

JURNAL

RESPIROLOGI

INDONESIA

Majalah Resmi Perhimpunan Dokter Paru Indonesia
Official Journal of The Indonesian Society of Respiriology



Respiratory Emergency in Hospitalized patient with Intrathoracic Malignancy at H. Adam Malik General Hospital

Concordance of TST and QFT-Plus, Sensitivity and Specificity of TST and QFT-Plus in Detection of LTBI in MDR TB Contact

Analysis of Comorbidity and Its Association with Disease Severity and Mortality Rate in Hospitalized COVID-19 Patients

Correlation between N-Acetyltransferase 2 (NAT2) Polymorphism Genotype with Plasma Isoniazid (INH) Concentration in MDR TB Patients Receiving Short Regimen in West Sumatera

Impact of Pulmonary Rehabilitation on Hospitalization Duration, IL-6 Levels, and Respiratory Muscle Power in Hospitalized Community-Acquired Pneumonia Patients

The Effect of Inspiratory Breathing Muscle Exercise Using Spirometer on Changes in Lung Function and Dyspnea Severity in Tuberculosis Pleurisy Patients

Risk Factors of Prolonged QTc Interval in Patients with Drugs-Resistant Tuberculosis

The Correlations Between Measurement of Lung Diffusing Capacity for Carbon Monoxide and The Severity Group of Asthma Patients in Persahabatan Hospital Jakarta

Safety of Favipiravir for Treatment of COVID-19: Latest Systematic Review

The Efficacy of Remdesivir in Reducing SARS-CoV-2 Viral Load and Its Safety on COVID-19 Patients: A Systematic Review

JURNAL RESPIROLOGI INDONESIA

Majalah Resmi Perhimpunan Dokter Paru Indonesia
Official Journal of The Indonesian Society of Respiriology

Editorial Advisory Board

M. Arifin Nawas
Faisal Yunus
Agus Dwi Susanto

Editorial-in-Chief

Fanny Fachrucha

Editorial Board

Feni Fitriani Taufik
Noni Novisari Soeroso
Tutik Kusmiati
A. Farih Raharjo
Ginangjar Arum Desianti
Irandi Putra Pratomo
Jamal Zaini
Mia Elhidsi

International Editorial Board

Guido Vagheggini
Mayank Vats
Motoyasu Kato
Ira Paula Wardono

Secretariat

Shalzaviera Azniatinesa
Suwondo
SST : Surat Keputusan Menteri Penerangan RI
No.715/SK/DitjenPPG/SST/1980 Tanggal 9 Mei 1980

Editorial Office

PDPI Jl. Cipinang Bunder, No. 19, Cipinang Pulo Gadung
Jakarta Timur 13240 Telp: 02122474845
Email : editor@jurnalrespirologi.org
Website : <http://www.jurnalrespirologi.org>

Publisher

The Indonesia Society of Respiriology (ISR)
Published every 3 months (January, April, July & October)

Jurnal Respiriologi Indonesia

2nd Rank Accreditation
According to the Decree of the Minister of Research and
Technology/Head of the National Research and Innovation
Agency of the Republic of Indonesia Number: 200/M/KPT/2020
December 23, 2020

JURNAL RESPIROLOGI INDONESIA

Majalah Resmi Perhimpunan Dokter Paru Indonesia
Official Journal of The Indonesian Society of Respiriology

VOLUME 42, NUMBER 1, January 2022

TABLE OF CONTENT

Original Article

- Respiratory Emergency in Hospitalized patient with Intrathoracic Malignancy at H. Adam Malik General Hospital* 1
Elizabeth Napitupulu, Noni Novisari Soeroso, Setia Putra Tarigan, Putri Eyoer
- Concordance of TST and QFT-Plus, Sensitivity and Specificity of TST and QFT-Plus in Detection of LTBI in MDR TB Contact* 9
Rullyano Hardian, Reviono, Harsini, Yusup Subagio Sutanto
- Analysis of Comorbidity and Its Association with Disease Severity and Mortality Rate in Hospitalized COVID-19 Patients* 18
Anthony Christanto, Aditya Sri Listyoko, Ngakan Putu Parsama Putra
- Correlation between N-Acetyltransferase 2 (NAT2) Polymorphism Genotype with Plasma Isoniazid (INH) Concentration in MDR TB Patients Receiving Short Regimen in West Sumatera* 26
Mega Senja, Masrul Basyar, Yessy Susanty Sabri, Afriani
- Impact of Pulmonary Rehabilitation on Hospitalization Duration, IL-6 Levels, and Respiratory Muscle Power in Hospitalized Community-Acquired Pneumonia Patients* 34
Santony, lin Noor Chozin, Teguh Rahayu Sartono, Rahmad, Harun Al Rasyid
- The Effect of Inspiratory Breathing Muscle Exercise Using Spirometer on Changes in Lung Function and Dyspnea Severity in Tuberculosis Pleurisy Patients* 43
Irmainsi, Herry Priyanto, Dewi Behtri Yanifitri
- Risk Factors of Prolonged QTc Interval in Patients with Drugs-Resistant Tuberculosis* 52
Andika Pradana, Katharine, Parluhutan Siagian
- The Correlations Between Measurement of Lung Diffusing Capacity for Carbon Monoxide and The Severity Group of Asthma Patients in Persahabatan Hospital Jakarta* 58
Bulkis Natsir, Faisal Yunus, Triya Damayanti
- ### Literature Review
- Safety of Favipiravir for Treatment of COVID-19: Latest Systematic Review* 67
Rizki Oktarini, Anna Rozaliyani, Ratika Rahmasari, Muhammad Alkaff, Rani Sauriasari
- The Efficacy of Remdesivir in Reducing SARS-CoV-2 Viral Load and Its Safety on COVID-19 Patients: A Systematic Review* 76
Afifah Fauziyyah, Ratika Rahmasari, Rani Sauriasari

Concordance of TST and QFT-Plus, Sensitivity and Specificity of TST and QFT-Plus in Detection of LTBI in MDR TB Contact

Rullyano Hardian, Reviono, Harsini, Yusup Subagio Sutanto

Department of Pulmonology and Respiratory Medicine Faculty of Medicine, Universitas Sebelas Maret, RSUD dr. Moewardi, Surakarta

Abstract

Background: Tuberculosis (TB) is an infectious disease and the main cause of world health problems. Not all individuals infected with *Mycobacterium tuberculosis* (Mtb) develop active TB. Latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation of the Mtb antigen with no evidence of clinically manifest active TB. Closed contact and household contact with MDR TB patients increases the risk of MDR TB transmission. There is no gold-standard test for LTBI. Tuberculin Skin Test (TST) and Quantiferon Gold Plus (QFT-Plus) examinations are used for LTBI diagnosis.

Methods: A cross-sectional diagnostic test of 32 MDR TB contacts, consisting of 16 household contacts and 16 close contacts, was conducted in April 2020 at Dr. Moewardi Surakarta Hospital.

Results: Positive TST results among MDR TB contacts were 18.8%, while QFT-Plus positive was 25%. The concordance level of TST and QFT-Plus was nearly perfect ($\kappa=0.818$, $p<0.001$). The sensitivity and specificity of QFT-Plus with household contacts as the gold standard were 37.5% and 87.5%, respectively. The sensitivity and specificity of TST with household contacts as the gold standard were 25% and 87.5%, respectively.

Conclusion: The concordance level of TST and QFT-Plus in the detection of LTBI in MDR TB contacts was very good. The TST can be used in place of QFT-Plus although QFT-Plus has better sensitivity. Both tests are useful for confirming TB infections. Both of these tests are not diagnostic, however they can be used to screen for LTBI in MDR TB contacts. (*J Respirol Indones* 2022; 42(1): 9–17)

Keywords: TST, QFT-Plus, Contact, MDR TB

Tingkat Kesesuaian TST dengan QFT-Plus Serta Sensitivitas dan Spesifisitas TST Dengan QFT-Plus dalam Mendeteksi LTBI pada Kontak TB MDR

Abstrak

Latar belakang: Tuberculosis (TB) merupakan penyakit infeksi penyebab utama masalah kesehatan dunia. Tidak semua individu terinfeksi *Mycobacterium tuberculosis* (Mtb) akan berkembang menjadi TB aktif. Infeksi tuberkulosis laten (LTBI) adalah keadaan respon imun persisten terhadap stimulasi antigen Mtb dengan tanpa adanya bukti dan tanda klinis TB aktif. Kontak serumah dan erat dengan pasien TB MDR meningkatkan risiko penularan TB MDR. Baku emas diagnosis LTBI saat ini tidak ada. Pemeriksaan Tuberculin Skin Test (TST) dan Quantiferon Gold Plus (QFT-Plus) digunakan untuk diagnosis LTBI.

Metode: Uji diagnostik cross sectional terhadap 32 kontak TB MDR, terdiri 16 kontak serumah, dan 16 merupakan kontak erat dilakukan pada April 2020 di RSUD dr. Moewardi Surakarta.

Hasil: Tingkat kesesuaian TST dan QFT-Plus adalah sangat baik ($\kappa = 0,818$, $p < 0,001$). Sensitivitas dan spesifisitas QFT-Plus dengan kontak serumah sebagai baku emas sebesar 37,5% dan 87,5%. Sensitivitas dan spesifisitas TST dengan kontak serumah sebagai baku emas sebesar 25% dan 87,5%.

Kesimpulan: TST positif pada kontak TB MDR didapatkan sebesar 18,8% sedangkan QFT-Plus positif sebesar 25%. Tingkat kesesuaian TST dengan QFT-Plus dalam deteksi LTBI pada kontak TB MDR adalah sangat baik. Pemeriksaan TST dapat menggantikan pemeriksaan QFT-Plus. QFT-Plus memiliki sensitivitas yang lebih baik. Kedua pemeriksaan baik untuk memastikan infeksi oleh TB. Kedua pemeriksaan kurang baik untuk diagnosis, namun masih dapat digunakan untuk skrining pada kontak TB MDR. (*J Respirol Indones* 2022; 42(1): 9-17)

Kata kunci: TST, QFT-Plus, Kontak, TB MDR

Correspondence: Rullyano Hardian

Email: rullyanoh@gmail.com

INTRODUCTION

Tuberculosis (TB) is an infectious disease that continues to be the leading cause of global health issues. *Mycobacterium tuberculosis* (Mtb) has been influencing and developing human existence for thousands of years. The success has persisted for thousands of years because it may remain latent, asymptomatic, and then reactivate as active TB. Not all individuals infected with Mtb will develop active TB. Tuberculosis is one of the top ten causes of mortality globally, as well as the primary cause of death from an infectious agent.¹⁻³

Not all individuals infected with Mtb will develop active TB. Fifty to 70% of individuals exposed to MTb can overcome their TB infection through innate or adaptive immune mechanisms. The remaining 30–50% will be active TB or LTBI. Latent tuberculosis infection (LTBI) is a state of persistent immune response to *Mycobacterium tuberculosis* antigen stimulation without any evidence or clinical signs of active TB. Individuals infected with MTb have a high risk of developing active TB. Every year, LTBI progression to active TB contributes to an increase in the incidence of active TB. Active tuberculosis occurred in 7.7% of LTBI patients after one year of infection and 14.2% at the end of 2020. Prevention of active TB originating from LTBI reactivation is an important component of the WHO End TB Strategy program. End TB program targets cannot be achieved without involving LTBI management.³⁻⁵

The large global burden of LTBI is a potential source of TB transmission in the future. The global burden of LTBI in 2016 was around 1.7 billion people, or a quarter of the world's population. The Southeast Asia region bears more than 40% of the global TB incident burden and nearly 35% of the world's LTBI burden. The burden on the Southeast Asian region is disproportionate, considering that only about 26% of the global population lives in this region. The current response to the TB situation in the Southeast Asia region needs to be accelerated as soon as possible to achieve significant progress

towards achieving the *End TB Strategy's* targets.³⁻⁵

Antimicrobial resistance is an increasingly serious threat to public health globally. Multidrug-resistant (MDR) Mtb strains, resistant to both first-line TB drugs (rifampin and isoniazid), are responsible for about a quarter of all deaths caused by antimicrobial-resistant infections. WHO data shows around 558,000 cases of MDR TB or Rifampicin resistant (RR) worldwide. Household and close contact with MDR TB patients increases the risk of MDR TB transmission. The latent TB patients who come into contact with MDR TB patients is a potential burden for increasing MDR TB incidence. Close contact with TB and MDR-TB patients, especially children and people living in low-income countries, is highly likely to develop MDR-TB. The risk of spreading the disease from index cases to contacts will increase if there is a delay in diagnosis and treatment. Research by Fox et al. (2017) in Vietnam found the prevalence of positive TST results in contacts with MDR TB patients was 40.8%. Husein et al. (2019) found that the prevalence of LTBI in the contact group with with TB in Duhok city, Iraq, was high at 41.3% (62/150). This burden must be addressed to prevent a global epidemic of MDR TB. Prevention of the increased incidence of MDR TB from latent TB caused by MDR strains is very important for the success of TB control programs.⁶⁻¹⁰

The diagnosis of LTBI can be a challenge because there is no gold-standard check. The number of bacteria in LTBI individuals is unknown, but it is believed to be so small that it is impossible to directly examine Mtb bacteria, so an immunological examination is carried out instead. The diagnosis of LTBI is made through the *tuberculin skin test* (TST) or the *interferon-gamma release assay* (IGRA). This research used QFT-Plus with the consideration of having better specificity and sensitivity. Because the QFT-Plus test is expensive and difficult to get in laboratory facilities, the TST is better-suited for situations in Indonesia with a high prevalence of tuberculosis. The TST is not only inexpensive, but also easy to do and obtain. The background of this study stems

from the disparity in data availability, diagnostic methods appropriate for Indonesian settings, and LTBI treatment of MDR TB contacts. This study aims to provide information regarding early detection of LTBI in MDR TB contacts.^{5,11}

Furthermore, this study was specifically done to compare the applicability of TST and QFT-Plus examination results in identifying LTBI in MDR TB contacts, as well as finding the difference in sensitivity and specificity of both tests in detecting LTBI in MDR TB contacts. Furthermore, this study was specifically done to compare the applicability of TST and QFT-Plus examination results in identifying LTBI in MDR TB contacts, as well as finding the difference in sensitivity and specificity of both tests in detecting LTBI in MDR TB contacts. By providing fundamental data of prevalence statistics and diagnostic procedures through this study, our research team hope this could be useful for future reference to establish LTBI detection and prevention strategies.

METHODS

This study is a cross-sectional diagnostic test study in which the independent and dependent variables were measured simultaneously for the TST and QFT-Plus examinations. The research was conducted at Dr. Moewardi Hospital, Surakarta Sragen, in April 2020 to meet the number of samples. The sample in this study was MDR TB contacts who were not sick with TB or had had TB disease. The inclusion criteria in this study were people >18 years of age who were willing to participate in the study. The exclusion criteria for this study were a person with clinical signs or symptoms of TB, or a history of TB, a history of taking anti-tuberculosis drugs (OAT), a history of severe allergic reactions or hypersensitivity to a previous TST examination (necrosis, ulceration, anaphylactic shock), or someone with comorbid disease and immunosuppressive disease (DM, clinical HIV, renal failure, and the use of corticosteroids). Subjects who do not return within 48–72 hours for a TST evaluation or withdraw are

considered discontinuous.

A person in contact with MDR TB patients who agreed and met the inclusion criteria was asked to sign an informed consent. The sample consisted of 32 MDR TB contacts, divided into 16 household contacts and 16 close contacts. Subjects who met the inclusion criteria were then given education and recorded data, including identity, history taking, physical examination, laboratory examination, TST examination, and QFT-Plus. Subjects are required to be re-examined within 48–72 hours for TST readings.

Data analysis is presented in the distribution of frequency and percentage. Kappa Cohen test was used to calculate the degree of concordance between TST and QFT-Plus. The correlation analysis used in this research is contingency coefficient analysis. Data on all variables were analyzed using SPSS 22 for windows. The non-existent gold standard for establishing the diagnosis of LTBI is a problem in determining the diagnostic accuracy of TST and IGRA. Comparing patients at high risk of exposure to active TB or patients with LTBI at high risk of acquiring active TB is an alternate method of determining sensitivity that cannot be tested directly.

RESULT

This study was conducted on 32 MDR TB contact respondents with the characteristics of gender, age, type of contact, education level, nutritional status (BMI), and BCG scar. Respondents in this study had a proportion of middle-aged (41–60 years) greater than other age groups, namely as much as 50%. The results of the QFT-Plus and TST that were positive were mostly found in respondents in the middle-aged group, namely 12%, with a total of 4 respondents, and 5.6% of respondents with positive QFT-Plus.

The number of female respondents was 17 (53.1%), while the number of male respondents was 15 (46.9%). The results of the positive QFT-Plus and TST examinations were mostly found in female respondents (18.8%), with a total of six respondents

and seven (21.9%) respondents with positive QFT-Plus.

Based on the type of contact (household contacts with close contacts), the number of respondents is the same, namely 16 people each, or 50% of the respondents. The results of positive TST and QFT-Plus examinations were more common in the household contact variable group than in close contacts, which was 12.5%, with a total of four respondents having positive TST results and six respondents (18.8%) having positive QFT-Plus results. This value is higher than the positive immunological examination results in close contact, namely two (6.3%) positive TST respondents and two (6.3%) positive QFT-Plus.

Most of the research respondents have a very high educational background or have a college education, as many as 15 (46.9%) respondents. Most of the research respondents were respondents with normal nutritional status, as many as 16 (50%), while for those with poor nutritional status, the

proportion was two (6.2%). Most of the research respondents were found to have BCG scars, as much as 75%.

Cross tabulation of positive QFT-Plus examination results with positive TST results in 6 (18.8%) respondents and positive QFT-Plus results with negative TST results in as many as 2 (6.3%) respondents. Negative QFT-Plus examination and positive-negative TST were not obtained in this study, so 0.0%. As many as 24 (75%) respondents obtained a negative QFT-Plus examination and a negative TST.

The degree of conformity (Kappa) of the TST examination with QFT-Plus in this study was 0.818 with a p-value of < 0.001 statistically significant. The data above shows that the level of conformity of the two examinations is very good (kappa value: > 0.8). The level of conformity of the TST examination with QFT-Plus in detecting LTBI in MDR TB contacts can be seen in Table 2.

Table 1. Characteristics of Research Subject

Characteristics	Total Subject n (%)	TST (+) n (%)	QFT-Plus (+) n (%)
Age			
Early adulthood (18–40) years)	14 (43,8%)	2 (6,3%)	3 (9,4%)
middle-aged (41–60)	16 (50%)	4 (12,5%)	5 (15,6%)
Older adults (>61)	2 (6,2%)	0 (0,0%)	0 (0,0%)
Gender			
Female	17 (53,1%)	6 (18,8%)	7 (21,9%)
Male	15 (46,9%)	0 (0,0%)	1 (3,1%)
Contact type			
Household Contact	16 (50%)	4 (12,5%)	6 (18,8%)
Close Contact	16 (50%)	2 (6,3%)	2 (6,3%)
Level of Education			
Low (Elementary)	6 (18%)	0 (0,0%)	0 (0,0%)
Medium (Junior High School or equivalent)	1 (3,1%)	1 (3,1%)	1 (3,1%)
High (Senior High School)	10 (31,3%)	2 (6,3%)	4 (12,5%)
Very high (College)	15 (43,8%)	3 (9,4%)	3 (9,4%)
Nutritional Status (BMI)			
Less BMI	2 (6,2%)	0 (0,0%)	0 (0,0%)
Normal BMI	16 (50%)	4 (12,5%)	5 (15,6%)
Excess BMI	14 (43,8%)	2 (6,3%)	3 (9,4%)
Scar BCG			
Exist	24 (75%)	5 (15,6%)	7 (21,9%)
None	8 (25%)	1 (3,1%)	1 (3,1%)

Table 2. Conformity of TST and QFT-Plus in detecting LTBI in MDR TB contacts

Group	TST		Total	Kappa (κ)	P
	Positive	Negative			
QFT-Plus	Positive	2	8	0,818	<0,01
	Negative	24	24		
Total	6	26	32		

Note: κ = kappa; P<0,001 means significant

Table 3. The results of the sensitivity test, the specificity of the QFT-Plus examination for MDR-TB household contacts

		Household Contact		Total
		Positive	Negative	
QFT-Plus	Positive	6	2	8
	Negative	10	14	24
	Total	16	16	32
Sensitivity	=	37,5%		
Specificity	=	87,5%		
Positive predictive value	=	75%		
Negative predictive value	=	58,3%		
Positive probability ratio	=	3		
Negative probability ratio	=	0,7		

The results of the QFT-Plus sensitivity test for MDR TB household contacts in this study were 37.5%. The sensitivity value obtained means detecting 37.5% of respondents with positive household contacts with QFT-Plus. The specificity value of the QFT-Plus examination on MDR TB household contacts is 87.5%, which means that the possibility of negative household contacts that can be excluded for respondents who have a positive QFT-Plus is 87.5%. The positive predictive value of QFT-Plus in this study was 75%, and the negative predictive value in this study was 58.3%. This study's QFT-Plus positive chance ratio was 3, with a

negative probability ratio of 0.7. The sensitivity and specificity of QFT-Plus to MDR TB household contacts can be seen in Table 3.

Table 4. Results of sensitivity test, specificity of TST examination for MDR TB household contacts.

		Household Contact		Total
		Positive	Negative	
TST	Positive	4	2	6
	Negative	12	14	26
	Total	16	16	32
Sensitivity	=	25%		
Specificity	=	87,5%		
Positive predictive value	=	66,6%		
Negative predictive value	=	53,8%		
Positive probability ratio	=	2		
Negative probability ratio	=	0,8		

The results of the TST sensitivity test for MDR TB household contact respondents in this study were found to be 25%. The sensitivity value obtained means that TST can detect 25% of respondents with positive household contacts. The specificity value of the TST on MDR TB household contacts is 87.5%, which means that the possibility of negative household contacts that can be excluded in respondents who have a positive TST is 87.5%.

Table 5. Correlation of research subject characteristics to QFT-Plus and TST

Characteristics	QFT-Plus (+) n (%)	QFT-Plus (-) n (%)	Total n (%)	P	TST (+) n (%)	TST (-) n (%)	Total N (%)	P
Gender				0.025				0.011
Female	7 (21.9)	10 (31.1)	17 (53.1)		6 (18,8)	11(34,4)	17 (53,1)	
Male	1 (3.1)	14(43.8)	15 (46.9)		0 (0)	15 (46,9)	15 (46,9)	
Age				0.578				0.590
Early adulthood (18–40 years)	3 (9.4)	11(34.4)	14 (43.8)		2 (6,3)	12 (37,5)	12 (43,8)	
middle-aged (41–60 years old)	5 (15.6)	11 (34.4)	16 (50)		4 (12,5)	12 (37,5)	16 (50)	
Older adults (>61 years)	0 (0)	2 (6.3)	2 (6.2)		0 (0)	2 (6,3)	2 (6,3)	
Contact Type				0.102				0.365
Household Contact	6(18.8)	10(31.3)	16 (50)		4(12,5)	12(37,5)	16 (50)	
Close Contact	2(6.3)	14(43.8)	16 (50)		2(6,3)	14(43,8)	16 (50)	
Level of education				0.094				0.125
Low (Elementary)	0 (0)	6 (18.8)	6 (18.8)		0 (0,0)	6 (18,8)	6(18,8)	
Medium (Junior High School)	1 (3.1)	0 (0)	1 (3.1)		1 (3,1)	0 (0)	1 (3,1)	
High (Senior High School)	4 (12.5)	6 (18.8)	10 (31.3)		2 (6,3)	8 (25)	10 (31,3)	
Very High (College)	3 (9.4)	12 (37.4)	15 (43.8)		3 (9,4)	12 (37,5)	15 (46,9)	
Nutritional Status (BMI)				0.578				0.590
Less BMI	0 (0)	2 (6.2)	2 (6.2)		0 (0)	2 (6,3)	2 (6,3)	
Normal BMI	5 (15.6)	11 (34.4)	16 (50)		4 (12,5)	12 (37,5)	16 (50)	
Excess BMI	3 (9.4)	11 (34.4)	14 (43.8)		2 (6,3)	12 (37,5)	14 (43,8)	
Scar BCG				0.346				0.601
Exist	7 (21.9)	17 (53.1)	24 (75)		5 (15,6)	19 (59,4)	24 (75)	
None	1 (3.1)	7 (21.9)	8 (25)		1 (3,1)	7 (21,9)	8 (25)	

The positive predictive value of TST in this study was 66.6%, and the negative predictive value in this study was 53.8%. The TST positive probability ratio is 2, and the negative probability ratio is 0.8. The sensitivity test and the specificity of TST for MDR TB household contacts can be seen in Table 4.

Male respondents tend to have a negative QFT-Plus examination (43.8%), while female respondents with a negative QFT-Plus examination are 31.3%. There was a significant correlation with gender and with QFT-Plus ($r=0.370$ and $P=0.025$) or TST ($r=0.411$ and $P=0.011$). This research did not find a statistically significant correlation between age, type of contact, education level, nutritional status, and BCG scar with the TST or QFT-Plus examination. In Table 5, the correlation between the characteristics of the research subjects (gender, age, type of contact, education level, nutritional status, and BCG scar) on the QFT-Plus and TST examinations can be seen.

DISCUSSION

This study obtained positive TST examinations from six (18.8%) subjects, while the QFT-Plus examination obtained more positive results, namely eight (25%) respondents. The number of positive TSTs on MDR TB contacts obtained in this study was less when compared to the study conducted by Nguyen et al. (2015) in Ho Chi Minh City, Vietnam, where subjects received positive TST in 39% of MDR TB contacts.¹²

At the positive QFT-Plus examination, with a positive TST, there were six subjects, or 18.8%, and at the positive QFT-Plus examination, with a negative TST, there were two subjects, or 6.3%. Two respondents with positive QFT-Plus and negative TST results have the characteristics that they are household contacts, are part of the young and middle-aged age groups, and have normal and excess nutritional status.

Negative QFT-Plus examination with negative TST obtained by 24 (75%) respondents. The number of negative TST in MDR TB contacts

obtained in this study was greater than the study results by Fox et al. (2017) on 147 contacts of MDR TB patients in Vietnam, where negative TST results were obtained by 59.18% subjects.⁶ The results of the TST and QFT-Plus examinations were negative 75% in this study, which could be due to several things. The first is that there are 75% of contacts who are not infected by Mtb. This is based on the theory that about 50–70% of individuals exposed to Mtb can overcome the infection (PDPI, 2016).⁵ Second, negative TST results in this study could be false negatives. False-negative TST results can occur because the infection occurred in less than 8–10 weeks. On the other hand, false-negative TST results can also occur due to long exposure and infection. Third, the results of the LTBI examination in many studies were negative. This could also be due to the fact that this study did not include vulnerable populations such as infants and children, especially those aged <5 years. In their study, Golla et al. (2017) found a prevalence of 44.7% of positive TST in children aged <5 years who were in contact with MDR TB patients.¹³

The level of conformity between TST and QFT-Plus as a diagnostic tool the LTBI degree of conformity (Kappa) TST examination with QFT-Plus was 0.818, with $P<0.001$ statistically significant. The excellent concordance rate means that the TST examination can detect LTBI in MDR TB contacts. Researchers have not received a study of the suitability of QFT-Plus with TST against MDR TB contacts (household and close contacts). The study of the QFT-Plus conformity test with TST was conducted by Venkatappa et al. (2019) in the United States, October 2016 to May 2017, on high-risk populations including close contacts, immigrants, homeless people, inmates, and those with a history of travel to countries with high TB rates. This study found that the level of conformity between QFT-Plus and TST was sufficient ($\kappa=0.46$).¹⁴ Abdulkareem's research (2019) in Kurdistan, Iraq, tested the suitability of QFT Plus - TST, conducted in May–October 2018 on 521 household contacts of active TB patients. This study found that the level of

conformity of the QFT-Plus examination with TST was good ($\kappa=0.679$).¹⁵

The TST examination has several disadvantages compared to the QFT-Plus, resulting in false positives and negatives.⁴ The excellent match rate between TST and QFT-Plus means that the TST examination can be used as a diagnostic tool to detect LTBI equivalent to QFT-Plus. The TST examination can replace the QFT-Plus examination for LTBI detection in MDR TB contacts.

The specificity value of QFT-Plus and TST is 87.5%, which means that this test is good for confirming LTBI in MDR TB contacts because of its high specificity. The low sensitivity value (QFT-Plus 37.5% vs. TST 25%) means that this test is less sensitive for diagnosing LTBI in MDR TB contacts, so additional tests are needed for diagnosis. The sensitivity and specificity of TST in LTBI for high-risk groups have been reported in several studies. A previous study by Sinaga (2017), which assessed the sensitivity of LTBI to CD4+ cell count 200 mm^3 , found that the TST sensitivity was 28.6%, and the specificity was 81.7%. The Triyoga study (2018) assessed the specificity and sensitivity of TST in medical personnel, finding a higher TST performance with a sensitivity of 33.33% and a specificity of 93.30%. This tool can still be used for screening to detect LTBI in MDR TB contacts. Despite getting low sensitivity on both examinations, this study shows that the sensitivity value of QFT-Plus is better than TST.^{11,16}

There is a significant correlation between gender and TST and QFT-Plus with a moderate correlation value because, in this study, the index cases of MDR TB were mostly male. Subjects with positive TST and QFT-Plus from the household contact group were partners (wives) of the index cases.

This study did not find a statistically significant correlation between age, education level, nutritional status, and BCG scar with TST or QFT-Plus examination. These results follow the research of Fox et al. (2017) on 180 respondents who were in contact with drug-sensitive TB patients and 147 respondents who had contacts with MDR TB

patients in Vietnam.⁶ There was no statistically significant relationship between age, gender, occupation, education level, and previous history of BCG immunization with positive TST.⁵ Based on age, the most positive TST was in the middle adult age group, which was 12.5% according to the research of Eom et al. (2017) in Busan, South Korea, for respondents aged >18 years who were household contacts of TB patients who received the highest number of positive TST in the middle-aged group, namely 36 out of 188 (19%) respondents.¹⁷

Poor nutritional status causes a person's susceptibility to infection, but a meta-analysis study by Saag et al. (2018) found that poor nutritional status did not significantly correlate with LTBI. A study by Chadra (2009) on children with Z-scores BMI also did not find an increase in the prevalence of positive TST in severe malnutrition compared to moderate degrees. This is in accordance with the WHO recommendation not to carry out systematic examinations for LTBI in people with poor nutritional status.¹⁸

The history of BCG vaccination had no effect on the QFT-Plus assessment. The TST examination may be influenced by a booster effect caused by a history of past BCG vaccine administration, although the World Health Organization maintains that vaccination history has a limited influence on the specificity of the tuberculin test since BCG cross-reactivity declines over time.³

The limitation of this study is that there is no gold-standard diagnostic test for LTBI. An alternative way of assessing sensitivity and specificity that cannot be assessed directly by comparing the gold standard is to compare subjects at high risk of exposure to active TB patients or subjects with LTBI who are at risk of developing active TB. Selection of household contacts as a substitute for the gold standard because they have a high risk of exposure to Mtb.^{19,20}

CONCLUSION

Because the TST and QFT-Plus have a high degree of concordance, the two tests can be utilized

interchangeably. QFT-Plus can be replaced by examination and vice versa. TST can be used instead of QFT-Plus to identify LTBI in MDR TB contacts. QFT-Plus has a sensitivity of 37.5% while TST has a sensitivity of 25%. In this investigation of MDR TB contacts, the QFT-Plus and TST exams demonstrated a high specificity of 87.5%.

The lack of a gold-standard necessitates consensus on a certain method to be utilized as the gold-standard, therefore it is recommended that cohort studies be employed for future study. Because the QFT-Plus test has higher sensitivity and specificity than TST, it is suggested for detecting LTBI in MDR TB contacts. Because the QFT-Plus test has higher sensitivity and specificity than TST, it is suggested for detecting LTBI in MDR TB contacts.

REFERENCES

1. World Health Organization. Global tuberculosis report 2019. Geneva; 2019.
2. Burhan E, Ramdhani RR, Zaini J. Proporsi tuberkulosis laten pada pasien kanker paru di Rumah Sakit Umum Pusat Persahabatan Jakarta. *J Respirologi Indones*. 2019;39(4):256–65.
3. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management [Internet]. Geneva: World Health Organization; 2018. Available from: <https://apps.who.int/iris/handle/10665/260233>
4. World Health Organization. South-East Asia Regional Action Plan on Programmatic Management of Latent Tuberculosis Infection [Internet]. New Delhi: World Health Organization. Regional Office for South-East Asia; 2019. Available from: <https://apps.who.int/iris/handle/10665/326897>
5. Perhimpunan Dokter Paru Indonesia. Pedoman tatalaksana infeksi TB laten. Indonesia; 2016.
6. Fox GJ, Anh NT, Nhung N V, Loi NT, Hoa NB, Ngoc Anh LT, et al. Latent tuberculous infection in household contacts of multidrug-resistant and newly diagnosed tuberculosis. *Int J Tuberc lung Dis*. 2017;21(3):297–302.
7. Lokhande RM, B F. Study of tuberculosis burden in adult house hold close contacts of sputum smear positive index cases of MDR tuberculosis. *Glob J Res Anal*. 2019;8(2):36–7.
8. Knight GM, McQuaid CF, Dodd PJ, Houben RMGJ. Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modelling. *Lancet Infect Dis*. 2019;19(8):903–12.
9. Hussein N, Balatay A, Almizori L, Saifullah H. A Study of The Prevalence of Latent Tuberculosis in Household Contacts of Patients with Active Tuberculosis in Kurdistan Region of Iraq: A Brief Report. *Int J Infect Press*. 2019;6(2):10–2.
10. Gaskell KM, Allen R, Moore DAJ. Exposed! Management of MDR-TB household contacts in an evidence light era. *Int J Infect Dis*. 2019;80S:S13–6.
11. Sinaga F, Reviono, Harsini. Validitas dan reliabilitas pemeriksaan TST dan T-SPOT dalam mendeteksi infeksi TB laten pada penderita infeksi HIV. *J Ilmu Kedokt Dan Kesehat*. 2017;4(4):248–59.
12. Anh NT, N N V, Loi NT, Nguyen K, A LN, Buu TN, et al. The prevalence of latent TB infection among household contacts of multi-drug resistant and new tuberculosis patients in Ho Chi Minh city, Vietnam. In: *The 5th Conference of the Union Asia-Pacific Region*. Sydney; 2015.
13. Golla V, Snow K, Mandalakas AM, Schaaf HS, Du Preez K, Hesselring AC, et al. The impact of drug resistance on the risk of tuberculosis infection and disease in child household contacts: a cross sectional study. *BMC Infect Dis*. 2017;17(1):593.
14. Venkatappa TK, Punnoose R, Katz DJ, Higgins MP, Banaei N, Graviss EA, et al. Comparing QuantiFERON-TB Gold Plus with Other Tests To Diagnose Mycobacterium tuberculosis Infection. *J Clin Microbiol*. 2019;57(11):e00985-19.

15. Abdulkareem FN, Merza MA, Salih AM. First insight into latent tuberculosis infection among household contacts of tuberculosis patients in Duhok, Iraqi Kurdistan: using tuberculin skin test and QuantiFERON-TB Gold Plus test. *Int J Infect Dis.* 2020;96:97–104.
16. Triyoga PA. Tingkat kesesuaian pemeriksaan tuberculin skin test (TST) dengan T-SPOT.TB, dan sensitivitas serta spesifitas TST DAN T-SPOT.TB dalam mendeteksi infeksi TB laten pada tenaga kesehatan. Universitas Sebelas Maret; 2019.
17. Eom JS, Kim I, Kim W-Y, Jo E-J, Mok J, Kim M-H, et al. Household tuberculosis contact investigation in a tuberculosis-prevalent country: Are the tuberculin skin test and interferon-gamma release assay enough in elderly contacts? *Medicine (Baltimore).* 2018;97(3):e9681.
18. Saag LA, LaValley MP, Hochberg NS, Cegielski JP, Pleskunas JA, Linas BP, et al. Low body mass index and latent tuberculous infection: a systematic review and meta-analysis. *Int J Tuberc Lung Dis.* 2018;22(4):358–65.
19. Girardi E, Angeletti C, Puro V, Sorrentino R, Magnavita N, Vincenti D, et al. Estimating diagnostic accuracy of tests for latent tuberculosis infection without a gold standard among healthcare workers. *Euro Surveill.* 2009;14(43):19373.
20. Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM. Evaluation of diagnostic tests when there is no gold standard. A review of methods. *Health Technol Assess.* 2007;11(50):iii, ix–51.