Original Article

Diagnostic value of GeneXpert MTB/RIF in bronchoalveolar lavage fluid for pulmonary non-tuberculosis mycobacterial in acid-fast stain smear-positive and GeneXpert MTB/RIF-negative cases

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Background: The identification of non-tuberculosis (TB) mycobacterial (NTM) infection remains a significant challenge. This study aims to investigate the diagnostic value of multicolour nested real-time fluorescence quantitative nucleic acid amplification detection technology [Xpert *Mycobacterium tuberculosis* (MTB)/rifampicin (RIF)] in bronchoalveolar lavage fluid (BALF) acid-fast smear-positive cases.

Methods: Between 1 January 2017 and 30 June 2022, 365 patients who underwent fibreoptic bronchoscopy and had positive acid-fast smears of BALF were examined using Xpert MTB/RIF. The mycobacteria growth indicator tube (MGIT) 960 was used for rapid sputum culture and traditional drug sensitivity testing. Combined with mycobacterial culture and drug sensitivity results, Xpert results of alveolar lavage fluid were analysed to guide diagnosis and treatment.

Results: The sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of Xpert detection for diagnosing NTM lung disease in acid-fast smear-positive cases were 100% (45/45), 99.68% (310/311), 97.83% (45/46) and 100% (310/310), respectively.

Conclusions: Xpert MTB/RIF in alveolar lavage fluid can not only detect RIF resistance but also distinguish pulmonary TB from NTM pulmonary disease in patients with positive acid-fast smears.

Keywords: Bronchoalveolar lavage fluid (BALF); acid-fast smear-positive; Xpert *Mycobacterium tuberculosis*/rifampicin (Xpert MTB/RIF); pulmonary tuberculosis (pulmonary TB); non-tuberculous mycobacterial lung disease

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Introduction

Non-tuberculosis (TB) mycobacterial (NTM) lung disease is a chronic lung disease caused by NTM infection, unlike TB, which is caused by *Mycobacterium tuberculosis* (MTB) complex infection. The incidence rate of NTM pulmonary disease is increasing yearly worldwide, especially in developed countries and regions (1). Furuuchi *et al.* indicate that NTM disease is rapidly increasing and has become a public health problem threatening human health (2). However, the diagnosis and treatment of NTM lung disease face many challenges, one of which is differentiating it from TB. Due to the lack of significant differences in clinical manifestations, imaging features and

sputum smear detection between NTM and MTB, and the fact that most patients have a history of underlying lung diseases (such as chronic obstructive pulmonary disease, bronchiectasis, etc., misdiagnosis or missed diagnosis is prone to occur (3). Bronchoalveolar lavage fluid (BALF) smear testing can only prove the presence of acid-fast bacteria but cannot distinguish whether it is an MTB or NTM infection (4). However, due to its simple and rapid operation, it is suitable for use in basic-level hospitals as a screening indicator for pulmonary TB (5). It is frequently reported that NTM infection is misdiagnosed and treated as TB in clinical practice, and NTM is naturally resistant to the commonly used primary and secondary anti-TB drugs in clinical practice, resulting in prolonged treatment (5,6). Therefore, in daily diagnosis and treatment work, NTM lung disease cannot be ignored.

To improve the diagnostic accuracy of NTM lung disease, faster, more sensitive and specific detection methods are needed. The multicolour nested real-time fluorescence quantitative nucleic acid amplification detection technology [Xpert MTB/rifampicin (Xpert MTB/RIF)] is a molecular detection technique based on nested real-time polymerase chain reaction (PCR). It can not only quickly detect TB but also detect rifampicin (RIF) resistance, providing a reference for clinical medication and being the preferred method recommended by the World Health Organisation (WHO) for diagnosing MTB complex (MTBC) (7). Several studies have mentioned the cross-reactivity between GeneXpert MTB/RIF and NTM, but it is not common (8,9). Early laboratory diagnosis of NTM infection using the Xpert method has important clinical application value in clarifying disease diagnosis, selecting treatment drugs and other aspects (10). The purpose of this study is to use Xpert MTB/RIF technology to predict the diagnosis of NTM lung disease in patients with positive acid-fast smears, evaluate its diagnostic efficiency and explore its potential value in reducing misdiagnosis and improving treatment decision-making. We present this article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1556/rc).

Highlight box

Key findings

- Xpert *Mycobacterium tuberculosis*/rifampicin (Xpert MTB/RIF) in alveolar lavage fluid can not only detect rifampicin resistance but also distinguish pulmonary tuberculosis (TB) from non-tuberculosis mycobacterial (NTM) pulmonary disease in patients with positive acid-fast smears.

What is known and what is new?

- GeneXpert MTB/RIF for rapid diagnosis of TB and rifampicin resistance.
- Xpert MTB/RIF in alveolar lavage fluid can not only detect rifampicin resistance but also distinguish pulmonary TB from NTM pulmonary disease in patients with positive acid-fast smears.

What is the implication, and what should change now?

- The GeneXpert MTB/RIF technology can be extended to the diagnosis of tuberculosis and can be combined with other NTB diagnostic methods.

Methods

Research participants

We retrospectively analysed 365 patients from Wenzhou Central Hospital, The Dingli Clinical Institute of Wenzhou Medical University, The Second Affiliated Hospital of Shanghai University between January 2017 and June 2022 who underwent bronchoscopy and found positive acid-fast smears in the lavage fluid. The patient selection criteria were as follows: (I) after bronchoscopy, it was found that the acid-fast smear of the lavage fluid was positive; (II) there was no clear diagnosis of pulmonary TB or non-tuberculous mycobacterial disease. The exclusion criteria were as follows: (I) patients who have received anti-TB or anti-non-tuberculous *Mycobacterium* treatment (whenever receiving treatment); (II) patients with other severe lung or systemic infections [Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) criteria for severe pneumonia] (11); (III) patients with immunodeficiency or immunosuppression; (IV) patients who are unable to provide sufficient lavage fluid samples. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the ethics committee of Wenzhou Central Hospital, The Dingli Clinical Institute of Wenzhou Medical University, The Second Affiliated Hospital of Shanghai University (ID: L2023-04-092). The ethics committee of the Wenzhou Central Hospital approved this study with a waiver of informed consent due to its retrospective nature.

BALF collection

Bronchoscopy was performed on all study participants, and 5–10 mL of BALF specimens were collected. Five mL or more of BALF samples were taken, and 0.5% N-acetyl-L-

cysteine-NaOH digestion solution was added according to the degree of turbidity. The mixture was shaken well (liquefaction time did not exceed 5 minutes) and centrifuged at 3,000 rpm for 20 minutes, and the precipitate was washed with 6.8% phosphate-buffered saline (PBS).

Acid-fast smear of BALF

Five mL of BALF was stained with Ziehl-Neelsen dye after being contaminated, centrifuged and dried.

Xpert MTB/RIF of BALF

BALF was added to the digestive solution for digestion. The digestive solution (including BALF) was then added to the washing solution in a 1:1 ratio, the test tube cap was tightened and the mixture was shaken with a vortex oscillator for 30 seconds. It was left to stand at room temperature for 15 minutes until no visible granular substances remained in the mixture. Two mL of the mixture was taken and added to the GeneXpert cartridge. The GeneXpert cartridge was then placed in the GeneXpert instrument for automatic detection (Xpert MTB/RIF detection kit, Cepheid, USA). The system automatically displayed the detection results after approximately 2 hours. Detailed operation procedures are provided in the manual.

Cultivation of Mycobacterium in BALF

Five mL of BALF was digested and washed before being cultured in mycobacteria growth indicator tubes (MGIT). Positive culture tubes required acid-fast staining confirmation and bacterial identification.

Identification of bacterial strains using the gene chip method

According to the instructions of the gene chip-based *Mycobacterium* species identification kit (CapitalBio Corporation, Beijing, China), 1 mL of the supernatant was taken. If there was a positive MGIT culture, 1 mL of bacterial suspension was taken and centrifuged at approximately 13,000 g in 1 mL of physiological saline for 1 minute. After processing with 1 mL of washing solution, it was centrifuged at 13,000 g for 5 minutes for precipitation. Fifty μL of cracking liquid was added, and the precipitate was resuspended. The mixture was heated and lysed at 100 ℃ for 10 minutes, then centrifuged at 13,000 g for 2 minutes, and the supernatant was the obtained genomic DNA template. The amplification tube of PCR amplification solution was taken and centrifuged at 5,000 g for 2 seconds, 4 μL of DNA template was added and the tube was placed in a PCR amplification device for the reaction. The reaction conditions and operations were followed according to the instructions.

Statistical analysis

Data were collected, and statistical analysis was performed using SPSS 20.0 software (IBM Corp., Armonk, NY, USA). The diagnostic efficiency of the above laboratory testing methods was evaluated using sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV). Count data were expressed in numbers or percentages. The hypothesis of data normality was tested using the Kolmogorov-Smirnov test. Sample size estimation was based on the Se and Sp formulas, efficiency analysis was based on sample size and effect size formulas and data transformation was performed using logarithmic or square root transformation.

Results

Clinical characteristics

All 365 cases were divided into the Xpert-positive group and Xpert-negative group based on Xpert MTB/RIF results. Among the 315 patients in the Xpert-positive group, there were 207 men and 108 women, aged between 13 and 79 years, with an average age of 41.77±16.35 years. Among them, there were 15 cases aged ≤17 years, 271 cases aged 18–65 years and 29 cases aged 66 years and above. Among the 50 Xpert-negative patients, there were 29 men and 21 women, aged between 32 and 77 years, with an average age of 59.48±11.82 years. Among them, there were no cases aged ≤17 years, 33 cases aged 18–65 years and 17 cases aged over 65 years. The age distribution of the groups showed statistical differences (P<0.001) (see *Tables 1*,*2*). There were statistically significant differences in the proportion of fever, cough, expectoration, haemoptysis, chest tightness, pleural effusion, bronchiectasis and pneumothorax between the groups (P<0.001), whereas no statistically significant difference was found in the proportion of chest pain, poor appetite, and cavity (P>0.05). The Xpert-negative group had more lesions in the upper and inferior lobes, and the difference was statistically

Table 1 Demographic information of patients (n=365)

Variables	Numerical value
Age (years), mean ± SD	44.2±12.6
Gender (male/female)	236/129
Positive rate of sputum smear (%)	76.7
Positive rate of BALF culture (%)	98.4
Positive rate of irrigation solution smear (%)	100
Positive rate of irrigation solution culture (%)	97.8
Xpert positivity rate of sputum (%)	86.3
Xpert positivity rate of BALF (%)	86.6
Diagnosis rate of pulmonary tuberculosis (%)	85.2
Diagnosis rate of non-tuberculosis mycobacterial disease (%)	12.3
Rifampicin resistance rate (%)	9.0
Xpert-positive rate (%)	86.3
Xpert-negative rate (%)	13.7

SD, standard deviation; BALF, bronchoalveolar lavage fluid.

Table 2 General demographic data

Variables	Xpert positive (n=315)	Xpert negative (n=50)	P valve
Gender			0.34
Male	207	29	
Female	108	21	
Age (years)			<0.001
≤17	15	0	
18–65	271	33	
≥66	29	17	
Average age, mean ± SD	41.77±16.35	59.48±11.82	

SD, standard deviation.

significant (P<0.001). The Xpert-negative group also had relatively larger lesions, with a statistically significant difference (P<0.001), as shown in *Table 3*. The acid-fast staining smears of the two groups indicated that the number of acid-fast bacilli in the Xpert-negative group was lower (*Table 4*).

Diagnostic value and efficiency evaluation of Xpert

Of the 365 patients included, 356 were BALF culture positive, and 9 were BALF culture negative. Among the 365 patients, 46 were smear-positive but Xpert-negative. Of these 46 patients, 45 were confirmed to have NTM infection through bacterial identification, whereas one patient's TB DNA test was positive. Among cases with a positive BALF smear and culture but negative Xpert, there was a 97.83% (45/46) probability of being diagnosed with NTM infection, whereas none of the Xpert-positive patients had NTM infection. The Se, Sp, PPV and NPV of Xpert detection for the diagnosis of NTM lung disease in acid-fast smear-positive cases were 100% (45/45), 99.68% (310/311), 97.83% (45/46) and 100% (310/310), respectively. In patients with pulmonary TB, the Se was 99.68% (310/311), Sp was 100% (45/45), PPV was 100% (310/310) and NPV was 97.83% (45/46). One patient with MTB was Xpert negative (see *Table 5*).

NTM strain identification results

Among all 45 cases of NTM species, *M. avium/intracellulare* (MAC) accounted for 88.89% (40/45), *M. chelonae/abscessus* for 6.67% (3/45) and the remaining *M. kansasii* and *M. marinum* accounted for 2.22% (1/45).

Discussion

Non-tuberculous mycobacterial disease is increasing yearly. Although BALF smear examination is the simplest and fastest method to detect mycobacteria, the traditional acid-fast bacilli smear and pulmonary computed tomography fail to distinguish non-tuberculous *Mycobacterium* from *M. tuberculosis* infection (12,13). At present, mycobacterial culture is still the gold standard for diagnosis. Although its Se is high, it is well known that mycobacterial culture takes a long time, typically 1–2 months, which greatly delays the accurate clinical diagnosis of non-tuberculous mycobacterial disease. As a result, some patients are misdiagnosed with TB. Additionally, non-tuberculous mycobacteria are naturally resistant to most anti-TB drugs (14). Once NTM lung disease is misdiagnosed, it may lead to the patient receiving the wrong treatment plan, delaying the optimal treatment time, resulting in poor prognosis and increasing the economic burden.

Table 3 The clinical characteristics and CT findings of the two groups were compared

Clinical characteristics	Xpert (–) (n=50)		Xpert (+) (n=315)		P
	n	(%)	n	(%)	
Fever	5	10.0	91	28.9	<0.001
Cough	40	80.0	308	97.8	<0.001
Expectoration	37	74.0	283	89.8	<0.001
Hemoptysis	14	28.0	36	11.4	<0.001
Chest tightness	14	28.0	21	6.7	<0.001
Chest pain	5	10.0	25	7.9	0.33
Fatigue	10	20.0	48	15.2	0.02
Poor appetite	11	22.0	54	17.1	0.12
Pleural effusion	3	6.0	45	14.3	<0.001
Bronchiectasis	24	48.0	9	2.9	<0.001
Pulmonary cavity	24	48.0	128	40.6	0.20
Pulmonary bullae	3	6.0	20	6.3	0.01
Pneumothorax	1	2.0	0	0	<0.001
The lesion size					<0.001
<2 cm	14	28	195	61.9	
≥2 cm	36	72	120	38.1	
Location of the lesion					
Upper lobe of lung	27	54	285	90.5	<0.001
Middle lobe of right lung	23	46	130	41.3	0.53
Inferior lobe of lung	16	32	215	68.3	<0.001
The lesions range					
Single lung lobe	11	22	112	35.6	0.06
Two lung lobes	14	28	73	23.2	0.46
>2 lung lobes	25	50	130	41.2	0.25

CT, computed tomography.

Table 4 Acid-fast smears were compared between the two groups

Grade	Xpert-positive (n=315)	Xpert-negative (n=50)
<1+*	64	20
1+	93	19
2+	74	9
3+	43	1
4+	41	1

*, 1–9 bacteria/300 fields of view (1,000×).

Cough, fatigue, haemoptysis, chest tightness and bronchiectasis were significantly higher in the Xpert-negative group than in the Xpert-positive group, whereas fever and pleural effusion were higher in the Xpert-positive group, with statistical differences, indicating that pleural effusion and bronchiectasis play an important role in distinguishing pulmonary TB from NTM, which is consistent with the studies (15,16).

Our studies indicate that NTM lung disease diagnosis

Table 5 Xpert diagnostic value and efficacy evaluation (cases)

Xpert MTB/RIF	*Mycobacterium* culture results			
	NTM	MTB	Negative	Total
Xpert–	45	1	4	50
Xpert+	0	310	5	315
Total	45	311	9	365

NTM, non-tuberculous mycobacteria; MTB, *Mycobacterium tuberculosis*; Xpert MTB/RIF, Xpert *Mycobacterium tuberculosis*/rifampicin (multicolor nested real-time fluorescence quantitative nucleic acid amplification detection technology).

should be considered clinically when the Xpert test yields a negative result. According to the guidelines for the diagnosis and treatment of non-tuberculous mycobacterial disease, a single experimental treatment for suspected NTM disease is not recommended. Instead, two or more sputum specimens need to be tested, and sputum or BALF culture identification or molecular biology testing is required (17). Based on the results of sterile identification, NTM disease can be misdiagnosed for an extended period. When conducting suspected MTB tests on patients, clinicians should be alert to the possibility of NTM infection when the sputum smear is positive and the Xpert test is negative. They should select NTM-related cultures and molecular biology identification for further diagnosis and timely treatment of patients. It is recommended to conduct additional tests for mycobacterial species identification and other specialised examinations to establish a basis for subsequent targeted and individualised treatment.

In the cases of mycobacterial culture with NTM, the main strain was MAC (88.89%), indicating that it is the most common clinical pathogen, which is consistent with the report by He *et al.*, as well as with reports from other regions of Zhejiang Province (18,19).

It is worth noting that we reported a false negative patient. The reasons for the unqualified samples include personal operation by technical personnel and excessively long specimens (20). Therefore, in clinical practice, when using Xpert MTB/RIF for testing, attention should be paid to controlling the quality of lavage fluid specimens according to regulations to avoid misdiagnosis or missed diagnosis caused by specimen factors. The limit of detection for TB DNA is 5×10^3 strains/mL, and the minimum detection limit for Xpert is 131 strains/mL. The minimum detection limit for *Mycobacterium* culture is 120 strains/mL. Thus, a situation may arise when the bacterial strain inside the tube is between 120 and 131 strains/mL.

To address these issues, future research can improve Xpert MTB/RIF technology, enhance its Se for detecting low bacterial content specimens, expand its detection range for resistance to other anti-TB drugs, increase its ability to identify non-TB *Mycobacterium* strains, optimise its detection process and cost-effectiveness and make it more suitable for clinical application and promotion.

There are some limitations in this study. First, the sample size is relatively small, which may affect the representativeness and generalisability of the results. Second, the research design is retrospective, and there may be some uncontrollable confounding factors and biases. Although Xpert MTB/RIF technology has the advantages of being fast, sensitive and specific, there are also some limitations, such as its inability to diagnose NTM separately, distinguish between live and dead bacteria, detect specific strains of NTM and address the possible causes and solutions for false positives or false negatives, which may be influenced by sample quality and quantity.

Conclusions

The Xpert method has good clinical value and application prospects in aiding the differentiation between preliminary NTM lung disease with smear-positive TB and pulmonary TB. A high suspicion of non-tuberculous mycobacterial disease is required in patients with a positive bronchoalveolar lavage (BAL) acid-fast smear and negative BAL GeneXpert MTB/RIF. However, there are limitations with the use of Xpert such as the possibility of false negatives or false positives. It detects only the presence of MTB and rifampin resistance, whereas resistance to other anti-TB drugs, such as isoniazid, cannot be detected. Clinically, it is necessary to combine mycobacterial culture, mycobacterial species identification and other laboratory tests.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1556/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1556/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1556/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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the ethics committee of Wenzhou Central Hospital, The Dingli Clinical Institute of Wenzhou Medical University, The Second Affiliated Hospital of Shanghai University (ID: L2023-04-092). The ethics committee of the Wenzhou Central Hospital approved this study with a waiver of informed consent due to its retrospective nature.

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