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Prevalence of Latent Tuberculosis Infection and its Associated Factors Among Diabetic Patients Availing Primary Health Care in Terengganu State, Malaysia

Nur Fatini Husain, Harmy Mohamed Yusoff*, Nurulhuda Mat Hassan and Aniza Abdul Aziz

Faculty of Medicine, Universiti Sultan Zainal Abidin, Kuala Terengganu, Malaysia

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ABSTRACT

Objectives: Diabetes mellitus (DM) patients are considered to be at high risk for contracting latent tuberculosis infection (LTBI). This study aimed to determine the prevalence of LTBI and its associated factors among diabetic patients attending primary care clinics in Terengganu state, Malaysia. ***Methods***: This cross-sectional study was conducted among diabetic patients attending 11 health clinics in the Terengganu region from June 2017 to November 2018. The selected participants were administered a tuberculin skin test (TST). Simple and multivariate logistic regressions were applied to evaluate the significant associated factors of LTBI. ***Results:*** The total number of participants were 703 DM patients. The factors found associated with LTBI were poor diabetic control status (odds ratio (OR) = 8.53; $p = 0.008$), being a healthcare worker (OR = 7.91; $p = 0.001$), history of contact with TB patients (OR = 5.69; $p < 0.001$), bronchial asthma (OR = 5.28; $p = 0.019$), coronary heart disease (OR = 3.45; $p = 0.026$), and nephropathy (OR = 0.34; $p = 0.040$). The presence of LTBI was found in 34 (4.8%) participants. ***Conclusions:*** At 4.8%, the prevalence of LTBI among DM patients in Terengganu is relatively low. Diabetics with poorly controlled blood glucose levels, nephropathy, bronchial asthma, coronary heart disease, history of TB patient contact, or working in the healthcare profession should be periodically tested for LTBI.

Tuberculosis (TB) has re-emerged as a major threat to public health. The World Health Organization (WHO) has reported that people infected with TB have increased from 8.6 million in 2013 to 9.9 million (with 1.3 million deaths) in 2020.[1,2] Furthermore, it is estimated that one in four people in the world is infected with latent tuberculosis infection (LTBI).[3] Moreover, 5–10% of those with LTBI may in time develop active TB.[1,4,5]

The prevalence of diabetes mellitus (DM) has also been increasing dramatically worldwide, with a 129.7% increase in prevalence from 1990 (211.2 million) to 2017 (476.0 million).[6] Historically, the incidence of TB has been high in diabetic patients whose lower immunity triples the risk of TB.[5,7,8] In addition to DM, smoking, older age, history of TB contact, working as a healthcare worker, and having other comorbidities increase the risk of TB.[8–11] Therefore, in populations with the above characteristics, it is essential to regularly screen for the prevalence of LTBI and TB and manage these conditions when identified.

Malaysia has an intermediate burden of TB.[12] This study aimed to determine the prevalence of LTBI and its associated factors among diabetic patients in primary care clinics in Terengganu state in the east coast of Malaysia to counter the effects of the dual problem of diabetes and TB in this population.[13]

METHODS

This community-based cross-sectional study was conducted from June 2017 to November 2018 among diabetic patients in 11 selected primary care clinics in the region of Terengganu. Government primary health clinics having family medicine specialists in Terengganu were categorized into three areas; central, north, and south. Using

*Corresponding author: ✉harmyusoff@unisza.edu.my

stratified random sampling, five of nine clinics in the central area, three of five clinics in the northern area, and three of six clinics in the southern area were selected.

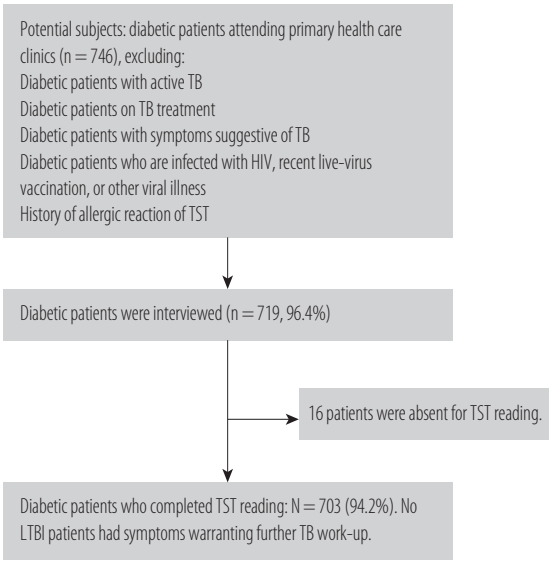
Ethical approval was given by the Human Research Ethics Committee Universiti Sultan Zainal Abidin and the National Medical Research and Ethics Committee (NMRR-16-1937- 30162).

The sample size for the study was calculated by using PS Software (Power and Sample Size Calculation version 3.1.6 by Vanderbilt University School of Medicine), assuming a 28.2% prevalence of LTBI,[14] 95% CI, 5% margin of error, and 1.96 value for the standard normal distribution. Assuming 20% non-participation and considering a cluster design effect, a minimum sample size of 746 was arrived at. Systematic random sampling with 1:3 ratios was then applied to choose samples among diabetic patients who attended the clinics during the study period.

All diabetic patients who fulfilled the inclusion criteria and were willing to participate in the study were eligible for participation. Inclusion criteria comprised: age ≥ 18 years, having been diagnosed with DM for at least 12 months, and having no mental health problems [Figure 1]. Exclusion criteria were being previously diagnosed with or currently having TB, being in an immunocompromised state (due to conditions such as HIV, malignancies, end-stage renal failure, or being on any immunosuppressive therapy), and with a history of allergic reaction to the tuberculin skin test (TST).

After receiving the respondent's written consent, the researcher interviewed and completed the case report form, which required information on socio-demographic data such as age, gender, marital status, education occupation, monthly household income, and place of residence. Also collected were history of contact with TB patients, smoking status, and presence of comorbidities such as asthma, hypertension, hyperlipidemia, and rheumatoid arthritis. Further clinical data was obtained from the patient's medical records in the clinic.

Patients who had no chest X-ray (CXR) done within one year were subjected to a new CXR. The results of all CXR were read by the medical doctor in each clinic and were verified by a research team member (a clinician), to exclude active TB. Thereafter, the tuberculin skin test (TST) was performed.



LTBI: latent tuberculosis infection; TST: tuberculin skin test.

Figure 1: The enrolment process of diabetic patients in the study.

The diagnosis of LTBI was confirmed by TST which uses a protein precipitate of heat-inactivated tubercle bacilli, known as purified protein derivative. The standard TST consists of an intracutaneous injection of 0.1 mL (5 tuberculin units) of purified protein derivative into the volar forearm. TST was administered by a trained staff nurse who also measured any induration (in mm) occurring 48–72 hours post-injection.[15] Indurated area refers to the raised region, not the surrounding erythema. The 'pen technique' was used by lightly drawing with a pen in the horizontal and vertical planes until the edge of the induration was reached to distinguish the indurated area from the surrounding erythema. The size of the reaction was indicated by the measurement of induration transversely to the long axis of the forearm from the most medial point.[16] The Development Group of CPG TB Malaysia (4th edition) suggests that a TST induration of ≥ 10 mm should be considered as a positive LTBI for high-risk individuals such as diabetic patients.[15,17]

Latent TB refers to inactive TB, which differs from active TB whereby the body is already affected by *Mycobacterium tuberculosis* complex, whereas in latent TB, the bacteria cause no symptoms of TB with normal CXR, negative sputum, and the individual does not feel sick.[4,6,18] To confirm the presence of inactive *M. tuberculosis* complex in the body, TST or interferon-gamma release assay (IGRA) test is required.[6,19]

DM was defined as Type 1 or Type 2 diabetes diagnosed using fasting plasma glucose of ≥ 7.0 mmol/L or random plasma glucose ≥ 11.1 mmol/L (single reading in a symptomatic patient and two readings in an asymptomatic patient) or modified oral glucose tolerance test of fasting ≥ 7.0 mmol and 2-hour postprandial of ≥ 11.1 mmol/L.[20]

IBM SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for statistical analysis. A 5% level of significance was set, *p*-value ≤ 0.05 or less was considered statistically significant. A descriptive statistic such as percentage, mean and SD for each variable was calculated to describe frequencies (n) and percentage (%) for categorical variables while mean and SD were used for numerical variables. This study also involved simple and multiple logistic regressions to determine the significance of association between the LTBI and related variables among diabetic patients. Variables having *p*-values ≤ 0.25 were included to proceed for further multivariable analysis. Also applied were goodness of fit tests such as classification table and area under the curve (ROC).

RESULTS

A total of 703 eligible diabetic patients attending selected health clinics in Terengganu participated in this study. Figure 1 shows the procedure to enroll the participants.

Table 1: Comparative characteristics of latent tuberculosis infection (LTBI) and non-LTBI participants of the study (N = 703).

Variables	Total, n (%)	No LTBI, n (%)	LTBI, n (%)	*p*-value
Mean age (SD)	58.9 (10.3)	59.1 (10.1)	58.9 (9.3)	0.888[a]
Gender				0.459[b]
Male	228 (32.4)	215 (94.3)	13 (5.7)	
Female	475 (67.6)	454 (95.6)	21 (4.4)	
Ethnicity				0.952[c]
Malay	702 (99.9)	668 (95.2)	34 (4.8)	
Chinese	1 (0.1)	1 (100)	0 (0.0)	
Marital status				0.426[c]
Single	17 (2.4)	17 (100)	0 (0.0)	
Married	585 (83.2)	555 (94.9)	30 (5.1)	
Divorced/separated	11 (1.6)	9 (81.8)	2 (18.2)	
Widowed	90 (12.8)	88 (97.8)	2 (2.2)	
Highest educational level				0.151[b]
No formal education	80 (11.4)	78 (97.5)	2 (2.5)	
Primary	261 (37.1)	251 (96.2)	10 (3.8)	
Secondary	303 (43.1)	287 (94.7)	16 (5.3)	
Diploma Degree/ Master/ Ph.D.	59 (8.4)	53 (89.8)	6 (10.2)	
Mean household monthly income (SD), RM	1790 (2787)	17734 (28 288)	2100 (1808)	0.031[b]
< 3000	574 (81.7)	551 (96.0)	23 (4.0)	
≥ 3000	129 (18.3)	118 (91.5)	11 (8.5)	
Occupation				< 0.001[b]
Not working	345 (49.1)	334 (96.8)	11 (3.2)	
Healthcare worker	26 (3.7)	20 (76.9)	6 (23.1)	
Non-healthcare worker	332 (47.2)	315 (94.9)	17 (5.1)	
Place of residency				0.616[b]
Rural	533 (75.8)	506 (94.9)	27 (5.1)	
Urban	170 (24.2)	163 (95.9)	7 (4.1)	
Smoking status				0.023[c]
Non-smoker	336 (47.8)	325 (96.7)	11 (3.3)	
Active smoker	49 (7.0)	42 (85.7)	7 (14.3)	
Ex-smoker	64 (9.1)	61 (95.3)	3 (4.7)	
Passive smoker	254 (36.1)	241 (94.9)	13 (5.1)	

Table 1: Comparative characteristics of latent tuberculosis infection (LTBI) and non-LTBI participants of the study (N = 703).

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Variables	Total, n (%)	No LTBI, n (%)	LTBI, n (%)	*p*-value
History contact with TB patient				< 0.001[c]
No	644 (91.6)	621 (96.4)	23 (3.6)	
Yes	59 (8.4)	48 (81.4)	11 (18.6)	
Obesity				0.711[b]
No	232 (33.0)	220 (94.8)	12 (5.2)	
Yes	471 (67.0)	449 (95.3)	22 (4.7)	
Hypertension				0.424[b]
No	141 (20.1)	136 (96.5)	5 (3.5)	
Yes	562 (79.9)	533 (94.8)	29 (5.2)	
Hyperlipidemia				0.526[b]
No	199 (28.3)	191 (96.0)	8 (4.0)	
Yes	504 (71.7)	478 (94.8)	26 (5.2)	
Bronchial asthma				0.062[b]
No	680 (96.7)	649 (95.4)	31 (4.6)	
Yes	23 (3.3)	20 (87.0)	3 (13.0)	
Rheumatoid arthritis				0.552[c]
No	687 (97.7)	654 (95.2)	33 (4.8)	
Yes	16 (2.3)	15 (93.8)	1 (6.2)	
Mean TST value (SD)	2.53 (3.7)			
Mean duration of diabetes (SD), years	6.83 (5.1)	6.86 (5.1)	6.24 (5.3)	0.487[a]
Types of medication				0.934[b]
Diabetic oral medication	414 (58.9)	393 (94.9)	21 (5.1)	
Insulin therapy	41 (5.8)	39 (95.1)	2 (4.9)	
Both	248 (35.3)	237 (95.6)	11 (4.4)	
Mean HbA_{1c} levels for the last one year (SD)	8.41 (3.2)	8.38 (3.3)	9.07 (2.5)	0.228[a]
Diabetic control status				0.010[b]
< 6.5	172 (24.5)	170 (98.8)	2 (1.2)	
≥ 6.5	531 (75.5)	499 (94.0)	32 (6.0)	
Microvascular complications				
Retinopathy				0.173[b]
No	484 (68.8)	457 (94.4)	27 (5.6)	
Yes	219 (31.2)	212 (96.8)	7 (3.2)	
Neuropathy				0.081[b]
No	469 (66.7)	451 (96.2)	18 (3.8)	
Yes	234 (33.3)	218 (93.2)	16 (6.8)	
Nephropathy				0.057[b]
No	498 (70.8)	469 (94.2)	29 (5.8)	
Yes	205 (29.2)	200 (97.6)	5 (2.4)	
Macrovascular complications				
Coronary heart disease				0.046[c]
No	661 (94.0)	632 (95.6)	29 (4.4)	
Yes	42 (6.0)	37 (88.1)	5 (11.9)	
Stroke				0.288[c]
No	681 (96.9)	649 (95.3)	32 (4.7)	
Yes	22 (3.1)	20 (90.9)	2 (9.1)	
Peripheral vascular disease				0.670[c]
No	670 (95.3)	638 (95.2)	32 (4.8)	
Yes	33 (4.7)	31 (93.9)	2 (6.1)	

HbA_{1c}: glycated hemoglobin; [a]: numerical variables using independent t-test; [b]: categorical variables using chi-square test; [c]: Fisher exact test; TST: tuberculin skin test.

The mean age of the respondents was 58.9±10.2 years. Females (67.6%) and married people (83.2%) were in the majority. The mean duration of the participants' diabetes was 6.8±5.0 years and the mean of glycated hemoglobin (HbA_{1c}) levels for the last one year was 8.4±3.2). Most (414; 58.9%) participants took oral medications to keep DM in control. Three-quarters (531; 75.5%) had HbA_{1c} levels ≥ 6.5 mmol/L in the previous one year. LTBI was found in 34 (4.8%) participants. Table 1 shows the comparative characteristics of the LTBI and non-LTBI participants.

In the multivariate analysis using forward logistic regression, there were significant associations between poor diabetic control ($p = 0.008$), healthcare workers ($p = 0.001$), history of TB contact ($p < 0.001$), bronchial asthma ($p = 0.019$), coronary heart disease ($p = 0.026$), and nephropathy ($p = 0.040$) with latent TB status [Table 2].

Participants with poorly controlled diabetes (HbA_{1c} > 6.5 mmol/L) had 8.53 times higher odds of having LTBI than those with good diabetic control (HbA_{1c} ≤ 6.5 mmol/L). Healthcare workers had 7.91 times higher odds of having LTBI than the unemployed; non-healthcare workers had 1.67 higher odds than the unemployed.

The participants who had contact with TB patients were 5.7 times more likely to have LTBI than those who did not. Patients with coronary heart disease had 3.5 greater odds of having LTBI compared to those without this condition. Patients with bronchial asthma had 5.3 times higher odds of having LTBI and nephropathy patients had 66% lower odds.

The model reasonably fits well. Model assumptions are met. There are no interaction and multicollinearity problems. Classification table (overall correctly classified percentage is 95.3%, which is > 70.0%) and ROC is 0.798 (95% CI: 0.73–0.87).

DISCUSSION

Accurate diagnosis of LTBI, establishing its local prevalence, and identifying the associated risk factors are vital for TB control in any population. WHO's End TB Strategy[21] recommends early screening for LTBI in countries with lower or intermediate TB incidence to reduce the incidence of TB cases.

Table 2: Multivariate analysis of the association between associated factors and latent tuberculosis infection (LTBI) status among diabetic patients (N = 703).

Variables	Simple logistic regression				Multiple logistic regression			
	Wald	B	OR (95% CI)	*p*-value	Wald	B	Adjusted OR (95% CI)	*p*-value
Diabetic control status								
No			1.00				1.00	
Yes	5.33	1.70	5.45 (1.29–22.99)	0.021	7.04	2.14	8.53 (1.75–41.61)	0.008
Occupational status								
Unemployed			1.00				1.00	
Healthcare workers	15.72	2.21	9.11 (3.06–27.15)	< 0.001	11.11	2.07	7.91 (2.34–26.70)	0.001
Non-healthcare workers	1.57	0.49	1.64 (0.76–3.55)	0.211	1.52	0.52	1.67 (0.74–3.80)	0.217
History of TB contact								
No			1.00				1.00	
Yes	21.18	1.82	6.19 (2.85–13.45)	< 0.001	16.15	1.74	5.69 (2.44–13.28)	< 0.001
Bronchial asthma								
No			1.00					
Yes	3.14	1.14	3.14 (0.89–11.14)	0.076	5.53	1.66	5.28 (1.32–21.13)	0.019
Coronary heart disease								
No			1.00				1.00	
Yes	4.43	1.08	0.34 (0.12–0.93)	0.035	4.95	1.24	3.45 (1.16–10.25)	0.026
Nephropathy								
No			1.00					
Yes	3.39	-0.91	0.40 (0.15–1.06)	0.065	4.23	-1.08	0.34 (0.12–0.95)	0.040

OR: odds ratio. Significant p-values are given in bold.

The current results indicate a low (4.8%) prevalence of LTBI among DM patients in Terengganu. The overall incidence of TB in Malaysia in the year 2021 was 97 per 100 000 people, which puts the country in the category of low-intermediate incidence of TB cases (< 100 TB cases per 100 000 people).[22] However, there are regional variations within Malaysia as shown by the high prevalence of LTBI in Seremban[23] (28.5%) and Kelantan[24] (11.4%), compared to our 4.8%. It may be instructive to take a closer look.

Data collection for the Seremban study was during 2014–2015.[23] The participants were older than ours (61.7 years vs. 58.9 years), and they would have had greater cumulative exposure to *M. tuberculosis*. Further, the Seremban study was based on patients attending a single clinic within a city, while our patients were from multiple clinics located in three locations in Terengganu state, giving us a much wider geoclimatic and ethnic representation. The location of the clinic in Seremban city also suggests that its subjects were more likely than ours to be exposed to an urbanized, industrialized, and thus relatively polluted environment.

The second study, conducted in a university clinic in Kelantan[24] during 2013–2015 on a DM population of mean age = 57.6, recorded a significantly lower prevalence of LTBI of 11.4% compared to the Seremban study, albeit more than twice as much as in the current study. Kelantan is less urbanized than Seremban which may partly explain the lower prevalence. Meanwhile, a reason for the higher prevalence of DM there compared to our study might be their poorer diabetic control status (HbA_{1c} = 8.82±2.10)[24] compared to ours (8.4±5.0). Hyperglycemia induces immune dysfunction with alteration of circulating levels of type 1 (interferon γ, interleukin 2, and tumor necrosis factor α) and type 17 (interleukin 17F) cytokines.[25] Therefore, poor glycemic control may influence the potential immunological mechanism, increasing the risk of LTBI in individuals with DM.

The wide variations in infection rates can strongly influence the incidence of TB in each country. For instance, many studies conducted in high TB incidence countries such as Mozambique, India, and South Africa have also reported a high prevalence of LTBI.[26–28]

Multivariate analysis identified six factors significantly associated with LTBI among DM patients — poor diabetic control status, being a healthcare worker, history of contact with TB patients, bronchial asthma, coronary heart disease, and nephropathy. Regarding glycemic control, our findings are consistent with studies in Mexico, USA, and India,[9,29–31] which also associated poor glycemic control with LTBI. Diabetic patients with immunocompromised states tend to have diminished cytokine levels, increasing their susceptibility to various pathogens including LTBI.[32]

In the current study, healthcare workers were significantly more likely to have LTBI than those working in other professions or unemployed. Likewise, previous studies have shown that the prevalence of LTBI in people who had a history of contact with TB patients increased by 1.14 to 1.32 times.[9,33] The prevalence of LTBI among healthcare workers may also increase with the number of years of work, being a smoker, or having diabetes.[8,34] A study from Malaysia showed that healthcare workers with a history of TB contact had 8.69 times higher odds of getting LTBI, while in Thailand, the risk of LTBI among nurses increased by 6% each year increase in age.[35,36] The association between age and LTBI among healthcare workers was also confirmed by studies in Italy and Oman.[34,37] Diabetic patients who live in the same house as TB patients are also at risk of being infected themselves, due to their weak immunity.[8]

Our results also agree with other studies that bronchial asthma is positively associated with LTBI. A study by Lee et al,[38] highlighted the association of consumption of the inhaled corticosteroid (ICS) with TB, where ICS decreases the local immunity of the lungs, facilitating the invasion of *M. tuberculosis*, leading to LTBI.

In our study, after adjusting for associated factors and other potential confounders, coronary heart disease was found significant to LTBI positivity. This was also in agreement with a Peruvian study which found that the adjusted risk of LTBI was 1.90 times higher in patients with acute myocardial infection (AMI) compared with no AMI, and also noted a higher prevalence of LTBI among AMI case-patient than in control (64% vs. 49%).[39]

However, we observed lower odds of LTBI among our patients with nephropathy. This was in contrast to previous studies which highlighted the increased risk of LTBI and active TB with chronic kidney disease.[40] This finding deserves further evaluation

and may be due to the impairment of the specific immune response in patients with chronic kidney disease in our patients towards the TST, leading to a lower reactivity. Other methods such as IGRA may perform better in elucidating LTBI in this group of patients.

To our knowledge, this is the first cross-sectional study to determine the associated factors of LTBI among diabetic patients conducted in a state in the east coast of Malaysia. It was a relatively large study that recruited patients in several primary care clinics across different regions of Terengganu, although it may not be absolutely representative of the diabetic population of the east coast of Malaysia.

Our study has several limitations. Being a cross-sectional study conducted within a limited period, we could identify only the associated factors rather than the actual risk factors. In view of the time and financial limitations, we used the TST instead of the more accurate IGRA test. Furthermore, this study did not compare the prevalence of LTBI between diabetic and non-diabetic patients.

CONCLUSION

The burden of LTBI is low among diabetic patients living on the east coast of Malaysia. However, screening for LTBI may be needed in diabetic patients with the associated factors of LTBI, namely having uncontrolled blood glucose level, nephropathy, bronchial asthma, coronary heart disease, history of TB contact, and working in the healthcare field. Efforts should be made to increase awareness of the benefit of improving blood sugar control in diabetic patients with LTBI.

Disclosure

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