme had screened almost 850,000 people for TB disease. This is an excellent achievement regarding the number of TB screening uptake. However, the number of positive yields for TB disease is still low. The MOH had set a target for 1% of positive yield out of the number of people screened for TB disease. Thus, the target has not been achieved yet.

Furthermore, the chosen people for TB screening are extensive. If any of the people had one of the criteria set as a high-risk group, he needs to be screened for TB disease. This is done based on one factor only. No other assessment has been done before the patient is advised to screen for TB disease. Therefore, the MOH may require many resources to screen this broad and large eligible population for TB disease.

As for smokers, there is no systematic screening for this population to be screened for TB disease other than if he is registered with KBM. Based on the data, the majority of smokers may not be screened yet for TB disease. This requires a new systematic screening method for this population to increase the uptake of TB screening among smokers in Malaysia.

1.8 Study rationale

This study aims to develop an innovative, validated multifactorial screening system known as TBRSS that can be used to screen TB diseases among smokers. This screening system can be a new method for screening among smokers in Malaysia. It will be done by assessing the smokers based on variables identified and listed on a form. Using a risk score, the community may know their specific risk of having TB disease, which can help them understand the threat for them to get TB disease. Therefore, they will be more likely to go for a TB screening test by knowing the risk.

This screening system will only consider the sociodemographic and medical background of the patient without any investigation and invasive test required for the risk to be calculated. Therefore, it will be easier to be conducted as a replacement for other TB screening methods. Also, this screening system can be used not only by the HCWs but also by other stakeholders such as community volunteers. Patients can also use this risk score to know their risk for TB disease.

Therefore, this scoring system may help increase the number of smokers screened for TB disease and increase the probability of detecting TB cases among smokers. Compared with only screened smokers attending the KBM, we can screen the smoker at large, even outside the health facilities and in the community.

Early screening and prompt treatment are essential as secondary prevention for TB disease. This new screening system will help the healthcare provider detect the TB cases earlier, facilitate them to undergo TB diagnostic tests and give the treatment as soon as possible if they are TB positive. This action can further reduce the transmission of TB disease among the population. Also, we can reduce the complication that might occur once they have TB disease and increase the likelihood of successful TB treatment.

Finally, the new screening system can potentially reduce further the incidence rate of TB cases among the population in Malaysia in line with the target set by SDG and WHO.

1.9 Research questions

1) What are the predictive factors for TB disease among smokers?

2) Is the newly developed screening system of TB among the smoker population validated and reliable to be used in the population?

3) What is the proportion of smokers coming for a diagnostic test to detect TB disease after different days?

4) Does the risk score effectively predict a smoker of high risk or low risk for TB disease?

5) Does the newly validated screening tool increase TB screening uptake among smokers?

1.10 Objectives

1.10.1 General objective

- To develop and evaluate the effectiveness of Tuberculosis Risk Score for Smoker (TBRSS) as a screening tool among smokers in improving TB screening uptake and detection.

1.10.2 Specific objective:

a) Phase 1

1. To describe the characteristics of smokers undergone TB screening.
2. To determine the predictors for TB disease among smokers.

b) Phase 2

3. To develop a new risk score for TB screening among the smoker population named TBRSS.
4. To validate the TBRSS as a new screening tool for TB disease among the smoker population.

c) Phase 3

5. To determine the accuracy of the TBRSS in predicting TB disease

6. To determine the proportion of patients coming for a diagnostic test for TB disease after being screened using TBRSS on different days.

7. To determine the changes in TB screening uptake and TB cases detection after implementing TBRSS.

1.11 Hypothesis

a) Phase 1

1. Social history, medical history, smoking history, contact or TB history and symptom history were significantly associated with TB disease.

b) Phase 2

2. The newly developed TBRSS is a validated and reliable TB screening system to be used in the smoker population.

c) Phase 3

3. The accuracy of the TBRSS in predicting TB disease among smokers is acceptable.

4. There is an increased in proportion of patients coming for a diagnostic test for TB disease after being screened using TBRSS.

5. The trend of TB screening increases in smokers after implementation of the TBRSS.

CHAPTER 2

LITERATURE REVIEW

2.1 TB and smokers

Many studies have been conducted to determine the relationship between smoking habits and TB disease. One study had reported that smoking habit might have reduced the smoker's immunological body response to the bacteria that may have infected the lung. They also reported that the smoke from cigarettes interferes with the ciliary function of the lung tissue causing it more susceptible for *Mycobacterium tuberculosis* to invade and infect the body with TB disease (Van Zyl Smit *et al.*, 2010).

It is vital to screen smokers for TB disease within the population. By being a smoker, the risk of having TB disease is higher than a non-smoker. A meta-analysis by Bates *et al.* (2007) showed that the risk of getting TB disease by a tobacco smoker is higher by 2.33 compared to non-smoker after adjusted to age and sex of the populations.

Besides that, being a smoker affects the outcome and course of TB treatment among them once they have been diagnosed with TB disease. In Penang, smoking is highly associated with prolonging the duration of treatment among TB patients compared to TB patients who are non-smokers (adjusted odds ratio (OR) = 2.43, 95% CI: 1.18, 5.03) (Atif *et al.*, 2014). Meanwhile, in Hong Kong, the rate of successful treatment in a TB patient reduced by smoking after controlling with other factors such as

baseline characteristics, comorbidities, the extent of lung disease, lung cavitation and bacteriology (Leung *et al.*, 2004). Among TB patients in Malaysia, smoking is significantly associated with unfavourable outcomes (adjusted OR = 1.15, 95% CI: 1.03, 1.28). These show that smoking is a poor predictor for TB disease and treatment outcomes for TB patients.

The prevalence of smokers among TB patients is high compared to the non-smoker group, as documented by a study in Penang (Awaisu *et al.*, 2010). About 54% of TB patients in Penang are current smokers or ex-smokers. Throughout Malaysia in 2011, the proportion of smokers among TB patients (34.0%) is higher compared to the proportion of diabetic patients (15.4%) and HIV patients (6.6%) (Liew *et al.*, 2015). This shows how important it is to tackle the issue of the smoker for TB disease. Even so, the focus of the high-risk group is not on the smoker population. The trend of TB patients who smoke is not documented and accounted for (JKNK, 2019b).

Furthermore, Basu *et al.* (2011) used mathematical modelling. They found out that if nothing had been done for the smoking habit in the population, it is estimated that there will be 101 million excess death due to TB by 2050. The target set by SDG can only be achieved after a delay of 35 years from the current target.

2.2 Predictors for TB disease

2.2.1 Among general populations

Generally, there are many predictors reported for TB disease. Each predictor may increase or decrease the risk for TB disease if present among the population.

a) Sociodemographic

Gender does play a role in determining whether a person has a high risk or low risk for TB disease. In South Korea, a prospective cohort study was conducted among smokers. The researchers found that male patients who smoke had a higher risk of TB than females (Jee *et al.*, 2009). However, based on a survey conducted in Taiwan, there is no association between male smokers and female smokers to TB disease after being stratified to smoking status (Lin *et al.*, 2009).

Age was also found to be associated with TB disease. A 12-year follow-up study conducted in Canada found that patients with age equal and younger to 10 years old had a higher risk to develop TB disease compared to those older than 10 years old with a hazard ratio (HR) of 5.49 (95% CI: 41.6, 7.24) (Morán-Mendoza *et al.*, 2010).

Researchers also found that person's BMI also plays a role in determining the risk for TB disease among the population. This has been reported by Leung *et al.* (2004), where the increase of every 1 kg/m^2 of a person's BMI, the person had a lower risk for active TB disease with adjusted HR of 0.87 (95% CI: 0.83, 0.92). In Peru, increasing BMI value is associated with a lower risk for TB disease by 13% (95% CI: 0.83, 0.91) (Saunders *et al.*, 2017).

A limited study reported the association between marital status with TB disease. In Taiwan, univariate analysis showed an association between the marital status and active TB disease. Still, multivariate analysis showed no association between marital status of a person with active TB disease (Lin *et al.*, 2009).

People who migrated had a higher risk of developing TB disease, especially those from a country with a high burden of TB disease. The duration of living in the new country increases the risk of developing TB disease and may increase the transmission of TB disease to the other population. A review was done based on the study among the migrants. The yield for active TB diseases was meagre when screened during the arrival of the migrated country. However, the reactivation of the latent TB infection may occur after one or two years since the arrival date, which has been concerning among researchers (Pareek *et al.*, 2016). Similarly, a meta-analysis by Chan *et al.* (2017) also reported a high cumulative incidence of TB cases detected during post-migration follow up among the migrants.

Another predictor for TB disease is the type of place a person is living. In Taiwan, a study by Chan *et al.* (2014) found that child contacts residing in the high-incidence area had a higher risk for TB disease than child contacts living in the non-high incidence area (adjusted HR = 8.2, 95% CI: 3.8, 18.0).

Due to high engagement with many patients, especially TB patients during services in the health centre, HCW was associated with an increased risk of having TB disease compared to other occupations. This includes all layers of HCW, including health attendants and drivers. A meta-analysis reported that HCW had a higher risk for active TB disease than the general population (Joshi *et al.*, 2006). Another meta-analysis showed that the pooled OR for HCW to get TB disease compared to the general population is 2.94 (95% CI: 1.67, 5.19) (Uden *et al.*, 2017). Comparing each level of HCW, those who are clinical staff and engaged longer with patients had a higher risk of developing TB disease (Tudor *et al.*, 2016).

In terms of education status, univariate analysis showed that patients with an education level less than elementary school had a higher risk for active TB disease compared to a patient who completed high school with a crude OR of 6.23 (95% CI: 3.21, 12.09) (Lin *et al.*, 2009). In California, poor education lead to a higher risk for TB disease among patients discharged from the hospital (Pablos-Méndez *et al.*, 1997).

Few studies also reported a person's income as a predictor of TB disease. Lin *et al.* (2009) found that a household with a low income had a higher risk for active TB disease than a household with a higher income (crude OR = 2.10, 95% CI: 1.22, 3.62).

b) History of TB and contact

Being a contact is also a crucial predictor in determining if a person has a high risk or low risk for TB disease. A meta-analysis reported that, based on multiple studies, contacts had a 2.3% of positive yield for active TB disease (Morrison *et al.*, 2008). Saunders *et al.* (2017) found that contacts who have been exposed to an index TB case for more than six hours per week in two weeks had an increased risk of developing TB disease by 80% compared to a non-contact person (95% CI: 1.3, 2.4).

Immunisation with the BCG vaccine has been widely used in many countries globally. Malaysia has introduced the BCG vaccine to all newborns as primary prevention for TB disease. In India, a person who was not vaccinated with the BCG vaccine had a higher risk for TB infection than a person who had been vaccinated with the vaccine (Dayal *et al.*, 2018). However, a study in Ethiopia showed no association of BCG vaccination with TST reactivity (Elias *et al.*, 2016).

A person who has a history of TB disease may have a higher risk of developing another TB disease than a person who never had TB before. Smoking further increases the risk of developing recurrent TB disease by 34% (95% CI: 1.2, 1.4) (Jee *et al.*, 2009). A study in Tanzania reported that patients with a previous history of more than one episode of TB disease had a higher risk to develop recurrence TB disease compared to those who had never had TB disease before (HR = 6.2, 95% CI: 2.2, 17.7) (Said *et al.*, 2017).

c) Medical and health characteristics

It is well-known that being a diabetic patient does increase the risk of a person having TB disease, especially if the patient had poor glycaemic control of his diabetes disease. This has been reported by Lee *et al.* (2016). They found that diabetic patients with poor glycaemic control had a higher risk of developing TB disease than a non-diabetic patients with an adjusted HR of 2.21 (95% CI: 1.63, 2.99). In a meta-analysis study, Al-Rifai *et al.* (2017) showed that the risk for a diabetic patient to get active TB disease compared to non-diabetic patient ranges between 1.55 and 6.00.

Being HIV positive patient may increase the risk of developing TB disease. This is due to the suppression of the immune system by HIV itself. In South Africa, it is reported that TB incidence increased among HIV positive miners compared to HIV-negative miners with an adjusted risk ratio of 2.90 (95% CI: 2.48, 3.38) (Sonnenberg *et al.*, 2005). Another prospective study in San Francisco found that homeless with HIV positive had a higher risk for TB disease compared to homeless with HIV negative (adjusted HR = 11.0, 95% CI: 4.6, 26.5) (Moss *et al.*, 2000).

There are a lot of other diseases that may cause immunosuppression in a patient other than diabetes mellitus and HIV positive. This includes renal failure, COPD, liver disease, ischaemic heart disease and transplant patients. A retrospective matched cohort study in Barcelona compared transplant recipients with the general population. The researchers found that patients who had multiple involvements of organ transplants had a higher risk of developing TB disease than the general population (Benito *et al.*, 2015).

d) History of TB symptoms

Most screening programs use symptomatic screening as one of the primary screening methods. Researchers in South Africa reported that person who had more than one symptom had a higher risk for active TB disease compared to a person who had only one symptom presented during the screening (adjusted OR = 3.45, 95% CI: 1.83, 6.49) (Hanifa *et al.*, 2017). They also reported that in univariate analysis, HIV patients who had symptoms more than one week are more likely to have active TB disease compared to a patient who had symptoms less than one week (cure OR = 4.36, 95% CI: 1.27, 13.64). While in Southern Brazil, if a prisoner had been experiencing the symptoms for more than five weeks, the risk for active TB disease increased with a higher prevalence ratio (Valença *et al.*, 2015).

2.2.2 Among smokers

A few studies have been reported as predictors for TB disease among smokers. The study design that reported these predictors consisted of different types of study designs. However, the number of predictors reported are minimal.