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Comparative efficacy of methods for early diagnosis of tuberculosis pleuritis with rifampicin-resistance

Altyn Almagambetova, Kalzhan Yermekbayeva, Daniyar Dilmagambetov, Galiya Tanzharykova, Bakytzhan Baisalbayev

Department of Phthisiology and Dermatovenereology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Republic of Kazakhstan

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SUMMARY

The purpose of the article was to explore the effectiveness of a complex morphological study of pleural biopsies and molecular genetic study (GeneXpert MBT/Rif) of pleural effusion in verifying the diagnosis of pleurisy of tuberculous aetiology.

The participants of the study were 120 patients with a exudative pleurisy who were admitted to the department of extrapulmonary tuberculosis of the Regional Phthisiopulmonology Center (RPPC) in Aktobe (Republic of Kazakhstan) in the period from 2018 to 2020.

Significant differences were obtained in the compared groups ($p<0.05$), which testifies to the rather high diagnostic efficiency of the GeneXpert MBT/RIF molecular genetic method in comparison with bacterioscopy in detecting *Mycobacterium tuberculosis* (MBT) in pleural fluid obtained by video thoracoscopy.

Using the GeneXpert method, positive results of the presence of MBT in the pleural fluid were obtained in 26.3% of patients of the main group, while in patients of the control group, MBT was detected only in 3.2% of cases by simple bacterioscopy ($p<0.05$). The high diagnostic efficiency of the GeneXpert express method (26.3%) is confirmed and proven by the "gold standard" of bacteriological examination of pleural fluid – the growth of MBT colonies in 24.6% of cases by the BACTEC MGIT-960 method and in 28.1% of cases of MBT growth on solid nutrient medium Lowenstein-Jensen in patients of the main group.

The combination of the invasive method of video thoracoscopy diagnostics with the GeneXpert microbiological express method for detecting MBT in the pleural fluid is today, the optimal method for early diagnosis of a drug-resistant form of exudative pleurisy of tuberculous etiology.

Keywords: Tuberculosis, pleurisy, GeneXpert, videothoracoscopy, drug resistance, mycobacterium tuberculosis.

INTRODUCTION

Tuberculosis remains one of the most common infectious diseases in the world. Despite the decrease in epidemiological indicators for tuberculosis in Kazakhstan, the problem of early diagnosis and adequate treatment of its extra-pulmonary forms remain relevant, due to the spread and growth of drug-resistant forms [1, 2]. Significant difficulties are caused by an early and timely diagnosis of one of the widespread forms of tuberculosis – exudative pleurisy of a specific aetiology. This phenomenon is explained by the limitations of traditional methods for diagnosing exudative pleurisy. More than 50 different somatic diseases are known (*e.g.*, congestive heart failure, pneumonia, lung cancer, tuberculosis, pulmonary embolism, rheumatoid arthritis, etc.), which are accompanied by the formation of effusion in the pleural cavity. Therefore, verification of tuberculous pleurisy requires an integrated approach to this problem [3].

Corresponding author
Altyn Almagambetova
E-mail: alt.almagambetova@gmail.com

Today, the diagnosis of tuberculous pleurisy, especially with drug resistance of *Mycobacterium tuberculosis* (MBT), is a difficult task and requires the use of modern research methods. The most informative and rapid methods for verifying the aetiology of pleural effusions are a complex morphological study of pleural biopsies and a molecular genetic study of the contents of the pleural cavity [4-8]. In 2010, WHO approved the polymerase chain reaction (PCR) method using the GeneXpert platform (Sunnyvale, California, USA). Many studies carried out in various laboratories around the world have established that the Xpert MBT/RIF diagnostic test has a significantly higher sensitivity than the Ziehl-Neelsen smear microscopy method, having a diagnostic specificity comparable to it [2, 9, 10].

According to many authors, the study of pleural fluid and pleural biopsy to determine MBT by the GeneXpert method has a higher sensitivity and contributes to the rapid diagnosis of tuberculous pleurisy [11-13]. Consequently, timely diagnosis and the appointment of early adequate treatment for patients with drug-resistant tuberculous pleurisy necessitates studying the effectiveness of the combined use of video thoracoscopy (VTS) and determining MBT in pleural effusion using the GeneXpert molecular genetic method.

In the Aktobe Regional Phthisiopulmonology Center (ARPPC), along with the traditional methods, modern methods of diagnosing tuberculosis are also used: GeneXpert in combination with a morphological examination of biopsy material obtained with VTS. The purpose of this study was to study the effectiveness of a complex morphological study of pleural biopsies and GeneXpert molecular genetic study of pleural effusion in verifying the diagnosis of pleurisy of tuberculous etiology.

PATIENTS AND METHODS

This research study was carried out from 2018 to 2020 at the ARPPC in Aktobe (Republic of Kazakhstan). To solve the set tasks, the participants of the study were 120 patients with clinical manifestations of exudative pleurisy and the presence of pleural effusion, who were admitted to the department of extrapulmonary tuberculosis. According to the purpose of the study, the patients were divided into two groups: the main group (57 patients), and the control group (63 patients). To obtain homogeneous results, the study excluded patients under the age of 15 and over 80 years old, as well as with mental illness in the acute phase, with the presence of severe concomitant pathology, and pregnant women. Before starting the work, all patients gave informed consent to participate in the research study.

All patients, according to the clinical protocol, underwent a set of diagnostic measures, including a general clinical examination, X-ray examination and laboratory investigation. The most common symptoms of respiratory tuberculosis, such as intoxication (weakness, sweating, fever, and weight loss) and bronchopulmonary-pleural syndromes were determined. In the history of the disease, special attention was paid to the onset of the disease (acute or gradual), the duration and dynamics of the process, the presence of previous anti-inflammatory treatment, and its effectiveness. The risk factors were ascertained: previously transferred tuberculosis, the presence of concomitant pathology, and contact with patients with tuberculosis.

In the main group of subjects (57 patients), VTS was performed using the Karl Storz video complex (Germany). Surgical interventions were performed under intubation anesthesia with the ability to turn off the operated lung from ventilation. Aspiration of exudate was carried out with the installation of drains. A pleural biopsy was performed from several places with further histological examination of the resulting pathological material. GeneXpert is a fully automated real-time PCR system that determines MBT DNA from pathological material samples with the determination of resistance to a highly effective anti-tuberculosis drug – rifampicin [14-16]. The volume of pathological material for research was at least 3-5 mL.

In the main group (57 patients), the pleural fluid taken during VTS was subjected to a molecular genetic study by the GeneXpert method with the determination of drug susceptibility to rifampicin. Patients in the control group (63 patients) underwent pleural puncture with determination of cell composition and microscopy on MBT according to Ziehl-Neelsen in aspirated fluid. At the same time, all patients of the main and control groups underwent inoculations of pleural fluid for liquid (automated system BACTEC MGIT 960) and solid Lowenstein-Jensen nutrient media. Mathematical pro-

cessing of the obtained data was carried out using the STATISTIKA 10 program. Analysis of indicators of microscopic examination and diagnostic test Xpert MBT/RIF of pleural fluid was carried out using the Pearson Chi-square contingency tables. Differences in indicators in the compared (main and control) groups were considered statistically significant at $p<0.05$.

RESULTS

Among the examined patients in the main group, there were 41 men (71.9%), and 16 women (28.1%); in the control group 46 (73%) and 17 (27%), respectively. The average age of the patients was 37.5±13.26 years. A significant part was unemployed persons: 73 (60.8%) cases; 34 (28.3%) were employed; 7 (5.8%) pensioners, 4 (3.3%) students and 1 (0.8%) disabled people. Contact with a tuberculosis patient was established in 8 (14.0%) patients in the main group and in 15 (23.8%) patients in the control group. In most cases, there was family contact, which occurred in 15 (65.2%) patients from the study groups. A history of previously transferred tuberculosis was indicated by 23 (19.2%) people, of which: 11 (47.8%) in the main group and 12 (52.2%) in the control group.

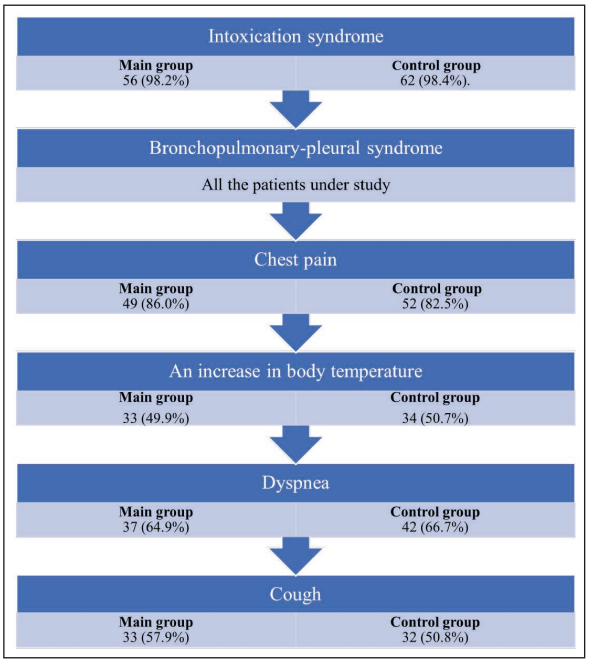

Figure 1 - Manifestations of intoxication and bronchopulmonary-pleural syndromes in patients with tuberculous pleurisy.

It is known that tuberculous pleurisy occurs with manifestations of intoxication and bronchopulmonary-pleural syndromes. In this case, the intoxication syndrome is accompanied by weakness, sweating, fever, and weight loss [17-19]. Bronchopulmonary-pleural syndrome (chest pain, shortness of breath, dry cough, occasionally with sputum production) occurred in all the patients under study (Figure 1).

Given the severity of clinical symptoms, with tuberculous pleurisy, the majority of patients were identified by referral – 117 (97.5%) people, of whom in the main group – 56 (98.2%) and in the control group – 61 (96.8%). Whereas, during the preventive examination – a medical examination that is conducted to assess an individual's overall health and identify potential health problems before they become serious, respectively, 3 (2.5%) patients, of them in the main group – 1 (1.8%) and in the control group – 2 (3.2%). According to the anamnestic data, the duration of the disease before the patients were admitted to the anti-tuberculosis hospital varied from 10 days to 1.5 months. The terms of admission to the hospital from the onset of clinical symptoms ranged from 10 days to 1 month – in 111 (92.5%) patients, of which 52 (91.2%) were patients of the main group, and 59 (93.7%) – control. In both groups, hospitalization for more than one month from the onset of clinical manifestations of the disease amounted to 9 (7.5%) cases, of which in the main group – 5 (8.8%), and in the control group – 4 (6.3%), respectively. It should be noted that the loss of time from the moment of illness to diagnosis increases the likelihood of complications.

In the main group of patients, an active specific process in the lung was diagnosed in 22 (38.6%) cases, residual changes after the postponed tuberculous process were found in 7 (12.3%) cases, there were no local changes in the lungs – in 28 (49.1%). In the control group – 26 (41.3%), 16 (25.4%), and 21 (33.3%) patients, respectively. In 40.8% of cases, local changes in the lungs were absent. In the absence of local changes in the lungs, the diagnosis of exudative pleurisy of tuberculous aetiology is difficult, which, in turn, proves the relevance of the chosen research goal. Secondary forms of tuberculosis were diagnosed in patients with an active pulmonary process. The analysis of the fre-

quency of concomitant diseases in patients with tuberculous pleurisy occurred in the main group in 17 (29.8%) cases and the control group – in 26 (41.3%) cases (Table 1).

Data given in Table 1 indicate that in the main group, chronic pyelonephritis was diagnosed in 35.3% of cases, iron deficiency anemia in 17.6%, chronic gastritis, diabetes mellitus and chronic cholecystitis in 11.8%, and 5.9%. In the control group, chronic pyelonephritis and iron deficiency anemia were diagnosed in 38.5% of cases, chronic gastritis, and rheumatoid arthritis were found in 7.7%, and benign prostatic hyperplasia and diabetes mellitus in 3.8%.

Most often, the localization of pleural effusion was unilateral and occurred in 114 (95.0%) patients, while bilateral pleural effusion was in 6 (5.0%) patients. In the main group, unilateral pleural effusion was found in 56 (98.2%) patients, of which right-sided in 32 (57.1%), left-sided in 24 (42.9%) patients. Unilateral pleural effusion in the control group was found in 58 (92.1%): right-sided in 27 (46.6%), left-sided in 31 (53.4%) subjects. Bilateral pleural effusion was observed in 1 (1.8%) patient in the main group and in 5 (7.9%) patients in the control group. There were no statistically significant differences in patients from the main and control groups according to the criterion of localization of pleural effusion ($p>0.05$). In laboratory examination of pleural fluid in 114 (95.0%) patients, serous exudate was of a lymphocytic nature, with an average value of the number of lymphocytes – 91.8±16.49%. According to numerous authors, the predominance of lymphocytes in the pleural fluid is only an indirect indicator of the tuberculous aetiology of exudative pleurisy [19-21].

In 57 (100%) patients of the main group, tuberculous eruptions with VTS were detected on both pleural layers, but more often on the parietal. The size of the rashes varied within 1-3 mm in diameter. According to the results of the histological examination in the main group of patients, tuberculosis was confirmed in all 57 patients. A biopsy specimen of the pleura revealed typical tuberculous granulomas, consisting of lymphoid and epithelioid cells, with the presence of Pirogov-Langhans cells and caseous necrosis. The pleural fluid evacuated during VTS was sent for microbiological diagnostics using the GeneXpert express method and determining the drug susceptibility of MBT strains to anti-tuberculosis drugs. A comparative assessment of the results of the effectiveness of the above methods for diagnosing MBT in the pleural fluid in patients of the main and control groups was carried out (Table 2).

As can be seen from the data in Table 2, in the study of exudate for the presence of the causative agent of tuberculosis in the control group by the microscopic method with Ziehl-Neelsen staining, in most cases (96.8%) MBT was not detected, while by the GeneXpert method, DNA of mycobacteria was detected in 15 (26, 3%) cases in the studied patients of the main group. Statistically, according to this criterion, the groups are reliably distinguishable ($p<0.05$).

Table 1 - Concomitant diseases in patients with tuberculous pleurisy.

N.	*Accompanying illnesses*	*Number of patients*	
		main	*control*
1	Iron-deficiency anaemia	3 (17.6%)	10 (38.5 %)
2	Chronic pyelonephritis	6 (35.3%)	10 (38.5%)
3	Glomerulonephritis	1 (5.9%)	–
4	Diabetes	2 (11.8%)	1 (3.8%)
5	Chronic gastritis	2 (11.8%)	2 (7.7%)
6	Chronic cholecystitis	2 (11.8%)	–
7	Rheumatoid arthritis	–	2 (7.7%)
8	Benign hyperplasia prostate	1 (5.9%)	1 (3.8%)

Table 2 - Comparative evaluation of the results of the study of pleural fluid by microscopy and GeneXpert.

Patient group	*Method research*	*The result of pleural fluid for MBT*			
		MBT (–)		*MBT (+)*	
		absolute number	*%*	*absolute number*	*%*
Main (n=57)	GeneXpert	42	73.7	15	26.3*
Control (n=63)	microscopy	61	96.8	2	3.2*

Note: *Reliability of differences when compared with the control group ($p<0,05$).

By the GeneXpert method, out of 15 (26.3%) positive results, rifampicin resistance was detected in 14 (93.3%) cases, and rifampicin sensitivity was preserved in 1 (6.7%) case. To confirm the diagnostic efficiency of the GeneXpert express method, pleural fluid was cultured on liquid (automated BACTEC MGIT 960 system) and solid Lowenstein-Jensen culture media, which are the "gold standard" for bacteriological diagnosis of tuberculosis [1]. The obtained results of the bacteriological examination of pleural fluid are shown in Table 3. According to Table 3, the growth of MBT colonies by bacteriological methods was revealed in patients of both the main and control groups. In particular, in the main group using the BACTEC MGIT 960 method, an increase in MBT was obtained in the pleural fluid in 24.6% of cases, on solid culture media of Lowenstein-Jensen in 28.1%. Almost similar results were obtained in the control group of the subjects, that is, in 23.8% and 28.6%, respectively. The growth of MBT colonies on solid and liquid nutrient media confirms the tuberculous aetiology of exudative pleurisy in both the main and control groups under study. At the same time, the method of simple bacterioscopy, used in the control group of the studied individuals, gave a positive result of the presence of MBT in the pleural fluid taken during pleural puncture only in 3.2% of cases. Whereas, in the main group by the GeneXpert method, MBT was found in the pleural fluid taken at VTS in 26.3% of cases. The above results prove the diagnostic efficiency and high sensitivity of the GeneXpert express method in comparison with simple bacterioscopy at an early stage in the diagnosis of exudative pleurisy of tuberculous etiology.

Subsequently, we carried out a comparative analysis of the bacteriological study of pleural fluid in patients of both groups in terms of MBT growth on different nutrient media. According to the analysis, in patients of the main and control groups, when inoculating pleural fluid on liquid nutrient media (BACTEC MGIT 960), the results of MBT growth were obtained on average on 27.6±4.27 and 27.5±5.05 days, on solid nutrient media. Lowenstein-Jensen media by 69.1±2.13 and 70.8±1.80 days, respectively, while the Xpert MBT/RIF test gave a positive result for the presence of MBT DNA in 26.3% of individuals from the main group during 2 hours of the first day of the study. Also, the above data prove the insufficient sensitivity of the simple microscopy method in the study of pleural fluid, in which MBT was found only in 2 cases (3.2%). Thus, this indicator confirms the advantage of the GeneXpert molecular genetic method over traditional methods of studying pleural fluid on the MBT.

Based on the objective of the study, compared the results of the drug susceptibility test (DST) of the tuberculosis pathogen to rifampicin using the Xpert MBT/RIF test and traditional methods of microbiological diagnostics (Table 4).

Table 3 - Results of growth of MBT colonies in pleural fluid on solid and liquid nutrient media.

Groups	*Automated system BACTEC MGIT 960*		*Solid culture media Lowenstein-Jensen*	
	absolute number	*%*	*absolute number*	*%*
Main (n=57)	14	24.6	16	28.1
Control (n=63)	15	23.8	18	28.6

Table 4 - Results of the MBT drug susceptibility test to rifampicin in the study group

Microbiological diagnostic methods	*Number of patients with MBT (+) in pleural fluid*	*DST results*			
		R-sensitive		*R-resistant*	
		absolute	*%*	*absolute*	*%*
BACTEC MGIT960	14 (24.6%)	1	7.1	13	92.9*
Lowenstein-Jensen	16 (28.1%)	2	12.5	14	87.5*
XpertMBT/RIF	15 (26.3%)	1	6.7	14	93.3*

Note: *Reliably with p<0,05.

According to Table 4, in the main group, when tested on the BACTEC MGIT analyzer, 960 out of 14 (24.6%) positive results of cultures on MBT in 1 (7.1%) case, sensitivity to rifampicin were preserved, in 13 (92.9%) cases revealed resistance of MBT to rifampicin. When inoculating pleural fluid on solid culture media of Lowenstein-Jensen, growth of MBT colonies was obtained in 16 (28.1%) cases, in 2 (12.5%) of which MBT strains are sensitive to rifampicin, and in 14 (87.5%) – MBT strains were resistant to rifampicin. When the Xpert MBT/RIF diagnostic test was performed, out of 15 (26.3%) positive results, rifampicin resistance was diagnosed in 14 (93.3%) cases, and rifampicin sensitivity was retained only in 1 (6.7%) case.

DISCUSSION

Tuberculosis remains a serious epidemiological threat worldwide. Timely and accurate detection of the disease provides effective treatment and control of the patient's condition. Early detection of MBT is also an effective method of preventing the incidence of latent tuberculosis infection of individuals from the risk group and infection of the population as a whole. The difficult situation with morbidity is complicated by the tendency to increase the resistance of many strains to antituberculosis drugs. Early detection of the causative agent of acid-resistant tuberculosis bacillus may prevent complications, making possible to start treatment with sensitive anti-tuberculosis agents in time, and alleviate the patient's condition. Considering the disappointing situation with the accuracy and timeliness of diagnosis of extrapulmonary forms of tuberculosis, including mycobacterial pleurisy with antibiotic resistance, many comparative studies appeared in recent years, including the use of the GeneXpert test for early detection of extrapulmonary tuberculosis. WHO also recommends early detection of extrapulmonary forms of tuberculosis using molecular genetic tests, namely Xpert MBT/Rif and Xpert MBT/Rif Ultra [26].

The results of many studies confirm the efficiency of the XpertMBT/Rif analysis for rapid detection of pleurisy of tuberculous etiology with mycobacterial resistance. A similar study in 2020 evaluated the efficiency of the GeneXpert system in detecting MBT in patients with signs of tuberculous pleurisy. One hundred and sixty patients underwent thoracoscopy under local anesthesia to obtain biopsy samples for final diagnosis verification. The GeneXpert tests were compared with the standard composite reference test (CRS) and the BACTEC MGIT 960 liquid culture system. The sensitivity and specificity of the GeneXpert test were determined, and the positive (PPV) and negative (NPV) predictive values were compared. The level of sensitivity of Xpert MBT/Rif was 68.8%, the level of specificity was 64.6%, the PPV of Xpert MBT/Rif was 56.4%, the NPV was 75.6%. The sensitivity of Xpert MBT/Rif relative to CRS was 69.0%, the specificity was 100.0%. The sensitivity of MGIT relative to Xpert MBT/Rif was 56.6%, and the specificity also was 100.0%. Among them, the ability to detect resistance to anti-tuberculosis drugs was assessed. MGIT culture identified resistant isolates in 12 of 13 patients. Xpert MBT/Rif detected all isolates resistant to rifampicin [27]. This study also confirms the feasibility of using the Xpert MBT/Rif method in clinical practice for accurate and early diagnosis of received thoracoscopic biopsy materials in patients with tuberculous pleurisy.

Also, the use of rapid diagnosis of tuberculosis in patients with pleural effusion was carried out by A.T. Kobra et al., Xpert MBT/Rif, adenosine deaminase (ADA) and Liquid Culture methods were compared 55 samples of pleural effusion were collected from patients from 10- to 75-year-old [28]. Using the Xpert MBT/Rif test, 36.75% of positive cases were identified, among which 55 were resistant to rifampicin. ADA analysis showed 29.09% positive results. The result of determining the effectiveness of tests for the rapid detection of MBT in patients with pleurisy shows high sensitivity (99%) and specificity (98%) of the Xpert MBT/Rif method, which means that this test is an early and accurate method for determining tuberculous pleurisy with resistance to mycobacteria.

An interesting case was published in 2022, describing data on the successful use of Xpert MBT/Rif in a patient with multidrug-resistant tuberculosis to isoniazid and rifampicin, who had a right-sided pleural effusion and pleural thickening. Scientists confirmed that in all cases of exudative or lymphocytic pleural effusion, pleural biopsy samples of patients should be examined by the Xpert MBT/Rif method, cultural analyzes, and a genotypic sensitivity test for early diagnosis and successful patient management [29]. A comparison of the complex

morphological study of pleural fluid biopsies and the molecular analysis of GeneXpert MBT/Rif pleural biopsies for the purpose of confirming the diagnosis of tuberculosis with other similar scientific studies of the early detection of MBT in patients with pleurisy showed high diagnostic efficiency of the Xpert MBT/Rif analysis. This molecular genetic analysis is simple and quick to use, unlike most complex morphological systems [30, 31].

This study made possible to fully analyze the efficiency of the GeneXpert method in detecting MBT in patients with unknown pleural effusion, using the information resource of our own sample of patients. Evaluation of the results was carried out using the microscopic method with staining according to Ziehl-Neelsen and molecular analysis by GeneXpert. Mycobacterial DNA was detected microscopically in 3.2% of cases, while the GeneXpert system detected 26.3% of MBT. The study made it possible to compare the results of the Xpert MBT/Rif method on the drug sensitivity of the tuberculosis bacillus with the methods of sowing on liquid nutrient media BACTEC MGIT 960 and Lowenstein-Jensen medium. The evaluation of the results showed a high efficiency of sensitivity and specificity in the detection of MBT in pleural fluid and a low probability of misdiagnosis by the GeneXpert method. As in most similar works, this study excludes factors that prevent heterogeneous research results. The patient cohort had similar characteristics, including clinical symptoms and a burdened epidemiological environment, including a family history of contact. General clinical, instrumental and laboratory examinations were carried out, the history of the disease, the duration of the pathological process before hospitalization to the phthisiopulmonology center were brought to the spotlight. It was noted that the severity of the disease and the risk of developing complications was lower in patients who had a shorter duration of the disease before hospitalization to the anti-tuberculosis hospital. Among the symptoms in all patients, intoxication and bronchopulmonary pleural syndromes prevailed, according to the diagnosis. Comorbidities of the patients, the presence of which complicated the patient's condition and the diagnostic process, were also considered.

The Xpert MBT/Rif method has been proven to be highly effective in pleural material obtained during video thoracoscopy under intubation anesthesia in patients with pleural effusion. The content of serous exudate with a predominance of lymphocytic cells (91.8±16.49%) in the pleural fluid was present in 95.0% of patients, which may indicate the patient's tuberculosis infection. Also, in favor of the GeneXpert method is the detection of MBT DNA in a smaller number of cases using the method of simple microscopy in the pleural fluid, in contrast to the molecular genetic method. The Xpert MBT/Rif test can be used to detect resistance to rifampicin. In this study, the Xpert MBT/Rif method identified 14 rifampicin-resistant results among 15 positive cases. To control the diagnostic efficiency of the Xpert MBT/Rif system, the results of sowing pleural fluid on the automated BACTEC MGIT 960 system and solid nutrient media were compared. Liquid media showed an increase in MBT of 24.6%, and Lowenstein-Jensen solid media - 28.1%. This study demonstrated the feasibility of using the Xpert MBT/Rif method in the early detection of tuberculous pleurisy, taking into account the high specificity and sensitivity of the method, which affects the results of patient treatment.

Consequently, the results indicate a fairly high efficiency of the molecular genetic rapid method GeneXpert, characterized by reliably proven positive results of MBT in pleural fluid with the determination of drug sensitivity of MBT to the main anti-TB drug (rifampicin) in the shortest possible time. GeneXpert – a method of molecular genetic detection of MBT in pleural fluid in combination with VTS plays a significant role in the early diagnosis of drug-resistant exudative pleurisy of tuberculous etiology. All patients, depending on the results of drug sensitivity, were prescribed timely, adequate treatment according to the category, which will undoubtedly affect the effectiveness of treatment of patients with a drug-resistant form of tuberculous pleurisy.

Today, according to many authors, there is a high incidence rate, accompanied by the presence of a significant proportion of drug-resistant forms of tuberculosis [22-25]. To prevent the spread of drug-resistant forms of tuberculosis, timely, early diagnosis and adequate treatment of patients with infectious forms are required. The use of endoscopic methods for the differentiation of isolated pleural lesions is a priority in the diagnostic plan, due to the high information content, both by identifying changes in the pleural leaves, and by ob-

taining material for morphological verification of the nature of pleurisy, which makes it possible to increase the level of verification of the aetiology of pleurisy to 100% of cases [3, 5]. Analysis of the data obtained, in particular, 100% histological confirmation of the tuberculous aetiology of the inflammatory process in the pleural cavity, corresponds to the literature data and indicates the need to use VTS with pleural biopsy to verify the diagnosis of tuberculous pleurisy.

The above data prove the insufficient sensitivity of the method of simple microscopy of the pleural fluid, in which MBT was detected only in 3.2% of cases. Obtained significant differences in the compared groups ($p<0.05$), which testifies to the diagnostic efficiency of the GeneXpert molecular genetic method in determining MBT in pleural fluid in comparison with the method of simple microscopy with Ziehl-Neelsen staining. The arsenal of traditional methods of culture research and determination of the sensitivity to MBT to anti-TB drugs is time-consuming and cumbersome. During this time, patients may undergo an inadequate course of treatment, the circulation of drug-resistant strains may continue, and the spectrum of MBT resistance may expand. The introduction of the high-tech method GeneXpert contributes to the timely and early diagnosis of tuberculous pleurisy. The GeneXpert molecular genetic method is a fast and reliable method for determining drug susceptibility to rifampicin, making it a reliable marker of multidrug-resistant tuberculosis (MDR-TB). The combination of VTS and the GeneXpert molecular genetic method will be an early and optimal way to verify the diagnosis of drug-resistant exudative pleurisy of tuberculous etiology.

The results of the study will contribute to the timeliness of identifying these patients, the adequacy and effectiveness of treatment, as well as shortening the time for differential diagnosis of exudative pleurisy, and preventing the development of complications. All patients with established drug resistance to rifampicin were prescribed timely, adequate treatment in accordance with the category, which will undoubtedly affect the effectiveness of treatment of patients with drug-resistant tuberculous pleurisy. The limitation of this study is that we could not specify how early was considered early for diagnosis, nor could report any differences in outcomes between individuals who were early diagnosed and those who were not.

CONCLUSIONS

Based on the research, the following conclusions were obtained:

1. The combined application of VTS and the GeneXpert molecular genetic method for determining MBT in pleural effusion allows a short time to verify the aetiology of exudative pleurisy. In 57 patients of the main group, in the pathological material taken from the pleural cavity with VTS, that is, in 100% of cases, the tuberculous aetiology of exudative pleurisy was histologically confirmed.
2. Using the GeneXpert method, positive results of the presence of MBT in the pleural fluid were obtained in 26.3% of patients of the main group, whereas, in patients of the control group, MBT was detected only in 3.2% of cases by the method of simple bacterioscopy ($p<0.05$).
3. The high diagnostic efficiency of the GeneXpert express method (26.3%) is confirmed and proven by the "gold standard" of bacteriological examination of pleural fluid – the growth of MBT colonies in 24.6% of cases by the BACTEC MGIT 960 method and in 28.1% of cases of MBT growth on solid nutrient media of Lowenstein-Jensen in patients of the main group.
4. The combination of the invasive method of VTS diagnostics with the GeneXpert microbiological express method for detecting MBT in the pleural fluid is today, the optimal method for early diagnosis of a drug-resistant form of exudative pleurisy of tuberculous etiology.

Conflict of interests
The authors declare that there is no conflict of interests.

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