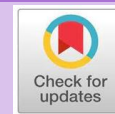**Original Article**

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Predictive Positive Value Xpert MTB/RIF in Detecting *Mycobacterium tuberculosis* on Adult Pulmonary Tuberculosis Patients in Dr. Soetomo Referral Hospital Surabaya Indonesia

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Abstract

Pulmonary tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* and transmitted via droplets. According to the WHO, TB cases in the world have reached ten million. Southeast Asia is the largest contributor, and Indonesia itself has the second-highest number in the world with an incidence of approximately 824,000 cases. The most common symptoms of active TB are cough, fever, weight loss, and night sweats. The diagnosis can be established upon the confirmation that one of the specimens contains *M.* tuberculosis. Xpert MTB/RIF provides results in less than 2 hours, whereas culture takes approximately 2-6 weeks. This research aims to evaluate the characteristics and determine the Predictive Positive Value (PPV) percentage of GeneXpert MTB/RIF, utilizing parameters derived from the gold standard examination results, namely culture. This research method is descriptive- analytic based on secondary data extracted from medical records of patients receiving care at the multi-drug resistant TB (MDR-TB) Outpatient Management at Dr. Soetomo Referral Hospital Surabaya from the period January 2019 – April 2022. The results showed that the PPV level of GeneXpert MTB/RIF in detecting the presence of *M. tuberculosis* is 90%. The diagnosis of pulmonary TB is also supported by the chest X-ray infiltrate's appearance and clinical symptoms of cough, weight loss, fever, and night sweats. Smoking and diabetes are the most common comorbid and risk factors in TB. The conclusion of this study is that the PPV for diagnosing adult pulmonary TB using the Xpert MTB/RIF is relatively high. This suggests the potential use of this method as a diagnosing tool for accurately diagnosing pulmonary tuberculosis.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb) and transmitted by droplets. Transmission of TB happens through the inhalation of nuclei droplets that contain the bacteria, and they will pass through the mouth, upper respiratory tract, bronchus, and alveolus.[1] The risk factors for tuberculosis are age, gender, smoking, alcohol consumption, comorbidity (diabetes, human immunodeficiency virus (HIV), hypertension, etc.), job, and poor ventilation, which will contribute to the exposure of the bacteria to the host immune system.[2]

Indonesia is the second country having the most cases, with 384 cases per 100,000 population. In Indonesia, East Java was the second province with the most TB cases, with 43,268 cases per year. Further, there are three Global High Burden Countries (HBCs) for TB, TB/HIV, and MDR/Rifampicin Resistant TB (MDR/RR TB), Indonesia, placed in a section that includes in all three sections of HBCs.[3] Tuberculosis is classified by the location (pulmonary or extrapulmonary), treatment history (new or relapse cases), medication sensitivity , and the HIV.[4] According to the WHO, pulmonary cases account for 90% of tuberculosis cases.[3]

Distinguishing tuberculosis involves categorizing it as either bacteriologically confirmed (with a positive GeneXpert/AFB/Culture test) or clinically confirmed (symptoms, risk factors, and chest X-ray support, but lacking bacteriologic confirmation). Typical symptoms include persistent cough, prolonged fever, night sweats, weight loss, and hemoptysis. GeneXpert serves as the primary screening tool for tuberculosis suspects, and a positive result requires confirmation through the gold standard culture test.[4]

Even though the culture method remains the gold standard for diagnosing tuberculosis, it has drawbacks, including test complexity and prolonged turnaround time (approximately 6-9 weeks).[5] In 2013-2014, Indonesia introduced GeneXpert, which based on nucleic acid amplification (NAAT), delivers results within two hours and employs molecular technology to identify rifampicin resistnce.[6,7] Targeting the *rpoB* gene, which plays a role in *Mycobacterium tuberculosis* replication and serves as a potential rifampicin target, allows simultaneous detection of the bacteria and rifampicin resistance through PCR technology.[8,9] Both culture methods and GeneXpert demonstrate high accuracy, with culture methods reaching 90% sensitivity and 100% specificity, and GeneXpert achieving 81.8% sensitivity and 96.5 specificity. [10,11] The aim of this study is to evaluate the accuracy (Predictive Positive Value) of GeneXpert MTB/RIF.

MATERIALS AND METHODS

Population and Sample

The data used in this research were secondary data, obtained from medical records of adult patients with lung tuberculosis multi-drug resistance at the Dr. Soetomo Surabaya General Hospital from the period January 1st, 2019, until April 31st, 2022. The sample used in this research is all medical records of adult MDR-TB patients (above 18 years old) that meet the inclusion criteria, including complete medical records.[12] The exclusion criterion was inpatient management. The total number of patients in the MDR-TB outpatient management is 255; the number of patients that meet all the criteria is 197.

Methods

This research design is an observational retrospective study, opting for a descriptive analytic approach to assess the high accuracy (predictive positive value) of GeneXpert as a screening for tuberculosis. The data were analyzed using Microsoft Excel version 16.65, applying the predictive value formula—calculated as true positives divided by the sum of true positives and false positives.

RESULTS AND DISCUSSION

The research results showed that the majority of patients with MDR-TB within the productive age group were between 18-45 years old. This finding aligns with the statement from the WHO that the highest incidence of cases falls within the 25-34 age range.[13] The risk of exposure of Mtb through pollution and smoking was higher in population above 15 years old. The increased risk for young people might be mainly because of the continued transmission within the community.[14] Based on this research; men are more likely to have tuberculosis. The WHO also stated that males have a 1.6-fold a higher risk than females. There are several factors that can cause this gender gap, such as biological differences, and men are also likely to have the risk factor associated with TB exposure. [13,15] At the MDR-TB outpatient department Dr. Soetomo Surabaya General Hospital, the majority of cases involve new cases, followed by relapse cases. Several hypotheses exist regarding the prevalence of relapse, including the likelihood that the immune systems of recently recovered individuals have not fully recovered. Other than that, individuals who have not fully completed treatment often reside in high-risk TB exposure environments, potentially explaining the elevated risk of

bacterial reactivation among these patients,[16] as shown in Table 1.

Table 1. Profile and diagnosed status of adult patients at MDR-TB outpatient department Dr. Soetomo Surabaya General Hospital, January 2019 – April 2022.

Predictor	Amount	Percentage
Age		
18-45	115	58.38
46-59	59	29.95
>60	23	11.67
Gender		
Male	101	51.27
Female	96	48.73
Diagnosed		
New cases	85	43.14
Relapse cases	60	30.45
Loss to follow-up	18	9.13
Failed treatment	18	9.13
Unstandardized treatment	5	2.53
Non-DOTS*	9	4.56
Unknown	2	1.02

*DOTS, directly observed treatment shortcourse

Risk factors and comorbidities such as smoking, alcohol consumption, diabetes, HIV, and immunosuppressive therapy significantly impact the treatment outcome and mortality rates of TB patients.[17] Table 2 shows that diabetes is the predominant comorbidity among the subjects in this study, consistent with previous research indicating a threefold increased risk of TB infection in individuals with diabetes. Alveoli play a crucial role in TB infections and their

replication.[18,19] Diabetes mellitus, with its potential to damage mediated cells and poor glycemic control, adversely impacts cytokine response, modifying the defense mechanisms in alveolar macrophages. Hyperglycemia disrupts the recruitment of neutrophil, movement of the monocyte, and phagocytosis of alveolar macrophage. Inactive T-Helper cell activation further hampers the release of the antigen-specific interferon gamma. Pulmonary microvasculature mutations and micronutrient deficiency contribute to the invasion and formation of TB.[20]

Another common comorbidity is HIV. The main effect of immunosuppressants on HIV is the loss of the CD4, which is the biggest contributor to establishment of TB. The increase of TNF-α could elevate the risk of developing TB. Decreasing apoptosis, increasing necrosis of macrophage from the infected HIV , and impeding the development of specific immune response may be associated with the immune system in HIV-infected individuals, which makes them susceptible to TB infections.[21]

Smoking and alcohol consumption are the main risk factors with infections such as TB.[19,21] Smoking has a significant role in the pathogenesis of tuberculosis, especially in ciliary dysfunction, decreasing immune system, and the damage of macrophage immune system that could be the underlying cause of TB infections. Smoking also decreases the production of IL-12, which affects infection on immunocompetent individuals.[19] Alcohol consumption adversely affects the immune system, which increases the risk of tuberculosis infection and the reactivation of latent tuberculosis. While macrophages play crucial role in eliminating various bacteria, alcohol consumption may compromise the responsiveness of alveolar macrophages to

new pathogens.[22]

Table 2. Comorbidities and risk factors of adult patients with MDR-TB at outpatient department Dr. Soetomo Surabaya General Hospital January 2019 – April 2022.

Predictor	Amount	Percentage
Comorbidities		
Diabetes Mellitus	70	35.53
Gastric problem	5	2.54
Hypertension	9	4.57
HIV	7	3.55
Malnutrition	1	0.50
None of the above	92	46.70
Risk Factors		
Smoking	71	36.04
Alcohol consumption	27	13.70
None of the above	99	50.25

Table 3 shows the X-ray manifestations in tuberculosis patients. While chest X-rays provide a rapid indication of pulmonary tuberculosis, their weakness lies in imaging pulmonary infections, as various infections have similar signs and symptoms.[23] In Indonesia, the regulation by the Ministry of Health stated that every patient suspected of tuberculosis with negative bacteriologic test result should undergo chest X-ray to confirm the diagnosis. If the chest X-ray leads to tuberculosis, it will declare "tuberculosis clinically confirmed."[4] In another study, it was stated that the common chest X-ray on suspect tuberculosis was infiltrate,[24] which was in line with this study, whose chest X-

ray examination was done when the patients first came in.

Table 3. The chest X-ray of adult patients in MDR-TB outpatient department at Dr. Soetomo Surabaya General Hospital January 2019 – April 2022.

CXR	Amount	Percentage
Cavity	56	28,43
Infiltrate	117	59,39
Nodule	2	1,01
Miliary	2	1,01
Fibrosis	95	48,22
Fibrothorax	4	2,03
Pleural effusion	6	3,00
Atelectasis	10	5,07
Consolidation	9	4,56

The prevalent clinical features observed in TB patients in this study are cough, weight loss, fever, and night sweats. Cough, particularly common in lung tuberculosis, plays a significant role in its transmission, as shown in Table 4.[25] Weight loss is a frequent occurrence in TB patients, attributed to the production of inflammatory mediators, ultimately leading to leptin suppression in the progression of TB.[26] Fever and night sweats are often interconnected, with secondary inflammation by the tubercle contributing to fever. Although the exact mechanism of the rising body temperature, mainly at night remains unclear, it may be a factor in the occurrence of night sweats.[27]

Table 4. Clinical manifestation of adult patients at MDR-TB outpatient department Dr. Soetomo Surabaya General Hospital January 2019 – April 2022.

Clinical manifestation	Amount	Percentage
Cough	188	95.43
Night sweats	89	45.18
Blood cough	47	23.86
Dyspnea	79	40.10
Weight loss	141	71.57
Fever	85	43.15
Chest pain	50	25.38

*One patient could have more than one clinical manifestation.

The predictive positive value indicates the percentage of people who have a positive result on the test and are confirmed to have the disease. A predictive positive value can be obtained by dividing the true positive by the addition of true positive and false positive.[28] A false positive percentage of 0.08% remains in this sample, indicating that, although the gold standard yielded negative results, the Xpert MTB/RIF produced a positive result. The CT Value result of Xpert may have been in the "low or very low" range or around 28.3, and the false positive may have resulted from the lack of bacterial growth on the culture technique.[29] Another contributing factor to the persistence of false positive results is the inability to culture *Mycobacterium tuberculosis* DNA, which may exist extracellular or in a non-intact cell. Consequently, the manufacturer of Xpert MTB/RIF recommends that Xpert MTB/RIF should be used in conjunction with the gold standard.[30] According to this study, 90% of patients with a positive result on Xpert MTB/RIF were confirmed to have the condition listed in Table 5. This result is consistent with the previous study. Permatasari et al. reported that the predictive positive value of Xpert MTB/RIF is 90%, whereas Allahyartorkaman et al. reported that it is 83.9%.[10,31]The ability of the positive predictive value on Xpert MTB/RIF to identify *Mycobacterium tuberculosis* is

crucial for diagnosing TB. Additionally, because it may provide information on rifampicin resistance, and may serve as the basis to precisely administer the treatment and as early as possible .[32]

Table 5. Culture test results of adult patients at MDR-TB outpatient department Dr. Soetomo Surabaya General Hospital January 2019 – April 2022.

	GeneXpert (+)
Culture (+)	180
Culture (-)	17

*Culture test for *Mycobacterium tuberculosis* and GeneXpert for MTB detected and rifampicin resistance.

STRENGTH AND LIMITATION

The strength of this study lies in the use of Xpert MTB/RIF as a diagnostic tool in Indonesia. However, the limitations of this study were due to its retrospective method and following the government program, where negative results in GeneXpert are not further confirmed through culture or the gold standard.

CONCLUSIONS

The predictive positive value of the diagnosing method using the Xpert MTB/RIF is 90% for adult patients, which is relatively high; therefore, this result potentially supports the applicability of the Xpert MTB/RIF as a diagnosing tool for accurately diagnosing pulmonary tuberculosis.

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CONFLICT OF INTEREST

All of the authors declare that they have no conflict of interest.

ETCHICAL CLEARANCE

All the protocol and the use of medical records for the data on this research are approved by Dr. Soetomo Surabaya General Hospital ethics committee (Ref. No.: 1055/LOE/301.4.2/1X/2022).

AUTHOR CONTRIBUTION

Every author has equally contributed to this research, from the design to the drafting and revision, and given their final approval of the article.

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