ORIGINAL ARTICLE

Latent Tuberculosis Infection among Household Contacts of Drug-sensitive Pulmonary Tuberculosis Patients: A Cross-sectional Study from Medan, Indonesia

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ABSTRACT

Background and Objective. The WHO advises the detection of cases of pulmonary tuberculosis (TB) in household contacts (HHCs). This activity allows for testing family members of TB patients for latent tuberculosis infection (LTBI) and detecting factors associated with LTBI. The purpose of this study is to identify LTBI and its associated factors among HHCs of TB patients.

Methods. An analytical cross-sectional study was conducted in Medan, Indonesia. Subjects were family members living in the same household as pulmonary drug-sensitive tuberculosis (DS-TB) patients and met the inclusion and exclusion criteria. Data collection involved interviews, chest X-rays, blood collection for Interferon-Gamma Release Assay (IGRA) analysis, and, if necessary, the Xpert MTB/RIF test to examine sputum. Subjects were classified as having LTBI if the IGRA test was positive, the chest X-ray results were normal or did not suggest TB, and there were no clinical symptoms indicative of tuberculosis.

Results. A total of 90 HHCs of TB patients were included; 30 subjects (29.41%) had LTBI, and 60 subjects (58.82%) did not have LTBI. The majority of subjects were female (76.6%), with a Mean±SD age and body mass index (BMI) of 41.17±15.33 years and 24.65±4.72, respectively. Variables such as gender, age, educational level, employment type, comorbidities, BMI, smoking, alcohol intake, and length of contact were not significantly associated with LTBI ($p>0.05$).

Conclusion. To achieve TB eradication, it is crucial to investigate household contacts of pulmonary TB patients. Individuals with LTBI can benefit from education and management of preventive TB treatment.

Keywords: household-contact (HHC) investigation, IGRA, latent TB infection (LTBI), pulmonary TB

INTRODUCTION

Tuberculosis (TB) is one of the common public health issues in tropical countries, especially in Indonesia. Since the world has been facing the COVID-19 pandemic, the surge in TB and HIV/AIDS cases has led to high morbidity and mortality worldwide. The latest global data from 2021 showed an increase in the number of TB cases compared to 2020. In 2021, there were 10.6 million TB cases, an increase of 4.5% from 10.1 million cases in 2020.[1] After India, Indonesia has the second-highest number of TB patients worldwide,

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with around 824,000 cases and 93,000 deaths caused by TB. Tuberculosis is the leading cause of death among communicable, maternal, neonatal, and nutritional diseases in Indonesia.[2]

To find latent tuberculosis infections (LTBI), which fall under the purview of TB control programs, and to intensify TB case finding, the WHO recommends actively and massively screening household contacts (HHCs) exposed to an index case of TB. The current strategy for eliminating TB also involves identifying individuals with LTBI, treating them, and offering tuberculosis preventive treatment (TPT).[3] In Indonesia, HHCs investigation and TPT have been included in the national tuberculosis control program to eliminate tuberculosis.[4]

It is estimated that 1.3–2.3 billion people worldwide, or roughly 25% of the global population, are infected with TB.[3,5] About 10% of infected individuals develop into active cases, and 90% remain with latent TB infection.[6] According to estimates, 5–10% of people with LTBI will reactivate to have active TB[7] and typically develop the active illness 1-2 years after infection[8].

Compared to the general population, household members who have close contact with active TB patients are more likely to contract the disease because they breathe the same air for longer periods. In low- and middle-income countries (LMICs), the prevalence of LTBI is 51.5%, and the prevalence of active TB is 3.1% among HHCs of TB patients, as revealed by Fox et al.[9] Age, gender, tobacco use, obesity, and having close contact with TB patients have all been linked to LTBI, according to a Chinese study.[10] An Indonesian study discovered association between LTBI and bedroom density, occupation type, and contact duration.[11]

The Interferon-Gamma Release Assays (IGRA) test is used in this study to examine for TB infection, circumventing some of the shortcomings of the Tuberculin Skin Test (TST), such as cross-reactivity in individuals who have received the Bacille Calmette-Guérin vaccination and non-TB *Mycobacteria* infections, as well as measurement errors related to induration size.

Tracing HHCs with active TB patients is important to identify TB and LTBI, and factors associated with LTBI. This activity can contribute to TB elimination by preventing the occurrence of pulmonary TB in the future. This study aimed to identify LTBI and factors associated with LTBI among family members in household contact with TB patients.

METHODS

Study Design and Setting

This research was a cross-sectional study and conducted in Medan city, Indonesia. Medan is an urban area and the capital of North Sumatra province in Indonesia with a population of 2,474,166 people.[12] TB patients, serving as the index case, were identified in several hospitals, clinics, and community health centers (Puskesmas) in Medan. The index case must be a pulmonary TB patient with sputum examination results positive for *Mycobacterium tuberculosis* and sensitive to Rifampicin, as determined using the Xpert MTB/RIF test. To confirm that the index case is a TB patient with positive *Mycobacterium tuberculosis* and Rifampicin-sensitive results from sputum examination, we referred to the data from SITB (Indonesian Tuberculosis Information System), the national TB patient data information system in Indonesia.

After identifying the index case, we proceeded to invite family members living in the same household with the index case to participate in the contact investigation study and this was obtained by consecutive sampling from October 1, 2023 to December 5, 2023. Several methods were used to disseminate information related to contact investigation activities, such as during patient treatment control visits at the TB DOTS polyclinic, while the patient was hospitalized, or by directly contacting the index case via telephone. Family members willing to participate in the contact investigation study were instructed to visit a designated hospital or clinic near their residence. Examinations of family members of TB patients (research subjects) were conducted at various health service locations in Medan, including Haji Adam Malik Hospital, Prof. dr. Chairuddin P. Lubis Universitas Sumatera Utara Hospital, Advent Hospital, and Medan Medical Centre (MMC) clinic.

Participants

Family members living in the same household as pulmonary DS-TB patients were selected as research subjects. Individuals aged ≥15 years old who were willing to participate in the study by signing an informed consent were recruited. Family members living in the same household as extrapulmonary TB patients and those diagnosed with pulmonary TB from the results of close contact investigations were excluded. The minimum number of research subjects was 99 people who were close contacts in the same household. This number was obtained using the Lemeshow formula with a 5% error rate and the estimated proportion of latent TB in close contacts in the same household from other previous studies was 47.7%.[13] In this study, the number of research subjects who were close contacts in the same household was 102 people.

Data Collection

After the study subjects signed an informed consent, contact investigation activities continued with several examination procedures to collect data. These included interviews, blood collection for IGRA examination, chest X-ray examination, and, if necessary, sputum examination. The IGRA (Interferon-Gamma Release Assays) test was conducted using the QuantiFERON TB-Gold Plus (QFT-Plus) with the ELISA examination technique. The interview items included demographic data, such as gender, age, occupation, and educational level. Height and weight were measured to determine nutritional status, and

questions regarding comorbidities, smoking history, alcohol consumption, and duration of contact were also asked. Chest X-ray and IGRA examinations were performed in the same day for all subjects participating in the contact investigation. If abnormalities were detected on the chest X-ray that clinically suggested pulmonary TB or the subjects has a symptom suggestive of TB, a sputum examination using the Xpert MTB/RIF test was conducted.

If the IGRA test was positive, the chest X-ray results were normal and did not suggest tuberculosis, and the subjects did not exhibit any clinical symptoms of tuberculosis, they were classified as having LTBI. Subjects were considered to be negative for LTBI if there were no symptoms of tuberculosis, the IGRA test results were negative, and the chest X-ray was normal. Subjects whose sputum examination results using the Xpert MTB/RIF test were positive and those whose clinical examination and chest X-ray results indicated TB were not included in the analysis.

The risk factors as independent variables were age, sex, type of occupation, educational level, nutritional status, comorbidity, smoking behaviour, alcohol consumption, and contact duration, and the dependent variable was Latent TB infection. Age, sex, type of occupation, educational status, comorbidity (defined as having one or more chronic condition apart from tuberculosis), smoking behavior, alcohol consumption, and contact duration were obtained by interview while nutritional status as Body Mass Index (BMI) was obtained by weight and height measurements of the subjects.

Statistical Analysis

Data were analyzed using the Chi-squared test or Fisher's exact test to identify associations between risk factors and the incidence of latent tuberculosis. Statistical significance was considered at $p<0.05$. All statistical analyses were performed using SPSS version 25 (IBM SPSS, New York, United States).

Ethical Considerations

The research design and procedure have been reviewed and approved by the Ethical Committee of Universitas Sumatera Utara on September 26, 2023, No. 971/KEPK/USU/2022. Each participant read, understand, sign, and possess a copy of their Informed Consent Form (ICF).

RESULTS

Among the 102 subjects who were family members of 62 TB patients, 30 subjects (29.41%) had LTBI and 60 subjects (58.82%) did not have LTBI. The remaining 12 subjects were diagnosed with pulmonary TB; six subjects with positive sputum results were sensitive to Rifampicin, and six other subjects were diagnosed with clinical TB from the chest X-ray examination.

Table 1 describes the characteristics of the household contacts as subjects based on the occurrence or absence of latent TB infection (n=90, univariate analysis).

Table 1. Characteristics of Research Subjects

Variable	Latent TB Infection			
	Positive (n=30)		Negative (n=60)	
	n	%	n	%
Age (years)				
15-25	5	5.6	10	11.1
26-35	6	6.7	15	16.7
36-45	2	2.2	9	10.0
46-55	11	12.2	13	14.4
>55	6	6.7	13	14.4
Sex				
Male	6	6.7	15	16.7
Female	24	26.6	45	50.0
Occupation				
Laborer/ farmer/ fisherman	1	1.1	11	12.2
Trader/ entrepreneur	1	1.1	3	3.3
Employed/ soldier/ officer/ civil servants	7	7.8	12	13.4
Student	3	3.3	7	7.8
Housewives/ unemployed	18	20.0	27	30.0
Level of education				
Elementary school	4	4.4	6	6.7
Junior high school	2	2.2	8	8.9
Senior high school	20	22.2	31	34.5
University	4	4.4	15	16.7
Nutritional status				
Obese	11	12.2	26	29.0
Overweight	4	4.4	10	11.1
Normal	13	14.4	21	23.4
Underweight	2	2.2	3	3.3
Comorbid				
Yes	2	2.2	8	8.9
No	28	31.1	52	57.8
Smoking behavior				
Yes	4	4.4	6	6.7
No	26	28.9	54	60.0
Alcohol consumption				
Yes	0	0.0	2	2.2
No	30	33.3	58	64.5
Contact duration				
≥5 hrs/day	26	29.0	47	52.2
<5 hrs/day	4	4.4	13	14.4

The majority age group for the LTBI group was 46-55 years, while for the non-LTBI group, it was the 26–35-year age group. A total of 76.6% of subjects were female, with 26.6% in the LTBI group and 50% in the non-LTBI group. Being a housewife or unemployed was found in 20% of the LTBI group and 30% in the non-LTBI group. The majority of subjects were in senior high school, with 22.2% in the LTBI group and 34.5% in the non-LTBI group. Normal weight was the most common in the LTBI group, while in the non-LTBI group, obesity was the most common. In both groups,

Table 2. Bivariate Analysis Results of Risk Factors of Latent TB Infection

Variable	Latent TB Infection				*p*	OR (95% CI)
	Positive (n=30)		Negative (n=60)			
	n	%	n	%		
Age					0.297	1.598 (0.661-3.866)
≥45 years	17	18.9	27	30.0		
<45 years	13	14.4	33	36.7		
Sex					0.597	0.750 (0.258-2.183)
Male	6	6.7	15	16.7		
Female	24	26.6	45	50.0		
Level of education					0.720	0.821 (0.280-2.410)
Low education (Elementary school + Junior high school)	6	6.6	14	15.6		
High education (Senior high school + University)	24	26.6	46	51.2		
Type of occupation					0.180	0.545 (0.224-1.328)
Outdoor [a]	12	13.3	33	36.7		
Indoor (Housewives/unemployed)	18	20.0	27	30.0		
Nutritional status					0.643	0.808 (0.327-1.992)
Not normal	18	20.0	39	43.3		
Normal	12	13.3	21	23.4		
Comorbid					0.486[b]	0.464 (0.92-2.337)
Yes	2	2.2	8	8.9		
No	28	31.1	52	57.8		
Smoking behavior					0.726 [b]	1.385 (0.359-5.335)
Yes	4	4.4	6	6.7		
No	26	28.9	54	60.0		
Alcohol consumption					0.551 [b]	0.383
Yes	0	0.0	2	2.2		N/A
No	30	33.3	58	64.5		
Contact duration					0.341	1.798 (0.531-6.802)
≥5 hrs/day	26	29.0	47	52.2		
≤5 hrs/day	4	4.4	13	14.4		

a – laborer/farmer/fisherman, trader/entrepreneur, employee/soldier/officer/civil servants, student, b – Fisher test

more subjects had no comorbidities (88.9%), did not smoke (88.9%), and did not consume alcohol (97.8%). Contact duration of ≥5 hours/day was the most common, with 29.0% in the LTBI group and 52.2% in the non-LTBI group.

Table 2 shows the summary statistics for LTBI positive vs negative, and the OR and p-value (bivariate analysis). Statistical analysis showed that there was no association between gender, educational level, age, type of work, tobacco use, nutritional status, comorbidities, contact duration, alcohol consumption, and the risk of LTBI (p>0.05).

DISCUSSION

In this study, of the 102 subjects who were HHCs of 62 pulmonary TB patients as index cases, it was found that 30 individuals (29.41%) had LTBI, and 60 individuals (58.82%) did not have LTBI. This rate is slightly higher than the average rate of latent TB infection stated by the WHO in 2016, with an estimated global prevalence of LTBI at 23%.[14] A comprehensive systematic review that summarizes 88 studies distributed across 36 countries showed that the global prevalence of LTBI was 24.8% based on the IGRA test, and 21.2% based on TST. This review involved a large number of subjects (67,167 subjects for the IGRA test, and 284,664 subjects for TST).[14] Another study by Fox et al. also revealed the prevalence of LTBI in close contacts of TB patients was 28.1% in high-income countries (HICs), while in lower middle-income countries (LMICs), it was 51.5%. Based on the type of contact, the prevalence of LTBI among HHCs between HICs and LMICs was 30% and 45.4%, respectively.[9] Different findings on latent TB infection rate can be caused by differences in the age of the study subjects, nutritional status, educational level, poor ventilation, overcrowding of places, and compliance in wearing masks.

Our study found that the youngest age of family members of HHCs was 15 years and the oldest was 76 years, with a mean ± SD age of 41.17 ± 15.33 years, and there were 19 subjects aged >55 years. This indicates that HHCs can occur at all ages, including old age, which is known as a vulnerable age. Our study shows no significant association between the age of HHCs of PTB patients and the risk of LTBI (p>0.05). This result was in line with the studies of Karbito et al. in

Indonesia[11], Odera et al. in Kenya[15], and Ghanaiee in Iran[16]. A study from India shows a surge in LTBI cases among HHCs of PTB from 47% at <6 years old to 53% between 6–14 years old. The increase in LTBI cases was also shown in the 15–45 years old group (78%), and in those >45 years old (85%).[17]

Some high-risk environments, including work offices and schools, are major contributors to the increased prevalence of LTBI in young adults due to the high frequency and duration of social contact, extensive use of public spaces, and contact at home with the index patient. Overcrowding and poor ventilation also contribute to TB transmission, suggesting that some transmission occurs outside the household.[17]

Regarding gender characteristics in this study, the majority of participants in both the LTBI and non-LTBI groups were female. This could be because most individuals who came forward during the contact investigation were women, as many men could not attend the sessions due to work commitments. This was also reflected in the employment status of the subjects in this research, with many being housewives or unemployed. There was no association between gender and LTBI in this study ($p>0.05$), a finding echoed by Dolla et al. in India.[17] However, a study by Chen et al. in China found a significant relationship between gender and LTBI; the risk of LTBI increased significantly among males (OR = 1.52; 95% CI: 1.33–1.75).[10] Another study examining the gender gap in LTBI risk discovered that men had a considerably higher proportion of LTBI than women. Yet, after adjusting for smoking habits, age, and other clinical variables, the study reaffirmed that the higher risk of LTBI was not associated with male gender.[18] The lack of an association between the incidence of LTBI and gender in our study could be due to the small number of male participants, which was only 23.4% of the total, leading to an unbalanced gender proportion that could influence the analysis results.

Regarding educational level, the majority of participants in this study had completed senior high school, and there was no association between educational level and the risk of LTBI ($p>0.05$). It is expected that individuals with a higher level of education would have greater knowledge about TB and LTBI. Research in a Canadian Urban Centre on Chinese immigrants regarding knowledge and perception of LTBI found low knowledge with a score of 40% regarding LTBI, with difficulty distinguishing between TB and LTBI.[19] Lack of knowledge about LTBI may deter household members of TB patients from participating in contact investigations, even when offered for free. Many in this study were also unwilling to participate in contact investigation activities, citing reasons such as fear of blood draws, lack of time due to work, fear of the results, and a desire to focus on family members with TB.

In this study, there was also no association between the types of work, which were divided into indoor and outdoor categories, and the risk of LTBI ($p>0.05$). The types of indoor work referred to in this research include housewives and those who are unemployed, while outdoor work encompasses laborers/ farmers/ fishermen, traders/ entrepreneurs, employees/ soldiers/ officers/ civil servants, and students. Different results were obtained in a research conducted in the city of Semarang, Indonesia, where contact duration, the type of occupation, and bedroom density were associated with latent TB infection. Fishermen/farmers/laborers had a risk of latent TB infection 7.04 times greater (AOR: 7.04; 95% CI: 1.70–29.02) as compared to housewives and the unemployed.[11] A research in Germany, a low-incidence nation of TB, using the IGRA test, compared the prevalence of latent TB based on the type of work of healthcare workers and non-healthcare workers, and found that healthcare workers were more at risk of contracting LTBI than non-healthcare workers.[20] The differing results in our research may be due to the analysis being carried out by only dividing the type of work into two categories: working indoors and outdoors.

In this study, no association was found between BMI and latent TB infection. This contrasts with a research in China which found that being overweight increased LTBI (OR: 1.36; 95% CI: 1.17-1.57).[10] A previous study has demonstrated that individuals with lower BMI had a higher chance of contracting tuberculosis.[21] However, it was not clearly stated how BMI impacted *M. tuberculosis* infection. Research on healthcare workers, another specific population, revealed inconsistent BMI results regarding LTBI risk.[22,23]

Our study found no association between comorbidities and an increased risk of LTBI ($p>0.05$). A comprehensive review consisting of 20 studies and involving 4,055,082 participants shows a significant association between LTBI and diabetes mellitus. This study compares cohort and cross-sectional studies with an RR of 1.62 and a CI value of 1.02 to 2.56 for cohort studies, while for cross-sectional studies, the OR value was 1.55 (95% CI: 1.30–1.84). The pooled OR was high in studies with healthcare workers OR: 5.27 (95% CI: 1.52–8.20), and refugees OR: 2.88 (95% CI: 1.93–4.29). Prediabetes was also associated with LTBI (OR = 1.36, 95% CI: 1.01–1.84).[24] In our study, only 10 subjects (9.8%) had comorbidities, and the presence of comorbidities was discovered only through interviews with subjects, without examinations such as blood sugar levels and HIV testing.

In our investigation, there was no association ($p>0.05$) between alcohol and smoking intake and the risk of LTBI. Other association studies found that tobacco use was a risk factor for LTBI.[18,25,26] Meanwhile, children exposed to passive smoking are also more likely to contract LTBI.[27] Exposure to cigarette smoke reduces the lung T-cells' ability to produce IFN-gamma when stimulated in vitro with antiCD3, which raises the risk of contracting *M. tuberculosis*.[28] Simultaneously, evidence suggests that tobacco use can damage macrophage control of *M. tuberculosis*, implicated in smoking-induced immunosuppression, which supports the possibility that tobacco use increases susceptibility to LTBI.[29] Individuals with alcohol use disorders (AUD) have a higher risk of both LTBI and active TB disease compared to those without AUD.[30] Alcohol consumption may promote *M. tuberculosis*

infection and evasion of host defences due to its effects on oxidative stress in the alveoli, impairments to the alveolar macrophage and epithelium, and other components of the lung's innate immune system.[31] Because most participants in our study were women, it is likely that very few of them smoked or drank alcohol. This may impact the analysis of the risk of LTBI in relation to alcohol and smoking.

The final variable examined in this study was the association between the duration of contact with TB patients and the risk of LTBI (p>0.05). This differs from the results of other studies from Indonesia (AOR: 4.70; 95% CI: 1.33–16.66)[11] and Thailand (OR: 9.15; 95% CI: 1.44-58.05)[32], which found a relationship between the duration of contact ≥5 hours/day and the risk of LTBI. The duration of contact provides an opportunity for family members living with a PTB patient to contract *M. tuberculosis*. The exposure to *M. tuberculosis* and the risk of LTBI increase with the length of contact time.

This study has several limitations. The unequal proportion of subjects based on gender has implications for the small number of smoking habits and alcohol consumption analyzed. Additionally, information regarding comorbidities was only obtained from interviews, so there may be individuals with comorbidities, especially diabetes mellitus and HIV, that are not known. This study also did not collect information on whether TB patients or their families as close household contacts wore masks or not while at home, which could possibly influence the occurrence of latent TB infection. Bias can occur in the selection of subjects since this research was only conducted in some places in the city of Medan, and did not represent the general LTBI prevalence in Medan. Bias during the interview can also occur such as questions about the duration of contact with TB patients at home, but can be overcome by choosing categorically 5 hours per day of contact with TB patients. This study also did not record the number and reason of subjects who refused to participate in the study. Further studies are needed with more study sites, risk variables, and data collection regarding the reasons for refusing to undergo contact investigation examinations.

However, this research was the first household contact investigation conducted in the city of Medan, Indonesia. Another advantage was that this study used the IGRA test to identify the presence of latent TB infection, chest X-rays were performed on all subjects, sputum examinations were carried out using the Xpert MTB/RIF test, and the determination of pulmonary drug-sensitive TB patients as index cases was carried out using the Xpert MTB/RIF test.

Despite the limitations mentioned above, this research provides important information about the high rate of latent TB infection among individuals living in the same household as TB patients. This underscores the significance of household contact investigations and the provision of Tuberculosis Preventive Treatment to individuals with latent tuberculosis infection, which will contribute to the global and particularly Indonesian efforts to eliminate TB.

CONCLUSION

The prevalence of latent TB infection among household contacts of active TB patients is notably high. Age, gender, level of education, type of occupation, nutritional status, comorbidities, duration of contact, smoking behavior, and alcohol consumption were not associated with latent TB infection. The findings of this study can serve as foundational data for further enhancing contact investigation activities for individuals living in the same household as pulmonary TB patients and for providing TB Preventive Treatment to those with latent TB infection.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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