IJTID. Volume 12 No 2 May-August 2024
Sinta 2 (Decree No: 105/E/KPT/2022)
e-ISSN: 2356-0991; p-ISSN:2085-1103
Available online at https://e-journal.unair.ac.id/IJTID

Original Article

IJTID
(INDONESIAN JOURNAL OF TROPICAL AND INFECTIOUS DISEASE)
Scientific Journal of Tropical and Infectious Disease

Correlation Between MTB/RIF Gene Xpert Cycle Threshold Values and Clinical Radiological Severity of Pulmonary Tuberculosis

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OPEN ACCESS

ARTICLE INFO

Received: February 29, 2024
Accepted: April 30, 2024
Published: August 30, 2024
Available online: August 30, 2024

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Keywords:
Cycle threshold (Ct) values
GeneXpert
Radiological
Severity
Tuberculosis

Abstract

The determination of bacterial load is essential for assessing disease severity, transmission rate, and prognosis. GeneXpert is a diagnostic test that provides Cycle Threshold (Ct) value as a potential measure of *Mycobacterium Tuberculosis* (Mtb) load. Despite its potential, there are limited reports exploring the relationship between Ct value and clinicoradiologial severity. This study aimed to correlate Ct value and clinicoradiological severity of pulmonary tuberculosis (TB). The study was a retrospective design using medical record data of confirmed TB patients from January to December 2022. These patients were identified based on GeneXpert test and classified as high, moderate, or low detection Mtb when Ct value was <16, 16-22, and 22-28, respectively. In assessing the severity of clinical using the Bandim score, thoracic TB lesions were categorized by chest X-ray into minimal, moderate, and advanced. Of the total of 90 TB patients the majority were males (78.9%) aged 46-65 years (59.0%), with comorbidities (95.0%). Most of the participants had mild clinical severity (44.4%), with Ct value of 16-22 (52.2%), and moderate lesions (35.6%). The most common lesions were fibroinfiltrates on the chest x-ray (61.1%). The Ct value of <16 had a significant correlation with clinical severity of TB ($p<0.05$) but no significant association with advanced lesions ($p>0.05$). Based on the results, Ct value had a strong correlation with clinical severity in pulmonary TB. In addition, it could be used as a predictor for managing pulmonary TB patients and an important indicator for control programs.

Cite this as: Merrina, R., Yanti, B., and Arliny, Y. (2024). Correlation Between MTB/RIF Gene Xpert Cycle Threshold Values and Clinical Radiological Severity of Pulmonary Tuberculosis. *Indonesian Journal of Tropical and Infectious Disease*, 12(2) : 73–81. https://doi.org/10.20473/ijtid.v12i2.55560

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb), which can be prevented and cured.[1] It is also a heavy burden in several Asian countries, particularly India, recognized as the biggest nation in Asia's southeast. Several studies have shown that India has the highest TB prevalence, with 210 occurrences per 100,000 people in 2021 as the yearly rate. Meanwhile, Indonesia has the third highest incidence of TB, having a yearly rate of 75.2% of pulmonary TB occurrences in 2021.[2] The gold standard for establishing a diagnosis of this disease is dependent on various microbiological tests, each with its unique advantages and limitations. Although microscopy has been reported to have high specificity, it is largely limited by low sensitivity. Applying culture to liquid and solid substances is an alternate method for identifying TB, but this method often causes delays in detection (6-8 weeks). According to previous studies, liquid media for culture, like the BacT/ALERT system, Mycobacterial Growth Indicator Tube (MGIT), Microscopic Observation Drug Susceptibility Assay (MODS), and Bactec 460TB system have the potential to offer faster results within 7 to 10 days. However, culture test is more expensive and requires subculture on solid media for optimization.[3] To overcome these limitations, several reports have proposed the use of Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), which is a computerized real-time genetic assay to identify rifampicin resistance and diagnose tuberculosis quickly. This assay is advised to be used as a first examination for people who may have multidrug-resistant tuberculosis (MDR-TB) or TB correlated with the human immunodeficiency virus.[4]

In 2013, the WHO issued a recommendation advocating for the adoption of Xpert as the first diagnostic examination among every adult and kids exhibiting TB symptoms.[4] The GeneXpert test uses advanced molecular technology to detect duplicated DNA sequences through real-time nested-Polymerase Chain Reaction (Rt-PCR) assays. In addition, the resultant Ct value serves as a semiquantitative measure, offering insight into the number of TB bacilli in sputum samples.[5] This test correlates Ct value with the number of acid-resistant bacilli observed through microscopy and the time required to produce a positive culture of Mtb using liquid culture system. Despite its potential, few researches have explored the correlation between Ct value and various clinical characteristics, such as the severity of TB, demographic of TB patient, severity of lung parenchymal damage, and drug resistance.

The Ct value in pulmonary TB plays a role in determining bacterial load, replication patterns, and patient prognosis.[6] A cohort study analyzed the relationship between the parameter and the clinical outcomes of pulmonary TB patients. The results showed that the lower the Ct value or the fewer the PCR machine rounds, the worse the clinical outcome due to higher replication and rapidly increasing bacterial load.[7] The parameter is typically categorized into high (22-28), medium (16-22), and low (<16) ranges, indicating varying levels of detectable Mtb concentration. The continuous variable Ct value has an inverse relationship with the quantity of Mtb that is present. In molecular rapid tests, it represents the number of times the PCR machine is spun to determine the presence of bacteria, where more spins indicate fewer bacteria, and vice versa. Low Ct value indicates that the machine rotates only a few times and the bacterial load is high due to high bacterial replication. The real-time Reverse Transcription - Polymerase Chain

Reaction (RT-PCR) Ct value represents the number of amplification cycles and is inversely related to viral load. The parameter can also be used semi-quantitatively to predict viral load, which offers valuable insights into disease prognosis.[8]

Several reports have discussed the correlation between GeneXpert and other TB screening modalities,[9,10] but there are limited studies analyzing the Ct value with clinical profiles and TB severity in pulmonary tuberculosis patients. Therefore, this study aimed to evaluate the correlation between the Ct value and the clinical profile and degree of severity pulmonary tuberculosis.

MATERIALS AND METHODS

Methods

This was a retrospective study, which was carried out based on patients' medical record data at the TB service center of Dr. Zainoel Abidin Hospital Banda Aceh from January 2020 to July 2021, for 19 months, with a total of 106 participants. The medical records were obtained.

Inclusion Criteria

Patients fulfilled the inclusion requirements with pulmonary TB based on GeneXpert MTB/RIF examination and had complete medical record data. In addition, eligible participants were aged ≥18 years with cough symptoms lasting more than two weeks, accompanied by sweating at night, loss of weight, shortness of breath, a high temperature, chest discomfort, and bloody cough.

Exclusion Criteria

Patients diagnosed with extra-pulmonary TB and patients diagnosed with drug-resistant pulmonary TB (DR-TB) were excluded from the study.

Sample Collection

Clinical data such as cough, sweating at night, loss of weight, shortness of breath, high temperature, chest discomfort, and bloody cough were then inputted for analysis and categorized into mild, moderate, and severe groups based on the Bandim TB score. It was based on these signs, symptoms, and indicators, such as tachycardia, anemia conjunctiva, positive lung auscultation findings, axillary temperature >37.0°C, and body mass index (BMI) of <18 in addition to clinical abnormalities.[11] Upper Mid Arm Circumference was not inputted as the data were not present in the medical records. Details of each patient's data were recorded in the data collection sheet. Ct values from GeneXpert were categorized as high, medium, and low. Mtb was deemed identified when a positive response with a Ct value of ≤38 was observed in at least two of the five probes. Semiquantitative estimation of the Bacilli concentration was performed using the Ct 22–28 range in the high category, indicating low detectable Mtb, Ct 16-22 in the medium category, indicating medium detectable Mtb, and Ct <16 in the low category, showing high detectable MTB.[8] In the assessment of chest X-ray, all radiologic lesions found on thoracic photographs, such as consolidation, nodular opacity, and cavities, were entered into the data collection sheet. Pleural effusion, pneumothorax, fibrosis, and hilar lymphadenopathy were also observed. The degree of disease extent based on chest X-ray was divided into (1) Minimal degree when the fibroinfiltrate lesion was slight with no demonstrable cavities, no change in lung volume, only above the second chondrosternal junction, and at the level of the fourth thoracic vertebra. (2) Moderate degree when the diffuse fibroinfiltrate lesion had moderate density and could extend to the entire lung on one side, there was a

cavity with a diameter of less than 4 cm. (3) Advanced degree, where the lesion was more extensive than the moderate degree.[12]

Data Analysis

Statistical indicators like frequency and percentage were computed for qualitative information, whereas mean and standard deviation (SD) were determined for quantitative data. Kruskal Wallis test was used to assess the association of Ct value with the clinical severity of pulmonary TB and the severity of radiology, which was considered significant when the p-value <0.05. Statistical analysis was performed using Statistical Product and Service Solutions (SPSS) version 23.0.

RESULTS AND DISCUSSION

Among the 90 patients with pulmonary TB in this study, 78.9% were males, 59% were aged 46-65 years, and 95.0% had comorbidities, with varying types, such as type 2 diabetes (29%), malnutrition (55%), hypertension (12%), heart disease (6%), and kidney function abnormalities (3%). The majority of pulmonary TB patients had mild clinical severity (44.4%), with clinical complaints of cough (94.4%), shortness of breath (52.2%), chest pain (57.8%), and anemia (83.3%). In addition, most of the participants showed medium Ct value (52.2%), chest X-ray with moderate lesion (35.6%), and decreased hemoglobin levels (83.3%), as shown in Table 1.

Table 1. Clinical characteristics of study participants.

Characteristics	Frequency (n)	Percentage (%)
Gender		
Male	71	78.9
Female	19	21.1
Age		
18-45 years	39	43.3
46-65 years	51	56.7
Comorbidities		
With comorbid	85	85.0
Without comorbid	5	5.0
Comorbid		
DM type 2	23	25.6
Malnutrition	50	55.6
Hypertension	11	12.2
Heart Disease	5	5.6
Acute Kidney Injury	3	3.3
Clinical symptoms		
Cough	85	94.4
Hemoptysis	24	26.7
Temperature >37°C	31	34.4
Night Sweats	23	25.6
Shortness of breath	47	52.2
Chest Pain	52	57.8
Abnormal Auscultation	43	47.8
Heart Rate >90	48	53.3
BMI <18	39	43.3
BMI <16	15	16.7
Anemia	75	83.3
TB severity (Bandim score)		
Mild degree	40	44.4
Moderate Degree	36	40.0
Severe Degree	14	15.6
GeneXpert		
High	19	21.1
Medium	47	52.2
Low	24	26.7
CT value Xpert		
Low	19	21.1
Medium	47	52.2
High	24	26.7
Hemoglobin Level		
Normal	15	16.7
Decreased	75	83.3
Chest X-Ray		
Minimal	17	18.9
Moderate	41	45.6
Advanced	32	35.6

The most common chest X-ray lesion shown in this study was fibroinfiltrate at 61.1%, followed by consolidation (23.3%), pleural effusion (16.7%), and pneumothorax (6%). Meanwhile, pneumothorax was not a typical TB lesion but could be secondary to Mtb infection, as shown in Figure 1.

Table 3. Correlation of GeneXpert Ct value with clinical radiological severity of TB patients

Variable	CT value GeneXpert						Total		OR (CI 95%)	p-value
	High		Medium		Low					
	n	%	n	%	n	%	n	%		
Clinical Severity										
Mild	12	30.0	24	60.0	4	10.0	40	100.0	1.357 (0.532-3.465)	0.006
Moderate	11	30.6	18	50.0	7	19.4	36	100.0		
Severe	1	7.1	5	35.7	8	57.1	14	100.0		
Chest X-Ray Severity										
Minimal	5	29.4	11	64.7	1	5.9	17	100.0	1.184 (0.369-3.804)	0.145
Medium	7	17.1	23	56.1	11	26.8	41	100.0		
Advanced	12	37.5	13	40.6	7	21.9	32	100.0		

Low Ct value examination had a significant correlation with severe clinical degree, while high Ct value had a significant association with mild clinical degree of pulmonary TB patients ($p<0.05$). Meanwhile, Table 3 indicates that there was no statistically significant correlation between Ct value and TB lesions based on chest X-ray.

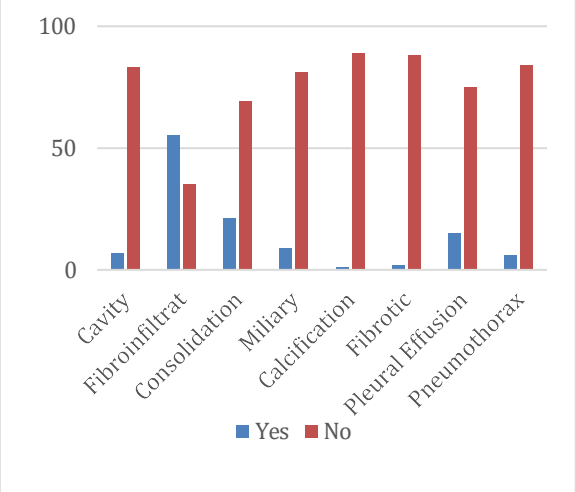

Figure 1. Distribution of typical TB lesions based on chest X-ray.

Receiver Operating Curve (ROC) analysis was used to assess predictors of pulmonary TB severity through Ct value. The results showed that the medium Ct value (C_T 16-22) could be used as a predictor of pulmonary TB severity with a sensitivity value of 92.9% and specificity of 30.3% ($p = 0.003$) (Figure 2).

The majority of pulmonary TB patients in this study were males, accounting for 78.0% of the total population, as shown in Table 1. This finding was supported by a meta-analysis showing that males were the predominant TB patients in low- and middle-income countries, with a male-to-female ratio of 2.21: 1.[13] According to the WHO, pulmonary TB cases in males are 1.8 times higher compared to females.[14] The majority of men as the characteristic findings of this study are similar to findings by Noviyani et al.[15]

The higher prevalence could possibly be caused by better access to health services[13]. Males were more susceptible to infection or at risk of exposure, and a higher prevalence of smoking was correlated with toxic lung injury, leading to decreased immune cell function and increased susceptibility.[14,16]

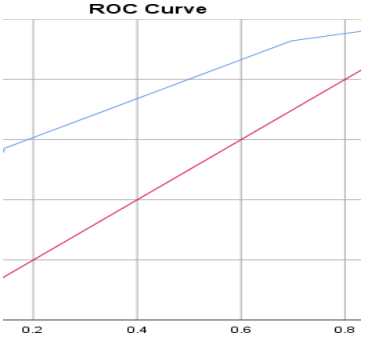

Figure 2. ROC curve (blue line) of Ct value on clinical severity of pulmonary TB.

Of the participants in the present research, 59.0% were between the ages of 46 and 65 of the total population, as shown in Table 1. Previous studies related to the occurrence of TB in Indonesia found that the highest prevalence was found among individuals aged ≥ 55 years.[15] The susceptibility of elderly individuals to TB infection correlated with increased vulnerability to infection and reactivation of Mtb infection. In addition, as people age, the lung's cellular and physiological alterations coincide, resulting in a low-grade oxidative state that is pro-inflammatory and persistent.[17] As a result, the stress response's homeostatic balance was upset, which increased the risk of oxidative stress, mitochondrial dysfunction, cell damage, decreased lung function, impaired immunosurveillance, and an increased vulnerability to respiratory and chronic illnesses like tuberculosis. These unfavorable changes were primarily brought on by inflammation and immuno-senescence. Decreased immunity, comorbidities, and its vulnerability to harmful medication side effects, among other things, puts aged people at an increased risk of tuberculosis (TB) illness and death.[18,19]

Based on the results, the most common thoracic photo findings found in samples with pulmonary TB were fibroinfiltrates at 61.1%, followed by consolidation at 23.3% (Figure 1). Furthermore, fibroinfiltrates were a combination of fibrosis and infiltrates. Fibrosis was caused by long-term lung tissue damage characterized by an abundance of extracellular matrix deposits in the airways, replacing typical lung parenchyma containing collagenous material that caused changes in structure, such as the lung wall's thickness and stiffness.[20] A study by Majdawati showed that 66% of patients showed infiltrate lesions, 36% had combined lesions, 8% had fibroinfiltrates, and 90% had no lesions. Infiltrate lesions and cavities unevenly distributed on chest X-ray were more often found in pulmonary TB cases with Mtb positive sputum results compared to sputum-negative cases. Infiltrates and cavities were the most common lesions found in patients with pulmonary TB.[21]

This study showed a significant correlation of Ct value with clinical severity of pulmonary TB, as shown in Table 3. The lower the Ct value, the more severe the clinical severity of patients with the condition. The medium Ct value (C_T 16-22) could be used to predict pulmonary TB severity with a sensitivity value of 92.9% and specificity of 30.3% (figure 2). Several studies had reported that GeneXpert examination played a role in determining bacterial replication by measuring Ct value and dividing Ct results into 3 groups, namely high <16, medium 16-22, and low 22-28.[22] Ct quantitatively described the number of mycobacteria, which was inversely related to the concentration of TB bacilli. A high Ct value indicated a high number of bacilli/bacterial load.[23] In line with previous reports, bacterial load was an early marker of TB infection severity. Furthermore, it played a role in the transmission of infection and propagation of mycobacterium as well as an important virulence factor. The findings showed that Ct value with high bacterial load had a significant correlation with low pulmonary TB severity. Studies that directly assessed the relationship between bacterial load and clinical severity of pulmonary TB were limited. Various references indicated the superiority of molecular testing using this PCR method to conventional sputum examination. Several studies have also compared the Ct value with others and investigated the relationship between the Ct category and its response to positivity

and cultured positivity using smear microscopy. A report assessing the Ct value of Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) with TB severity in India showed the absence of a correlation between the Ct value of CBNAAT and clinical profile of pulmonary TB, possibly due to the small number of samples.[8,24] Another study exploring bacterial load and inflammatory reaction with clinical severity in pneumonia showed that increased bacterial load correlated with manifestations of high fever (>39.1°C). In addition, low Ct value correlated with more invasive bacterial activity and complications of pneumonia.[25]

STRENGTH AND LIMITATION

This investigation was restricted to clinical observations made after the fact using patient medical record data. Moreover, it was conducted in a single study center and did not include a control group. Therefore, various places need to be studied in order to produce a validated result for more exact and accurate results as well as greater generality of the findings.

CONCLUSIONS

In conclusion, Ct value had a significant correlation with pulmonary TB. In addition, the diagnostic accuracy set at medium Ct value (CT 16-22) could predict pulmonary TB severity. Based on these findings, Ct value could be used as a predictor for managing pulmonary TB patients and an important indicator for TB control programs.

ETHICAL CLEARANCE

The research protocol was approved by Ethics Committee Approval from the Organizational Ethics Committee (Note Number 146/ETIK-RSUDZA/2023).

ACKNOWLEDGMENT

We appreciate the assistance with this research provided by the medical record team of Dr. Zainoel Abidin Hospital.

FUNDING

Sponsorship was not provided for this study.

CONFLICT OF INTEREST

There is absolutely no conflict of interest with this study.

AUTHOR CONTRIBUTION

The study was designed by BY and RM. Reviewing the literature was done by YA. With collaboration from all authors, BY and YA analyzed the statistical data, RM prepared the paper, and RM collected data in the clinics.

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