VALIDATION AND EFFECTIVENESS OF A NEW SCREENING TOOL FOR PULMONARY TB DETECTION AMONG DIABETIC PATIENTS IN KELANTAN

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by

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We want to express our gratitude to Allah SWT for allowing to help us endlessly in finishing the research of Validation and Effectiveness of A New Screening Index (TBDM-PT) For TB Detection Among Diabetic Patients In Kelantan. This TBDM-PT, considered a pioneer development tool for TB screening among DM patients, can be used as an official screening tool to increase the TB detection rate among DM patients especially in primary healthcare settings.

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DECLARATION

I, Muhammad Ikhwan Bin Ismail, declare that the work presented in this thesis is originally mine. The information that has been derived from other sources is clearly indicated in the thesis.

Muhammad Ikhwan Bin Ismail

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AFB	Acid Fast-Bacilli
AUC	area under the curve
BCG	*Bacille Calmette-Guerin*
BMI	body mass index
CXR	chest X-ray
COPD	chronic obstructive pulmonary disease
DM	Diabetes Mellitus
F-CVI	factor-level content validity index
FVI	face validity index
HCW	health care worker
HIV	human immunodeficiency virus
HRG	High Risk Group
HUSM	Hospital Universiti Sains Malaysia
NPV	negative predictive value
OR	odds ratio
PPV	positive predictive value
RR	risk ratio
S-CVI/Ave	scale-level content validity index, averaging method
SD	standard deviation
SDG	Sustainable Development Goal
SPSS	Statistical Package for Social Studies
T2DM	Type 2 Diabetes Mellitus
TB	TB
TBIS	TB Information System
TBDM-PT	TB Diabetes Mellitus Predictive Tool
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

LIST OF APPENDICES

ABSTRAK

VALIDASI DAN KEBERKESANAN ALAT SARINGAN BARU BAGI SARINGAN TUBERKULOSIS PARU-PARU DI KALANGAN PESAKIT DIABETES MELLITUS DI KELANTAN

Latar Belakang: Tuberkulosis (TB) merupakan satu penyakit berjangkit yang merbahaya di seluruh dunia. Penyakit Kencing Manis (DM) meningkatkan risiko pesakit untuk dijangkiti TB sehingga empat kali ganda berbanding dengan bukan pesakit DM. Kedua-duanya adalah penyakit kronik yang boleh wujud bersama dan mempengaruhi satu sama lain dalam pelbagai cara. Dengan peningkatan pesakit DM masa ini, kadar jangkitan TB di seluruh dunia akan meningkat. Sehingga kini tiada alat saringan TB berupa borang risiko khusus bagi pesakit DM sebelum menjalani ujian diagnosa TB menyebabkan kurangnya pengesanan TB paru-paru dalam kalangan pesakit DM.

Objektif: Kajian diadakan bagi menentukan faktor-faktor yang menyumbang kepada penyakit TB paru-paru dalam kalangan pesakit DM, memformulasikan alat permarkahan saringan TB (TBDM-PT) dan mengesahkan keberkesanan pemarkahan risiko jangkitan TB dan menilai keberkesanan alat ini bagi mengesan TB dalam kalangan pesakit DM di klinik kesihatan di Kelantan.

Kaedah: Kajian ini mengandungi tiga fasa. Kajian kes kawalan bagi fasa pertama melibatkan 270 orang pesakit DM sama ada menghidap TB (n=90) dan bukan pesakit TB (n=180). Kriteria inklusi termasuk berstatus penyakit DM berumur 18 tahun ke atas dan dalam temujanji klinik kesihatan. Data-data pesakit diambil dari kad rekod pesakit DM, borang TBIA 10A-1 dan laman web Pendaftaran Diabetes Kebangsaan

(NDR) (26 item). Regresi logistik mudah dan berganda telah digunapakai untuk menganalisa data-data tersebut. Dalam fasa 2, alat saringan pemarkahan risiko, TBDM-PT dirangka berdasarkan regresi logistic berganda dan metod kawasan bawah lengkung (AUC). Kajian validasi konten melibatkan sembilan pakar dalam penyakit TB. Nilai faktor indek pengesahan konten (F-CVI) dan skala purata indeks pengesahan konten (S-CVI/Ave) diperolehi. 20 petugas kesihatan di klinik kesihatan dipilih untuk kajian validasi pemuka dan nilai indeks pengesahan pemuka (FVI) diperolehi.

Kajian Pilot melibatkan 34 pesakit DM yang telah menjalankan saringan TB di klinik kesihatan dalam jajahan Kota Bharu dalam tiga bulan sebelum dilakukan bagi menentukan prestasi diagnostik bagi TBDM-PT seperti ketepatan, sensitivity, specificity, nilai jangkaan positif (PPV) dan nilai jangkaan negative (NPV).

Kajian eksperimental kuasi bagi fasa 3 di mana Kota Bharu dipilih sebagai kumpulan intervensi, menggunakan TBDM-PT sebagai alat saringan manakala Pasir Mas sebagai kumpulan kawalan menggunakan kaedah saringan sedia ada. Pesakit disusuli selama empat bulan sehingga pesakit selesai menjalani ujian diagnosa Pulmonary TB sebagai hasil kajian primary (*primary outcome*) manakala hasil kajian sekunder (*secondary outcome*) adalah jangkitan TB laten (*LTBI*). Kadar insiden dan nisbah risiko (RR) digunakan dalam Analisa perbandingan untuk menunjukkan keberkesanan alat saringan

Keputusan: Majoriti pesakit adalah perempuan (56.7%) dan berumur 60 tahun ke atas (60.7%). Tujuh faktor (item) dikenalpasti berkait rapat secara analisa statistik dengan risiko penyakit TB; lelaki (Adj OR: (95% CI); 2.78 (1.17-6.63)), Indeks jisim badan (BMI) <23kg/m2 (Adj OR: (95% CI); 7.22 (2.74-19.04)), tempoh menghidap DM ≤ 10 tahun (Adj OR: (95% CI); 2.90 (1.13-7.39)), tiada parut BCG (Adj OR: (95%

CI);19.76 (2.98-130.9)), paras HbA1C dalam 6 bulan ≥8% (Adj OR: (95% CI);19.76 8.31 (3.28-21.05)), sejarah batuk melebihi dua minggu (Adj OR: (95% CI); 31.08 (11.64-82.98))dan sejarah demam melebihi dua minggu (Adj OR: (95% CI); 6.25 (1.15-33.99)). Sejarah kontak TB didapati berkait rapat secara klinikal dengan risiko penyakit TB melalui konsultasi bersama pakar TB dan dimasukkan sebagai item saringan sebagai risiko tinggi dalam TBDM-PT. Nilai-nilai F-CVI dan S-CVI/Ave mencapai tahap yang diterima pakai bagi validasi alat saringan yang sepatutnya. Kajian pilot menunjukkan ketepatan adalah 58.8% dengan nilai sensitivity 83%, specificiti 54%, nilai jangkaan positif (PPV) 28% dan nilai jangkaan negativ (NPV) 94%. Seramai 227 pesakit DM menjalani kajian experimental, nisbah risiko (RR) bagi pengesanan penyakit TB adalah 3.29; 95%CI (1.12,9.69), manakala pengesanan TB laten (*LTBI*) melibatkan 223 pesakit DM mendapati nisbah risiko (RR) adalah 3.67; 95%CI (1.01,12.76)

Kesimpulan: TBDM-PT adalah alat saringan pemarkahan risiko Pulmonari TB yang baru dirangka dan telah divalidasi. Ia berkesan meningkatkan kadar deteksi tiga hingga empat kali ganda bagi penyakit TB dan jangkitan TB latent dalam populasi pesakit DM. Rekomendasi adalah kajian in perlu ditambah baik dengan kajian kos efektif sebelum digunakan di klinik kesihatan.

Kata kunci: Tuberkulosis, kencing manis, alat saringan, keberkesanan, validasi, klinik kesihatan

ABSTRACT

Introduction: Tuberculosis (TB) is a dangerous infectious disease worldwide. Diabetes mellitus (DM) increases the risk of infection up to four times compared to non-DM patients. With the increase in DM patients, the rate of TB infection is increasing worldwide. Until now, there is no specific TB screening tool for DM patients causing the lack of Pulmonary TB detection among DM patients.

Objective: To determine the factors that contribute to Pulmonary TB disease among DM patients, formulate a TB screening scoring tool and confirm the effectiveness of the Tuberculosis Diabetes Mellitus Predictive Tool (TBDM-PT) in Kelantan.

Methodology: This study consists of three phases. The case-control study for the Phase 1 involved 270 DM patients either suffering from TB (n=90) and non-TB patients (n=180). DM disease status, age 18 years and above and in the health clinic appointment were included in the analysis. Patient data was taken from the DM medical record, TBIS 10-1A form and National Diabetes Registry (NDR) website. Simple and multiple logistic regression was used to analyze the data. During Phase 2, the risk score was formulated based on multiple logistic regression and the area under the curve (AUC) method. The content validation study involved nine experts in TB management. The values of the factor content validation index (F-CVI) and the average index to the content validation index at the scale level (S-CVI/Ave) were obtained. Twenty health workers in health clinics were selected for face validation studies and face validation index (FVI) values were obtained.

A pilot study involving 34 DM patients who had undergone TB screening at a health clinic in the Kota Bharu district three months prior, was conducted to determine the

diagnostic performance for TBDM-PT such as accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

In a quasi-experimental study for phase 3, Kota Bharu was selected as the intervention group, using TBDM-PT as a screening tool while Pasir Mas was the control group using existing screening methods. The patient was followed up for four months until the patient completed the Pulmonary TB diagnosis test as the primary outcome while the secondary outcome was the latent TB infection (LTBI). Incidence rates and risk ratios (RR) were used in comparative analysis to demonstrate the effectiveness of screening tools

Result: The majority of patients were female (56.7%) and aged 60 years and above (60.7%). Seven factors (items) were identified to be closely related by statistical analysis to the risk of TB disease; male (Adj OR: (95% CI); 2.78 (1.17-6.63)), Body mass index (BMI) <23kg/m2 (Adj OR: (95% CI); 7.22 (2.74-19.04)), duration of DM ≤ 10 years (Adj OR: (95% CI); 2.90 (1.13-7.39)), no BCG scar (Adj OR: (95% CI);19.76 (2.98-130.9)), HbA1C level in 6 months ≥8% (Adj OR: (95% CI);19.76 8.31 (3.28-21.05)), history of cough over two weeks (Adj OR: (95% CI); 31.08 (11.64-82.98)) and history of fever over two weeks (Adj OR : (95% CI); 6.25 (1.15-33.99)). TB contact history was found to be clinically closely related to the risk of TB disease through consultation with a TB specialist and was included as a screening item as a high risk in TBDM-PT.

The F-CVI and S-CVI/Ave values reached the accepted adequate screening tool validation level. The pilot study showed the accuracy was 58.8% with a sensitivity 83%, specificity 54%, positive predictive value (PPV) 28% and negative predictive value (NPV) 94%. A total of 227 DM patients underwent an experimental study, the risk ratio (RR) for the detection of TB disease was 3.29; 95%CI (1.12,9.69), while

detection of latent TB (LTBI) involving 223 DM patients found the risk ratio (RR) was 3.67; 95%CI (1.01,12.76)

Conclusion: TBDM-PT is a newly developed and validated Pulmonary TB risk scoring tool. It effectively increases the detection rate three- to fourfold of Pulmonary TB disease and latent TB infection in the DM patient population. The recommendation is that this study needs to be improved with cost-effective studies before being used in health clinics.

Keywords: Tuberculosis, Diabetes Mellitus, screening tool, efficacy, validation, health clinic

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

TB is a disease caused by *Mycobacterium tuberculosis*. It commonly affects the lungs but may manifest in any body part, including the skin, brain, intestine, and kidney. Since *Mycobacterium tuberculosis* was first identified on 24 March 1882, the disease burdens have impacted worldwide. Various strategies have been implemented in handling the TB (TB) program. By concept, the elimination of Tuberculosis can be achieved through two mechanisms: either reducing the pool of latently infected persons via screening or interrupting the transmission at any point possible (Heffernan *et al.*, 2018). Since 1994, WHO has recommended a Directly Observed Treatment, Short-course (DOTS) strategy including technical and managerial components, given that one-third of cases do not take medication as prescribed (WHO, 1999). With DOTS implementation, the cure rate rises to 95%, especially in poorer countries (Davies, 2003). As one of the most cost-effective interventions, this method has been maintained as a standard procedure until now (Davies, 2003). Subsequently, in achieving the full-scale DOTS implementation in meeting the TB-related Millennium Developmental Goal (MDG), the WHO recommended the Stop TB Strategy in 2006 (Uplekar and WHO, 2006). The main objective of these strategies is to reduce the global burden of TB by 2015 with a specified indicator for monitoring. In 2015, WHO promoted the Sustainable Developmental Goals, detailed explicitly in SDG 3 (Good Health and Well Being), to end the disease epidemic by 2030. In addition, to increase

TB detection, the WHO introduced systematic screening for TB guidelines in 2013 (WHO, 2013).

1.2 GLOBAL TB BURDEN

TB remains the most common death involving one single pathogen worldwide, with an estimated 10 million TB cases reported in 2019 (Chakaya *et al.*, 2021). While progress is being made globally in ending TB, the process needs to be faster, with the significant concern of inadequate TB detection. About 2.9 million (29%) TB patients were not reported in 2019 alone and have been under the radar (Chakaya *et al.*, 2021). Between 2015 and 2020, global TB incidence reduced by 2% per year with an 11% overall reduction; however, the target milestone for the End TB Strategy is a 20% reduction in TB incidence (WHO, 2021a). Within the same period, Global TB detection and treatment show a 9.2% reduction in TB deaths, while the milestone for the Ending TB strategy is to reduce TB deaths by about 35% (WHO, 2021a). In addition, 47% of people still face catastrophic costs globally for TB treatment (WHO, 2021a). This achievement justifies the need for intensive screening and control measures globally.

1.3 GLOBAL TB-DM BURDEN

Diabetes Mellitus (DM) is a severe non-communicable disease worldwide. The result of urbanisation, population aging, alteration in diet habits, and reduced activity patterns, which cause obesity, may be the cause of the increase in the prevalence of DM. With about 462 million (6.28%) individuals are affected by Type 2 DM, estimated more than 1 million deaths reported due to DM in 2017, which puts DM as

the ninth leading cause of mortality and seventh among causing disability and years of life lost (DALY) (Khan *et al.*, 2020). Besides, the rise of DM individuals is expected to rise further to 642 million in 2040 globally (Al-Rifai *et al.*, 2017).

The relationship between TB and DM (TB-DM) was first described by Avicenna (980-1027 AD) more than 1000 years ago (Mudla, 2014). Since then, it's been triggering a variety of epidemiological studies. Diabetes has been identified as a risk factor for developing TB (Ahmad *et al.*, 2020). The weak immunity developed by the progress of DM may be the factor that contributes to several complications. TB-DM patients had a higher mortality rate (10.3%) than TB-only patients (7.6%), with nearly a 3-fold increase in total death (Adjusted OR 2.75; 95% CI 1.40, 5.39) and death during TB therapy (Adjusted OR 2.43; 95% CI 1.13, 5.23) (Nguyen and Graviss, 2019). Besides, as the result of the suboptimum physiological function of the lung due to DM causes the delay in clearance of the TB bacteria, which results in the spreading of the disease being prolonged and infecting many more people (Mudla, 2014).

The prevalence of TBDM was higher in low and middle-income countries. Of the ten countries with the highest number of DM patients, six of them have been identified as "high burden" for TB by the World Health Organisation (WHO) (Restrepo, 2016).

1.4 BURDEN OF TB-DM IN MALAYSIA

About 2/3 of global TB is in the western Pacific region, where Malaysia has been included. Malaysia had been classified as an intermediate or moderate TB burden in 2020, where the TB incidence reported is 92/per 100,000 population (Mohd Hassan *et al.*, 2021). The incidence trend in Malaysia started to be 61/100,000 in 1990 and subsequently rose to 79/100,000 in 2011 with aggressive screening and intervention.

The incidence trend kept fluctuating until 2018, when the incidence plateau at 92/100,000 until 2020 (NSP, 2016).

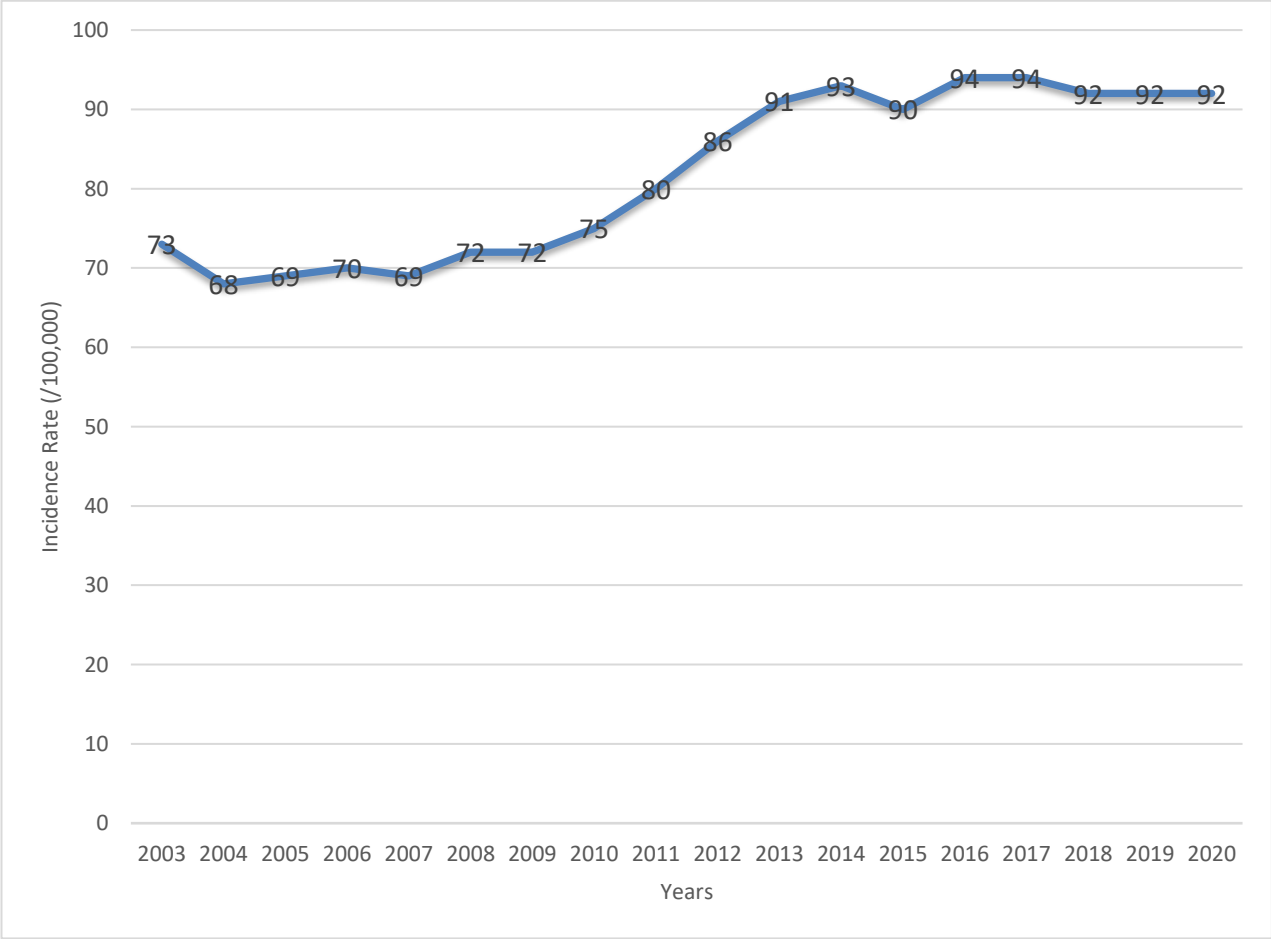


Figure 1.1: Incidence rate of TB in 2003-2020 Malaysia (WHO, 2020)

TB alone ranked at 3rd highest incidence rate and highest mortality rate among communicable diseases in Malaysia, with an estimated 6 deaths per 100,000 population (MOH and WHO, 2019). It has caused by 47,736 Disability Life years lost (DALYs), accounting for 0.9% of overall DALYs in Malaysia, predominantly affecting males aged 24-54 years old which indicates the burden of disease in contributing to significant premature mortality and years lived with disability among adulthood (Nasaruddin *et al.*, 2015).

Concomitantly rising with TB, Diabetes prevalence showed an incremental trend from 2011 until 2019, from 7.2% in 2011 to 8.3% in 2015 and 9.4% in 2019 (NHMS, 2019). Another worrying issue is the prevalence of a rise in blood sugar without knowing or having been diagnosed with DM, drastically increasing from 4% in 2011 to 8.4% in 2019 (NHMS, 2019). Even though comparatively, DM risk is low (3-fold) as compared with the HIV risk (20-fold) of being infected with TB, looking at the increasing prevalence of DM, the contribution of DM to TB is expected to be much higher (Restrepo, 2016).

Even though there is evidence of a reduction in the cases of TB in analysis from 2012 until 2016, there is an increasing incidence of DM among TB patients (Ahmad *et al.*, 2020). A recent study suggests that the risk of TB among DM patients was 1.8-9.5 times higher compared to non-DM patients in Asian countries (Zheng *et al.*, 2017). This condition results in an implication of query whether we are screening enough for identifying TB among DM patients.

1.5 TB IN KELANTAN

From 2019 until 2021, the trend of TB detection showing reducing in trend. The notification rate for TB significantly shows a reduction in trend from 64.2/100,000 population in 2019 down to 44.9/100,000 population in 2021 (JKNK, 2021). The pandemic of Covid-19 probably has an impact on TB case detection due to reduced human resources and increased work burden among healthcare workers. However, the current issue is due to low detection or miss diagnosis, there is a high probability of spreading of disease among undetected TB to the community afterward.

Among TB patients in Kelantan year 2021, estimated about 35.5% are diabetes which considered the highest as compared with a smoker (33.8%) and HIV patients (5.7%) (JKNK, 2021)

1.6 HIGH-RISK GROUP FOR TB

The term "high-risk groups" refers to a broad spectrum of people who have particular traits or health conditions that make them more susceptible to contracting TB or developing the disease. These populations, who include migrants from high-incidence environments, refugees, and asylum seekers, are more susceptible to contracting TB because of things like living in cramped quarters, being uprooted, and having little access to healthcare (Dobler *et al.*, 2018). In addition, there is a higher chance of TB reactivation in people with weakened immune systems, such as those who have DM, HIV infection, organ transplants, or systemic lupus erythematosus (Ai *et al.*, 2016; Cheng *et al.*, 2019). The rationale of this group has been emphasize for regular TB screening is because the late diagnosis and large pool of LTBI undetected among the high-risk group including DM patients may contribute to continuous and sustained TB spread among the population which contributes to a very slow reduction of TB incidence rate (Lönnroth *et al.*, 2013). By priorities a high-risk group for TB screening, may improve the detection rate and reduce the TB complication.

1.7 SYSTEMATIC HIGH-RISK GROUP (HRG) SCREENING

In theory, systematic screening for active TB can be done for the whole population (mass screening) or for specific risk groups. It can attack both persons who seek

medical attention (with or without symptoms or indications consistent with TB) and those who do not seek medical attention (because they do not perceive that they have a health problem that warrants medical attention, because barriers make it difficult to access health care, or for other reasons) (WHO, 2013). However, achieving the whole population for doing TB screening seems to be unrealistic with the increasing trend of other disease burdens and limited human resources. Besides, a study done in 1974 found that it is recommended to discontinue the practice of randomly selecting cases of tuberculosis by mobile mass radiography due to expensiveness of mass radiographs (WHO, 2013). Thus, Since 2013 WHO has introduced the Systematic High-Risk Group Screening for TB detection among smokers, diabetic patients, and immunosuppress patients (WHO, 2013). The principle of this screening is provider-initiated where it requires the provider to identify the higher risk based on certain criteria for TB screening (WHO, 2013). With a similar aim to improve TB detection, Malaysia started to implement the HRG screening in 2015 (Mohd Hassan *et al.*, 2021). In addition, as Malaysia categorized a moderate TB burden, the recommended screening method is targeted at the High-Risk group, including DM, as it may increase the risk for active TB disease (Lee *et al.*, 2018). The TB screening tests available recommended by WHO are the chest x-ray, symptom status screening, and tuberculin skin test (TST) (WHO, 2021b).

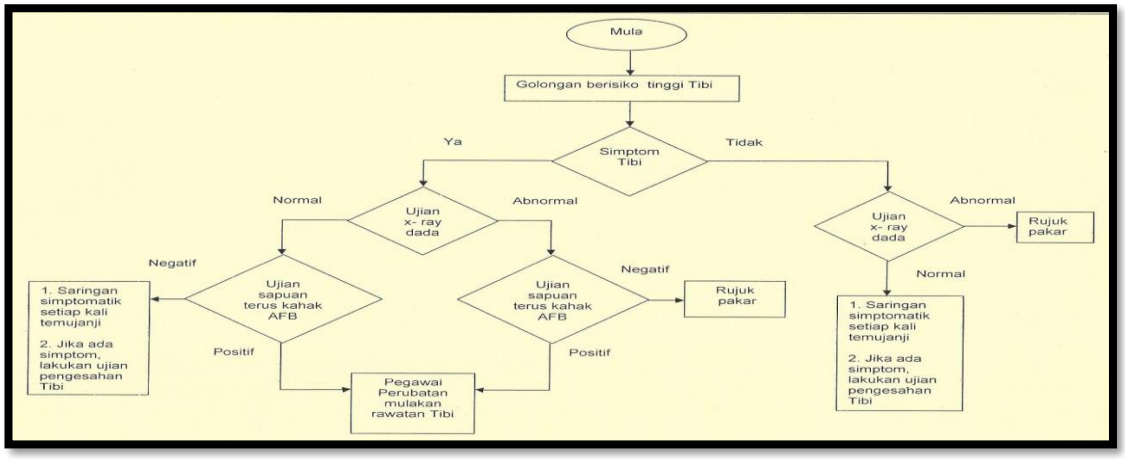
1.8 TB SCREENING AMONG DM PATIENT

Patients with DM should be screened for TB because there is a reciprocal association between these two illnesses. Despite attempts to enhance preventative measures, the burden of TB persists, particularly in developing countries. Therefore, it is imperative

to recognize and manage risk factors like DM (Yorke *et al.*, 2017). Research demonstrated that TB cases among DM patients can be presented with delayed sputum conversion that requires a routine TB screening to avoid miss diagnosis (Nair *et al.*, 2013). Furthermore, it has been shown that diabetes and tuberculosis coexist can lead to higher hospitalization rates, mortality rates, and consequences such as renal impairment. These findings emphasize the significance of early TB detection and treatment in DM patients (Basir *et al.*, 2019; Sembiah *et al.*, 2020).

Since 2013, WHO has introduced the concept of TB screening among High-Risk Groups (HRG) including Diabetes Mellitus, undernourished, elderly, immigrants, and many more (WHO, 2013). Malaysia has implemented HRG screening among DM patients since 2015 (Mohd Hassan *et al.*, 2021). Annually, all DM patients should be screened for TB. However, since challenges in the TB program in Malaysia have been known to have low human resources or understaffing, it's been difficult to screen 100% of DM patients every year (Abd Rahman and Mokhtar, 2015). The only tool available for help in the selection of high-risk for TB is by using the symptomatic screening tool which provided by WHO that has been used worldwide (Roberts *et al.*, 2021). There were no other criteria related to glycaemic control that can be used to determine the risk of TB among DM patients available so far. Thus, every medical officer has been trained to keep on high suspicious of any symptom relevant to TB symptoms among DM patients as the symptoms might be different from non-DM patients (Gil-Santana *et al.*, 2016). This might explain the possibility of the highest cost to detect one TB case among DM patients (RM 13,214.26) as the expected high denominator for screening as compared to the positive TB cases (Mohd Hassan *et al.*, 2021). Figure 1.2 demonstrates how TB screening among HRG including DM patients done in healthcare facilities in Malaysia. All HRG screened for TB symptoms and

tested accordingly either with chest x-ray for asymptomatic or with sputum examination if symptomatic. It indicates that all HRG patients will undergo the TB diagnostic test regardless of other factors besides symptoms alone. This may result in an expected high denominator for those who went for TB screening and cause a low TB detection rate.



(MOH, 2016)

Figure 1.2: TB Screening among HRG in Malaysia Healthcare Facility flow chart

Sputum samples from DM patients who were suspected of TB were requested for testing, involving sputum for AFB and for *Mycobacterium Tuberculosis* culture and sensitivity (MTB C&S). Chest X-rays were carried out as part of TB screening among DM patients in addition to sputum analysis. TB-suggestive lung abnormalities, such as infiltrates, cavities, or nodules, can be seen on chest X-rays. In DM patients, radiological findings in conjunction with clinical symptoms and test data can help with the diagnosis of Pulmonary TB.

From TB screening among DM patients in Kelantan between 2019 and 2021, as shown in Figure 1.3, it showed the lowest yield for TB case detection as compared to other TB High-risk groups listed by WHO. This happened due to too much screening for TB among DM patient however only small portion of sample confirmed as TB based on diagnostic testing.

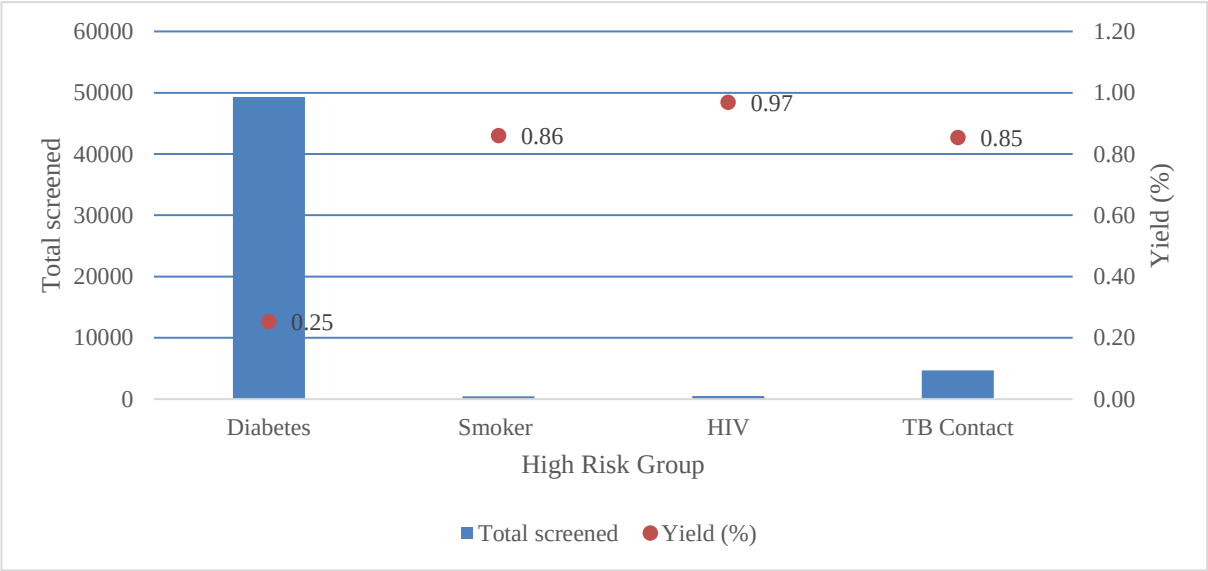


Figure 1.3: HRG TB Screening Yield in Health Clinic in Kelantan Between 2019-2021

1.9 PROBLEM STATEMENT

The existing systematic screening suggested by WHO provides a starting point to improve the TB screening strategy. However, the outcome of systematic screening, especially TB screening among DM patients, is not excellent. In addition, there were no screening tools for TB screening among DM patients used worldwide. Besides having DM as the only risk factor for TB infection, limited knowledge of other criteria related to sociodemographic and glycaemic control may further contribute to the risk of TB.

The yield of TB-diagnosed diseases among DM patients is the lowest as compared to other high-risk group TB screening where it costs RM 13,214.26 per one TB case detected (Mohd Hassan *et al.*, 2021). A low screening yield may result in extra costs for the screening budget, compromising other health programs. Thus, this population

needs a new, focused systematic screening strategy to enhance the acceptance of TB screening among DM patients in Malaysia.

1.10 STUDY RATIONALE

A criteria or additional screening test algorithm may help select only the most high-risk patients. As far as the literature has been explored, there are limitations regarding factors associated with TB disease among DM patients. Instead, the global study focuses mainly on DM disease among TB patients (Dabhi *et al.*, 2020). Thus, it doesn't provide a solid list of risks among DM patients to be screened for TB. DM patients are also more likely to experience LTBI reactivation-related active TB development (Öhd *et al.*, 2020). However, the available references do not adequately address the particular variations in TB symptoms between DM and non-DM individuals with LTBI. Limited literature describing the variation of symptoms does lead to an undetected pool of LTBI among DM patients. A finding from a TB review study in Malaysia from 2000 until 2013 found that about 91% of TB with DM patients, having a Pulmonary TB smear Positive (Swarna Nantha, 2014). It may be due to the immunological impairment of DM patients, causing delayed clearance of *Mycobacterium TB* bacteria in the lung (Mudla, 2014). These findings are consistent with another study where TB patients with no DM are more prone to contract extra-pulmonary TB (Lin *et al.*, 2009). The finding justifies that the risk of disease transmission among TBDM is higher in the population than in other TB patients.

With all the problem statements above, developing specific criteria may guide the screening process. The criteria may include a social aspect in predicting the risk of TB among DM patients as it has been more accurate (Htet *et al.*, 2021).

This study may provide a scoring system to prioritise the high-risk group for TB screening instead of pooling all the DM patients in the same risk group, which results in a low yield in TB detection.

By prioritising the risk group, the burden of healthcare workers in managing the TB program will be significantly reduced. These may help in providing more quality services to patients in need. The validated tools will guide in achieving the End TB strategy and SDG target, as the accurate screening tool may improve the detection rate among high-risk groups.

1.11 RESEARCH QUESTIONS

i. What are the factors associated with TB disease among Diabetes patients?

ii. Does the newly developed screening tool (TBDM-PT) valid and reliable to be used in the population?

iii. Does the rate of TB detection increase after using the TBDM-PT for TB screening in Diabetic patients as compared to the current TB screening program in Kelantan?

iv. Does the rate of LTBI detection increase after using the TBDM-PT for TB screening in Diabetic patients as compared to the current TB screening program in Kelantan?

1.12 OBJECTIVE

1.12.1 General

To validate a new TB screening Tool and evaluate its effectiveness in TB detection among DM patients in Kelantan.

1.12.2 Specific

i. To determine the factors associated with TB disease among DM patients in Kelantan.

ii. To develop, validate, and determine the accuracy of the TBDM-PT for TB detection among DM patients in Kelantan

iii. To compare the rate of Pulmonary TB disease (primary outcome) among DM patients between using TBDM-PT vs the current screening program.

iv. To compare the rate of LTBI (secondary outcome) between using TBDM-PT and the current screening program.

1.13 HYPOTHESIS

i. Sociodemographic factors, clinical factors, behavioral factors, and comorbidity including diabetic control are significantly associated with the risk of TB disease

ii. The newly developed tool (TBDM-PT) is a valid and reliable tool to predict the TB risk among DM patient

iii. There is a difference between the rate of TB disease detection among DM between using the TBDM-PT or the current screening program

iv. There is a difference between the rate of Latent TB Infection (LTBI) detection among DM between using the TBDM-PT or the current screening program

CHAPTER 2

LITERATURE REVIEW

2.1 FACTOR ASSOCIATED WITH TB DISEASE

The literature review has been done broadly by using multiple search engines available about the association that may cause the risk of TB and available screening tools related to TB worldwide a comprehensive review of the existing literature has been conducted to explore the factors associated with the risk of TB among DM and general population. Besides, available screening tools for TB on a global scale have also been explored.

2.1.1 DM History

Immunity of individuals plays a vital role in contributing to the risk of TB. Generally, any infectious disease, including TB, may be stopped or protected by our immunity. The general population is at risk of TB infection since immunity level varies among individuals (Nathella and Babu, 2017). However, the risk multiplied for DM patients. Multiple studies suggest that due to the immunological impairment caused by DM, the risk of being infected by infectious disease increases. In the peripheral blood mononuclear cells (PBMC) of DM patients, there was a substantial drop in cluster of differentiation 4 (CD4+) and cluster of differentiation 8 (CD8 T) cell subsets, indicating hyperimmune reactivity and an increased risk of infection with a variety of pathogens, including *Mycobacterium Tuberculosis* (Ponnana *et al.*, 2020). This finding has been proven by a systematic review finding that the risk of DM patients being

infected by TB increases with a risk ratio (RR) of 3.11(95% CI 2.27,4.26), as compared to non-DM patients (Restrepo, 2016). Generally, most of the studies are related to Type 2 DM and the risk of TB, even though Type 1 DM is the more severe form (Sruthi *et al.*, 2021). This finding is due to very few samples for Type 1 DM to be analysed. However, a population-based historical study in Taiwan involving 5195 Type 1 DM patients showed the risk of TB was 4.36 (95% CI 2.43,7.36) times greater than the general population (Shen *et al.*, 2014). In addition, TB in Type 1 DM is more toward the active stage rather than the passive. A finding from four prospective, 16 retrospectives, and 17 case-control studies, the finding shows that the risk of active TB among DM was 3.59 fold (95% CI 2.25,5.73), 1.55 fold (95% CI 1.39,1.72), and 2.09 fold (95% CI 1.71,2.55) respectively as compared to non DM patient (Al-Rifai *et al.*, 2017). Based on the age-stratified analysis, the age factor, especially for those under 40 years old with DM, increases the risk of getting TB compared to those aged 40 and above with DM (Hayashi and Chandramohan, 2018). DM control is related to prognosis, determining an individual's immunity strength. An uncontrol DM hemoglobin A1C (HbA1C) ≥7.0% showing the risk of positive sputum culture even after 2 months of anti-TB treatment with an odds ratio of 4.316 (95% CI 1.31,14.27; $p = 0.017$) (Park *et al.*, 2012). This finding is due to higher glucose levels that may interrupt Peripheral Blood Mononuclear Cell (PBMC) proliferation involved in immunity response (Ponnana *et al.*, 2020). Besides, being uncontrol DM was an independent risk factor for TB treatment failure or death with an adjusted odd ratio of 4.11; (p =0.022) (Yoon *et al.*, 2017). A study done in Malaysia, specifically in Kelantan, found that only 37.4% adhere to a diabetic diet, with only 20% of patients having HbA1C levels <7.0% (Ahmad *et al.*, 2014). Another indicator that determines the risk of being infected by TB is the duration of being diagnosed as DM. A study

shows that more than 10 years of being diagnosed with DM, a higher risk of being infected by TB by the adjusted odd ratio of 8.89 (95% CI 1.88,58.12) as compared with 0-5 years duration of being diagnosed as DM (Amare *et al.*, 2013). DM is genetically predisposed, and there is a potential for a diagnosis of DM, especially in the early phase of the disease.

It has been discovered that DM therapy affects DM patients' risk of tuberculosis. For example, a systematic study revealed that prescribing metformin may lower the incidence of tuberculosis in diabetics (Yu *et al.*, 2019). Additionally, as DM itself increases TB disease activity and therefore the spread of TB, metformin has been suggested as a potential protective medication against TB in individuals with DM. This is because increased DM prevalence has resulted in greater rates of TB infection (Fu *et al.*, 2021).

2.1.2 Elderly

Due to several aging-related variables as well as the co-morbidity of diabetes mellitus (DM) and tuberculosis (TB), the senior population with DM is at an elevated risk of developing TB. Research has repeatedly shown that among people with diabetes mellitus, being older is a substantial risk factor for tuberculosis (TB). Elderly diabetes patients have been discovered to have a remarkably high prevalence of tuberculosis (TB), indicating that this group is susceptible to tuberculosis infection (Workneh *et al.*, 2017). Moreover, studies have shown a substantial correlation between a person's age and their chance of contracting tuberculosis (TB) in those who have diabetes mellitus (DM), with age being recognized as a critical factor influencing TB-DM comorbidity (Viswanathan *et al.*, 2012). Besides, the discovery that diabetes mellitus is the primary risk factor for a significant percentage of adult tuberculosis cases,

especially in those between the ages of 35 and 60, highlights the increased mortality risk associated with the disease in older diabetes patients (Restrepo, 2016).

2.1.3 Family History of DM

Multifactorial factors, including environmental factors, may influence the genetic element before it's been expressed phenotypically (Alam *et al.*, 2019). A higher risk of TB has been linked to genetic predisposition, especially in the setting of diabetes. Due to the higher sensitivity of type 2 diabetics to TB infection, this genetic predisposition to diabetes has also been associated with an increased risk of TB (Lin *et al.*, 2015b). Furthermore, it has been demonstrated that genetic variables significantly influence the susceptibility to TB infection. Differences in the genetic background of the human host might affect the course of TB infection subsequent to exposure to comparable risk factors (Kramnik *et al.*, 2000). This further supported by risk of being infected by TB disease was found to increase with an odd ratio of 5.85 (95% CI 4.44,7.69) as compared to individuals with no family history of DM (Wang *et al.*, 2013; Workneh *et al.*, 2017). These factors contribute to an individual's susceptibility to TB infection and the subsequent development of the disease.

2.1.4 History of TB Contact

Exposure to TB infection can be either through household contact or environmental exposure, especially when it involves an occupation. It mainly correlates with the bacteria concentration and duration of human exposure (Kozińska and Augustynowicz-Kopeć, 2016). Close area with inadequate ventilation area predisposes TB infection to available exposure (Kozińska and Augustynowicz-Kopeć, 2016). DM

patients who have TB household contact are substantially more likely to develop TB than individuals who do not with high odd ratio (OR) 95% CI of 63.29 (95 % CI: 4.42, 83.10) (Fibriana *et al.*, 2020). A systematic review found that the risk of an individual being infected by TB is high when having contact with a TB patient in a family with an adjusted odd ratio of 9.4 (95% CI 1.82, 48.50) as compared with an individual with no TB contact in the family household (Amare *et al.*, 2013). For exposure at the workplace, specifically among healthcare workers, a procedure involving managing TB patients promotes a higher risk. It's not necessary to manage a specimen at the laboratory. In fact, normal verbal conversation or procedures may increase the risk of infection (Nienhaus *et al.*, 2014). Several studies in systematic review found that an estimated 27% up to 81% of TB cases among healthcare workers are attributed to exposure in healthcare settings (Baussano *et al.*, 2011; Narasimhan *et al.*, 2013). In addition, compared with the general population, the risk of LTBI was greater among healthcare workers, with an odd ratio of 2.27 (95% CI 1.61, 3.20) (Uden *et al.*, 2017). This finding justifies that the healthcare worker profession is associated with a high risk of TB infection.

2.1.5 Anaemia

Anaemia, have been linked to worse health outcomes in people with DM. Anaemia has been connected to a higher risk of tuberculosis development and is a common comorbidity in patients with diabetes mellitus. Anaemia may weaken the immune system, increasing a person's vulnerability to *Mycobacterium TB* infection, according to studies (Orsolin *et al.*, 2020). Anaemia defined as reduces one or more red blood cell (RBC) indices (Broadway-Duren and Klaassen, 2013). Low blood haemoglobin (Hb) concentration (less than 11.0 g/dl for 6–59-month-old children, 11.5 g/dl for 5–

11-year-old children, 12.0 g/dl for 12–14-year-old children and non-pregnant women (for age 15 and up), 11.0 g/dl for pregnant women, and 13.0 g/dl for adult men for age 15 years and above is characterised as anaemia. It's often associated with DM, in which iron and erythropoietin deficiency type is dominantly involved, and it may aggravate the risk of developing diabetes-related microvascular and macrovascular complications (Sahay *et al.*, 2017). Furthermore, anaemia has been associated with an increased risk of adverse pharmacological reactions to anti-TB drugs in people with DM, which could complicate the course of TB treatment (Aweis and Suleiman, 2020). Generally, the risk for anaemic individuals to get TB is 3.56 (95% CI 2.53,5.01) higher than non-anaemic individuals. Similarly, a cohort study show that the Hazard Ratio (HR) of TB to be contracted is 2.01(95% CI 1.70,2.37) higher for anaemic individual as compared to non-anaemic and the HR increase synchronise with the anaemia severity of HR 1.37 (95% CI 0.92,2.05), 2.08 (95% CI 1.14,3.79), and 2.66 (95% CI 1.71, 4.13) for mild, moderate, and severe anaemia, respectively (Gelaw *et al.*, 2021).

2.1.6 Urbanisation

Globally, urbanisation is an ongoing process that inevitably involves social and economic development. It involves the migration of humans to seek economic opportunity. The projection of the urbanisation process has been expected to rise from 49% (3.2 billion) in 2005 to 60% (4.9 billion) population in 2030 globally (Liang and Wang, 2020). Urban in Malaysia is defined as gazetted areas with adjoining built-up areas with a combined population of 10,000 or more (Yaakob *et al.*, 2012). Until 2021, Malaysia's urban population was estimated at 77.7%, with an average growing rate of 1.64% (Knoema, 2021). The drastically increasing population may increase density and lead to a massive slum area. The over-density population are at risk of spreading

infectious disease, especially airborne ones like TB. This finding has been proven by a systemic review where urban residents increase the risk of infection with an adjusted odd ratio of 5.5 (95% CI 1.07, 28.20) compared to rural residents (Amare *et al.*, 2013).Obesity Another study in Malaysia also shows a positive correlation for urban residents being at high risk of being infected by TB (ρ=0.884) (Kaur *et al.*, 2020). In addition, DM patients living in high-density areas or urban areas, especially those presenting with atypical symptoms of TB, may complicate the diagnosis and treatment. These may lead to delayed detection and increase the risk of transmission (Al-Rifai *et al.*, 2017).

2.1.7 Education Status

An education status difference does show the significant demand in health literacy for understanding information and proceeding with inquiry or treatment (Green, 2022). The education status of individuals with DM plays a significant role in influencing the risk of TB. A poor health-seeking habits and delayed healthcare seeking have been associated to low educational status, and these factors may accelerate the advancement of tuberculosis in individuals with diabetes mellitus (Felicia *et al.*, 2019). Low educational status has also been connected to noncompliance with TB treatment plans, which can lead to treatment failure and the emergence of drug-resistant TB strains (Nandakumar *et al.*, 2013). This fact has also been applied to the general population's TB risk. A finding from the study shows that the main risk factor for TB was not having a university-level education with an odd ratio of 4.45 higher (95% CI 1.50,13.17; p = 0.007) as compared to the university level and above (Jiamsakul *et al.*, 2018).

In conclusion, a person's education level has a big impact on how likely they are to have tuberculosis. Low educational status has been linked to poor health-seeking

habits, a lack of information about tuberculosis, and socioeconomic inequities, all of which raise the risk of tuberculosis among people with diabetes mellitus.

2.1.8 Marital status

Being in a relationship like marriage provides social support and influence in daily decision-making, including health. It's all about the effect of "cohesive marriage" on physical and mental health (Kiecolt-Glaser and Newton, 2001). Through the influence, the individuals in marriage are aware of the importance of the relationship. They are responsible for maintaining the harmony of the relationship, including self-concern about health and completion of any treatment needed (Young *et al.*, 2014). Being married shows a 69% protective effect from TB compared with single, separated or divorced with an odd ratio of 0.31 (95% CI 0.14, 0.72) (Young *et al.*, 2014). However, there are contradicting findings where a study involving elderly TB shows that being once in a relationship, either married or divorced, had a risk of infected TB disease by the adjusted odd ratio of 3.2 (95% CI 1.34,7.57) and 6.9 (95% CI 2.78,17.3) respectively as compared to the group who never been in marriage (Murali *et al.*, 2021). In addition, couples with DM are more likely to have a strict routine, including regular care on medication, partner medication, and ambulation help, especially for elderly, if necessary. Thus, low immunity due to DM and routine close contact with a partner may increase the risk of disease transmission, including TB (WHO, 2007).

2.1.9 Smoking

An important topic of research is the relationship between smoking and the risk of tuberculosis (TB) in people with diabetes mellitus (DM). For those with diabetes

mellitus, smoking has been found to be a major risk factor for tuberculosis (TB). Smoking has been shown to have negative effects on inflammation, insulin resistance, and dyslipidaemia. These findings point to a possible mechanism by which smoking promotes the development of diabetes mellitus and its related problems (Chang, 2012). Smoking association with the risk of TB has been debated for more than 100 years (van Zyl Smit *et al.*, 2010). Smoking itself causes ciliary dysfunction, reducing the number of macrophages, CD4, and CD8 cell levels, decreasing immunity and increasing susceptibility toward TB infection (van Zyl Smit *et al.*, 2010). Active or passive smoking is an accelerating factor for TB infection (de Vargas *et al.*, 2021). The latter is more related to indoor air pollution involving smoking households. About 7.1% of all TB patients with a relative risk of 1.6 (95% CI, 1.2,2.1) are attributed to smoking behaviour globally (WHO, 2021a). A systematic review shows that smoking does increase the risk of TB infection with a relative risk of 2.3-2.7 compared with non-smokers (Narasimhan *et al.*, 2013). In addition, smoking may increase the risk of latent TB activation, TB recurrence and TB mortality (de Vargas *et al.*, 2021).

2.1.10 Underweight

Being underweight has been known as an established risk factor that may contribute to risk for active TB. The prevalence of underweight in TB patients is significantly three-fold higher as compared with normal BMI (Badawi *et al.*, 2020). It was estimated that every 1 unit increase in BMI causes a 2% reduction in TB incidence (Badawi *et al.*, 2020). Given the fact that the underweight (<18.5kg/m2) and DM type 2 are independent risks of TB, the risk escalates as the BMI drops and reaches a maximum-to-hazard ratio of 8.30 (95% CI 4.4,15.5) (Harries, 2019). However, for diabetic patients, the statistics show that more than 80% found out to be with BMI of >23kg/m2

(Ahmad *et al.*, 2014). Thus, identifying the group of underweight DM patients for TB screening may be justifiable to rule out TB infection. The person may be underweighted as a result of an underlying tuberculosis infection.

2.1.11 HIV patients

One important factor that has been repeatedly found to significantly increase the risk of tuberculosis (TB) in people with diabetes mellitus is the incidence of HIV among TB patients. Research has indicated that HIV is more common in TB patients, especially when diabetes is present. This highlights the mutually reinforcing effect of HIV and diabetes on the risk of tuberculosis (Kumar *et al.*, 2023; Tulu *et al.*, 2021; Villalva-Serra *et al.*, 2022). Additionally, a higher risk of multidrug-resistant tuberculosis (MDR-TB) has been linked to the coexistence of HIV and diabetes mellitus (DM), highlighting the intricate issues presented by the convergence of these diseases (Onuka *et al.*, 2017).

Generally, infection with the human immunodeficiency virus (HIV) increases an individual's risk of TB by a large margin. Many researches have repeatedly shown that those living with HIV/AIDS have a higher risk of TB. For example, a meta-analysis conducted revealed that those living with HIV/AIDS were 3 times more likely to develop pulmonary TB than people without the virus (Rumkhullah *et al.*, 2018). According to other literature, patients receiving antiretroviral medication (ART) for suppressed HIV infection had a fourfold greater risk of getting TB (Azevedo-Pereira *et al.*, 2023). Late-stage HIV infection was also found to increase the chance of developing TB by a factor of 20 in latently infected persons (Azevedo-Pereira *et al.*, 2023). Basically, at any phase of HIV infection, there is a significant risk of getting TB infection. The risk of getting TB worsen if the patient also having DM.

2.1.12 Alcoholism

The relationship between alcohol use and DM patients' risk of tuberculosis has been investigated in this regard. Research has demonstrated that alcohol misuse, which is frequently linked to unhealthy risk behaviors, can hasten the course and intensity of disease and raise the possibility of tuberculosis in individuals with diabetes mellitus (Ahmad *et al.*, 2020). Furthermore, drinking alcohol has been connected to weakened immune system response to novel infections, worsened malnourishment, and decreased immune system function, all of which can raise the risk of tuberculosis in people with diabetes mellitus (Choi *et al.*, 2021). It is noteworthy that several characteristics, such as gender, lifestyle, and socioeconomic level, may have an impact on how much alcohol is consumed and the risk of tuberculosis among people with diabetes mellitus. For instance, it has been noted that men are more prone than women to abuse alcohol, behavior that increases the chance of acquiring MDR-TB (Pan *et al.*, 2023). Research also has shown that alcoholics are more likely than non-alcoholics to transmit MDR-TB, raising the prospect of both increased transmission and recurrence of the disease in this population (Rajendran *et al.*, 2021).

2.2 AVAILABLE TB SCREENING TOOLS

Screening tools are tools designed for distinguishing between individuals with a high probability of being infected or not. It must subsequently be followed by a diagnostic test for confirmation (WHO, 2021b). The selection of a screening method might change based on the resources, knowledge, and unique context of the healthcare facility. To increase the precision of TB diagnosis, combination techniques, such as the use of symptom-based screening combined with diagnostic tests supplemented with additional TB risk-associated factors, are frequently used. Populations at