

GeneXpert MTB/RIF combined with conventional methods for tuberculosis in Shanghai Regional Medical Center: a retrospective diagnostic study

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Background: At present, the diagnosis of tuberculosis (TB) is still challenging, and improving the efficiency of diagnosis can help prevent and control TB. This retrospective clinical study aimed to assess the diagnostic efficiency of GeneXpert MTB/RIF for pulmonary TB.

Methods: A total of 620 newly-diagnosed patients who visited the pulmonary clinic of Shanghai Tongren Hospital between 2018 and 2021 were enrolled in the study. All 620 patients had acid-fast Bacilli (AFB) identified by Ziehl Neelsen staining (ZNS) test, BECTEC MGIT 960 liquid culture (LC), and GeneXpert MTB/RIF assay (GX). A total of 53 patients also underwent interferon- γ release assay (IGRA). The diagnostic efficacy of ZNS, LC, GX alone or in combination in pulmonary TB was evaluated, with clinical diagnosis as the gold standard. Moreover, the IGRA for pulmonary TB diagnosis was preliminarily assessed.

Results: Eventually, 185 cases were clinically confirmed (which included 36 etiologically negative cases) in the total enrolled 620 first-diagnosed patients. Overall, the 3 methods ZNS, LC, and GX showed sensitivities of 55.68%, 64.32%, and 68.64%, specificities of 98.39%, 95.40%, and 99.08%, positive predictive values (PPV) of 93.64%, 85.61%, and 96.95%, and negative predictive values (NPV) of 83.92%, 86.28%, and 88.14%, respectively. The GX method showed the highest specificity and PPV for a solitary single method, with 99.08% and 96.95%, respectively. Regarding pairwise combination methods, all showed superior sensitivity to a single test, reaching a maximum of 80.00%. Among them, the LC + GX combination showed both the highest sensitivity (80.00%) and NPV (91.78%), and the corresponding area under the receiver operating characteristic curve (0.875) was the largest. Among the 53 patients who underwent IGRA testing, 42 were positive (including 4 etiologically negative cases), and 11 were negative. The overall sensitivity of IGRA for diagnosing pulmonary TB was 90.00%, specificity was 27.27%, PPV was 42.86%, and NPV was 81.82%.

Conclusions: The GX method shows promise as a first-line diagnostic method for pulmonary TB. Furthermore, the sensitivity was significantly improved when combined with LC. This combination will screen out some etiologically negative patients plus IGRA, so their combination is recommended for practice optimization.

Keywords: Pulmonary tuberculosis; acid-fast bacilli smear microscopic examination; liquid culture; GeneXpert MTB/RIF; interferon-γ release assay (IGRA)

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Introduction

Tuberculosis (TB) is a global health problem which is predominantly caused by Mycobacterium tuberculosis (Mtb) infection (1). Around 1.2 million people die of TB worldwide each year, with nearly 10 million new cases (2). Its most common form is pulmonary TB, which is easily transmitted by aerosol droplets. If disease detection and treatment are delayed, the chance of transmission will increase (3). Therefore, rapid and accurate diagnosis of Mtb is an essential component of treating TB and reducing its global burden (4). Smear microscopy and culture are usually used as routine methods to detect *Mtb* in laboratories. The basic principle of acid-fast smear microscopy is identifying acid-fast Bacilli (AFB) (5) in smears by Ziehl-Neelsen staining (ZNS). It has fast detection speed and easy to popularize. But it requires a high bacterial content in the sample, resulting in its low sensitivity. So it is not conducive to the diagnosis of TB alone (6). The "gold standard" for TB laboratory examination and diagnosis is Mtb culture, such as Lowenstein-Jensen (L-J) method and MGIT 960 method (7). L-J method has a high detection rate, but it takes a long time, which is not conducive to the early diagnosis of TB. Moreover, the operation of L-J method is cumbersome, and there are pollution risks in the process of operation, which may lead to false negative results and easily aggravate the patient's condition. Compared with L-J method, MGIT 960 method optimized the operation steps before inoculation (such as neutralization centrifugal collection), thus improving the positive rate of Mtb culture. Meanwhile, its decontamination reagent was milder and more efficient, and its fluorescent substrate was added into the special culture tube to facilitate observation of bacterial growth. Further shorten the judgment time of results. GeneXpert MTB/RIF (GeneXpert) is a semi-quantitative gene detection technology based on nucleic acid amplification (8). It based on the principle of fluorescence quantitative polymerase chain reaction (PCR): Mtb and its drug resistance can be detected directly from the patient's sputum and other specimens at the same time (9). The whole detection time is about 2 h, and the sensitivity and specificity are high, which can provide rapid accurate identification of mycobacterium TB and its drug resistance detection. The

purpose of this study was to evaluate the value of GeneXpert in the diagnosis of TB and to preliminarily evaluate the application effect of combined detection of GeneXpert and other conventional methods in the field to provide a reference plan for the prevention and treatment of TB. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/ article/view/10.21037/atm-22-1374/rc).

Methods

General information

A total of 620 newly-diagnosed patients in the pulmonary outpatient department of Tongren Hospital from 2018 to 2021 were enlisted to this study (patients with suspected pulmonary TB in imaging or clinical manifestations were divided or referred to the pulmonary outpatient department, and those who visited the pulmonary outpatient department for the first time were called newly-diagnosed patients). All patients underwent (AFB) smear microscopic examination by ZNS, BECTEC MGIT 960 liquid culture (Liquid Culture), and GeneXpert simultaneously. Some patients (n=53) underwent interferon- γ release array (IGRA) testing. The inclusion criteria were as follows: complete medical history and laboratory examination results. The exclusion criteria were as follows: lung tumors or other primary tumors; and severe autoimmune diseases. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Tongren Hospital, Shanghai Jiao Tong University School of Medicine (No. 2022-007) and informed consent was provided by all participants.

Reagents and instruments

The AFB reagent was purchased from Zhuhai BASO Biotechnology Co., Ltd. (Guangdong, China). A liquid culture monitor and support kit was purchased from Becton, Dickinson, and Co. (BD; Franklin Lakes, NJ, USA). The GeneXpert instrument and detection kit was bought from Cepheid, USA. The IGRA reagent was purchased from QIAGEN (Hilden, Germany).

Inspection method

All participants collected 3 sputum samples once a day for 3 consecutive days for examination. The 3 samples were mixed and examined by AFB smear microscopy. The mixed samples were taken for GeneXpert and liquid culture, respectively. Additionally, 4 mL peripheral blood of 53 participants was placed into a heparin lithium anticoagulant vacuum tube for IGRA.

AFB smear microscopic examination by ZNS

First, the serial number was marked on a clean slide. The examiners removed about 0.05 mL of cheese-like, pus-like, or bloody sputum sample with a bamboo stick, and smeared it evenly onto an oval sputum film measuring 10×20 mm. After the smear had naturally dried, the ZNS method was adopted: firstly, the slide was heated with carbolic acid reddening agent for initial dyeing for 5 minutes; the excess dye solution was rinsed with running water; hydrochloric acid alcohol was added to decolorize it; and it was then rinsed with running water. Finally, methylene blue was added for re-dyeing for 30 seconds, followed by rinsing with running water. After the slide had dried, a microscopic examination was carried out. Diagnostic results were based on the laboratory rules for TB.

BECTEC MGIT 960 liquid culture

The liquid culture was carried out based on the BD BACTEC MGIT 960 system operation manual (BD, USA). First, 2% NALC NaOH sample pretreatment solution was prepared by taking about 2 mL sputum sample into a 50 mL centrifuge tube, adding 1-2 times the amount of freshly prepared pretreatment solution according to the characteristics of the sample. The cover was tightened, the tube was shaken for 30-60 seconds, followed by standing at room temperature for 15-20 minutes. Sterile phosphate-buffered saline (PBS; pH 6.8) was added to about 50 mL, the tube was centrifuged at 3,000 g ×15 minutes, the supernatant was removed, and 1-3 mL PBS was added to the suspension precipitation. Then, 0.5 mL of the suspension was transferred into an MGIT culture tube with 0.8 mL mycobacterium culture additive added in advance and placed on the machine for detection. The specimens with positive culture were first stained with acid-fast solution. The specimens with positive acidfast staining reported a positive culture of fast acid Mtb.

When BACTEC MGIT 960 indicated negative results after 48 days of specimen culture, it was reported that the culture of acid-fast *Mtb* was negative.

GeneXpert MTB/RIF detection

The operation was in strict accordance with the operating instructions of the GeneXpert MTB/RIF system. Firstly, the sputum sample was thoroughly mixed with the treatment solution at a ratio of 1:2. After digestion and treatment for 15–20 minutes, 2 mL of the reaction mixture was sucked up with a sampling gun and slowly put it into the reaction box. The box was then put into the detection module for subsequent reaction: (I) the sample was automatically cleaned and filtered, (II) after ultrasonic lysis, DNA fragments were formed and purified, (III) DNA reacted with PCR reagent, and (IV) semi-nested real-time fluorescence quantitative nucleic acid amplification detection. The results were determined by the fluorescence signal measured by the GeneXpert system and the built-in algorithm.

IGRA

The patient's anticoagulant peripheral blood (within 2 h after extraction) was mixed and put it into the test tubes, a positive control tube and negative control tube (1 mL/tube). After mixing, the specimen was incubated in a constant temperature incubator at 37 °C and 5% CO₂ for 20–24 hours. It was centrifuged at 3,000–5,000 rpm for 10 minutes followed by ELISA detection and the results were interpreted according to the kit's instructions.

Observation index

This study was a diagnostic study, and the clinical diagnosis was the gold standard. The diagnostic performance indexes of central nervous system (CNS), Liquid Culture, and GeneXpert were compared and jointly analyzed by statistical methods. The existing IGRA test results were preliminarily analyzed. All the diagnostic performance indexes analyzed included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Statistical analysis

The data were statistically analyzed by R (Version 4.1.0; The R Foundation for Statistical Computing, Vienna,

Page 4 of 8

 Table 1 Socio-demographic, laboratory data of the studied cases

Category	Total (n=620)
Age (years) [mean (SD)]	47.49 (18.98)
Gender (%)	
Male	366 (59.0)
Female	254 (41.0)
Sample (%)	
Lavage solution	1 (0.2)
Watery sputum	145 (23.4)
Saliva-like	66 (10.6)
Bloody phlegm	11 (1.7)
Sample type (%)	
Morning phlegm	361 (58.2)
Alveolar lavage fluid	1 (0.2)
Instant sputum	188 (30.3)
Nocturnal sputum	70 (11.3)

SD, standard deviation.

Table 2 Separate test rest	ults for the 3	methodologies
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Detection method	Overall (n=620)	Neg (n=435)	Pos (n=185)	P value
LC (%)				
Neg	481 (77.6)	415 (95.4)	66 (35.7)	<0.001
Pos	139 (22.4)	20 (4.6)	119 (64.3)	
ZNS (%)				
Neg	510 (82.3)	428 (98.4)	82 (44.3)	<0.001
Pos	110 (17.7)	7 (1.6)	103 (55.7)	
GX (%)				
Neg	489 (78.9)	431 (99.1)	58 (31.4)	<0.001
Pos	131 (21.1)	4 (0.9)	127 (68.6)	

ZNS, Ziehl Neelsen staining; LC, BECTEC MGIT 960 liquid culture; GX, GeneXpert MTB/RIF assay; Neg, negative; Pos, positive.

Austria). The measurement data were expressed as mean \pm standard deviation ($\bar{x}\pm s$) using *t*-test. The count data were expressed as rate (%), using chi-square. Two-sided test, P value <0.05 indicated a statistically significant difference.

Results

General characteristics of patients and sample description

Among the 620 newly diagnosed patients, 366 were male, and 254 were female. Their ages ranged from 13 to 93 years, and the median age was 48 years (interquartile range 30 to 63 years). The samples submitted for examination included sputum and alveolar lavage fluid. Sputum samples incorporated immediate sputum, morning sputum, and night sputum; the sputum properties included water sample, blood nature, and saliva sample (*Table 1*).

Clinical diagnosis results of patients and separate test results of 3 methodologies

Among 620 suspected pulmonary TB patients, 185 pulmonary TB patients and 435 non-pulmonary TB patients were clinically diagnosed. Among them, 110 cases were CNS-positive (17.7%), 139 cases were Liquid Culture-positive (22.4%), and 131 cases were GeneXpert-positive (21.1%) (*Table 2*). The cross-coverage relationship of the samples of the 3 methodologies is shown in *Figure 1*.

Joint detection and analysis results of three methodologies

We carried out 2 or 3 combinations of the 3 methods for statistical analysis, as follows *Table 3*.

Taking the clinical diagnosis results as the reference standard, the diagnostic performance indexes of CNS, Liquid Culture, and GeneXpert method were determined separately and jointly

We applied CNS, Liquid Culture, and GeneXpert alone to diagnose pulmonary TB. GeneXpert had the highest sensitivity (68.65%), specificity (99.08%), PPV (96.95%) and NPV (88.14%); CNS had the lowest sensitivity (55.68%), PPV (93.64%), and NPV (83.92%); the lowest PPV was Liquid Culture (85.61%). The sensitivity (any combination of 2 or 3 methods) was improved, in comparison to that of single detection, by up to 80.00%. Among all methods (single or combined detection), the sensitivity of "Liquid Culture + GeneXpert" and "CNS + Liquid Culture + GeneXpert" were the highest, both at 80.00%; the specificity (99.08%) and PPV (96.95%) of GeneXpert were the highest. The NPV

Annals of Translational Medicine, Vol 10, No 10 May 2022

Page 5 of 8



Figure 1 Total number of samples tested by 3 methodologies and distribution of Neg-Pos cases. ZNS, Ziehl Neelsen staining; LC, BECTEC MGIT 960 liquid culture; GX, GeneXpert MTB/RIF assay; Neg, negative; Pos, positive.

Table 5	Joint test	results	for th	e 3 I	netnoa	ologies

Detection method	Overall (n=620)	Neg (n=435)	Pos (n=185)	P value	
ZNS + LC (
Neg	463 (74.7)	412 (94.7)	51 (27.6)	<0.001	
Pos	157 (25.3)	23 (5.3)	134 (72.4)		
ZNS + GX (%)				
Neg	481 (77.6)	425 (97.7)	56 (30.3)	<0.001	
Pos	139 (22.4)	10 (2.3)	129 (69.7)		
LC + GX (%)					
Neg	450 (72.6)	413 (94.9)	37 (20.0)	<0.001	
Pos	170 (27.4)	22 (5.1)	148 (80.0)		
ZNS + LC + GX (%)					
Neg	448 (72.3)	411 (94.5)	37 (20.0)	<0.001	
Pos	172 (27.7)	24 (5.5)	148 (80.0)		

ZNS, Ziehl Neelsen staining; LC, BECTEC MGIT 960 liquid culture; GX, GeneXpert MTB/RIF assay; Neg, negative; Pos, positive.

(91.78%) of the "Liquid Culture + GeneXpert" combination was the highest (*Table 4*), and had the largest area under the receiver operating characteristic (ROC) curve (ROC =0.875; *Figure 2*).

Taking the clinical diagnosis results as the reference standard, the diagnostic performance indexes of IGRA

Of the 53 patients who underwent the IGRA testing based

 Table 4 The diagnostic performance indexes of individual detection

 and joint detection

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Detection method	Sensitivity	Specificity	PPV	NPV
LC	0.643243	0.954023	0.856115	0.862786
ZNS	0.556757	0.983908	0.936364	0.839216
GX	0.686486	0.990805	0.969466	0.881391
ZNS+LC	0.724324	0.947126	0.853503	0.889849
ZNS+GX	0.697297	0.977011	0.928058	0.883576
LC+GX	0.8	0.949425	0.870588	0.917778
ZNS + LC + GX	0.8	0.944828	0.860465	0.917411

ZNS, Ziehl Neelsen staining; LC, BECTEC MGIT 960 liquid culture; GX, GeneXpert MTB/RIF assay; PPV, positive predictive value; NPV, negative predictive value.

on the existing clinical decision, 42 were positive (4 cases were negative for TB), and 11 were negative. The overall sensitivity of IGRA for diagnosing TB was 90% (18/20), specificity 27.27% (9/33), PPV 42.86% (18/42), and NPV 81.82% (9/11) (*Table 5*).

Discussion

In recent years, TB incidence and infection rates have risen, showing an increasing trend (10). The TB caused by Mtb complex infection has remained the leading public health problem globally. The emergence of drug-resistant TB, especially RIF and multi-drug resistant TB, has greatly hindered the progress of controlling this disease. The



Figure 2 ROC curves of individual detection and joint detection of 3 methodologies. ROC, receiver operating characteristic; ZNS, Ziehl Neelsen staining; LC, BECTEC MGIT 960 liquid culture; GX, GeneXpert MTB/RIF assay; AUC, area under curve.

Table 5 Diagnosis results of IGRA (cases)				
Clinical diagnosis	IG	Total		
	Neg	Pos	TOLAI	
Neg	9	24	33	
Pos	2	18	20	
Total	11	42	53	

IGRA, interferon- γ release assay; Neg, negative; Pos, positive.

diagnosis of pulmonary TB is based on etiology (including bacteriology and molecular biology) examination. In this study, we conducted a comprehensive analysis for diagnosis with epidemiological history, clinical manifestations, chest imaging, associated auxiliary assessment, and differential diagnosis. The etiological and pathological results were used as the basis for diagnosis. However, due to the lack of rapid and accurate diagnostic methods for TB, the diagnosis of etiologically negative TB cases remains a challenge worldwide (11).

In this study, we were able to identify almost all cases with positive CNS examination or Liquid Culture, and even some specimens with negative smear examination, by using the GeneXpert method. Our results are consistent with those of a previous clinical study (12), which suggested that the laboratory uses the GeneXpert method to improve the positive detection rate of CNS-negative cases, especially for some community hospitals and suburban hospitals that cannot establish well-equipped laboratory infrastructure (13). In this study, our data showed that the sensitivity and specificity of GeneXpert detection were increased compared with the smear method. As confirmed by another study, this is an important point to explain that the GeneXpert test can improve the positive rate of the Mtb test (14). The smear method is a relatively simple, cheap method applicable to all hospitals. However, due to the inconsistent level of equipment and inspectors in hospitals, the diagnostic value of the smear method cannot be standardized, and the difference between hospitals is significant (15).

The isolation and culture of *Mtb* is the "gold standard" for the etiological diagnosis of TB. The International Tuberculosis and Lung Association recommends improved Roche culture as a reference method for the isolation and cultivation of Mtb. However, the improved Roche culture method takes a long time (usually 5-8 weeks), which is not conducive to the early diagnosis and timely treatment of pulmonary TB. The BACTEC MGIT 960 is an improved rapid liquid culture method wherein BBL PANTA[™] antibacterial agent and oleic acid-albumin-dextrose-catalase (OADC) nutrient medium are added to the medium (16). A fluorescent substance is used as a growth indicator of mycobacteria, which can rapidly increase the bacteria and be identified by the detection system. The average detection time of Mtb is 14.4 days. The diagnosis time of positive results has been significantly accelerated, while the

Annals of Translational Medicine, Vol 10, No 10 May 2022

negative results usually take 48 days, which is still a long waiting cycle. In this study, a total of 139 positive cases were identified in the detection of suspected pulmonary TB patients in our hospital by MGIT 960, of which 119 cases were clinically diagnosed as pulmonary TB. There were 20 false-positive results (14.39%), which may have been because some of the strains were non-tuberculous mycobacteria. The actual diagnostic value of the liquid culture method will also vary among hospitals due to the differences in environment, operator level, and experience.

GeneXpert is an automated PCR test using a molecular platform. Its sample processing, PCR amplification, and detection are integrated into an independent test unit. After loading, all detection steps are fully automated and independent (9). The rapid detection of drug resistance of *Mtb* and RIF by GeneXpert can help doctors judge whether a patient has TB patients or drug-resistant strains at the same time. A study in Switzerland and South Korea has also shown that the semi-quantitative results of GeneXpert are positively correlated with the isolation and culture results of Mtb (17). The "low", "medium", and "high" levels in GeneXpert test results also indicate that the probability of smear-positive in patients is higher, which suggests that the transmission potential of Mtb is high. In contrast, patients with negative GeneXpert results can be considered smearnegative, which may correspond to limited TB transmission potential (18,19). In this study, the sensitivity, specificity, PPV, and NPV of GeneXpert in the diagnosis of pulmonary TB were better than smear and liquid culture, and the combined detection can further improve the sensitivity.

Based on existing clinical decisions, some cases were tested for IGRA in this study (n=53). The preliminary evaluation of the relevant data showed that IGRA has higher sensitivity (90%) and low specificity (27.27%) in diagnosing pulmonary TB. Nonetheless, its value in the auxiliary diagnosis of negative cases of pulmonary TB is worthy of attention. It can be applied to joint detection in the future to accumulate more clinical evaluation data.

The drug resistance of RIF was characterized by routine drug sensitivity testing and GeneXpert testing. In a study conducted in 10 provinces in Western and Northwest Iran, the sensitivity and specificity of GeneXpert in detecting RIF resistance were 71% and 100%, respectively (20). However, in our study we detected 9 drug-resistant strains (all RIF-resistant). Due to the limited data in this regard, we have not evaluated the ability of the GeneXpert method to identify RIF resistance efficiency. It is necessary to accumulate more clinical cases and further study the drug resistance of *Mtb* in the future.

In this study, the data of patients from the Shanghai area who were admitted to our hospital were studied, showing that GeneXpert as a diagnostic tool for TB detection has high sensitivity and specificity, which is reliable for early diagnosis of TB. GeneXpert can be combined with liquid culture and IGRA for clinical application. The goal is to diagnose TB earlier and more accurately, thereby helping to control the spread of disease and improve the process of TB prevention, management, and treatment.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1374/rc

Data Sharing Statement: Available at https://atm.amegroups. com/article/view/10.21037/atm-22-1374/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm. amegroups.com/article/view/10.21037/atm-22-1374/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Tongren Hospital, Shanghai Jiao Tong University School of Medicine (No. 2022-007) and informed consent was provided by all participants.

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Zhang et al. GeneXpert MTB/RIF in the diagnosis of TB

Page 8 of 8

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