

Comparison of Tuberculin Skin Test and Interferon-Gamma Release Assay in the Diagnosis of Latent Tuberculosis Infection among Indonesian Health-care Workers

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Abstract

Background: Health-care workers are groups that are close contact with tuberculosis (TB) patients. As an alternative to the tuberculin skin test (TST), there is interferon-gamma release assay (IGRA) for the diagnosis of latent TB infection (LTBI). The objective of this study is to compare TST and IGRA in the diagnosis of LTBI among Indonesian health-care workers. **Methods:** This study design was a cross-sectional study. TST results are consistent for LTBI if there is induration ≥ 10 mm in individuals without previous TST, or ≥ 15 mm in participants with a history of previous TST. Medical history interview, physical examination, chest X-ray, and sputum smear examination were performed to exclude active TB infection. **Results:** Among 84 healthcare workers, the prevalence of LTBI was 51.2% by IGRA and 29.8% by TST with sufficient agreement ($\kappa = 0.34$). Age and low education were significantly correlated with the positive results of IGRA ($P < 0.05$); meanwhile smoking status was correlated with TST ($P < 0.05$). **Conclusion:** The prevalence of LTBI is higher with IGRA as compared to TST, with sufficient agreement and there is significant correlation between age and low education with the results of IGRA and in smoking status with TST.

Keywords: Interferon-gamma release assay, latent tuberculosis infection, tuberculin skin test

INTRODUCTION

Tuberculosis (TB) remains a leading cause of mortality worldwide and the WHO reported in 2017 that Indonesia is the second ranked for active cases of TB.^[1] About 10% of people infected with *Mycobacterium tuberculosis* (MTB) will develop active TB and become ill during their lives while others become latent.^[2]

A screening tests available for latent TB infection (LTBI) diagnosis are tuberculin skin test (TST) and interferon-gamma release assay (IGRA). Although routine testing is not recommended, in specific groups, the two tests become very useful, such as healthcare workers in close contact with active TB patients.^[3] The TST is often used to screen individuals of LTBI but cannot be used to distinguish whether MTB infection is active or latent.^[4]

The comparison of TST and IGRA in the diagnosis of LTBI among Indonesia health-care workers is still unknown. The purpose of this study is to reveal the prevalence of LTBI in

healthcare workers using IGRA and TST. The study also aimed to compare the TST and IGRA in the diagnosis of LTBI among Indonesian health-care workers as well as the associated factors from the participants' characteristics. Finally, we will define the cutoff point of TST as screening tests in health workers in countries with high TB incidence rates using IGRA and also determine the agreement between TST and IGRA results.

METHODS

The study design was a cross-sectional study. The study was conducted in the Community Lung Health Center (Balai Besar Kesehatan Paru Masyarakat [BBKPM]),

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Bandung, West Java Province, Indonesia, from January to April 2015. The population targets are all health-care workers in BBKPM Bandung. The inclusion criteria were participants aged ≥ 18 years old, health-care workers in contact with active pulmonary TB patients (lung clinic, lung infection wards, microbiology, laboratory, pharmacy, and radiology), has been working in the TB unit BBKPM for more than 2 months, willing to participate by signing informed consent. The exclusion criteria were a history of TB treatment, being treated for TB, active TB, pregnant women, and HIV positive. Sampling was done by total sampling. The variables studied were age, gender, nutritional status, education, socioeconomic status, type of employment, length of employment, location, level of occupational risk, Bacillus Calmette-Guérin (BCG) vaccination, and smoking status. The study protocols include signing the informed consent of research, obtaining basic data by medical interview, physical examination, chest X-ray examination, acid-fast bacilli (AFB) sputum smear (three times), and MTB culture, blood sampling, and the TST procedure. The entire series of studies conducted in BBKPM Bandung and IGRA-QuantiFERON TB Gold (IGRA-QFT) examination conducted at the Laboratory of Immunology and Biomolecular Universitas Pajajaran, Bandung, Indonesia. This study has been approved by the Institutional Review Board of Faculty of Medicine Universitas Indonesia (Ethical Clearance No. 59/UN2.F1/ETIK/2014).

The conformity level in this study is represented by the Kappa value κ . If the Kappa value κ is 0, it means that the conformity as observed was purely due by chance, meanwhile conformity level as high as 1, it reflects a perfect true conformity. The data collected was processed and analyzed using Statistic Package for Social Science (SPSS) version 20 (IBM Corp, Armonk, New York, USA). The regression logistic test was used to determined *P* value in comparing data between groups. $P < 0.05$ was considered to be statistically significant.

RESULTS

From initially 96 health workers, there were 12 participants that were excluded (3 pregnant women, 8 participants had a history of TB treatment and one subject with active pulmonary TB). The characteristics of 84 participants were described in Table 1. The number of females was slightly more than males 51.2% versus 48.8%, respectively. The participants were a predominantly young aged group with mean age 38.06 years, undergraduate education, a high socioeconomic status, normal nutrition status, have been vaccinated with BCG, paramedics type of work, working period ≤ 10 years, working location of clinics, and the risk level of work was dominantly high-risk groups.

First, we determined the prevalence of LTBI using IGRA and TST and analyzed the risk of LTBI by each subject's demographic variables. The prevalence of LTBI in this study, as reflected by IGRA-positive results, was 51.2% and from the results of a positive TST was 29.8%. The 41–50 years

Table 1: The distribution by sociodemography

Variable	Frequency, n (%)
Age (year)	
21-30	21 (25.0)
31-40	30 (35.7)
41-50	22 (26.2)
≥ 51	11 (13.1)
Total	84 (100)
Sex	
Male	41 (48.8)
Female	43 (51.2)
Total	84 (100)
Nutritional status	
Underweight	2 (2.4)
Normal	54 (64.3)
Overweight	28 (33.3)
Total	84 (100)
Type of work	
Paramedic	52 (61.9)
Nonparamedic	32 (38.1)
Total	84 (100)
Length of work (years)	
≤ 10	47 (56.0)
11-20	21 (25.0)
≥ 21	16 (19.0)
Total	84 (100)
Location	
Outpatient clinic	31 (36.9)
Laboratory	10 (11.9)
Radiology and pharmacy	12 (14.3)
Registration	11 (13.1)
Others	20 (23.8)
Total	84 (100)
Mantoux (mm)	
Positive (≥ 10)	16 (19.0)
Negative (< 10)	68 (81.0)
Total	84 (100)
IGRA-QFT	
Positive	43 (51.2)
Negative	41 (48.8)
Total	84 (100)

IGRA-QFT: IGRA-QuantiFERON TB Gold, IGRA: Interferon-gamma release assay, TB: Tuberculosis

aged group, low education group, and group without history of BCG vaccination, have the significant highest risk of getting IGRA-positive ($P < 0.05$), meanwhile females, lower socioeconomic class, smokers, abnormal nutritional status, paramedic workers, working period of more than 21 years, work location in clinics, work risk level, were not significantly contributed to higher risk of having positive IGRA results [Table 2]. As for TST test, the smokers have a significant increased risk of having positive TST test ($P < 0.05$), meanwhile age, gender, level of education, socioeconomic status, nutritional status, history of BCG vaccination, type of work, working duration, working location, and working risk level, were not associated with positive TST result [Table 3].

Table 2: Sociodemography relationship with interferon-gamma release assay-QuantiFERON tuberculosis Gold in healthcare workers

Variables	Latent TB infection			P	OR (95% CI)
	Positive, n (%)	Negative, n (%)	Total, n (%)		
Age (years)					
≥51	5 (45.5)	6 (54.5)	11 (100)	0.216	2.67 (0.56-12.62)
41-50	14 (63.6)	8 (36.4)	22 (100)	0.011*	5.60 (1.48-21.13)
31-40	19 (63.3)	11 (36.7)	30 (100)	0.007*	5.53 (1.58-19.27)
21-30	5 (23.8)	16 (76.2)	21 (100)		1.00
Sex					
Female	23 (53.5)	20 (46.5)	43 (100)	0.666	1.21 (0.51-2.84)
Male	20 (48.8)	21 (51.2)	41 (100)		1.00
Education					
Low	7 (87.5)	1 (12.5)	8 (100)	0.051	8.61 (0.99-74.57)
Middle	10 (55.6)	8 (44.4)	18 (100)	0.427	1.54 (0.53-4.46)
High	26 (44.8)	32 (55.2)	58 (100)		1.00
Social economy					
Low	1 (50.0)	1 (50.0)	2 (100)	0.915	0.85 (0.05-14.30)
Middle	7 (41.2)	10 (58.8)	17 (100)	0.355	0.60 (0.20-1.77)
High	35 (53.8)	30 (46.2)	65 (100)		1.00
Smoking status					
Nonsmoker	38 (54.3)	32 (45.7)	70 (100)	0.097	0.66
Smoker	5 (35.7)	9 (64.3)	14 (100)	0.487	1.08
Nutritional status					
Underweight	0	2 (100)	2 (100)	0.999	-
Normal	29 (53.75)	25 (46.35)	54 (100)		1.00
Overweight	14 (0.0)	14 (0.0)	28 (100)	0.750	0.86
Vaccination history BCG					
No	16 (72.7)	6 (27.3)	22 (100)	0.022*	3.46
Yes	27 (43.5)	35 (56.5)	62 (100)		1.00
Type of work					
Paramedic	24 (46.2)	28 (53.8)	52 (100)	0.241	0.59
Nonparamedic	19 (59.4)	13 (40.6)	32 (100)		1.00
Length of work (years)					
≥21	11 (68.8)	5 (31.2)	16 (100)	0.077	2.97
11-20	12 (57.1)	9 (42.9)	21 (100)	0.268	1.80
≤10	20 (42.6)	27 (57.4)	47 (100)		1.00
Occupational risk					
High risk	22 (48.9)	23 (51.1)	45 (100)	0.527	1.57
Medium risk	15 (51.7)	14 (48.3)	29 (100)	0.651	1.40
Low risk	6 (60.0)	4 (40.0)	10 (100)		1.00

*Statistically significant. TB: Tuberculosis, BCG: Bacillus Calmette-Guérin, OR: Odds ratio, CI: Confidence interval

Next, we examined the cutoff point to have sensitivity and specificity of the IGRA test by using the TST test as the gold standard [Table 4]. We obtained the 80.0% sensitivity and 61% specificity at the cutoff point of TST >10 mm, while the 75.6% sensitivity and 72.1% specificity at cutoff point >5 mm. Data specificity was used as a reference of test screening in health-care workers at risk of being infected with TB. In this study, the highest specificity was found at the point of induration ≥5 mm.

We then analyzed the agreement between IGRA and TST that were calculated at various point of cut induration, ≥5 mm, ≥6 mm, ≥7 mm, ≥8 mm, ≥9 mm, and ≥10 mm and obtained a value of conformity amounting to 66.5% with $\kappa = 0.34$ [Table 5].

The highest agreement value (72.4%) was found in the cutoff point of TST induration ≥6 mm ($\kappa = 0.48$) and ≥5 mm ≥5 mm ($\kappa = 0.48$) with a degree of agreement was moderate degree.

Finally, we reveal the discordant between the tuberculin test and IGRA-QFT by sociodemographic variables. We obtained the highest discordant in participants with a higher socioeconomic characteristics found in 25 participants ($\kappa = 0.26$) as shown in Table 6. The highest discordant were found in the group of age ≥51 age years old, female, high education level, and higher socioeconomic status in the TST (-)/IGRA (+).

The highest discordant between tuberculin test and IGRA-QFT based on nutritional status and a history of BCG vaccination

Table 3: Sociodemography relationship with tuberculin skin test in healthcare workers

Variables	TST			P	OR (95% CI)
	Positive, n (%)	Negative, n (%)	Total, n (%)		
Age (years)					
≥51	4 (36.4)	7 (63.6)	11 (100)	0.923	0.93
41-50	6 (27.3)	16 (72.7)	22 (100)	0.451	0.61
31-40	7 (23.3)	23 (76.7)	30 (100)	0.258	0.49
21-30	8 (38.1)	13 (61.9)	21 (100)		1.00
Gender					
Female	13 (30.2)	30 (69.8)	43 (100)	1.999	1.05
Male	12 (29.3)	29 (70.7)	41 (100)		1.00
Education					
Low	1 (12.5)	7 (87.5)	8 (100)	0.300	0.32
Middle	6 (33.3)	12 (66.7)	18 (100)	0.855	1.11
High	18 (31.0)	40 (69.0)	58 (100)		1.00
Social economy					
Low	1 (50.0)	1 (50.0)	2 (100)	0.505	2.61
Middle	6 (35.3)	11 (64.7)	17 (100)	0.541	1.42
High	18 (27.7)	47 (72.3)	65 (100)		1.00
Smoking status					
Nonsmoker	22 (31.4)	48 (68.6)	70 (100)	0.455	0.91
Smoker	11 (78.6)	3 (21.4)	14 (100)	0.005*	1.47
Nutritional status					
Underweight	1 (50.0)	1 (50.0)	2 (100)	0.468	2.86
Normal	14 (25.9)	40 (74.1)	54 (100)	0.000	1.59
Overweight	10 (35.7)	18 (64.3)	28 (100)	0.357	1.00
BCG					
No	7 (31.8)	15 (68.2)	22 (100)	1.00	1.14
Yes	18 (29.0)	44 (71.0)	62 (100)		1.00
Type of work					
Paramedic	7 (13.5)	45 (86.5)	52 (100)	0.103	0.39
Nonparamedic	9 (28.1)	23 (71.9)	32 (100)		1.00
Length of work (years)					
≥21	6 (37.5)	10 (62.5)	16 (100)	0.021*	5.04
11-20	5 (23.8)	16 (76.2)	21 (100)	0.166	2.62
≤10	5 (10.6)	42 (89.4)	47 (100)		1.00
Working location					
Clinic	5 (16.1)	26 (83.9)	31 (100)	0.246	0.45
Laboratory	1 (10.0)	9 (90.0)	10 (100)	0.245	0.26
Radiology and pharmacy	1 (8.3)	11 (91.7)	12 (100)	0.179	0.21
Registration	3 (27.3)	8 (72.7)	11 (100)	0.873	0.87
Others	6 (30.0)	14 (70.0)	20 (100)		1.00
Occupational risk					
High risk	13 (28.9)	32 (71.1)	45 (100)	0.571	1.63
Medium risk	10 (34.5)	19 (65.5)	29 (100)	0.399	2.10
Low risk	2 (20.0)	8 (80.0)	10 (100)		1.00

*Logistic regression test. BCG: Bacillus Calmette-Guérin, OR: Odds ratio, CI: Confidence interval, TST: Tuberculin skin test

was seen in participants (23 participants) with a history of BCG vaccination ($\kappa = 0.23$). The largest discordant was found in overweight participants and those with a history of BCG vaccination in the TST (-)/IGRA (+).

The highest discordant based on working characteristics was seen in participants with working period ≥ 21 years ($\kappa = 0.43$) and places of work category “other” ($\kappa = 0.44$). The biggest discordant was found in paramedics group and length of work

11–20 years group only in TST (-)/IGRA (+), meanwhile in the work risk level variable, the biggest discordant was found lower risk jobs at TST (+)/IGRA (-).

DISCUSSION

LTBI is important to be taken into account when evaluating TB infection control program. Investigating the prevalence of LTBI and the risk factors in the community might improve

Table 4: Cutoff point of tuberculin skin test

	TST cut-off point (mm)				
	≥5	≥6	≥7	≥8	≥10
Sensitivity (%)	75.6	78.4	77.5	79.3	80.0
Spesificity (%)	72.1	70.2	64.2	63.6	61.02

TST: Tuberculin skin test

Table 5: Agreement between tuberculin skin test and interferon gamma release assay-QuantIFERRON tuberculosis Gold

Results	TST cutoff point (mm)					
	≥5	≥6	≥7	≥8	≥9	≥10
Positive TST/positive IGRA	31	29	24	23	20	20
Negative TST/negative IGRA	29	33	34	35	36	36
Positive TST/negative IGRA	10	8	7	6	5	5
Negative TST/positive IGRA	12	14	19	20	23	23
Agreement (%)	72.4	72.4	67.8	69.0	66.5	66.5
κ (95% CI)	0.48	0.48	0.39	0.39	0.34	0.34

CI: Confidence interval, TST: Tuberculin skin test, IGRA: Interferon gamma release assay

the health policy. However, finding a suitable diagnostic tool to determine LTBI is an issue that needs to be confirmed. The current study compares the TST and IGRA to diagnose LTBI in population at risk of having LTBI.

This study involved nearly an equal amount of men and women which was different with study by Adams *et al.* that had more women than men.^[5] The participants working characteristics, such as type of work, length of work, place of work and level of occupational risk, provide an overview of risk factors that are directly related to work-associated LTBI. The working characteristics were comparable with the study by Torres Costa *et al.* in Portugal who found that all participants with BCG vaccination history were mostly paramedics that consisted of nurse 45% and doctors 17.3%, and the largest group based on service employment year was <5 years.^[6]

Our study found the prevalence of LTBI in healthcare workers using IGRA and TST were 51.2% and 29.8%, respectively. The biggest TST induration was found at ≥ 5 mm with a prevalence of 61.9%. Our LTBI prevalence by TST is lower than study by Martin *et al.*, who found TST positive prevalence was 53%.^[7] Furthermore, Drobniewski *et al.* in Russia reported that the prevalence of LTBI in health-care workers using IGRA-QFT was 40.8%.^[8] In this study, positive IGRA results were associated with age, education, and no history of BCG vaccination. Older age had an increased risk of positive IGRA with may be due to the immune system. However, the WHO reported in 2011 that the impact of immunosuppression on the IGRA validity is still unknown.^[4]

The majority of participants with low education have positive IGRA results, in contrast to the high education group. This may be related to low awareness to protect themselves from becoming infected with TB. A study by Grodzińska-Jurczak

et al. shows an insignificant correlation between low education and health knowledge.^[9] The group that did not receive BCG vaccination are associated with increased risk of positive IGRA. This shows that those with no BCG vaccination will be more susceptible to TB infection which is consistent with the study by Chan *et al.*, who found that the BCG vaccine has a protective effect on adults.^[10]

Smoking status is associated with positive TST result in this study, which is consistent with the study by Horne *et al.*, who found that smoking was independently associated with a significant increase in risk for LTBI.^[11] Lindsay *et al.* showed that cigarette smoke exposure increased the risk of TB infection, reduced the function of bronchial epithelial cilia, reduced the ability of alveolar macrophages, and impaired immune response to bacteria.^[12]

Nutritional status was not associated with positive IGRA result; however, underweight was associated with positive TST results. This is quite consistent with the study by Ryadinency *et al.*, who showed that the nutritional status in children is one of the risk factors that influence a children's susceptibility to TB infection.^[13]

There were no significant risks in working variables with positives TST and IGRA results. Our findings are different with study by Harada *et al.*, who reported that working experience as health officer more than 5 years, and has worked as a nurse in the TB inpatient ward, were significantly associated with LTBI.^[14] The consistent findings was showed by Pai *et al.*, in which working duration is a significant risk.^[15] A study by Plitt *et al.* stated that the type of work affects the positivity of TST result.^[16]

This study intended to see the cutoff point of TST based on the sensitivity and specificity of IGRA-QFT on health workers in countries with a high burden TB. The currently recommended TST results ≥ 10 mm and IGRA QFT ≥ 0.35 IU/ml as a positive cutoff showed 80% sensitivity and 61% specificity, but when using a different cutoff level will change the sensitivity and specificity. Specificity was used as a reference of screening tests in health-care workers at risk of becoming infected with TB. In one Canadian study, the specificity of IGRA was 97.7% and was more specific than the TST in participants that have had BCG vaccine.^[17]

The conformity level in this study is consistent with previous studies, such as the study by Lamberti *et al.*,^[18] who obtained $\kappa = 0.28$ in the UK, Al Hajoj *et al.*^[19] who obtained $\kappa = 0.312$ in Saudi Arabia, Adams *et al.*,^[5] with $\kappa = 0.28$ in South Africa, and Ratnatunga *et al.*^[20] in Sri Lanka found $\kappa = 0.30$. Taken together, the conformity level in the current study is comparable with other study and sufficiently reflects the real condition in the population.

The study limitations are it lacks of baseline profile of TB participants before LTBI before working in study place. This study also did not involve patients with AFB smear-positive active TB population as a positive control group. Finally, as a consequence of a cross-sectional methodology, the participants were only viewed at the time the study was conducted.

Table 6: Discordant between interferon-gamma release assay-QuantiFERON tuberculosis gold and tuberculin skin test based on sociodemography

Variable	Agreement between TST and IGRA-QFT		Discordant/total	Percentage			
	Percentage	κ (95% CI)		+TST/+IGRA	-TST/+IGRA	-TST/-IGRA	+TST/-IGRA
Age (year)							
21-30	76.2	0.52	4/21	9.5	14.3	71.4	4.8
31-40	56.7	0.23	15/30	23.3	40	26.7	10
41-50	72.7	0.49	5/22	45.5	18.2	31.8	4.5
≥51	54.5	0.22	4/11	9	36.4	54.6	0
Sex							
Female	66.1	0.34	16/43	23.3	30.2	39.5	7
Male	64.8	0.30	12/41	24.4	24.4	46.3	4.9
Education							
Low	49	0.15	2/8	62.5	25	12.5	0
Middle	72.2	0.47	4/18	33.3	22.2	44.5	0
High	66.5	0.35	22/58	15.5	29.3	46.6	8.6
Social economic							
Low	100	1.00	0/2	50	0	50	0
Middle	77.5	0.48	4/17	23.5	17.7	58.8	0
High	60.5	0.26	25/65	23.1	30.8	37	9.1
Smoking status							
Nonsmoker	50	0.18	28/70	24.3	30	42.9	2.8
Smoker	47.6	0.13	2/14	28.6	14.3	57.1	0
Nutritional status							
Underweight	100	-	0/2	0	100	0	0
Normal	61.9	0.28	18/54	27.8	25.9	38.9	7.4
Overweight	67.8	0.36	9/28	17.9	32.1	46.4	3.6
BCG							
No	69.2	0.42	5/22	50	22.7	27.3	0
Yes	63.5	0.23	23/62	14.5	29	48.4	8.1
Type of work							
Paramedic	63.4	0.23	19/52	12	52	2	34
Nonparamedic	68.7	0.42	10/32	28	41	0	31
Length of work (years)							
≥21	68.7	0.43	5/16	38	31	0	31
11-20	57.1	0.20	9/21	19	38	5	38
≤10	68.1	0.28	15/47	11	57	0	32
Location							
Clinic	61.3	0.21	12/31	13	48	3	36
Laboratory	70.0	0.29	3/10	10	60	0	30
Radiology and pharmacy	66.7	0.23	4/12	8	59	0	33
Registration	63.6	0.35	4/11	27	37	0	36
Others	70.0	0.44	6/20	30	40	0	30
Occupational risk							
High risk	31.1	0.39	31/45	4.4	26.7	24.4	44.4
Medium risk	41.1	0.16	17/29	13.8	27.6	20.7	37.9
Low risk	40.0	0.71	6/10	10.0	30.0	10.00	50.0

IGRA-QFT: IGRA-QuantiFERON TB Gold, IGRA: Interferon-gamma release assay, TB: Tuberculosis, CI: Confidence interval, TST: Tuberculin skin test, BCG: Bacillus Calmette-Guérin

CONCLUSION

Healthcare workers exposed to active TB patients have a higher prevalence of LTBI by positive IGRA test results than the TST. TST induration ≥5 mm can be used as a cutoff point for screening tests on health workers in countries with high

TB burden. Age, lower education, smoking and have not received BCG vaccination were the risk factors of LTBI in health workers.

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Conflicts of interest

There are no conflicts of interest.

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