RESEARCH ARTICLE / ARAŞTIRMA

DOI: 10.4274/mjima.galenos.2024.23055.13
Mediterr J Infect Microb Antimicrob 2024;13:23055.13
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2024.23055.13

# Evaluation of the Xpert MTB/RIF Test Performance in the Diagnosis of Suspected *M. tuberculosis* in Pulmonary and Extrapulmonary Clinical Specimens

## Tüberküloz Şüpheli Hastaların Pulmoner ve Ekstrapulmoner Örneklerinde Xpert MTB/RIF Testinin Tanısal Performansının Değerlendirilmesi

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## Abstract

**Introduction:** The aim of this study was to evaluate the performance of the Xpert MTB/RIF test in the diagnosis of *M. tuberculosis* in pulmonary and extrapulmonary clinical specimens with positive or negative smears.
**Materials and Methods:** Between January 2018 and December 2021, a total of 2082 samples were examined, including 1526 respiratory samples and 556 non-respiratory samples. The samples processed for culture were inoculated into Löwenstein Jensen medium and Mycobacteria Growth Indicator Tube (MGIT) tubes, then MGITs were loaded into the MGIT 960 automated system. The Xpert MTB/RIF molecular test was performed to all samples according to the manufacturer's recommendations.
**Results:** *M. tuberculosis* was grown in culture in 153 (7.3%) of all samples, and the Xpert MTB/RIF test was positive in 203 (9.7%). ARB, MTB/RIF test and culture positivity in lung samples are; 86 (5.6%), 175 (11.4%) and 129 (8.4%), respectively. In extrapulmonary samples; the positivity was 7 (1.2%), 28 (5%) and 24 (4.3%). When mycobacterial culture results are accepted as reference, the sensitivity was 53.6% and the specificity was 99.4% for the Ehrlich-Ziehl-Neelsen staining method. For respiratory samples, these values were 58.1% and 99.2%; for extrapulmonary samples, sensitivity and specificity were 29.2% and 100%, respectively. For all the samples examined with The Xpert MTB/RIF test; sensitivity, specificity; positive predictive value; and negative predictive value were calculated as 89.5%, 96.6%, 67.5% and 99.1%, respectively.
**Conclusion:** The sensitivity and specificity rates of the Xpert MTB/RIF test used in this study in non-respiratory samples were found to be slightly lower than in respiratory samples. It had high sensitivity and specificity rates in both sample groups. It was observed that The Xpert MTB/RIF test was a very fast and requiring low workload.
**Keywords:** Xpert MTB/RIF, *Mycobacterium tuberculosis*, rapid diagnosis, Bactec MGIT 960

## Öz

**Giriş:** Bu çalışmanın amacı, yayma pozitif veya negatif olan pulmoner ve ekstrapulmoner klinik örneklerde *Mycobacterium tuberculosis (M. tuberculosis)* tanısında Xpert MTB/RIF testinin performansının değerlendirilmesidir.
**Gereç ve Yöntem:** Ocak 2018-Aralık 2021 tarihleri arasında 1526 solunum yolu örneği ve 556 solunum yolu dışı toplam 2082 örnek incelenmiştir. Kültür için işlenmiş örneklerden, Löwenstein Jensen besiyerine ve Mycobacteria Growth Indicator Tube (MGIT) 960 otomatize sistemine yüklenen MGIT tüplerine, üreticilerin önerileri doğrultusunda ekim yapıldı. Tüm örneklerde Xpert MTB/RIF moleküler testi üretici firmanın önerileri doğrultusunda çalışılmıştır.

**Cite this article as:** Terzi HA, Aydemir Ö, Karakeçe E, Demiray T, Köroğlu M, Altındiş M. Evaluation of the Xpert MTB/RIF Test Performance in the Diagnosis of Suspected *M. tuberculosis* in Pulmonary and Extrapulmonary Clinical Specimens. Mediterr J Infect Microb Antimicrob. 2024;13:23055.13.

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**Received/Geliş Tarihi:** 02.11.2023 **Accepted/Kabul Tarihi:** 25.07.2024
**Published:** 30.07.2024

## Öz

**Bulgular:** Tüm örneklerin 153'ünde (%7,3) kültürde *M. tuberculosis* üremiş ve 203'ünde (%9,7) Xpert MTB/RIF testi pozitif bulunmuştur. Akciğer örneklerindeki ARB, MTB/RIF testi ve kültür pozitifliği sırasıyla; 86 (%5,6), 175 (%11,4), 129 (%8,4) iken; akciğer-dışı örneklerde bu değerler; 7 (%1,2), 28 (%5), 24 (%4,3) olarak bulunmuştur. Mikobakteriyel kültür sonuçları referans alındığında; çalışmamızda Ehrlich-Ziehl-Neelsen boyama yönteminin tüm örneklerdeki duyarlılığı; %53,6, özgüllüğü; %99,4; akciğer örnekleri için bu değerler sırasıyla; %58,1 ve %99,2; akciğer dışı örnekleri için ise %29,2 ve %100 olarak bulunmuştur. İncelenen tüm örnekler için Xpert MTB/RIF testinin duyarlılığı; %89,5, özgüllüğü; %96,6, pozitif öngörü değeri; %67,5 ve negatif öngörü değeri; %99,1 olarak hesaplanmıştır.

**Sonuç:** Bu çalışmada kullanılan Xpert MTB/RIF testinin solunum yolu dışı örneklerdeki duyarlılık ve özgüllük oranları solunum yolu örneklerine göre biraz daha düşük bulunmuştur. Her iki örnek grubunda da yüksek duyarlılık ve özgüllük oranlarına sahip olduğu, çok hızlı ve düşük iş yükü gerektiren bir test olduğu görülmüştür.

**Anahtar Kelimeler:** Xpert MTB/RIF, *Mycobacterium tuberculosis*, hızlı tanı, Bactec MGIT 960

## Introduction

According to the 2021 report of the World Health Organization (WHO), tuberculosis (TB) resulted in approximately 9.9 million new cases and 1.5 million patient deaths in 2020, and it still maintains its importance as a serious public health problem all over the world[1].

Although the microscopy method used in TB diagnosis today has high specificity values, it cannot help make a diagnosis in a short time due to its low sensitivity. Culture methods, which are currently used as the gold standard, have high sensitivity and high specificity. However, since the time it takes to give results is long, delays in diagnosis and treatment occur, and patient losses may occur during the waiting period for the result. Therefore, rapid diagnosis and initiation of effective treatment are prerequisites for the successful implementation of TB control programs[1,2].

Two groups of drugs are used in TB treatment: primary and secondary. While the primary drugs are isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin and thiacetazone; secondary drugs are more toxic and less tolerated drugs such as rifabutin, rifapentine, cycloserine, ethionamide, amikacin, kanamycin, capreomycin and paraaminosalicylic acid, levofloxacin, moxifloxacin and gatifloxacin[3].

Chromosomal mutations in *Mycobacterium tuberculosis (M. tuberculosis)* usually cause resistance to a single drug. However, bacteria resistant to more than one drug can be seen in the future with the accumulation of resistance. The situation of having resistance to at least isoniazid and rifampicin from anti-tuberculosis drugs is called multidrug-resistant (MDR) TB[4]. Cases resistant to a fluoroquinolone and an injectable second-generation drug (amikacin, kanamycin and capreomycin) in addition to isoniazid and rifampicin resistance are called extensively drug-resistant (XDR) TB according to the WHO report[5]. In recent years, the frequency of MDR and XDR *M. tuberculosis* strains causing TB has increased. Due to the impracticality of conventional diagnostic tests, their long time to complete, and their inadequacy in species-level typing, the Centers for Disease Control and Prevention has recommended the use of the fastest methods available for the diagnosis of *M. tuberculosis* in addition to standard tests in diagnostic mycobacteriology. One of these, the Xpert MTB/RIF test (Cepheid, Sunnyvale, CA, USA), has been used in recent years as an easy and rapid nucleic acid amplification test that can detect the presence of *M. tuberculosis* directly from the patient's sample in less than two hours[6].

This study aimed to evaluate the performance of the Xpert MTB/RIF test in the diagnosis of *M. tuberculosis* in pulmonary and extrapulmonary clinical samples with positive or negative smear results in our TB diagnostic laboratory over a 4-year period.

## Materials and Methods

This study was approved by the Sakarya University Faculty of Medicine Ethics Committee (ethics committee approval no: 176, date: 31.05.2023).

### Samples Included in the Study

Clinical samples of patients who were sent to the medical microbiology laboratory for routine TB polymerase chain reaction (PCR) with clinical suspicion of TB between January 2018 and December 2021 were included in the study. A total of 2,082 samples [1,526 respiratory tract samples: sputum, bronchoalveolar lavage (BAL); 556 non-respiratory tract samples: sterile body fluids (peritoneal fluid, pleural fluid, synovial fluid, biopsy), urine, cerebrospinal fluid (CSF)] were examined.

### Processing of Samples and Culture

After homogenization and decontamination of clinical samples, Ehrlich-Ziehl-Neelsen (EZN) and Auramine-Rhodamine staining methods were used for microscopic examination. Samples processed for culture were inoculated into 200 µl of Löwenstein

Jensen (LJ) medium (Salubris, Turkey) as solid medium and into Mycobacteria Growth Indicator Tube (MGIT) tubes (BD, Franklin Lakes, NJ, USA) containing modified Middlebrook 7H9 liquid medium according to the manufacturers' recommendations. The inoculations made into solid medium were incubated at 37 °C for 6-8 weeks, and the liquid medium was incubated with BACTEC MGIT 960 for 6 weeks. If there was no growth at the end of this period, the sample was evaluated as negative. In case of growth, the immunochromatographic method (BD MGIT TB Identification Test, Becton Dickinson, USA) detecting MPT 64 antigen was used for the identification of *M. tuberculosis* complex.

### Xpert MTB/RIF Test

Xpert MTB/RIF test was performed according to the manufacturer's recommendations. Decontaminated samples were mixed with a sample reagent containing sodium hydroxide and isopropyl alcohol at a ratio of 2 to 1 and kept at room temperature for 15 minutes. Then, 2 ml of this mixture was loaded into the test cartridge and the cartridge was placed in the Xpert device. After the test was completed in approximately 120 minutes, the obtained data were evaluated and recorded with a computer program.

### Statistical Analysis

Number and percentage were used to define the data. The results of the Xpert MTB/RIF test were compared with the results of the culture method, which is the gold standard in TB diagnosis. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated and performance evaluation was performed (Statistical Package for the Social Sciences statistics 21.0, IBM, USA).

## Results

Of the 2,082 clinical samples included in the study, 1,526 (73%) were lung samples and 556 (27%) were extrapulmonary samples. Of the respiratory tract samples, 552 were sputum samples and 974 were BAL samples. Of the extra-respiratory tract samples, 371 were sterile body fluids samples (peritoneal fluid, pleural fluid, synovial fluid, biopsy), 39 were urine samples, and 146 were CSF samples.

*M. tuberculosis* grew in culture in 153 (7.3%) of all samples, and the Xpert MTB/RIF test was positive in 203 (9.7%). In the EZN staining of the samples, acid-fast bacteria (ARB) positivity was detected in 93 (4.5%) samples. In lung samples, ARB, MTB/RIF test and culture positivity rates were 86 (5.6%), 175 (11.4%) and 129 (8.4%), respectively, while in extrapulmonary samples these values were 7 (1.2%), 28 (5%) and 24 (4.3%) (Tables 1, 2).

Among the samples with negative ARB results, 55 (55/1989, 2.7%) samples that could not be confirmed by culture and were found positive only by Xpert MTB/RIF test were evaluated as false positive (FP). Among the ARB positive samples, 11 (11/93, 11.8%) samples that could not be confirmed by culture and were found positive only by Xpert MTB/RIF test were evaluated as FP (Tables 1, 2).

**Table 1. Evaluation of Xpert MTB/RIF test in AFB positive and negative respiratory tract samples**

| Sample type | ARB (+) | | | | ARB (-) | | | |
|---|---|---|---|---|---|---|---|---|
| | Xpert MTB/RIF/Culture | | | | Xpert MTB/RIF/Culture | | | |
| | +/+ | -/- | +/- | -/+ | +/+ | -/- | +/- | -/+ |
| Sputum (n=552) | 30 | 0 | 3 | 2 | 19 | 479 | 13 | 6 |
| BAL (n=974) | 42 | 0 | 8 | 1 | 25 | 859 | 35 | 4 |
| Total (n=1526) | 72 | 0 | 11 | 3 | 44 | 1338 | 48 | 10 |

Sensitivity: 89.9%; Specificity: 95.8%; PPV: 66.3%; NPV: 99.0%.

ARB: Acid-resistant bacteria, BAL: Bronchoalveolar lavage, PPV: Positive predictive value, NPV: Negative predictive value

**Table 2. Evaluation of Xpert MTB/RIF assay for ARB positive and ARB negative non-respiratory samples**

| Sample type | ARB (+) | | | | ARB (-) | | | |
|---|---|---|---|---|---|---|---|---|
| | Xpert MTB/RIF/Culture | | | | Xpert MTB/RIF/Culture | | | |
| | +/+ | -/- | +/- | -/+ | +/+ | -/- | +/- | -/+ |
| Sterile (n=371) | 7 | 0 | 0 | 0 | 11 | 345 | 5 | 3 |
| CSF (n=146) | 0 | 0 | 0 | 0 | 3 | 141 | 2 | 0 |
| Urine (n=39) | 0 | 0 | 0 | 0 | 0 | 39 | 0 | 0 |
| Total (n=556) | 7 | 0 | 0 | 0 | 14 | 525 | 7 | 3 |

Sensitivity: 87.5%; Specificity: 98.7%; PPV: 75%; NPV: 99.4%.

ARB: Acid-resistant bacteria, Sterile: Peritoneal fluid, pleural fluid, synovial fluid, biopsy, PPV: Positive predictive value, NPV: Negative predictive value, CSF: Cerebrospinal fluid

Most of the FP results (59/66) were from lung samples. However, when the epicrisis reports of 66 patients evaluated as FP were examined, it was determined that 31 of these patients had previously been diagnosed as having TB clinically or radiologically and were receiving anti-tuberculosis treatment. The decrease in the number of bacilli and/or dead bacilli due to anti-tuberculosis treatment explains the ARB and culture negativities. Therefore, it could be concluded that only 35 patients were detected to have FP with the Xpert MTB/RIF test.

Again, while the Xpert MTB/RIF test was negative in a total of 13 (13/1989) samples, 10 of which were lung samples and 3 were extrapulmonary samples, the culture results of these samples were found to be positive and these results were evaluated as false negative (FN). In addition, FN results were encountered in 3 lung samples of ARB positive samples. False negative results were encountered in a total of 16 samples. When mycobacterial culture results were taken as reference, the sensitivity and specificity of the EZN staining method in our study were found to be 53.6% and 99.4% in all samples, and these values were found to be 58.1% and 99.2% for lung samples and 29.2% and 100% for extrapulmonary samples, respectively. For all samples examined, the sensitivity of the Xpert MTB/RIF test was calculated as 89.5%, specificity as 96.6%, PPV as 67.5% and NPV as 99.1%. The sensitivity, specificity, PPV and NPV values of the Xpert MTB/RIF test in lung and extrapulmonary samples are shown in Tables 1 and 2.

## Discussion

Today, traditional diagnostic methods such as ARB staining and culture are still used in the diagnosis of TB. However, it is thought that highly sensitive molecular tests such as Xpert MTB/RIF can replace stained microscopic examination in a short time due to their ability to simultaneously detect gene regions related to drug resistance in addition to the agent[1,2,6,7]. In this study, the performance of the Xpert MTB/RIF test in the diagnosis of *M. tuberculosis* was investigated.

Stained microscopic examinations are frequently used as a faster and cheaper test compared to culture in the detection of *M. tuberculosis*. While the sensitivity of ARB staining increases to 89.5% in lung samples, it can decrease to 2% in extrapulmonary samples. When the sensitivity results were compared with the Xpert MTB/RIF test in the same studies, it was reported that the Xpert MTB/RIF test was more sensitive[8,9]. In the study by Bunsow et al.[8], the sensitivity of ARB was calculated as 89.5% in lung samples and 16.6% in extrapulmonary samples, and the Xpert MTB/RIF test was found to be much more sensitive (97.1% and 33.3%, respectively). In our study, the sensitivity of ARB was calculated as 53.6% for all samples, 58.1% in lung samples and 29.2% in extrapulmonary samples, and the Xpert MTB/RIF test was found to be much more sensitive (89.9%, 87.5% and 89.5%, respectively). In various studies, the sensitivity of the Xpert MTB/RIF test was reported as 73.3-100%, specificity as 93-93.3%, PPV as 86.5-96% and NPV as 95.6-98.5%[8-11]. In our study where a total of 2082 samples were examined, ARB, Xpert MTB/RIF and culture positivity rates were determined as 4.5%, 9.8% and 7.3%, respectively. In this study, the sensitivity, specificity, PPV and NPV of the Xpert MTB/RIF test were determined as 89.5%, 96.6%, 67.5% and 99.1%, respectively. The reason for the low sensitivity of Xpert MTB/RIF was found to be patients who were previously diagnosed as having TB and were using medication among the patients with FP TB (culture negative, PCR positive). Our results are consistent with the literature. In some studies, the sensitivity of the Xpert MTB/RIF test was found to be much higher (88-100%) than the rates determined in this study. However, it was observed that a large part of the samples examined in these studies consisted of lung samples with high bacilli load, and especially patients with clinically suspected TB were selected[8,12]. In addition, it is stated that the reason for the variability in sensitivity is due to the differences in the types of samples studied, sample quality, composition of the clinical sample studied, especially in extrapulmonary samples, in terms of salt, protein and cellular residues[6,9,13]. In the literature, the sensitivity of the Xpert MTB/RIF test for respiratory tract samples alone has been reported as 77.5-100%, specificity as 94.3-100%, and PPV and NPV as 86.5-95.7% and 91.7-99.5%, respectively[10,11,14-18]. The highest sensitivity rates among respiratory tract samples were shown in sputum and BAL samples[6,8,19]. In this study, the sensitivity, specificity, PPV and NPV determined in respiratory tract samples were found to be consistent with other studies in the literature (89.9%, 95.8%, 66.3%, 99%, respectively). In our study, it is also observed that the sensitivities of respiratory tract samples are higher. However, it is understood from the PPV rates that the true positive detected with Xpert MTB/RIF, especially in respiratory samples, is low. The performance of the new version of the same kit used in our laboratory for the last 2 years may have played a role in this change. While specificity has high values in almost all studies, it is observed that the variability in sensitivity is due to the difference in the type of sample studied and factors such as bacilli load[19,20]. The very low detection limit of the new version may be the reason for the higher number of FP [while the detection limit for Xpert is 112.6 bacterial colony-forming units (CFU) per ml, for Xpert Ultra it is 15.6 CFU per ml][21]. However, being able to detect very low levels of bacteria in clinical samples is of vital importance in the diagnosis of some patients. The clinician's knowledge of the features of the kit used and the laboratory's close communication with the clinics will prevent errors. In fact, the evaluation of the results obtained with this new version of the kit together with the clinical characteristics of the patient, microscopy and especially culture results should not be ignored in the diagnosis of TB. In addition,

the manufacturer emphasizes that the Xpert MTB/RIF test has been validated only for pulmonary samples/sputum. This aspect of the kit should be shared with clinicians and included in the test result reports.

### Study Limitations

The high cost of the Xpert MTB/RIF test used in this study limits its widespread use in routine by all microbiology laboratories. In addition, the fact that it has been validated only for sputum-BAL samples and that FP results can be obtained, albeit rarely, with the new version of the kit with a low limit of detection (LOD) is an important disadvantage. The fact that a larger number of pulmonary and extrapulmonary samples and another molecular method could not be included in the study due to economic possibilities can be counted among the limitations of this study.

## Conclusion

As a result, the sensitivity and specificity rates of the Xpert MTB/RIF test used in this study were found to be slightly lower in non-respiratory samples than in respiratory samples. It was observed that the Xpert MTB/RIF test had high sensitivity and specificity rates in both sample groups, and was a very fast and low-workload test. However, in order to prevent errors in diagnosis due to the low positive results obtained with the kit with a low LOD, microscopy and culture results and clinical findings of the patients should be interpreted together.

### Ethics

**Ethics Committee Approval:** This study was approved by the Sakarya University Faculty of Medicine Ethics Committee (ethics committee approval no: 176, date: 31.05.2023).

**Informed Consent:** It is not necessary.

### Authorship Contributions

Concept: H.A.T., Ö.A., M.K., Design: H.A.T., Ö.A., M.K., Data Collection or Processing: H.A.T., Ö.A., M.K., Analysis or Interpretation: H.A.T., Ö.A., M.K., Literature Search: H.A.T., Ö.A., E.K., T.D., M.K., M.A., Writing: H.A.T., Ö.A., M.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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