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RESEARCH ARTICLE

GeneXpert MTB/RIF and GeneXpert MTB/RIF ultra in tuberculosis diagnosis: A comparative evaluation

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ABSTRACT

GeneXpert MTB/RIF and GeneXpert MTB/RIF ultra in tuberculosis diagnosis: A comparative evaluation

Introduction: *Recent studies have shown that Gene Xpert MTB/RIF (Xpert) and Gene Xpert MTB/RIF ultra (Xpert-U) tests outperform traditional microbiological methods in detecting tuberculosis (TB) and identifying rifampicin resistance. This research aimed to examine their diagnostic accuracy and clinical relevance.*

Materials and Methods: *This retrospective cohort study included patients aged 18 years and older with pulmonary or extrapulmonary samples analyzed by Xpert, Xpert-U, and conventional diagnostic methods between January 2016 and June 2020. The diagnostic performance of Xpert and Xpert-U was compared across four patient groups: A) Microscopy-culture-positive pulmonary TB, B) Microscopy-negative, culture-positive pulmonary TB, C) Pulmonary TB cases, and D) Extrapulmonary TB cases.*

Results: *A total of 1.366 samples (1.280 pulmonary, 86 extrapulmonary) were analyzed using Xpert and Xpert-U, including 1.042 males (76.3%) and 324 females (23.7%), with an average age of 54 years. For pulmonary TB, Xpert showed an overall sensitivity of 99.29% and specificity of 49.23%. Xpert-U demonstrated similar sensitivity at 98.56%, with an improved specificity of 89.66%. In extrapulmonary TB, Xpert-U achieved 100% sensitivity with a specificity of 70.59%.*

Conclusion: *Xpert and Xpert-U tests offer high sensitivity for detecting Mycobacterium tuberculosis, greatly improving the timely diagnosis and management of TB, especially in cases with low bacterial loads or drug resistance.*

Key words: *GeneXpert assays; Mycobacterium tuberculosis; pulmonary tuberculosis; rifampin resistance*

ÖZ

Tüberküloz tanısında GeneXpert MTB/RIF ve GeneXpert MTB/RIF ultra: Karşılaştırmalı bir değerlendirme

Giriş: *Son çalışmalar, GeneXpert MTB/RIF (Xpert) ve GeneXpert MTB/RIF ultra (Xpert-U) testlerinin, tüberküloz (TB) tespitinde ve rifampisin direncini belirlemede geleneksel mikrobiyolojik yöntemlere göre üstün olduğunu göstermektedir. Bu araştırma, bu testlerin tanısal doğruluğunu ve klinik önemini incelemektedir.*

Materyal ve Metod: *Bu retrospektif kohort çalışmasına, Ocak 2016 ile Haziran 2020 arasında Xpert, Xpert-U ve geleneksel tanı yöntemleri ile analiz edilen akciğer veya akciğer dışı örnekleri bulunan, 18 yaş ve üzeri hastalar dahil edilmiştir. Xpert ve Xpert-U'nun tanısal performansı dört hasta grubunda karşılaştırılmıştır: A) Mikroskopi-kültür pozitif akciğer TB, B) Mikroskopi negatif, kültür pozitif akciğer TB, C) Akciğer TB vakaları ve D) Akciğer dışı TB vakaları.*

Bulgular: *Toplamda 1.366 örnek (1.280 akciğer, 86 akciğer dışı) Xpert ve Xpert-U kullanılarak analiz edilmiştir. Çalışmaya 1.042 erkek (%76.3) ve 324 kadın (%23.7) dahil edilmiş olup, hastaların ortalama yaşı 54'tür. Akciğer TB için Xpert, %99.29 duyarlılık ve %49.23 özgüllük göstermiştir. Xpert-U, benzer bir duyarlılıkla (%98.56), daha yüksek bir özgüllük sağlamıştır (%89.66). Akciğer dışı TB'de ise Xpert-U, %100 duyarlılık ve %70.59 özgüllük elde etmiştir.*

Sonuç: *Xpert ve Xpert-U testleri, Mycobacterium tuberculosis tespitinde yüksek duyarlılık sunarak düşük bakteriyel yük veya ilaç direnci olan vakalarda TB'nin zamanında teşhis ve yönetimini büyük ölçüde iyileştirmektedir.*

Anahtar kelimeler: *GeneXpert testleri; Mycobacterium tuberculosis; pulmoner tüberküloz; rifampisin direnci*

INTRODUCTION

According to the World Health Organization's 2023 Global Tuberculosis (TB) Report, TB remains a major global health concern. In 2022, an estimated 10.6 million people worldwide developed the disease, reflecting a slight increase from prior years. Of these, about 7.5 million cases were diagnosed and reported, underscoring ongoing challenges with under-reporting and under-diagnosis. TB also remains one of the top causes of death from infectious diseases, with approximately 1.3 million fatalities globally (1).

TB diagnosis involves detecting *Mycobacterium tuberculosis* (MTB) *complex* bacteria in clinical samples. Culture testing remains the gold standard for confirming TB in the laboratory as it allows for drug-susceptibility testing by growing the bacteria. However, it has drawbacks, as susceptibility tests performed in automated liquid media take 5-8 days after culture growth, while those on solid media, such as Lowenstein-Jensen (LJ), can require 4-5 weeks (2). In addition, diagnosis is difficult due to the low number of bacilli in extrapulmonary TB forms (3).

In recent years, TB diagnosis has greatly advanced with the use of polymerase chain reaction (PCR) to directly detect MTB DNA from clinical samples. Multi-drug resistant-TB (MDR-TB) poses a major global health challenge, complicating TB control due to resistance to first-line drugs like rifampicin. Rapid diagnostics such as the Gene Xpert *M. tuberculosis*/rifampicin resistance (Xpert) and Gene Xpert MTB/RIF (Xpert-U) ultra tests are essential for early rifampicin resistance detection, enabling timely and effective treatment adjustments (4).

This study aimed to assess the diagnostic accuracy and clinical significance of the Xpert and Xpert-U tests for diagnosing TB and identifying rifampicin resistance.

MATERIALS and METHODS

Study Design and Data

This retrospective cohort study assessed the capacity, diagnostic efficiency, and clinical relevance of the Xpert and Xpert-U molecular diagnostic methods for detecting TB and rifampicin resistance compared to the gold standard culture method. The study was approved by the Local Ethics Committee (Decision no: 03, dated: 18.08.2020) and conducted in accordance with the Declaration of Helsinki principles. Approval was also obtained from the relevant institutional board (Decision no: 51, dated: 29.09.2020) following a thesis evaluation. This study was designed retrospectively, utilizing anonymized data, and therefore, the requirement for individual informed consent was waived.

Our study was designed retrospectively, and samples collected during the clinical evaluation of the patients and recorded in laboratory databases were analyzed. Although it is recommended to examine three consecutive samples for the diagnosis of pulmonary TB, the number of samples collected from each patient in routine clinical practice varies. In our study, some patients had three consecutive samples taken, while others had only a single sample. All available samples from each patient were analyzed in our study, and further prospective studies are needed to evaluate the impact of consecutive samples on diagnostic accuracy.

The study was conducted in a region with a moderate TB incidence in Türkiye. However, the hospital where the study was carried out serves as a national reference center for TB diagnosis and treatment. This institution accepts patients requiring advanced diagnostic evaluation not only from across the country but also from abroad. As a result, the patient population included in this study may differ from the national TB prevalence, as it predominantly consists of cases referred for further examination and specialized care.

In this retrospective cohort study, we included patients aged 18 years and older who underwent Xpert, Xpert-U, and conventional diagnostic tests (Microscopy, culture, drug susceptibility testing, histopathology) for pulmonary and extrapulmonary samples at our institution. The study covered two-time frames: January 2016-December 2018 (First period) and March 2019-June 2020 (Second period). We evaluated the diagnostic performance of Xpert (First period) and Xpert-U (Second period) across patient groups: A) Microscopy and culture positive pulmonary TB, B) Microscopy negative but culture positive pulmonary TB, C) All pulmonary TB cases, and D) Extrapulmonary TB.

Each sample underwent acid-fast staining by Kinyoun method, culture on LJ medium, and cultivation with drug susceptibility testing for streptomycin, isoniazid, rifampicin, and ethambutol using the BACTEC 960 (MGIT) system (BD Biosciences, Sparks, MD). Molecular diagnostic tests, Xpert or Xpert-U (Cepheid Inc., USA), were used in the first and second periods, respectively, to detect *M. tuberculosis* complex and rifampicin resistance in clinical samples.

Statistical Analysis

We analyzed the data using SPSS 25.0 (Statistical Package for Social Sciences 25.0) software. Patient characteristics were presented using descriptive statistics, such as mean ± standard deviation and frequency (percentage). The Kolmogorov-Smirnov test was employed to determine the distribution of continuous data. Categorical variables were analyzed with the chi-square and Fisher's exact tests as appropriate in contingency tables, whereas student's t-test or Mann-Whitney U test was performed as appropriate for comparison of continuous variables. A p value equal to or less than 0.05 was considered statistically significant for all data.

RESULTS

A total of 1.366 samples (1.280 pulmonary, 86 extrapulmonary) were analyzed using Xpert and Xpert-U.

Based on clinical, bacteriological, radiological, and pathological assessments, 833 patients were diagnosed with pulmonary TB, 29 with extrapulmonary TB, and 13 had both forms (Classified as pulmonary TB). Acido-resistant bacillus (AFB) microscopy was conducted for all samples, revealing 805 (58.9%) positive and 561 (41.1%) negative results; 786 of the positive samples were pulmonary, and 19 were extrapulmonary. Culture growth was observed in 738 of the samples, including 719 pulmonary and 19 extrapulmonary samples.

Gene Xpert MTB/RIF Test Results

Clinical samples from 571 patients were analyzed using Xpert, comprising 510 pulmonary and 61 extrapulmonary samples. This group included 451 males (79%) and 120 females (21%) with an average age of 56.9 ± 9.7 years. Based on clinical, bacteriological, radiological, and pathological data, 472 patients were diagnosed with pulmonary TB.

Among the lung samples tested with Xpert, 464 were positive and 46 negative. Xpert showed a sensitivity of 99.29% and specificity of 49.23%, with a statistically significant diagnostic accuracy (p= 0.000) (Table 1).

AFB microscopy was positive in 445 lung samples and negative in 65. The sensitivity and specificity of Xpert in AFB-positive cases were 99.50% and 47.62%, respectively, while for AFB-negative cases, sensitivity was 95.65% and specificity 51.11% (Table 2).

Rifampicin resistance was detected in 18 pulmonary samples using Xpert, showing 94.12% sensitivity and 99.56% specificity (Table 3).

Of the 61 extrapulmonary samples tested with Xpert, 15 patients were diagnosed with extrapulmonary TB. Xpert results for these samples were 11 positives and 50 negatives, with a sensitivity of 90.91% and specificity of 98% for extrapulmonary TB. However, the diagnostic accuracy for extrapulmonary TB was not statistically significant (p= 1.000) (Table 1).

Gene Xpert MTB/RIF Ultra Tests Results

Clinical samples from 795 patients were tested using Xpert-U, including 770 pulmonary and 25 extrapulmonary samples. This group consisted of 591 males (75.4%) and 204 females (24.6%) with an average age of 53.8 ± 9.7 years. Pulmonary TB was diagnosed in 361 patients based on clinical, bacteriological, radiological, and pathological data.

Among the lung samples analyzed with Xpert-U, 341 were positive and 429 negative, yielding a sensitivity of 98.56% and specificity of 89.66%. The diagnostic accuracy of Xpert-U was statistically significant (p= 0.000) (Table 1).

AFB microscopy was positive in 341 samples and negative in 429. For AFB-positive cases, Xpert-U's sensitivity was 98.97% and specificity 48.00%; for AFB-negative cases, sensitivity was 80.00% and specificity 94.58% (Table 2).

Rifampicin resistance was detected in 11 pulmonary samples using Xpert-U, with a sensitivity of 100% and specificity of 99.61% (Table 3).

In the extrapulmonary group, 25 samples were analyzed with Xpert-U, diagnosing extrapulmonary TB in 14 patients. Of these samples, 13 were positive and 12 negative, with a sensitivity of 100% and specificity of 70.59%. The diagnostic accuracy of Xpert-U in extrapulmonary TB was not statistically significant (p= 0.063) (Table 1).

Table 1. Diagnostic performance of Xpert and Xpert-U for pulmonary and extra-pulmonary tuberculosis

Test	Sample Type	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Xpert	Pulmonary TB	99.2	49.2	95	97
Xpert-U	Pulmonary TB	98.5	89.6	96.7	98.1
Xpert	Extra-pulmonary TB	90.9	98	91.6	98
Xpert-U	Extra-pulmonary TB	100	70.5	85.7	100

TB: Tuberculosis, Xpert-U: GeneXpert-ultra, PPV: Positive predictive value, NPV: Negative predictive value.

Table 2. Correlation of Xpert, Xpert-U, culture and microscopic examination in extrapulmonary samples

		Culture (n= 61)		ARB Microscopy + (n= 445)		ARB Microscopy - (n= 65)	
Xpert (n= 61)		+	-	Culture +	Culture -	Culture +	Culture -
	+	10	1	7	1	3	0
	-	1	49	0	1	1	48
		Culture (n= 770)		ARB Microscopy + (n= 341)		ARB Microscopy - (n= 429)	
Xpert-U (n= 25)		+	-	Culture +	Culture -	Culture +	Culture -
	+	8	5	8	2	0	3
	-	0	12	0	0	0	12

ARB: Acido-resistant bacillus, Xpert-U: GeneXpert-ultra.

Table 3. Comparison of Xpert and Xpert-U for detection of RIF resistance

Test/RIF Resistance		Culture		
		Positive	Negative	Total
Xpert	Positive	16	2	18
	Negative	1	491	492
	Total	17	493	510
Xpert-U	Positive	8	3	11
	Negative	0	759	759
	Total	8	762	770

RIF: Rifampicin, Xpert-U: GeneXpert-ultra.

DISCUSSION

This study, with its large patient cohort, enhances the understanding of Xpert and Xpert-U's diagnostic accuracy and clinical relevance in detecting TB and rifampicin resistance. Our findings confirm the high sensitivity of these tests, even in cases with low bacillary loads, demonstrating their effectiveness across both pulmonary and extrapulmonary TB. By examining both sample types within a single extensive cohort, this study expands upon the comprehensive work done in the literature, broadening their scope and integrating new findings into a unified analysis (4,5). This study contributes to these extensive studies by providing novel insights into the diagnostic improvements associated with Xpert-U, particularly in terms of sensitivity and specificity in diverse patient populations.

Despite TB being a treatable condition, it remains a global health challenge (1). Control efforts hinge on improved detection and timely diagnosis. This study underscores the diagnostic utility of the Xpert and Xpert-U tests for both pulmonary and extrapulmonary TB, especially in regions with high TB incidence. While PCR-based molecular tests have advanced microbial diagnostics significantly, understanding their specific applications, strengths, and limitations is essential for optimizing their use.

Our results show that Xpert has a sensitivity of 99.29% and specificity of 49.23% in diagnosing pulmonary TB. Sensitivity values in the literature vary widely due to factors such as sample type, bacillary content, disease stage, and technical proficiency, with previous studies reporting ranges from 43% to 100% (6-8). Studies conducted in low-TB-incidence regions, such as the United States, have reported lower sensitivity rates around 46%, while countries with moderate TB prevalence, including ours, report sensitivity rates of 80-100% (9,10). The high sensitivity we observed may be attributed to the high culture positivity (82%) and AFB microscopy positivity (87%) in our samples. Xpert-U demonstrated increased sensitivity (98.56%) but slightly lower specificity (89.66%) than Xpert, aligning with previous findings indicating higher diagnostic accuracy in AFB-negative and low-bacillary cases (7).

Specificity values for Xpert and Xpert-U vary significantly based on region and patient history, and in our study, Xpert showed a relatively low specificity of 49.23%, likely due to our hospital being a reference center for TB, which, by accepting both domestic and international patients, accommodates a higher number of TB cases than the national prevalence in Türkiye. Furthermore, Xpert tests' inability to distinguish live from dead bacilli can lead to persistent positivity even after TB treatment completion (11). Studies from various regions align with our findings, demonstrating that the specificity of Xpert can decrease in areas with high TB prevalence and incidence, such as India, particularly in certain patient populations (5,12). Furthermore, research indicates that the specificity of the Xpert MTB/RIF test may vary in high-prevalence settings, especially among previously treated patients, due to its inability to distinguish between live and dead bacilli (13).

For rifampicin resistance, Xpert showed a sensitivity of 94.12% and specificity of 99.56%, consistent with prior reports (94-100% sensitivity and 97-100% specificity). Xpert-U's melting temperature analysis increases its ability to detect silent mutations and enhances accuracy for rifampicin resistance (14). Our findings also identified that Xpert-U may detect mixed infections with non-*tuberculous mycobacteria*, as reported in similar studies (15,16).

Extrapulmonary samples pose unique challenges. In our study, Xpert and Xpert-U demonstrated sensitivities of 90.91% and 100%, respectively, which exceed the sensitivity ranges reported in meta-analyses for Xpert (75-85% sensitivity and 83-88% specificity) (17,18). Literature suggests that Xpert-U outperforms Xpert in sensitivity for extrapulmonary TB due to its lower analytical detection limit (5). Large-scale study conducted in South Africa emphasized that specificity remains consistently high (99%), supporting its use as a primary diagnostic tool, particularly in settings with high TB prevalence and among difficult-to-diagnose patient groups, such as those with extrapulmonary TB (19). However, the limited number of extrapulmonary samples in our study constrained statistical significance.

This study benefits from a large sample size and comprehensive analysis across pulmonary and extrapulmonary cases. By focusing on a high-prevalence setting, it provides real-world insight into Xpert and Xpert-U performance. However, as a retrospective, single-center study at a thoracic specialty hospital, generalizability is limited, particularly regarding extrapulmonary TB. The relatively low number of

extrapulmonary samples may also affect statistical power. Additionally, limited access to Xpert and Xpert-U outside of central laboratories in our country and their higher costs present challenges in routine use.

CONCLUSION

In conclusion, Xpert and Xpert-U tests offer highly sensitive, rapid diagnosis for TB, particularly in high-burden settings. While effective for pulmonary TB and rifampicin/MDR-TB, caution is necessary in interpreting results, particularly where specificity may be impacted by previous TB treatment. These tests support the early diagnosis of AFB-negative and extrapulmonary TB cases, though conventional methods should accompany their use in final diagnostic decisions. Their limitations, including high costs and limited availability in certain regions, underscore the need for integrated diagnostic approaches that include molecular testing alongside traditional methods.

Statement of Ethics

The study was approved by the Local Ethics Committee (Decision no: 03, dated: 18.08.2020) and conducted in accordance with the Declaration of Helsinki principles. Approval was also obtained from the University of Health Sciences (Decision no: 51, dated: 29.09.2020) following a thesis evaluation. This study was designed retrospectively, utilizing anonymized data, and therefore, the requirement for individual informed consent was waived.

Data Availability Statement

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Health Sciences University Dr. Suat Seren Chest.

Ethical Committee Approval: This study was approved by Health Sciences University Dr. Suat Seren Chest Ethics Committee (Approval number: 03, Date: 18.08.2020).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: İT, SAÖ
Analys/Interpretation: İT, YV, SAÖ, CB
Data acqusition: İT, OK, SAÖ, CB
Writing: İT, OK, SAÖ
Clinical Revision: SAÖ, OK
Final Approval: İT, SAÖ

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