

Diagnostic Performance of Molecular Rapid Test in Establishing Diagnosis of MDR-TB

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ABSTRACT

Tuberculosis (TB) is a global health problem and is the leading cause of morbidity and mortality in many developing countries. Multidrug-Resistant Tuberculosis (MDR-TB) becomes one burden of health problems, considering its high morbidity and mortality rates. The establishment of MDR-TB diagnosis remains a challenge, according to its requirement of advanced devices and methods, while bacterial culture as the gold standard is expensive and takes a long time. This study aims to evaluate the diagnostic performance of the Molecular Rapid Test or MRT (GeneXpert) in establishing MDR-TB diagnosis using Mycobacteria Growth Indicator Tube (MGIT) culture as the gold standard. This study involved 51 subjects, consisting of 26 (51%) male and 25 (49%) female adult patients with suspected TB treated at dr. Ario Wirawan Lung Hospital (RSPAW) Salatiga. The mean age of research subjects in this study was 48.2+16.35 years (17-79 years). The MRT for TB and MDR-TB detection showed 13 and 7 true positives, 32 and 43 true negatives; sensitivity of 68.4% and 87.5%, specificity of 100% and 100%, Positive Predictive Value (PPV) of 100% and 100%, Negative Predictive Value (NPV) of 84.2% and 97.7%, respectively. A specific analysis to diagnose MDR-TB by MRT on TB patient groups showed seven true positives, 0 false positives, 11 true negatives, and one false negative; sensitivity of 87.5%, specificity of 100%, PPV of 100%, and NPV of 91.7%, and respectively. For establishing the diagnosis of MDR-TB, MRT provides excellent specificity. One false-negative MDR-TB in MRT results is likely resistant to other antibiotics than Rifampicin.

Keywords: Tuberculosis, MDR, rapid molecular test, acid-fast bacteria, diagnostic performance

INTRODUCTION

Tuberculosis (TB) is a global health problem and a significant cause of morbidity and mortality. This condition is exacerbated by the increasing incidence of Multidrug-Resistant Tuberculosis (MDR-TB). The delay in diagnosis and compliance to treatment contributes significantly to the low cure rate. Therefore, various strategies are continuously developed to improve patient compliance with medication to increase the cure rate.¹ Multidrug-resistant tuberculosis is a TB strain that has been resistant to the two main drugs for first-line TB treatment.²

Bacterial culture is still the gold standard for the laboratory diagnosis of TB disease, as the gold standard of TB diagnosis.³ Contrastingly, although microscopic examination of Acid Fast Bacteria (AFB) is not the gold standard, it is more accessible, more efficient, inexpensive, and widely available in all laboratory units.⁴ The need for rapid TB diagnosis is driving a revolution in the development of GeneXpert as one of the molecular diagnostic instruments for TB. This Molecular Rapid Test (MRT) can be

performed on various specimens, such as urine, cerebrospinal fluid, peritoneal fluid, and pleural fluid.⁵ GeneXpert is able to detect Rifampicin-resistant *Mycobacterium tuberculosis* (MTB). One study reported that 95% of Rifampicin-resistant isolates were also resistant to isoniazid, thereby being practically used to diagnose MDR-TB.⁶

GeneXpert has been used in dr. Ario Wirawan Lung Hospital (RSPAW) Salatiga since July 2014; however, there has been no research on the diagnostic performance of GeneXpert in this hospital.

METHODS

This study used a cross-sectional design and was performed from April to June 2020. The study aimed to evaluate the diagnostic performance of the Molecular Rapid Test (GeneXpert) in the diagnosis of MDR-TB. Subjects were all adult patients treated at RSPAW Salatiga with suspected TB. Inclusion criteria were age above 16 years, cough with phlegm for two weeks or more, and no improvement of cough with non-OAT treatment. In addition, patients with leprosy co-infection were excluded from this study.

Sputum was collected from all patients for TB and MRT (GeneXpert) microscopic examination at RSPAW Salatiga. In contrast, the bacterial culture of Mycobacteria Growth Indicator Tube (MGIT) and Drug Susceptibility Test (DST) was carried out at Semarang Health Laboratory Center. The results were analyzed, and sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were calculated, with MGIT culture as the gold standard.

The research has obtained ethical clearance from the Health Research Ethics Commission, Faculty of Medicine, Gadjah Mada University/Dr. Sardjito Hospital, Yogyakarta with number Ref. No.: KE/FK/0496/EC/2020.

RESULTS AND DISCUSSIONS

This study involved 51 patients consisting of 26 (51%) male and 25 (49%) female subjects ranging from 17 to 79 years old. The characteristics of the

Table 1. Characteristics of research subjects

Variable	Value
Gender, n (%)	
Female	25 (49%)
Male	26 (51%)
Age, average±SD	48.2±16.4
<18 years	1 (2%)
18–60 years	39 (76.5%)
>60 years	11 (21.6%)
Occupation, n (%)	
Farmer/labor	17 (33.3%)
Housewife	8 (15.7%)
Self-employed	7 (13.7%)
Employee	11 (21.6%)
Student/retirement	8 (15.7%)
Earning, n (%)	
<2.5 million	31 (60.8%)
2.5-4.9 million	12 (23.5%)
5-7.5 million	7 (13.7%)
>7.5 million	1 (2%)

Table 4. MDR detection: comparison between RMT and MGIT culture

RMT	MGIT Culture		Total
	MDR	Non-TB or non-MDR-TB	
Rifampicin-resistant detected	7	0	7
Rifampicin-resistant not detected	1	43	44
Total	8	43	51

Comparison between microscopic examination of AFB and MGIT culture showed that all smear-positive results were confirmed on MGIT culture, and no false-positive results were found. Comparison between the microscopic examination of AFB and MGIT culture to detect MTB showed a specificity of 100% and sensitivity of 68.4%. Positive predictive value and NPV were 100% and 84.2%, respectively (Table 2).

Table 2. Comparison between microscopic examination of AFB and MGIT culture

Microscopic Examination	MGIT Culture		Total
	Positive	Negative	
Positive	13	0	13
Negative	6	32	38
Total	19	32	51

In contrast to the microscopic examination of AFB, the RMT examination in this study was sensitive. The sensitivity, specificity, PPV and NPV of RMT to detect MTB were 94.7%, 68.8%, 64.3% and 95.7%, respectively (Table 3). The previous study to evaluate the performance of GeneXpert in diagnosing pulmonary tuberculosis (TB) in China showed 84.0%, 87.8%, 78.2%, and 87.2%, respectively.⁷

Table 3. MTB detection: comparison between RMT and MGIT culture

RMT	MGIT Culture		Total
	Positive	Negative	
MTB detected	18	10	28
MTB not detected	1	22	23
Total	19	32	51

The sensitivity, specificity, PPV, and NPV of RMT to detect Rifampicin-resistant *Mycobacterium tuberculosis* were 87.5%, 100%; 100%; and 97.7%, respectively (Table 4).

Table 5. MDR detection: comparison between RMT and MGIT culture among TB patients

RMT	MGIT Culture		Total
	MDR	Non-MDR-TB	
Rifampicin-resistant TB detected	7	0	7
Rifampicin-resistant TB not detected	1	11	12
Total	8	11	19

The analysis was continued by excluding the non-TB patients. There were 19 TB patients, 8 MDR-TB patients, and 11 non-MDR-TB patients. The sensitivity, specificity, PPV, and NPV were 87.5%; 100%; 100%; and 91.7%, respectively (Table 5).

Microscopic examination of AFB is a specific but insensitive test, while TCM is a sensitive and non-specific examination in diagnosing TB. The number of bacteria influences the microscopic examination of AFB in the sputum specimen, which minimizes the possibility of detecting bacteria despite TB infection. A molecular test using GeneXpert detects genes of MTB bacteria, thereby increasing the potential to diagnose TB despite a small number of bacteria present in the sputum.

For MDR-TB diagnosis in TB and non-TB populations, molecular tests using GeneXpert showed excellent specificity. The specificity of GeneXpert remains high in the diagnosis of MDR-TB among TB patients. The high specificity also sensitivity was reported in a systematic review to determine the diagnostic accuracy of Xpert MTB/RIF. The sensitivity and specificity in detecting Rifampicin resistance in adults with presumptive Rifampicin-resistant tuberculosis were 96% (94% to 97%) and 98% (98% to 99%).⁸ However, the sensitivity of Xpert varied across different types of specimens. The systematic review, including 66 unique studies, reported low sensitivity (31%) in pleural tissue compared to 97% in bone or joint fluid.⁶ In a study to detect MDR-TB in central Malawi, GeneXpert MTB/RIF was used to confirm a positive result of one sample that was found to have discordant results between the microscopic examination (negative) and the tuberculosis CX-test, a non-commercial, thin-layer agar-based tuberculosis culture method (positive).⁹

The results of this study may differ from previous studies, possibly due to differences in the number of cases at the study site. Studies in Pakistan and Spain have shown that different diagnostic performance of GeneXpert is related to differences in endemicity in both areas. High sensitivity and specificity of a diagnostic test found in this study greatly assist the

therapeutic steps of TB. By detecting drug-resistant TB, therapeutic measures and infection control can be more effectively carried out.¹⁰ One study also reported that GeneXpert showed good performance in areas with low incidence, i.e., in Kuwait with an incidence of TB 23/100,000 cases, and only ~1% was MDR-TB.¹¹

CONCLUSIONS AND SUGGESTIONS

Molecular Rapid Test (GeneXpert) is a sensitive test, while the microscopic examination of AFB is a specific test for the diagnosis of TB. GeneXpert analysis shows excellent specificity in diagnosing MDR-TB.

Molecular rapid tests and microscopic examinations are suggested to be routinely carried out together for the diagnosis of TB, with the follow-up by MGIT culture for the diagnosis of MDR-TB, which is available at RSPAW Salatiga. Bacterial culture and DST need to be supported by providing standardized facilities and infrastructure at least Biosafety Level II. Molecular Rapid Test (GeneXpert) is proposed as a molecular test in external quality assurance.

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