Value of ultrasound-guided puncture combined with GeneXpert MTB/RIF technology in the diagnosis of pleural tuberculosis

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Abstract. The aim of the present study was to analyze the pathological and laboratory findings of pleural lesions post ultrasound-guided biopsy and to assess the diagnostic utility of percutaneous ultrasound-guided puncture combined with GeneXpert *Mycobacterium tuberculosis* (MTB)/resistance to rifampin (RIF) in pleural tuberculosis (TB) diagnosis. A retrospective analysis was conducted on 46 patients who underwent ultrasound-guided biopsy at the Shandong Public Health Clinical Center (Shandong Chest Hospital) between April 2018 and April 2021. Of these, 27 patients were diagnosed with pleural TB, while 19 were confirmed to have non-pleural TB. Preoperative examinations were negative for all patients. Under ultrasound guidance, tissue samples were obtained through puncture for subsequent pathological and laboratory examination. All collected samples were subjected to acid fast staining, *M. tuberculosis* culture and GeneXpert MTB/RIF (Cepheid). The sensitivity, specificity and area under curve (AUC) value were compared across methods. Rifampicin drug susceptibility was detected using the proportional method and compared with results obtained from GeneXpert MTB/RIF. The sensitivity and specificity of acid-fast staining, *M. tuberculosis* culture and GeneXpert MTB/RIF in diagnosing pleural TB were 18.52 and 100.00%, 14.81 and 100.00, 96.30 and 94.74%, respectively. Consistency analysis demonstrated that the GeneXpert MTB/RIF technique exhibited good agreement (κ=0.91), whereas the agreement for acid fast staining (κ=0.16) and *M. tuberculosis* culture (κ=0.13) was poor. Data analysis was performed by combining the results of the three detection methods with pathological findings. The diagnostic value for pleural TB was highest for GeneXpert MTB/RIF technology combined with pathology (AUC value=0.97), followed by *M. tuberculosis* culture combined with pathology (AUC value=0.94) and acid-fast staining combined with pathology (AUC value=0.94). No surgical complications were observed. Of the 27 samples, 4 tested positive using the *M. tuberculosis* culture method. Rifampicin resistance was detected from the bacterial colonies through the proportional method, with results consistent with those obtained from the GeneXpert MTB/RIF method. Ultrasound-guided percutaneous biopsy is considered a safe and effective approach for diagnosing pleural TB, Its sensitivity is much higher than that of pleural effusion, Moreover, there is currently limited research on ultrasound-guided pleural biopsy combined with laboratory testing worldwide. Ultrasound-guided puncture combined with GeneXpert MTB/RIF technology is of significant value in the diagnosis of pleural TB and in determining rifampicin resistance.

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. According to World Health Organization (WHO), TB ranks among the 10 leading causes of death globally and is the leading cause of mortality from a single infectious agent (1). While pulmonary tuberculosis is the most common manifestation, global statistics from 2019 indicate that ~16% of global tuberculosis cases were extrapulmonary (1). Extrapulmonary tuberculosis can affect nearly any organ, most frequently involving the lymph nodes, followed by pleural TB (2). Studies have demonstrated that the proportion of extrapulmonary tuberculosis cases among total tuberculosis cases has been gradually increasing (3,4). Pleural TB is prone to misdiagnosis due to its atypical clinical symptoms, lack of characteristic imaging manifestations, challenges in specimen acquisition, low etiology positivity rate, and difficulties in diagnosis. In a number of cases, confirmation is required through

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Abbreviations: TB, tuberculosis; WHO, World Health Organization; ROC, receiver operating characteristic curve; CRS, Common Reporting Standard; AUC, area under curve

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biopsy. Ultrasound offers portability and high resolution and ultrasound-guided puncture biopsy provides real-time imaging, safety and ease of operation. It is an effective method for diagnosing pleural TB and is crucial for differentiating pleural TB from other infectious and non-infectious diseases (5). Conventional methods for detecting tuberculosis include smear microscopy, culture and cytology; however, these methods possess certain limitations. Mycobacterial culture can serve as a reference standard but is time-consuming and requires skilled personnel for operation. Cytological methods for detecting lymphadenopathy necessitate expert interpretation and smaller laboratories often lack the necessary equipment, such as fluorescence or LED microscopes. These factors hinder the accurate and prompt diagnosis of patients with lymphatic tuberculosis in low-resource settings (6). Real-time fluorescence quantitative nucleic acid amplification using GeneXpert *M. tuberculosis* (MTB)/resistance to rifampin (RIF), a novel diagnostic technology for tuberculosis (6), can detect *M. tuberculosis* complex DNA. This method allows for the detection of rifampicin resistance-related mutations in the rpoB gene during the identification of *M. tuberculosis* complex, facilitating early and rapid diagnosis while effectively minimizing the risk of cross-contamination. Additionally, GeneXpert MTB/RIF (Cepheid) is less influenced by the presence of anti-tuberculosis drugs (6). Additionally, enhanced sensitivity, specificity and accuracy in detecting rifampicin resistance are notable advantages of this method. The present study aimed to investigate the value of ultrasound-guided pleural TB puncture combined with GeneXpert MTB/RIF in diagnosing pleural TB. However, among all the searches, there is only one study that confirms the diagnosis of pleural TB by ultrasound-guided pleural biopsy combined with GeneXpert MTB/RIF, indicating that this is still not widely promoted or used and has not been recognized by clinical doctors. The present study also aimed to further confirm the diagnostic value and significance of this study for pleural TB (7).

Materials and methods

Patients. The pathology, acid fast staining, *Mycobacterium* culture and GeneXpert results of patients with pleural lesions who underwent ultrasound-guided biopsy between April 2018 and April 2021 at the Shandong Public Health Clinical Center (Shandong Chest Hospital) were retrospectively analyzed. Diagnosis of tuberculosis was conducted following the guidelines set forth by the WHO (1) and the clinical diagnostic standards established by the Chinese Medical Association for tuberculosis (8). Clinically diagnosed TB patients met the following criteria: i) Presence of clinical symptoms consistent with tuberculosis; ii) imaging highly suggestive of tuberculosis; and iii) satisfactory response to anti-tuberculosis treatment (9). All lesions were routinely examined by ultrasound prior to biopsy. Clinical case data were collected, including patient age, sex, comorbidities, laboratory examination results and treatment response. None of the patients received treatment before biopsy. A flow diagram illustrating the study process is provided (Fig. 1). The patients with TB included 19 males and 8 females, with ages ranging from 16-56 years and a mean age of 23.7±14.1 years. Pulmonary tuberculosis was present as a complication in 17 cases.

All methods were carried out in accordance with relevant guidelines and regulations. The present study protocols were approved by the Ethics Committee of Shandong Public Health Clinical Center (Shandong Chest Hospital; approval no. 2021XKYYEC-33).

Ultrasound puncture. Based on the location of pleural lesions, patients were positioned differently, including sitting, supine, lateral or prone. The optimal puncture pathway for accessing pleural lesions was determined. This pathway was designed to avoid the ribs and to run obliquely at a shallow angle to the pleural plane, thereby facilitating the visualization of the puncture needle, enabling the acquisition of a greater volume of pleural tissue, and minimizing the risk of lung tissue puncture. Color Doppler flow imaging was employed to assess the blood supply to the lesion, ensuring that large blood vessels along the puncture pathway were avoided and that the pleural tissue with blood supply was targeted. The needle entry point was identified and marked accordingly. Routine disinfection was performed and a sterile towel was placed over the area. Local infiltration anesthesia was administered. An ultrasonic diagnostic instrument (Philips Q5; Philips Healthcare) equipped with a convex array probe (C5-1) operating at a frequency of 1 to 5 MHz was used. Puncture was carried out according to the predetermined pathway using a No. 18 semi-automatic cutting biopsy needle (18G; 10 cm; Becton, Dickinson and Company). The needle was inserted under real-time ultrasound guidance (Fig. 2A and B). Once the needle tip was observed to reach the target area, the biopsy gun was activated to obtain a tissue sample. Depending on the specimen condition, tissue acquisition was performed 2-3 times. The changes in chest pain, dizziness and chest tightness were monitored during the procedure. Postoperatively, ultrasonography was conducted to assess for complications such as hemoptysis, pneumothorax and bleeding. Pathological examination, acid fast staining, *M. tuberculosis* culture and GeneXpert testing were performed in all cases. Specimens were fixed in 10% formalin solution for 18-24 h at 20-35˚C and subsequently submitted for pathological analysis.

Histopathological examination. The specimens were dehydrated using a gradient of ethanol from low to high concentration and embedded in high concentration paraffin. Subsequently, they were sectioned at 15-30 μm. A 4 μm color band was prepared for staining (Fig. 3A and B), followed by pathological diagnosis.

Acid fast staining was performed using an acid fast staining solution (Zhuhai Beso Biotechnology Co., Ltd.), experienced laboratory doctors applied the modified alkaline reddening method to conduct the procedure. The staining temperature was 60˚C for 5 min. The results were determined according to the reagent instructions.

M. tuberculosis culture was carried out using the *Mycobacterium* culture monitoring system and reagents provided by BACTEC MGIT 960 (Becton, Dickinson and Company) for strain identification, following the manufacturer's instructions and specifications. GeneXpert MTB/RIF detection was performed using the GeneXpert MTB/RIF and an automated detection platform [GeneXpert (Cepheid)]. Samples were pretreated according to the operating procedures, and automatic detection and result interpretation were conducted as per the guidelines.

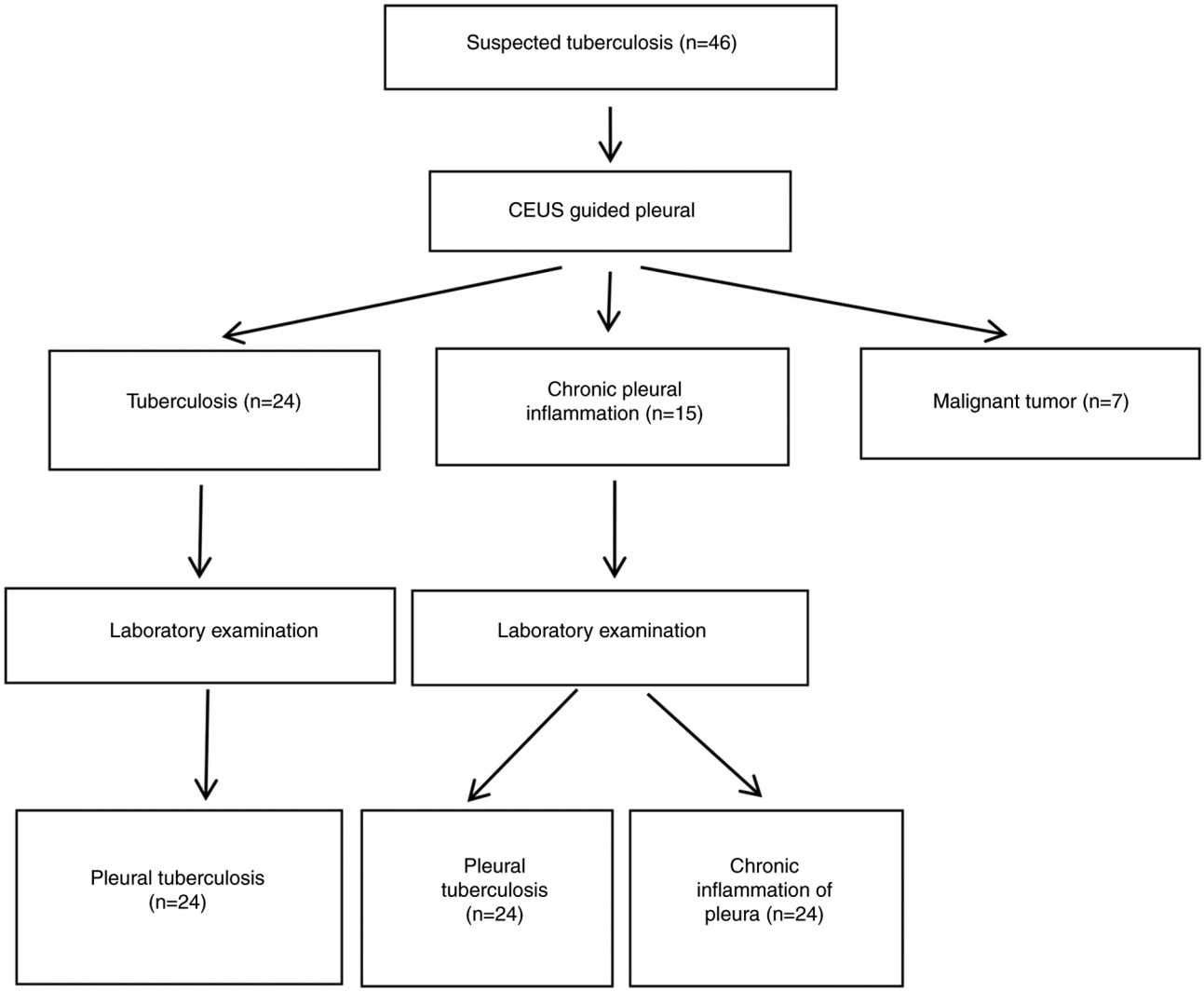

Figure 1. Flow diagram. CEUS, contrast-enhanced ultrasound.

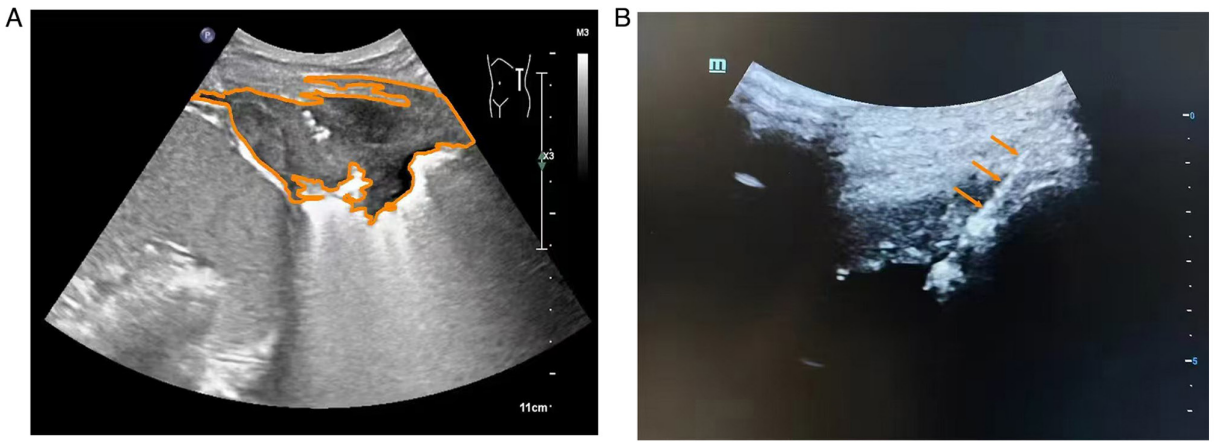

Figure 2. Ultrasound images. (A) Ultrasound imaging can clearly display pleural hypoechoic lesions, outlined by orange lines in the figure. (B) When performing biopsy on pleural lesions under ultrasound display, ultrasound can clearly show the biopsy needle (orange arrow).

Statistical analysis. The database was established and statistically analyzed using SPSS 24.0 (IBM Corp.). Indicators for statistical description include mean, standard deviation, frequency and composition ratio. Data following a normal distribution were expressed as mean and standard deviation, while non-normally distributed data were reported as median and interquartile range (m±IQR). Statistical inference was conducted using ROC curve

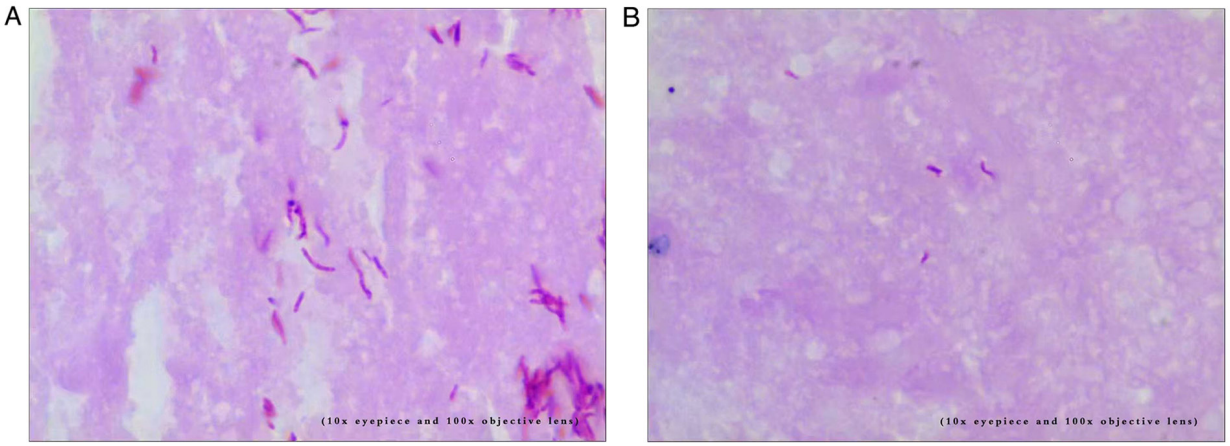

Figure 3. Acid resistant staining image. (A) The figure clearly shows the acid fast staining results of a patient with pleural tuberculosis. *M. tuberculosis* was stained blue. Magnification, x1,000. There are a large number of *M. tuberculosis*; (B) The figure clearly shows the acid fast staining results of another patient with pleural tuberculosis. *M. tuberculosis* was stained blue. Magnification, x1,000. The number of *M. tuberculosis* is relatively small.

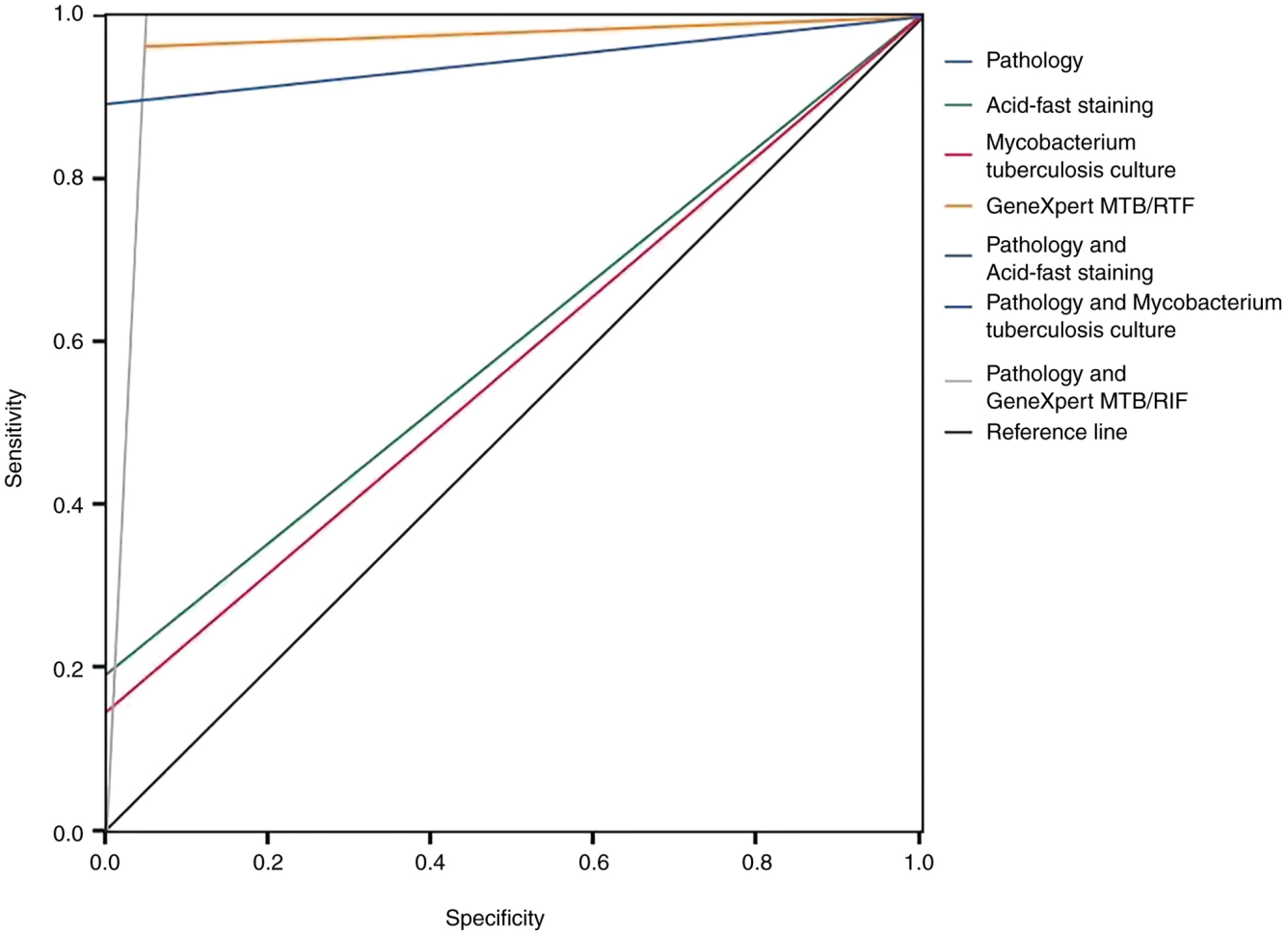

Figure 4. ROC curve of pathology and three test techniques in the diagnosis of pleural tuberculosis. ROC, receiver operating characteristic curve; MTB/RIF, *Mycobacterium tuberculosis*/resistance to rifampin.

analysis, κ-value, sensitivity, specificity, positive predictive value and negative predictive value. P<0.05 was considered to indicate a statistically significant difference. The optimal diagnostic threshold was determined using the Jordan index (Fig. 4).

Results

Using Common Reporting Standard (CRS) as a reference, 27 patients were diagnosed with tuberculous nodal pleurisy (Fig. 1), including 19 males and eight females, with ages

Table I. Diagnosis results of pathology and three detection techniques for pleural tuberculosis.

Detection techniques	Detection result	Clinical comprehensive diagnosis		
		Chest wall tuberculosis (n)	Non chest wall tuberculosis (n)	Total (n)
Pathology	Positive	24	0	24
	Negative	3	19	22
	Total	27	19	46
Acid-fast staining	Positive	5	0	5
	Negative	22	19	41
	Total	27	19	46
Mycobacterium tuberculosis culture	Positive	4	0	4
	Negative	23	19	42
	Total	27	19	46
GeneXpert MTB/RIF	Positive	26	1	27
	Negative	1	18	19
	Total	27	19	46
Pathology and Acid-fast staining	Positive	24	0	24
	Negative	3	19	22
	Total	27	19	46
Pathology and *Mycobacterium* tuberculosis culture	Positive	24	0	24
	Negative	3	19	22
	Total	27	19	46
Pathology and GeneXpert MTB/RIF	Positive	27	1	28
	Negative	0	18	18
	Total	27	19	46

MTB/RIF, *Mycobacterium tuberculosis*/resistance to rifampin.

ranging from 16-56 years and a mean age of 23.7±14.1 years. Pulmonary tuberculosis was present as a complication in 17 cases.

Pathological results. Ultrasound-guided pleural biopsy was conducted based on the microscopic observation of fibrous tissue or mesothelial cells. Pleural tissue was successfully obtained from all 46 patients, with a success rate of 100% (46/46). The length of the puncture tissue strips ranged from 0.5-1.8 cm. Pathological diagnosis revealed malignancy in seven cases, tuberculosis in 24 cases and chronic inflammation in 15 cases. Among the 15 cases of chronic pleural inflammation, three were ultimately diagnosed as tuberculous pleurisy. The pathological diagnosis of malignancy was consistent with the final clinical diagnosis, accounting for 15.21% (7/46) of all biopsies. Using CRS as a reference, 27 patients were ultimately diagnosed with tuberculous pleurisy, based on clinical manifestations, imaging examination and diagnostic treatment results.

Laboratory results. Among the 27 patients with pleural TB, *M. tuberculosis* culture was positive in four cases, acid-fast staining (Fig. 3A and B) was positive in 5 cases, and GeneXpert MTB/RIF was positive in 26 cases (Table I). The positive diagnostic rates for *M. tuberculosis* culture, acid-fast staining and GeneXpert MTB/RIF were 14.81, 18.52 and 96.30%, respectively. Among the 27 confirmed cases of pleural TB, GeneXpert MTB/RIF exhibited the highest positive rate, with the combination of GeneXpert MTB/RIF and pathology yielding a positive rate of 100%. GeneXpert MTB/RIF was positive in all four culture-positive cases. In 15 cases where *M. tuberculosis* culture and acid-fast staining were negative and GeneXpert MTB/RIF was positive. Finally, chest wall tuberculosis was ultimately diagnosed. GeneXpert MTB/RIF increased the pathogenic-positive detection rate of tissue biopsy specimens by 55.56% (15/27). The κ-value for GeneXpert MTB/RIF technology as shown in Table II was 0.91; the κ-values for acid-fast staining and *M. tuberculosis* culture were 0.16 and 0.13, respectively. The AUC value for GeneXpert MTB/RIF technology was 0.96, while the AUC values for acid-fast staining and *M. tuberculosis* culture were 0.59 and 0.57, respectively. The positive diagnostic rate, AUC and κ-values for the combination of pathology and GeneXpert MTB/RIF were 100.00%, 0.94 and 0.92, respectively, all of which were higher than those for the combination of pathology with acid-fast staining or *Mycobacterium tuberculosis* culture.

Table II. Diagnostic value of pathology and three detection techniques for pleural tuberculosis.

Detection techniques	AUC	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	κ-value	P-value	Total coincidence rate (%)	Jordan index (%)
Pathology	0.944	88.89	100.00	100.00	86.36	0.869	0.000	93.48	88.89
Acid-fast staining	0.593	18.52	100.00	100.00	46.34	0.158	0.047	52.17	18.52
Mycobacterium tuberculosis culture	0.574	14.81	100.00	100.00	45.24	0.126	0.079	50.00	14.81
GeneXpert MTB/RIF	0.955	96.30	94.74	96.30	94.74	0.910	0.000	95.65	91.03
Pathology and Acid-fast staining	0.944	88.89	100.00	100.00	86.36	0.869	0.000	93.48	88.89
Pathology and *Mycobacterium* tuberculosis culture	0.944	88.89	100.00	100.00	86.36	0.869	0.000	93.48	88.89
Pathology and Gene Xpert MTB/RIF	0.974	100.00	94.74	96.43	100.00	0.955	0.000	97.83	94.74

Results showed that the AUC of pathology combined with GeneXpert MTB/RIF was the largest. AUC, area under curve; MTB/RIF, *Mycobacterium tuberculosis*/resistance to rifampin.

Complications of ultrasound-guided puncture. None of the 46 patients experienced complications such as hemoptysis, pneumothorax and hemothorax; Only one patient presented with a pleural reaction characterized by dizziness and nausea, with an incidence rate of 1% (1/46). After bed rest, the symptoms resolved and the puncture was successfully repeated, allowing the procedure to be completed without further issues.

Discussion

Pleurisy is a common clinical condition, and tuberculous pleurisy is a form caused by *M. tuberculosis* infection. The underlying mechanism involves the entry of *M. tuberculosis* and tuberculous proteins into the pleural space, triggering a significant pleural reaction, primarily characterized by pleural effusion and pleural thickening (9). The clinical symptoms of tuberculous pleurisy are nonspecific, making diagnosis challenging. Routine diagnostic methods often fail to achieve definitive results. Imaging examinations play a crucial role in detecting pleural lesions, however, diagnosis requires pathological and laboratory confirmation. According to the 2010 guidelines of the British Thoracic Society for the diagnosis and management of unilateral pleural effusion in adults, when the nature of pleural effusion cannot be determined through ultrasound-guided aspiration, it is recommended that pleural biopsy be performed under imaging guidance to further clarify the nature of the lesion (10). Historically, Cope biopsy needles and Abrams biopsy needles were used for percutaneous pleural biopsy; however, these methods provided limited tissue samples and were associated with significant trauma, making complications such as pneumothorax and bleeding more likely (11,12). Defrancis *et al* (13) first introduced closed pleural biopsy into clinical practice, and through continuous refinement, it has become a primary diagnostic method for pleural lesions. Nevertheless, variations in guiding techniques have led to differences in the sensitivity and specificity for diagnosing pleural diseases (13). Thoracoscopic biopsy has been shown to enhance the diagnostic accuracy of GeneXpert MTB/RIF for tuberculosis (14), but the procedure is associated with greater trauma and carries a risk of postoperative infection and tuberculosis transmission. Ultrasound-guided biopsy, characterized by high precision, minimal invasiveness and safety, allows for accurate specimen collection, facilitating both pathological and laboratory examinations.

Pleural TB has been recognized for a long time. When the duration of tuberculous pleurisy exceeds 4 weeks, the positive rate of pleural biopsy is markedly reduced (15). Most cases of pleural TB involve paucibacillary disease (caused by a small number of bacteria), which reduces the sensitivity of traditional smear microscopy for diagnosis. In resource-limited settings, *Mycobacterium* culture and histological examination are not widely available due to the long culture time and the need for

fully equipped laboratories. GeneXpert MTB/RIF is an automated PCR test capable of accurately detecting tuberculosis and rifampicin resistance in sputum samples (16). Based on a systematic review (17), the World Health Organization issued recommendations regarding extrapulmonary tuberculosis, stating that GeneXpert MTB/RIF can be used as an alternative to conventional methods (such as routine microscopy, culture or histopathology) to detect specific non-respiratory specimens from patients with suspected extrapulmonary tuberculosis.

GeneXpert MTB/RIF is a diagnostic test used for detecting the DNA of the *M. tuberculosis* complex. Upon identification of the *M. tuberculosis* complex, mutations related to rifampicin resistance in the rpoB gene are detected. Test results can be obtained within 2 h after the initiation of the test, requiring only minimal technical time. Unlike traditional nucleic acid amplification tests, GeneXpert MTB/RIF integrates sample processing, PCR amplification and detection into a single self-contained test unit (18). Following sample loading, all analytical steps are all fully automated and self-sufficient. GeneXpert MTB/RIF employs molecular beacon technology to detect rifampicin resistance. Molecular beacons are nucleic acid probes that can identify and report the presence or absence of normal, favorable and wild type sequences of the rpoB gene.

In the present study, the positive rate of GeneXpert MTB/RIF combined with pathology was found to be 100%, while the positive rate of GeneXpert MTB/RIF alone was 96.30% (26/27), both of which were higher than the rates observed for acid-fast staining and tuberculous culture. The three detection methods were analyzed in conjunction with pathology for data evaluation. The diagnostic value for pleural TB was determined to be as follows: GeneXpert MTB/RIF technology combined with pathology (AUC value=0.97) > tuberculosis culture combined with pathology (AUC value=0.94)=acid-fast staining combined with pathology (AUC value=0.94). The positive rate of GeneXpert MTB/RIF in the present study was higher than that reported in previous studies involving ultrasound-guided or closed pleural biopsy (19).

Some researchers consider the clinical diagnosis of tuberculous pleurisy and tuberculous pericarditis to be the gold standard. GeneXpert MTB/RIF demonstrates high sensitivity (90.0 and 72.0%) and specificity (100.0% for both) (20), which is consistent with the findings of the present study. Additionally, research has been conducted regarding the value of GeneXpert MTB/RIF in detecting drug-resistant tuberculous pleurisy. Among 60 patients with tuberculous pleurisy, GeneXpert MTB/RIF confirmed the presence of rifampicin resistance genes in 10 cases, while only five cases were identified using the proportional method (21).

In the present study, four cases tested positive using the *M. tuberculosis* culture method. The colonies were evaluated using the proportional method, and the results were consistent with those obtained from the GeneXpert MTB/RIF method. A limitation of this study may be attributed to the small volume of positive tuberculosis culture data included. Numerous studies have demonstrated that GeneXpert MTB/RIF is highly valuable for diagnosing extrapulmonary tuberculosis, including lymphatic tuberculosis, spinal tuberculosis, urinary tuberculosis and nervous system tuberculosis (22-25). Additionally, there are studies confirming its diagnostic value in pleural TB (26). The findings of the present study align with these previous results. The positive rate of GeneXpert MTB/RIF, along with its AUC and κ-values were higher than those of acid-fast staining and tuberculosis culture. Furthermore, in the analysis of all combined experiments, the positive rate, AUC and κ-values for GeneXpert MTB/RIF combined with pathology were also the highest.

The consistency analysis indicated that GeneXpert MTB/RIF technology demonstrated good consistency (κ=0.91), whereas acid-fast staining (κ=0.16) and tuberculosis culture (κ=0.13) exhibit poor consistency. This may be attributed to the limited number of cases included. Although GeneXpert MTB/RIF facilitates the detection of *M. tuberculosis* and rifampicin resistance, it cannot fully replace traditional methods for assessing rifampicin resistance. The total number of cases included in the present study was not particularly large. The diagnosis of tuberculosis relies not only on pathological findings but also on etiological assessments. Most patients included in the present study were clinically suspected of having tuberculosis, resulting in a specificity of 100%, which is consistent with numerous research findings and does not impact the generalizability of the results.

In conclusion ultrasound-guided percutaneous biopsy, in conjunction with laboratory examination, is recognized as a safe and effective method for diagnosing pleural TB. The combination of ultrasound-guided puncture and GeneXpert MTB/RIF exhibits high sensitivity and specificity, demonstrating significant value in the diagnosis of pleural TB and the detection of rifampicin resistance.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

QY and YQ made substantial contributions to conception and design. QY and JC made substantial contributions to acquisition of data. FX, JC and SJ made substantial contributions to analysis and interpretation of data. YQ and QY wrote the manuscript. QY and FX constructed figures. JC and QY constructed the tables. YQ and SJ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study met the conditions of the Helsinki declaration. All methods were carried out in accordance with relevant

guidelines and regulations and all experimental protocols were approved by the Ethics Committee of Shandong Public Health Clinical Center (Shandong Chest Hospital; approval no. 2021XKYYEC-33). Informed consent was waived by the Ethics Committee of Shandong Public Health Clinical Center (Shandong Chest Hospital)/2021XKYYEC-33 for this study due to retrospective nature.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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