



RESEARCH ARTICLE

Retrospective data analysis on the prevalence and demographic risk factors for latent tuberculosis infection (LTBI) cases from a private laboratory in Malaysia

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ABSTRACT

Tuberculosis (TB) is a critical disease that predominantly affects the lungs. This disease remains a global health threat. Currently, the incidence of TB is estimated to be 92 cases in every 100 000 population. However, latent TB infection (LTBI) cases among Malaysians are another great health concern that requires immediate steps to be taken to detect, diagnose, and treat LTBI as one of the key strategies to end TB. Although individuals with LTBI are unlikely to infect others, the threat of infection is still imminent as these individuals can potentially develop into active TB cases. As such, this study aims to identify the prevalence of LTBI among asymptomatic individuals that underwent QuantiFERON®-TB Gold Plus test from a private laboratory in Malaysia to determine the association between the risk factors and the detected LTBI cases. A retrospective study was conducted by analyzing the archive records of 3 877 samples from January 2021 to March 2022. The cases underwent QuantiFERON®-TB Gold Plus tests for LTBI at Premier Integrated Labs. This study underlines that those who were LTBI positive had a prevalence of 638/3 877 (16.46%) with males contributing to 343/638 cases (53.76%). Furthermore, the majority of the positive cases were between the age of 30-43 years old with 197/638 (30.88%), and Chinese ethnicity with 225/638 (35.27%). The risk factors significantly associated with LTBI cases were age ($p = 0.001$) and ethnicity ($p = 0.001$). The prevalence of LTBI determined through this study is considered remarkably low for an intermediate TB burden country. Although LTBI is not contagious, specific clinical and preventative considerations are needed for the diagnosis, treatment, and implementation of appropriate safety measures to curb the spread of TB in Malaysia.

Keywords: Latent tuberculosis infection; tuberculosis; prevalence; QuantiFERON®-TB Gold Plus; *Mycobacterium tuberculosis*.

INTRODUCTION

Tuberculosis (TB) is known as one of the top 10 causes of death from a single infectious agent worldwide in humans among adults and youth (WHO, 2020). Despite great efforts to eradicate the disease, TB cases in Malaysia are still a major public health threat. Although the rate of BCG vaccination coverage is high. Globally, it is estimated in 2019 about 10 million people fell ill from TB in which there were estimated 1.2 million TB deaths among HIV-negative people and an additional 208 000 deaths among HIV-positive people (WHO, 2020). Malaysia is categorized as an intermediate TB burden country with a cumulative incidence of 92 per 100 000 population (Menziés *et al.*, 2018; Atiqah *et al.*, 2023). TB has been identified as the highest contributor to death in Malaysia compared to other infectious diseases. Statistics from the Ministry of Health Malaysia show that TB is the second highest infectious disease after hand, foot, and mouth disease (HFMD) (Joshi *et al.*, 2007).

Mycobacterium tuberculosis (MTB) is an airborne bacterium released by an active TB patient through coughing or sneezing which can remain in the air for some time, infecting other people (Ahmad, 2011; Azit *et al.*, 2019). Approximately 90% of infected patients can fight the infection through the formation of granulomas without developing clinical symptoms of TB. Thus, granulomas are present in people with healthy immune systems because the immune system can contain or eliminate the infection and prevent disease symptoms from developing (Jo *et al.*, 2013). MTB could remain alive, non-replicating within the granuloma in a dormant state or inactive phase for years (latent state). Latent tuberculosis infection (LTBI), which is characterized as asymptomatic and non-infectious, is a persistent immunological response to MTB. Without proper diagnosis, intervention, and management, 5-15% of LTBI instances progress to active TB throughout the patient's lifetime (Blumberg & Ernst, 2016; WHO, 2020). Reactivation is the term used to describe this situation. Several risk factors, such as comorbid conditions that

could compromise immunity and the length of time a patient has been exposed to LTBI, have been shown to influence reactivation rates (Kiazzyk & Ball, 2017; Gupta *et al.*, 2020). Previous studies have identified that approximately 70% of TB cases occur due to the reactivation of past infections. Although those who have had the infection recently have a higher risk of developing active TB than those who have had it for longer, the rate of LTBI reactivation decreases over time (Gupta *et al.*, 2020).

LTBI cases among Malaysians are another great health concern that requires immediate steps to be taken to detect, diagnose and treat LTBI as one of the key strategies to eliminate TB (Makeswaran *et al.*, 2022). Although individuals with LTBI are unlikely to infect others, the threat of the infection is still imminent as these individuals can potentially develop into active TB. For many years, LTBI was detected through tuberculin skin test (TST), but now with an alternative immunodiagnostic approach using whole blood-based QuantiFERON technology that offers efficient and high-throughput, LTBI can be detected effectively (Abdalahamid *et al.*, 2010; Fernandes *et al.*, 2018). The most recent generation of interferon-gamma release assay (IGRA) tests is the fourth generation QuantiFERON®-TB Gold-Plus (QFT®-Plus) and it has been implemented in many hospitals worldwide since it was introduced in 2015 (Almohaya *et al.*, 2020). The sensitivity and specificity of QFT®-Plus in screening for LTBI in children at aged 1-4 years were 75% and 100% respectively (Borkowska-Tatar *et al.*, 2021), whilst the sensitivity and specificity of the test in screening for LTBI in old populations (without histories of TB) in Taiwan were 100% and 95.1% (Chien *et al.*, 2018). Both TST and IGRA are indirect tests based on the host's immune response to TB and do not directly assess nor detect the bacteria. However, IGRA tests are more sensitive for the diagnosis of tuberculosis (TB) because it is not affected by bacillus Calmette-Guérin (BCG) vaccination nor by non-tuberculosis mycobacterial infections compared to TST (Yilmaz *et al.*, 2012). It is also not dependent on the injection method that requires the use of purified protein derivatives and does not involve interpretation of induration size to be read at 48-72 hours (CDC, 2023).

It is estimated that around one in four global populations suffer from LTBI and few of them can suffer from active TB if they are from a high-risk group. Various risk factors reported being associated with LTBI including smoking habits, HIV infection, immunosuppression, male gender, and younger age as well as the risk of developing active TB following infection depending on the quality of the immune defense mechanisms and the time elapsed since the infection (Watkins & Plant, 2006; Zwerling *et al.*, 2012; Jo *et al.*, 2013; Chu *et al.*, 2014; Klein & Flanagan, 2016). The estimated lifetime risk is about 5-10%, higher in small children, immunocompromised individuals, and shortly (within 1-2 years) after contact with an active TB case (Zwerling *et al.*, 2012). With limitations to clinical data and vaccination status, therefore, this study aims to investigate the prevalence of LTBI in Malaysia as detected via QuantiFERON®-TB Gold-Plus (QFT®-Plus) in the asymptomatic patients-based sample and to determine the relationship between LTBI with age, gender, and ethnicity.

MATERIALS AND METHODS

Study population and source of data

This was a retrospective study of 3 877 samples that screened for LTBI at Premier Integrated Labs, Kuala Lumpur, Malaysia, between January 2021 and March 2022. Samples obtained were from Pantai Hospitals all over Malaysia, as well as those from government and private clinics. The inclusion criteria are 1) samples from asymptomatic individuals seen in primary care that did not undergo the QFT®-Plus screening test, and 2) complete demographic information for each participant (age, gender, and ethnicity). The exclusion criteria were the individuals with blood samples that did not

follow the requirements of the specifications of the QFT®-Plus test such as no sufficient volume of blood, overfilled and not following collection guidelines. The sociodemographic features (gender, age, and ethnicity) of the subjects were recorded as presented in Table 1. This study was approved by the Research Ethics Committee Universiti Kebangsaan Malaysia (Human) (UKM PPI/111/8/JEP-2022-089). Written consent was also obtained and documented before the execution of the study.

QuantiFERON-TB Gold Plus assays

QFT®-Plus testing was performed on blood samples collected in accordance with the QFT®-Plus manufacturer's instructions (QuantiFERON®-TB Gold Plus, Qiagen, Hilden, Germany). The whole blood (5 ml) was drawn into blood-collecting vessels containing lithium-heparin. Briefly, 1 ml of the peripheral blood was transferred into each of four blood collection tubes: nil tube or negative control, the mitogen tube or positive control and the TB specific antigen tube (TB1 and TB2) containing specific antigens (early secretory antigenic target 6 and culture filtrate protein 10) for *M. tuberculosis*. The contents of each tube were mixed and the tubes were incubated at 37°C for 16 to 24 hours within 16 hours of collection. Then they were centrifuged at 2 500 rpm for 15 minutes at room temperature. The serum was stored at 4°C following incubation until examination. The concentration of IFN- γ in each sample was determined by the QFT®-Plus ELISA (enzyme-linked immunosorbent assay) kit. The results (IU/ml) were interpreted according to the criteria provided in the manufacturer's guidelines. LTBI was defined as a positive test when either the TB1 or TB2 tubes of the 4 tubes (Nil, TB1, TB2, Mitogen) was above the Nil IFN- γ IU/ml value. The blood test results may be negative, positive, or indeterminate. A positive test result, however, does not distinguish between active and latent TB or predict the risk of progression from latent to active TB but it may help in screening TB infection in normal population.

Statistical analysis

Data were presented as frequencies and percentages for categorical and continuous variables. The sociodemographic factors such as gender, age groups, and ethnicity were compared using the chi-square test. Multivariable logistic regression analysis was conducted to assess the associations of selected independent variables with LTBI cases. The model fit was assessed using Hosmer-Lemeshow goodness-of-fit test, where a p-value greater than 0.05 means that the model is a good fit. A similar approach was also used to identify risk factors for the results of the LTBI cases. Adjusted odds ratio (aOR) with a 95% confidence interval (95% CI) and Wald p-value were reported in all the regression analysis results to show the strength of association between independent and outcome variables. All data preparation, calculations, and analyses were performed using Microsoft Excel and Statistical Package for the Social Sciences, version 26 (SPSS® IBM Corp., Chicago, IL, USA). The level of significance was set at a p-value less than 0.05.

RESULTS

This study investigates LTBI cases handled by Premier Integrated Labs, over fifteen months and compares the demographic characteristics of these patients. Between January 2021 and March 2022, a total of 4 125 patients were identified. Only 3 877 patients, however, have complete demographic data and met all the criteria. The demographic characteristics of the study subjects were recorded, including their age, gender, and ethnicity. The patients were primarily males (56.05%), Malay (36.83%), and aged 30-43 (32.65%). (Table 1). According to the QFT®-Plus test results, 683 (16.46%) of the suspected LTBI patients tested positive for LTBI. The majority of the cases, 2 853 (73.59%), were LTBI-negative, while the remaining 386 (9.96%) had indeterminate results, as shown in Figure 1.

Table 1. Sociodemographic characteristics of the study population (n = 3877)

Variables	Frequencies (n)	%
<i>Gender</i>		
Male	2173	56.05
Female	1704	43.95
<i>Age</i>		
<15	200	5.16
15-29	868	22.39
30-43	1266	32.65
44-59	854	22.03
≥60	689	17.77
<i>Ethnicity</i>		
Chinese	1304	33.63
Malay	1428	36.83
Indian	371	9.57
Others	774	19.96

Table 2. Sociodemographic characteristics of positive latent tuberculosis infection patients (LTBI) (n = 638)

Variables	LTBI cases (n, %)
<i>Gender</i>	
Male	343 (53.76)
Female	295 (46.24)
<i>Age</i>	
<15	24 (3.76)
15-29	140 (21.94)
30-43	197 (30.88)
44-59	151 (23.67)
≥60	126 (19.75)
<i>Ethnicity</i>	
Chinese	225 (35.27)
Malay	198 (31.03)
Indian	57 (8.93)
Others	158 (24.77)

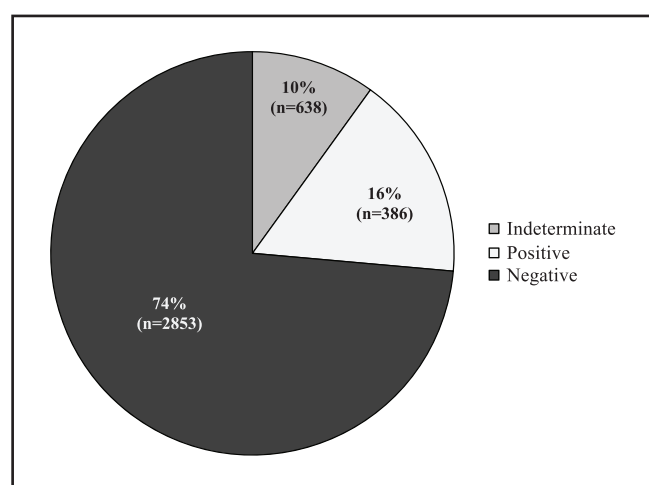


Figure 1. QuantiFERON®-TB Gold Plus results from n=3877 samples.

According to the study, males had the highest LTBI prevalence of 343/638 (53.76%), while females had 295/638 (46.24%) (Table 2). The 30-43 age group had 197/638 (30.88%) patients diagnosed with LTBI, followed by the 44-59 age group (23.67%). The average age of the patients was 42.76 years, ranging from 1 to 93 years old. Table 2 shows that Chinese ethnicity had a higher risk of LTBI with 225/638 (35.27%). Table 3 shows no significant difference in age groups or ethnicity with genders of subjects with LTBI positivity (2= 3.507, p = 0.477 and 2= 3.507, p = 0.477, respectively).

Table 3. Independent risk factors associated with latent tuberculosis infections by Chi-square analysis

Risk factors	Positive LTBI cases, n (%)		χ ²	P value
	Male	Female		
<i>Age</i>				
<15	15 (4.37)	9 (3.05)	3.507	0.477
15-29	69 (20.12)	72 (24.41)		
30-43	102 (29.74)	94 (31.86)		
44-59	84 (24.49)	67 (22.71)		
≥60	73 (21.28)	53 (17.97)		
<i>Ethnicity</i>				
Malay	107 (31.20)	91 (30.85)	2.901	0.407
Chinese	127 (37.03)	98 (33.22)		
Indian	25 (7.29)	32 (10.85)		
Others	84 (24.49)	74 (25.08)		

Multivariate analysis was used to evaluate the parameters that were significantly associated with positive and negative LTBI outcomes. Age and ethnicity are the risk factors that were shown as predictors that increase the predictive ability of the test model which were significantly related to the positive QFT®-Plus outcomes, as shown in Table 4. An increase of one year in age results in a 0.8% (95% CI 0.4% to 1.3%) increase in the likelihood of having LTBI.

Table 4. Independent risk factors associated with QFT®-Plus result from multivariate binary logistic regression

Risk factors	QFT-Plus test result, n (%)		Coefficient (B)	Wald X ²	P value	aOR (95% CI)
	Positive	Negative				
<i>Gender</i>						
Male	343 (53.76)	1634 (57.27)	Ref	Ref	Ref	Ref
Female	295 (46.24)	1219 (42.73)	0.119	1.812	0.178	1.13 (0.95, 1.34)
<i>Age</i>	638 (18.28)	2853 (81.72)	0.008	11.602	0.001***	0.80 (0.40, 1.30)
<i>Ethnicity</i>						
Chinese	225 (35.27)	901 (31.58)	Ref	Ref	Ref	Ref
Malay	198 (31.03)	1136 (39.82)	0.291	7.104	0.008	1.4 (1.08, 1.66)
Indian	57 (8.93)	271 (9.50)	0.151	0.836	0.361	1.16 (0.84, 1.61)
Others	158 (24.77)	519 (18.19)	0.477	15.983	0.001	1.61 (1.28, 2.04)

Model fit measures: Deviance 34.837, Cox and Snell R square 0.010, Nagelkerke R square 0.016. aOR: Adjusted odds ratio. CI: Confidence Interval.

DISCUSSION

Deaths due to TB in Malaysia recorded an increment of 12% in 2022 compared to 2021. The rise could be attributed to latent tuberculosis reactivation, which has been linked to COVID-19 cases. This is a major concern because reactivation can have serious health consequences if not detected and treated promptly. Thus, efforts to increase detection rates through early screening are critical and should be stepped up if necessary. Following that, this research was carried out to determine the prevalence of current LTBI cases in a Malaysian scenario.

There was a total of 4 125 individuals that underwent QFT®-Plus test from January 2021 to March 2022. However, only 3 877 patients that fulfilled all the inclusion and exclusion criteria were included in this study. Based on the descriptive analysis, 386 (16%) cases were detected as positive for LTBI whereas the majority were negative (n=2 853, 74%). The detected positive cases of LTBI reflect the number of potential cases of MTB reactivation and community transmission of TB if not being followed up or appropriately managed. Besides that, QFT®-Plus test results also indicate that a total of 638 (10%) patients have indeterminate results. Previous studies have shown that immunocompromised individuals and cancer patients with indeterminate results are associated with the elderly, children under five years of age, individuals receiving immunosuppressive therapy, having lymphocytopenia and hypoalbuminemia (Kobashi *et al.*, 2009; Richeldi *et al.*, 2009). A study conducted by Richeldi *et al.* (2009), found that the abnormal content of white blood cells with a low percentage and lymphocyte numbers were associated with indeterminate results. This situation impairs the reaction of the immune cells, CD4+ and CD8+ T lymphocytes towards ESAT6 and CFP10 antigens affecting the IFN- γ production *in vitro*. Other previous studies also reported that the relatively high frequency of indeterminate results is likely to be a consequence of the high proportion of individuals who had conditions that could affect their immune responses, for instance, chronic inflammatory diseases, lack of nutrition, or could also be due to technical issues regarding improper handling and transport of the blood samples (Calabrese *et al.*, 2015; Brown *et al.*, 2017; Oh *et al.*, 2019; Ahn *et al.*, 2021).

The results of the current population-based retrospective study showed that most of the patients detected with positive LTBI were males, which is consistent with most research reports that show high proportions of active TB or LTBI among male adults (He *et al.*, 2012; Ting *et al.*, 2014; He *et al.*, 2015; Ahmad *et al.*, 2021). Several studies found that men are more susceptible to bacterial, parasitic, fungal, and viral infections (Bernin & Lotter, 2014; Klein & Flanagan, 2016; Vom Steeg & Klein, 2016; Jacobsen & Klein, 2021), meanwhile, women are at a higher risk of getting autoimmune diseases such as systemic lupus erythematosus (SLE) and multiple sclerosis (MS) (Fairweather & Rose, 2004; Angum *et al.*, 2020). Sex hormones have been linked to the development of sex differences in the immune response to infections (Jacobsen & Klein, 2021). Gender differences in health and lifestyle habits may result in differences in infection risk factors. This could be due to exposure to smoking habits and alcohol consumption (Fernandes *et al.*, 2018; Oh *et al.*, 2023), as well as social contact factors, as the prevalence of LTBI was higher in males in the current study (involving occupational exposure) (Dodd *et al.*, 2016; Jacobsen & Klein, 2021). Chronic exposure to cigarette smoke can reduce the percentage of dendritic cells in the lungs, induce changes in the expression of stimulation molecules and weaken the response of CD4+ and CD8+ cells in the process of fighting infection or inflammation (Erawati & Andriany, 2020). The process of neutralizing microorganisms also will decrease as well as the immune system to fight against foreign pathogens such as viruses or bacteria which then increase the risk of various infections (Robbins *et al.*, 2004).

Further analysis shows that patients between the age of 30 and 43 were most diagnosed with LTBI compared to other age groups with 197 (30.88%) cases. The age of the patients within this range in the present study was similar to previous reports (Belo & Naidoo, 2017; Almohaya *et al.*, 2020; Gray *et al.*, 2020). Similar results were also reported by a Nigerian study performed prospectively on pulmonary TB patients which recorded the highest prevalence in the same group (Imam & Oyeyi, 2008). This proves that LTBI cases increase among young middle-aged groups (30-50 years) generally reflecting accumulated exposure over previous decades as this age was the “golden time” of a person who has accumulated life experience, and professional skills and reached the peak of potential abilities as well as social maturity and career (Dyussenbayev, 2017). Chinese ethnicity was found to have a higher risk of getting LTBI which accounted for 225 cases (35.27%), followed by Malay (198, 31.03%), Indian (57, 8.93%), and others (158, 24.77%). Previous studies conducted among Singapore healthcare workers discovered that while Chinese as a single race have the highest prevalence of TB cases, but come in second with 19.2%, trailing the other smaller ethnicities group that exclude Malays and Indians (52.3%) (Chia *et al.*, 2020). This could be attributed to a genetic predisposition that can affect the immune system of a specific population, making them more susceptible to certain infections and diseases (Abel *et al.*, 2018).

According to previous research, the risk factors of age and ethnicity are less debated in terms of their relationship in determining the sex disparities (gender) of LTBI patients. Only a few studies examined into the relationship between gender and sociodemographic risk factors (age and ethnicity), and its validity is still being debated. An independent Chi-square test was used in this study only to reveal that there was no significant difference in age groups and race between male and female LTBI patients. Similarly, a previous study on TB patients found no significant differences between pulmonary TB patients' gender and the risk factor of age (Imam & Oyeyi, 2008). There has been a lack of research into the relationship between ethnicity and health.

This study also aims to explore the predictors for positive and negative QFT®-Plus results for LTBI. Since few studies have identified age, gender, and ethnicity which are more focused on healthcare workers as a predictor in determining the QFT-Plus result (Abdalhamid *et al.*, 2010; Chu *et al.*, 2014; Almohaya *et al.*, 2020), we chose to identify the associated risk factors that could be in a population-based study. From the analysis of the overall model for the logistic regression, the risk factors of age and ethnicity show a significant predictive model with a significant correlation respectively. Meanwhile, gender does not play a role in determining the positive and negative results for LTBI. The male gender is not a factor with a substantial impact after adjusting for age, smoking history, and other clinical characteristics (Ting *et al.*, 2014). This result may explain why in the multivariate risk analysis, there was no significant difference between males and females, which also suggested that gender is only a complicated reflection of multiple factors such as gender issues, behavior, social activities, pregnancy, and other risk factors for TB infection (Imam & Oyeyi, 2008).

Age is always reported as a risk factor for positive LTBI tests. An increase of one year in age results in a 0.8% (95% CI 0.4% to 1.3%) increase in the likelihood of having LTBI. Advancement in age was previously demonstrated to be a significant predictor of LTBI incidence and men aged 34 years and older were found to be at an increased risk of LTBI (Byng-Maddick & Noursadeghi, 2016; Almohaya *et al.*, 2020). The increase of LTBI prevalence with age is a well-known observation previously reported either with QuantIFERON-Gold In-Tube (Harada *et al.*, 2006; Jo *et al.*, 2013) or TST (Rutanga *et al.*, 2015). Previous studies also found that the age group between 30 to 59 years has a high risk of LTBI, where the

increased risk of infection among individuals aged 35 to 60 years is probably explained by a prolonged cumulative exposure that could be occupational and/or non-occupational such as the type of work, the duration of exposure and environment factors (Zwerling et al., 2012; CDC, 2016; Belo & Naidoo, 2017; Sabri et al., 2019; Almohaya et al., 2020). A study by Rafiza et al. (2011) shows that employment factors show a significant link to the high prevalence of LTBI for individuals whose employment period exceeds 11 years and above (Rafiza et al., 2011; Oh et al., 2019). Other research findings show that people over 50 years old have a significant relationship with LTBI (Abbas et al., 2010; Almohaya et al., 2020). This may be due to age-related changes to the immune system in the phenotype and function of macrophages, which might be expected to compromise their role in protection against TB (Byng-Maddick & Noursadeghi, 2016).

Similar to the current study, the risk factors of ethnicity were found to increase the risk of a positive LTBI result (Gray et al., 2020). Ethnicity seems to remain an independent factor in the association of LTBI (Chia et al., 2020). It is still unclear whether the relationship is related to lifestyle, dietary habits, or certain personal beliefs, but this may have implications for targeted screening of risk groups in the future. Apart from that, only a few studies were found in investigating the association between ethnicity determining the positive result of LTBI. Thus, the risk factors of ethnicity remain in question about the role and its association in determining the infectivity of LTBI, especially in the general population in Malaysia. Targeting the high-risk and vulnerable groups for TB or LTBI can aid in early detection and treatment, reducing the risk of transmission of the infection among people.

Comparing QuantiFERON to TST in a fictitious scenario that looked at rising LTBI prevalence and rising TB reactivation rates revealed QuantiFERON to be more affordable. TST's lesser sensitivity as compared to QuantiFERON resulted in more false negative results, which meant that a larger percentage of the population eventually developed active TB. Similarly, there were more false positives due to TST's inferior specificity in a BCG population compared to QuantiFERON, which led to an increase in the number of patients undergoing unnecessary prophylactic medication. As a result, more patients had side effects from the medication. Moreover, unnecessary preventative care for false positives increased the expense of TST instead.

This study acknowledges several limitations that warrant consideration. Due to the retrospective nature of the study, which was limited to diagnostic laboratory findings and inaccessible medical records, clinical histories and radiological findings were not fully accessible. This limitation potentially compromised the ability to thoroughly evaluate the association of clinical factors such as smoking exposure, disease status and workplace hazards (e.g. healthcare workers), with the study outcomes. Future research efforts should prioritise improving data collection methods and accessing more detailed clinical and radiological information in order to enhance the study findings. However, despite these limitations, the current study managed to identify demographic-based risk factors that pose a higher risk for developing TB disease in certain individuals. Screening for LTBI in populations at increased risk is recommended (US Preventive Services Task Force, 2023)

CONCLUSIONS

Controlling the spread of tuberculosis remains a formidable challenge, as the TB pathogen can remain dormant in humans for years. The advent of QuantiFERON®-TB Gold Plus, on the other hand, has the ability to detect latent tuberculosis infection in patients. Our study sheds light on key demographic trends, revealing that LTBI is notably prevalent among men, individuals aged 30-43, and those of Chinese ethnicity, with age and ethnicity identified as significant

risk factors. It is imperative that we prioritize widespread screening for LTBI within the general population and intensify efforts to identify high-risk individuals for TB reactivation and transmission. Furthermore, timely surveillance and monitoring are essential to track changes in LTBI prevalence, tuberculosis incidence and healthcare utilization patterns thus enabling us to plan targeted interventions effectively. Implementing these strategies will pave the way for comprehensive healthcare initiatives aimed at eradicating tuberculosis in Malaysia.

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Conflict of Interest

The author declares that they have no conflict of interests.

REFERENCES

- Abbas, M.A., AlHamdan, N.A., Fiala, L.A., Alenezy, A.K. & Alqahtani, M.S. (2010). Prevalence of latent TB among health care workers in four major tertiary care hospitals in Riyadh, Saudi Arabia. *Journal of the Egyptian Public Health Association* **85**: 61-71.
- Abdalahamid, B., Hinrichs, S.H., Garrett, J.L., O'neill, J.M., Hansen-Cain, K.M., Armbrust, A.A. & Iwen, P.C. (2010). Utilization of the QuantiFERON-TB Gold test in a two-step process with the tuberculin skin test to evaluate health care workers for latent tuberculosis. *Journal of Clinical Microbiology* **48**: 2955-2956. <https://doi.org/10.1128/jcm.02253-09>
- Abel, L., Fellay, J., Haas, D.W., Schurr, E., Srikrishna, G., Urbanowski, M., Chaturvedi, N., Srinivasan, S., Johnson, D.H. & Bishai, W.R. (2018). Genetics of human susceptibility to active and latent tuberculosis: present knowledge and future perspectives. *The Lancet Infectious Diseases* **18**: e64-e75. [https://doi.org/10.1016/s1473-3099\(17\)30623-0](https://doi.org/10.1016/s1473-3099(17)30623-0)
- Ahmad, N., Baharom, M., Aizuddin, A.N. & Ramli, R. (2021). Sex-related differences in smear-positive pulmonary tuberculosis patients in Kuala Lumpur, Malaysia: prevalence and associated factors. *PLoS One* **16**: e0245304. <https://doi.org/10.1371/journal.pone.0245304>
- Ahmad, S. (2011). Pathogenesis, immunology, and diagnosis of latent *Mycobacterium tuberculosis* infection. *Journal of Immunology Research* **2011**: 814943. <https://doi.org/10.1155/2011/814943>
- Ahn, S.S., Kim, H.W. & Park, Y. (2021). Frequency and factors of indeterminate QuantiFERON-TB Gold In-Tube and QuantiFERON-TB Gold PLUS test results in rheumatic diseases. *Journal of Clinical Medicine* **10**: 4357. <https://doi.org/10.3390/jcm10194357>
- Almohaya, A., Aldrees, A., Akkielah, L., Hashim, A.T., Almajid, F., Binmoammar, T. & Barry, M.A. (2020). Latent tuberculosis infection among health-care workers using QuantiFERON-TB Gold-Plus in a country with a low burden for tuberculosis: prevalence and risk factors. *Annals of Saudi Medicine* **40**: 191-199. <https://doi.org/10.5144/0256-4947.2020.191>
- Angum, F., Khan, T., Kaler, J., Siddiqui, L. & Hussain, A. (2020). The prevalence of autoimmune disorders in women: a narrative review. *Cureus* **12**: e8094. <https://doi.org/10.7759/cureus.8094>
- Atiqah, A., Tong, S.F. & Nadirah, S. (2023). Treatment outcomes of extended versus nonextended intensive phase in pulmonary tuberculosis smear positive patients with delayed sputum smear conversion: a retrospective cohort study at primary care clinics in Kota Kinabalu. *Malaysian Family Physician* **18**: 2. <https://doi.org/10.51866/oa.191>
- Azit, N.A., Ismail, A., Ahmad, N., Ismail, R. & Ishak, S. (2019). Factors associated with tuberculosis disease among children who are household contacts of tuberculosis cases in an urban setting in Malaysia. *BMC Public Health* **19**: 1432. <https://doi.org/10.1186/s12889-019-7814-x>
- Belo, C. & Naidoo, S. (2017). Prevalence and risk factors for latent tuberculosis infection among healthcare workers in Nampula Central Hospital, Mozambique. *BMC Infectious Diseases* **17**: 408. <https://doi.org/10.1186/s12879-017-2516-4>
- Bernin, H. & Lotter, H. (2014). Sex bias in the outcome of human tropical infectious diseases: influence of steroid hormones. *The Journal of Infectious Diseases* **209**: S107-113. <https://doi.org/10.1093/infdis/jit610>
- Blumberg, H.M. & Ernst, J.D. (2016). The challenge of latent TB infection. *JAMA* **316**: 931-933. <https://doi.org/10.1001/jama.2016.11021>

- Borkowska-Tatar, D., Krasiboska, M. & Augustynowicz-Kopet, E. (2021). QuantiFERON-TB Gold Plus test in diagnostics of latent tuberculosis infection in children aged 1-14 in a country with a low tuberculosis incidence. *Polish Journal of Microbiology* **70**: 461-468. <https://doi.org/10.33073/pjm-2021-042>
- Brown, J., Kumar, K., Reading, J., Harvey, J., Murthy, S., Capocci, S., Hopkins, S., Seneviratne, S., Cropley, I. & Lipman, M. (2017). Frequency and significance of indeterminate and borderline Quantiferon Gold TB IGRA results. *European Respiratory Journal* **50**: 1701267. <https://doi.org/10.1183/13993003.01267-2017>
- Byng-Maddick, R. & Noursadeghi, M. (2016). Does tuberculosis threaten our ageing populations? *BMC Infectious Diseases* **16**: 119. <https://doi.org/10.1186/s12879-016-1451-0>
- Calabrese, C., Overman, R.A., Dusetzina, S.B. & Hajji-Ali, R.A. (2015). Evaluating indeterminate interferon- γ release assay results in patients with chronic inflammatory diseases receiving immunosuppressive therapy. *Arthritis Care and Research* **67**: 1063-1069. <https://doi.org/10.1002/acr.22454>
- Centers for Disease Control and Prevention (CDC). (2016). Basic TB Facts. [https://www.cdc.gov/tb/topic/basics/default.htm#:~:text= Tuberculosis%20\(TB\)%20is%20caused%20by,with%20TB%20bacteria%20becomes%20sick](https://www.cdc.gov/tb/topic/basics/default.htm#:~:text= Tuberculosis%20(TB)%20is%20caused%20by,with%20TB%20bacteria%20becomes%20sick). Accessed 2 April 2023
- Centers for Disease Control and Prevention (CDC). (2023). Testing for TB infection. <https://www.cdc.gov/tb/topic/testing/tbtesttypes.htm>. Accessed 6 February 2024
- Chia, S.Z.G., How, K.B.M., Chlebicki, M.P., Ling, M.L. & Gan, W.H. (2020). A retrospective review of tuberculosis exposure among health care workers in a tertiary hospital. *American Journal of Infection Control* **48**: 650-655. <https://doi.org/10.1016/j.ajic.2019.10.014>
- Chien, J.-Y., Chiang, H.-T., Lu, M.-C., Ko, W.-C., Yu, C.-J., Chen, Y.-H. & Hsueh, P.-R. (2018). QuantiFERON-TB Gold Plus is a more sensitive screening tool than QuantiFERON-TB Gold In-Tube for latent tuberculosis infection among older adults in long-term care facilities. *Journal of Clinical Microbiology* **56**: 10.1128/jcm.00427-00418. <https://doi.org/10.1128/jcm.00427-18>
- Chu, H., Shih, C.J., Lee, Y.J., Kuo, S.C., Hsu, Y.T., Ou, S.M., Shih, Y.N., Tarng, D.C., Li, S.Y., Chen, Y.T. et al. (2014). Risk of tuberculosis among healthcare workers in an intermediate-burden country: a nationwide population study. *Journal of Infection* **69**: 525-532. <https://doi.org/10.1016/j.jinf.2014.06.019>
- Dodd, P.J., Looker, C., Plumb, I.D., Bond, V., Schaap, A., Shanaube, K., Muyoyeta, M., Vynnycky, E., Godfrey-Faussett, P., Corbett, E.L. et al. (2018). Age- and sex-specific social contact patterns and incidence of *Mycobacterium tuberculosis* infection. *American Journal of Epidemiology* **183**: 156-166. <https://doi.org/10.1093/aje/kwv160>
- Dyussenbayev, A. (2017). Age periods of human life. *Advances in Social Sciences Research Journal* **4**: 258-263. <https://doi.org/10.14738/assrj.46.2924>
- Erawati, M. & Andriany, M. (2020). The prevalence and demographic risk factors for latent tuberculosis infection (LTBI) among healthcare workers in Semarang, Indonesia. *Journal of Multidisciplinary Healthcare* **13**: 197-206. <https://doi.org/10.2147/JMDH.S241972>
- Fairweather, D. & Rose, N.R. (2004). Women and autoimmune diseases. *Emerging Infectious Diseases* **10**: 2005-2011. <https://doi.org/10.3201/eid1011.040367>
- Fernandes, P., Ma, Y., Gaedert, M., Tsacogianis, T., Marques-Rodrigues, P., Fregona, G., Loomans, A., Jones-Lopez, E.C., Dietze, R., Ellner, J.J. et al. (2018). Sex and age differences in *Mycobacterium tuberculosis* infection in Brazil. *Epidemiology and Infection* **146**: 1503-1510. <https://doi.org/10.1017/S0950268818001450>
- Gray, B.J., Perrett, S.E., Gudgeon, B. & Shankar, A.G. (2020). Investigating the prevalence of latent Tuberculosis infection in a UK remand prison. *Journal of Public Health* **42**: e12-e17. <https://doi.org/10.1093/pubmed/fdy219>
- Gupta, R.K., Calderwood, C.J., Yavilinsky, A., Krutikov, M., Quartagno, M., Aichelburg, M.C., Altet, N., Diel, R., Dobler, C.C., Dominguez, J. et al. (2020). Discovery and validation of a personalized risk predictor for incident tuberculosis in low transmission settings. *Nature Medicine* **26**: 1941-1949. <https://doi.org/10.1038/s41591-020-1076-0>
- Harada, N., Nakajima, Y., Higuchi, K., Sekiya, Y., Rothel, J. & Mori, T. (2006). Screening for tuberculosis infection using whole-blood interferon-gamma and Mantoux testing among Japanese healthcare workers. *Infection Control and Hospital Epidemiology* **27**: 442-448. <https://doi.org/10.1086/504358>
- He, G., Li, Y., Zhao, F., Wang, L., Cheng, S., Guo, H., Klena, J.D., Fan, H., Gao, F., Gao, F. et al. (2015). The prevalence and incidence of latent tuberculosis infection and its associated factors among village doctors in China. *PLoS One* **10**: e0124097. <https://doi.org/10.1371/journal.pone.0124097>
- He, G.X., Wang, L.X., Chai, S.J., Klena, J.D., Cheng, S.M., Ren, Y.L., Ren, L.P., Gao, F., Li, Y.Y., He, G.M. et al. (2012). Risk factors associated with tuberculosis infection among health care workers in Inner Mongolia, China. *The International Journal of Tuberculosis and Lung Disease* **16**: 1485-1491. <https://doi.org/10.5588/ijtld.12.0193>
- Imam, T. & Oyeyi, T. (2008). A retrospective study of Pulmonary Tuberculosis (PTB) prevalence amongst patients attending infectious diseases hospital, in Kano, Nigeria. *Bayero Journal of Pure and Applied Sciences* **1**: 10-15. <http://doi.org/10.4314/bajopas.v1i1.57503>
- Jacobsen, H. & Klein, S.L. (2021). Sex differences in immunity to viral infections. *Frontiers in Immunology* **12**: 720952. <https://doi.org/10.3389/fimmu.2021.720952>
- Jo, K.W., Hong, Y., Park, J.S., Bae, I.G., Eom, J.S., Lee, S.R., Cho, O.H., Choo, E.J., Heo, J.Y., Woo, J.H. et al. (2013). Prevalence of latent tuberculosis infection among health care workers in South Korea: a multicenter study. *Tuberculosis and Respiratory Diseases* **75**: 18-24. <https://doi.org/10.4046/trd.2013.75.1.18>
- Joshi, R., Patil, S., Kalantri, S., Schwartzman, K., Menzies, D. & Pai, M. (2007). Prevalence of abnormal radiological findings in health care workers with latent tuberculosis infection and correlations with T cell immune response. *PLoS One* **2**: e805. <https://doi.org/10.1371/journal.pone.0000805>
- Kiazky, S. & Ball, T.B. (2017). Latent tuberculosis infection: An overview. *Canada Communicable Disease Report* **43**: 62-66. <https://doi.org/10.14745/ccdr.v43i34a01>
- Klein, S.L. & Flanagan, K.L. (2016). Sex differences in immune responses. *Nature Reviews Immunology* **16**: 626-638. <https://doi.org/10.1038/nri.2016.90>
- Kobashi, Y., Sugiu, T., Mouri, K., Obase, Y., Miyashita, N. & Oka, M. (2009). Indeterminate results of QuantiFERON TB-2G test performed in routine clinical practice. *European Respiratory Journal* **33**: 812-815. <https://doi.org/10.1183/09031936.00075008>
- Makeswaran, P., Shah, S.A., Safian, N., Muhamad, N.A. & Harith, A.A. (2022). Determinants of delayed tuberculosis treatment among patients in Selangor: a study protocol. *PLoS One* **17**: e0266746. <https://doi.org/10.1371/journal.pone.0266746>
- Menzies, N.A., Hill, A.N., Cohen, T. & Salomon, J.A. (2018). The impact of migration on tuberculosis in the United States. *The International Journal of Tuberculosis and Lung Disease* **22**: 1392-1403. <https://doi.org/10.5588/ijtld.17.0185>
- Oh, A.L., Makmor-Bakry, M., Islahudin, F. & Wong, I.C.K. (2023). Prevalence and predictive factors of tuberculosis treatment interruption in the Asia region: a systematic review and meta-analysis. *BMJ Global Health* **8**: e010592. <https://doi.org/10.1136/bmjgh-2022-010592>
- Oh, J., Park, H.D., Kim, S.Y., Koh, W.J. & Lee, S.Y. (2019). Assessment of vitamin status in patients with nontuberculous mycobacterial pulmonary disease: potential role of vitamin A as a risk factor. *Nutrients* **11**: 343. <https://doi.org/10.3390/nu11020343>
- Rafiza, S., Rampal, K.G. & Tahir, A. (2011). Prevalence and risk factors of latent tuberculosis infection among health care workers in Malaysia. *BMC Infectious Diseases* **11**: 19. <https://doi.org/10.1186/1471-2334-11-19>
- Richeldi, L., Losi, M., D'Amico, R., Luppi, M., Ferrari, A., Mussini, C., Codeluppi, M., Cocchi, S., Prati, F., Paci, V. et al. (2009). Performance of tests for latent tuberculosis in different groups of immunocompromised patients. *Chest* **136**: 198-204. <https://doi.org/10.1378/chest.08-2575>
- Robbins, C.S., Dawe, D.E., Goncharova, S.I., Pouladi, M.A., Drannik, A.G., Swirski, F.K., Cox, G. & Stimpfli, M.R. (2004). Cigarette smoke decreases pulmonary dendritic cells and impacts antiviral immune responsiveness. *American Journal of Respiratory Cell and Molecular Biology* **30**: 202-211. <https://doi.org/10.1165/rcmb.2003-0259OC>
- Rutanga, C., Lowrance, D.W., Oeltmann, J.E., Mutembayire, G., Willis, M., Uwizeye, C.B., Hinda, R., Bassirou, C., Gutreuter, S. & Gasana, M. (2015). Latent tuberculosis infection and associated factors among health care workers in Kigali, Rwanda. *PLoS One* **10**: e0124485. <https://doi.org/10.1371/journal.pone.0124485>
- Sabri, A., Quistebert, J., Naji Amrani, H., Abid, A., Zegmout, A., Abderrhamani Ghorfi, I., Souhi, H., Boucaid, A., Benali, A., Abilkassem, R. et al. (2019). Prevalence and risk factors for latent tuberculosis infection among healthcare workers in Morocco. *PLoS One* **14**: e0221081. <https://doi.org/10.1371/journal.pone.0221081>

- Ting, W.Y., Huang, S.F., Lee, M.C., Lin, Y.Y., Lee, Y.C., Feng, J.Y. & Su, W.J. (2014). Gender disparities in latent tuberculosis infection in high-risk individuals: a cross-sectional study. *PLoS One* **9**: e110104. <https://doi.org/10.1371/journal.pone.0110104>
- US Preventive Services Task Force. (2023). Screening for latent tuberculosis infection in adults: US Preventive Services Task Force recommendation statement. *JAMA* **329**: 1487-1494. <https://doi.org/10.1001/jama.2023.4899>
- Vom Steeg, L.G. & Klein, S.L. (2016). Sex Matters in infectious disease pathogenesis. *PLOS Pathogens* **12**: e1005374. <https://doi.org/10.1371/journal.ppat.1005374>
- Watkins, R.E. & Plant, A.J. (2006). Does smoking explain sex differences in the global tuberculosis epidemic? *Epidemiology and Infection* **134**: 333-339. <https://doi.org/10.1017/s0950268805005042>
- World Health Organization (WHO). (2020). Global Tuberculosis Report 2020. <https://www.who.int/teams/global-tuberculosis-programme/overview>. Accessed 3 April 2023
- Yilmaz, N., Zehra Aydin, S., Inanc, N., Karakurt, S., Direskeneli, H. & Yavuz, S. (2012). Comparison of QuantiFERON-TB Gold test and tuberculin skin test for the identification of latent *Mycobacterium tuberculosis* infection in lupus patients. *Lupus* **21**: 491-495. <https://doi.org/10.1177/0961203311430700>
- Zwerling, A., van den Hof, S., Scholten, J., Cobelens, F., Menzies, D. & Pai, M. (2012). Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review. *Thorax* **67**: 62-70. <https://doi.org/10.1136/thx.2010.143180>