

Efficacy of the Xpert MTB/RIF Assay in Multidrug-Resistant Tuberculosis

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Background: Half a million new cases of multidrug-resistant tuberculosis (MDR-TB) are registered annually, and therefore, the issue of the development of new fast and reliable methods for diagnosis of tuberculosis (TB) remains urgent in modern phthisiology.

Aims: The aim of this study was to investigate the effects of the Xpert MTB/RIF molecular genetic method on the diagnosis, clinical and radiological features, and efficacy of treatment of MDR-TB.

Materials and Methods: Patients with MDR-TB were divided into two groups. The first (study) group included patients ($n=412$) in whom a mutation in the gene responsible for the presence of *Mycobacterium tuberculosis* (MTB) and resistance to rifampicin were detected using the Xpert MTB/RIF assay. The second group consisted of patients ($n=540$) in whom TB was diagnosed using bacterioscopy and multidrug resistance was detected using inoculation on dense and liquid culture media. The results of bacterioscopic, bacteriological, molecular genetic, clinical studies and the efficacy of the treatment of 952 patients with MDR pulmonary TB were studied. The result of GeneXpert MTB/RIF was compared with the results of sputum bacterioscopy and culture methods on a dense Levenshtein–Jensen nutrient medium and on a liquid nutrient medium in a BACTEC 960 automated microbiological system.

Results: The “Successful treatment” outcome (“cured” and “treatment completed”) prevailed among patients who underwent timely diagnosis of MDR-TB using the Xpert MTB/RIF assay and reached 73.8%. In the second group of patients, it was 49.3% ($p=0.000$).

Conclusion: Timely diagnosis of MDR-TB using the Xpert MTB/RIF assay increased the efficacy of anti-TB chemotherapy.

Keywords: multidrug-resistant tuberculosis (MDR-TB), bacterioscopy, bacteriological method, Xpert MTB/RIF

Introduction

TUBERCULOSIS (TB) is responsible for more than a million deaths annually and is still one of the most important public health problems worldwide.¹ A major problem is a stable form of TB; according to the World Health Organization (WHO), half a million new cases are registered each year. Drug-resistant TB has high mortality rates due to complexity and high cost of its therapy. Waiting for the results of drug resistance tests leads to a delayed initiation of adequate therapy and, naturally, to an increase in the costs of chemotherapy.^{2–4}

The issue of *Mycobacterium tuberculosis* (MTB) drug resistance poses a great threat to therapy of TB and remains subject to increased control regarding global security in health care.^{5–8} The steady increase in the spread of resistant strains of MTB is of particular concern, especially strains

with broad and multiple drug resistance (BDR-TB and multidrug-resistant tuberculosis [MDR-TB], respectively), which are the greatest threat. MDR-TB is TB that does not respond to at least isoniazid and rifampicin, the two most powerful anti-TB (ATB) drugs. To date, MDR-TB is one of the main factors leading to increased mortality and reduced efficacy of treatment.^{9–12}

Therefore, developing new fast and reliable methods for diagnosis of TB remains urgent.¹³ Recently, the GeneXpert MTB/RIF (Cepheid, California) assay has been widely used. The Xpert MTB/RIF assay is a fast computerized test, which enables detection of MTB DNA and its resistance to rifampicin directly in sputum within 2 hours.¹⁴

The WHO recommends molecular genetic methods (MGM), in particular DNA strip technology, as quick methods for determining the drug sensitivity of MTB.^{15–17} The basis for these recommendations was the results of the studies, which

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demonstrated high accuracy and reliability of the method for TB and MDR-TB detection.^{18,19} Currently, MGM diagnostics of TB and MDR-TB are widely used and are major methods for MDR-TB detection worldwide, including Kazakhstan.^{15,16,20–23} To date, MGM for diagnosis of TB enable both early and timely diagnosis of an active specific process and prescribe necessary timely and adequate treatment, especially compared with culture methods.^{13,24,25}

The issues related to laboratory diagnosis of TB and drug resistance are of particular importance. Timely and accurate detection of TB and the spectrum of drug resistance of the pathogen within the shortest period from the moment of sampling, as well as further adequate control of the efficacy of chemotherapy, is one of the most important factors, which determine the success of anti-TB programs. Equally important is a well-considered use of available methods and rational design of patient screening schemes, which, together with qualitative diagnostics, ensure rational use of resources.^{26,27}

The aim of this study was to investigate the effects of the Xpert MTB/RIF MGM on the diagnosis, clinical and radiological features, and efficacy of treatment of MDR-TB.

Materials and Methods

Retrospective cohort study

A retrospective cohort study was performed (Fig. 1). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable

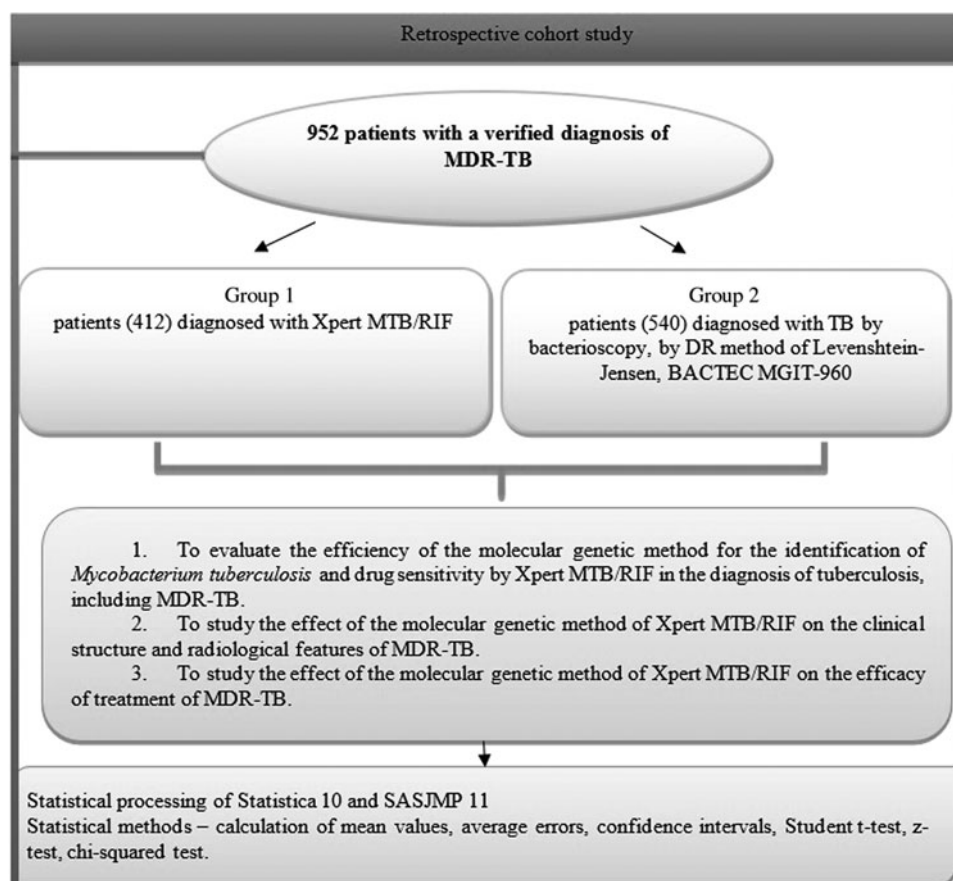
ethical standards. Informed consent was obtained from all individual participants included in the study. The objects of the study to assess the impact of molecular genetic diagnostic methods on the efficacy of treatment of MDR-TB included 952 patients older than 18 years with a verified diagnosis of MDR-TB in the Karaganda region from 2013 to 2014.

To solve the tasks and evaluate the studied parameters depending on the detection method, MDR-TB patients were divided into two groups. The first (study) group included patients ($n=412$) in whom Xpert MTB/RIF revealed a mutation in the gene responsible for the presence of *MTB* in the body and drug resistance to rifampicin, and the second group included patients ($n=540$) in whom TB was diagnosed by bacterioscopy method and multidrug resistance was identified on solid and liquid culture media by inoculation. In the course of the work, a retrospective selective statistical study was performed. Medical records of inpatients were used as accounting forms.

The results of bacterioscopic, bacteriological, molecular genetic, clinical studies and the efficacy of the treatment of 952 patients with MDR pulmonary TB were studied. The result of GeneXpert MTB/RIF was compared with the results of sputum bacterioscopy and culture methods on a dense Lowenstein–Jensen (LJ) nutrient medium and on a liquid nutrient medium in a BACTEC 960 automated microbiological system. For all three studies, sputum was taken from the same sample.

Cultural studies of the diagnostic material were performed on dense egg media of Lowenstein–Jensen according to appendix 17 of the Order of the Ministry of Health and Social Development of the Republic of Kazakhstan No. 19, dated

FIG. 1. Study model.



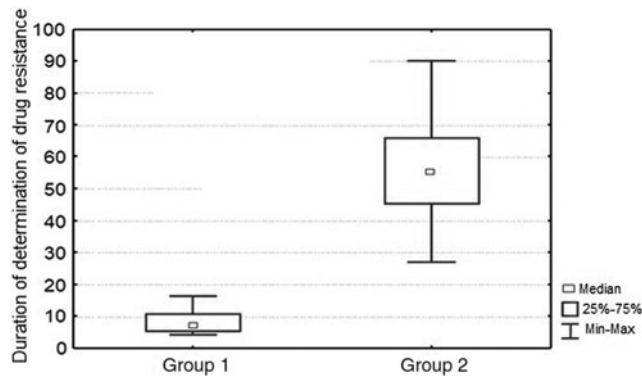


FIG. 2. Dependence of initiation of chemotherapy on the timing of drug resistance.

August 22, 2014 “On approval of the Instructions for the Organization and Implementation of Preventive Measures for Tuberculosis” (hereinafter referred to as the Order No. 19). Incubation of *MTB* in a solid nutrient medium is performed for 8 weeks. A positive seeding result is confirmed by: the growth of colonies on solid nutrient media not earlier than 3–4 weeks of incubation; microscopic confirmation of the acid resistance of the microorganism according to Ziehl–Nielsen from a grown colony. To determine the drug resistance of *MTB* to ATB drugs, the proportional method on the Lowenstein–Jensen medium is used. The stability of the tested strains is determined by the ratio of the number of colonies grown on a medium with drugs to the number of colonies grown on a medium without drugs.

The cultural diagnosis of TB was performed in laboratories on the automated system BACTEC MGIT 960 using liquid media in accordance with appendix 18 of the Order No. 19. In the event of *MTB* growth (up to the level of 105–106 CFU/1 mL of medium), the device evaluates the sample as positive and flashes and/or sounds a signal. If there is no growth for 6 weeks (42 days), the device evaluates the sample as negative. To confirm positive results, smears are prepared from each MGIT tube, which undergo Ziehl–Nielsen staining in accordance with general recommendations. Testing for resistance to ATB drugs is performed on the BACTEC MGIT 960 apparatus on the basis of the method of proportions; to avoid false sensitivity results, lower concentrations of pure ATB drug substances are used than on solid media. Upon completion of the test (14–21 days), a message appears on the device on the readiness of the results.

MGM for the diagnosis of TB and determination of drug sensitivity (Xpert MTB/RIF) were performed according to appendix 18 of the Order No. 19. The identification of ri-

TABLE 1. DISTRIBUTION OF THE PATIENTS BY SOCIAL STATUS

Social status	Group 1 (n=412), n (%)	Group 2 (n=540), n (%)	p
Unemployed	267 (64.8)	379 (70.2)	0.0783
Employed	77 (18.7)	91 (16.9)	0.4612
Homeless	21 (5.1)	26 (4.8)	0.2231
Student	21 (5.1)	14 (2.6)	0.0419*
Pensioner	26 (6.3)	30 (5.6)	0.6237

* $p < 0.05$, statistically significant differences.

TABLE 2. PATIENT DISTRIBUTION BY CASE TYPE

Parameter	Group 1 (n=412), n (%)	Group 2 (n=540), n (%)	p
New	163 (39.6)	150 (27.8)	0.0001*
Treatment after interruption	33 (8.0)	70 (13.0)	0.0148*
Transfer	33 (8.0)	48 (8.9)	0.6300
Failed treatment	21 (5.1)	92 (17.0)	0.0001*
Recurrence	108 (26.2)	109 (20.2)	0.0280*
Other	54 (13.1)	71 (13.1)	0.9851

* $p < 0.05$, statistically significant differences.

fampicin resistance is based on the identification of mutations in the *rpoB* gene (encoding the beta subunit of RNA polymerase). Xpert MTB/RIF is a fully automated real-time polymerase chain reaction system that simultaneously detects the *MTB* complex DNA and gene mutations in the *rpoB* codon associated with rifampicin resistance in the course of 2 hours.

Statistical data analysis

Two groups were compared on a quantitative scale using the nonparametric Mann–Whitney test. Comparison of the relative frequency of the parameter in various independent populations was carried out using the z -test. The statistical significance of different values for binary and nominal parameters was determined using the chi-square test. The analysis of changes for binary variables was carried out using the McNemar test. To describe quantitative parameters, we used the means and standard deviations in the format “ $M \pm S$.”

The level of statistical significance was fixed at the error probability level of 0.05. Statistical processing of data was performed using the Statistica 10 and SAS JMP 11 software.

Results and Discussion

Characteristics of the groups of patients according to major parameters

The use of the Xpert MTB/RIF express method in the diagnosis of TB allowed to detect the resistance of *MTB* to ATB drugs much faster than other methods—within 7 days from diagnosis to the start of therapy (interquartile range

TABLE 3. DISTRIBUTION BY DIAGNOSIS IN THE GROUPS

Parameter	Group 1 (n=412), n (%)	Group 2 (n=540), n (%)	p
Focal TB	5 (1.2)	6 (1.1)	0.8835
Disseminated TB	13 (3.2)	12 (2.2)	0.3724
Infiltrative TB	309 (75.0)	368 (68.1)	0.0208*
Caseous pneumonia	8 (1.9)	10 (1.9)	0.9196
Tuberculoma	12 (2.9)	8 (1.5)	0.1271
Cavernous TB	5 (1.2)	8 (1.5)	0.7242
Fibrous-cavernous TB	49 (11.9)	122 (22.6)	0.0001*
Tuberculous pleurisy	7 (1.7)	6 (1.1)	0.4387
Miliary TB	4 (1.0)	0 (0.0)	0.0218*

* $p < 0.05$, statistically significant differences.
TB, tuberculosis.

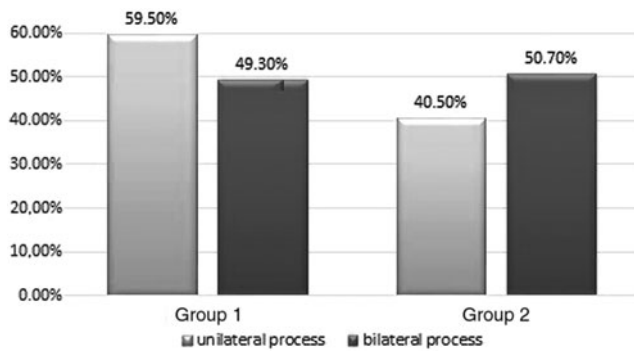


FIG. 3. Localization of pulmonary process.

[IQR] 5.0–11 days). The Lowenstein–Jensen method revealed resistance for 55 days from diagnosis to initiation of therapy (IQR 45–66 days), $p=0.000$ (Fig. 2).

Studies performed in South Africa,^{28,29} India,³⁰ and Russia³¹ displayed similar results; thus, according to Russian authors, the time to determine the drug sensitivity of *MTB* was reduced to 6 days (IQR 5–9 days) (MGM) compared with 22 days (IQR 20–28 days) (BacTAlert) and 65 days (IQR 60–82 days) (LJ) in patients excreting *MTB*.

To study the effect of the MGM of Xpert *MTB*/RIF on the clinical and radiological features and treatment efficacy of MDR-TB, we studied the gender, age, and social composition of patients and analyzed cases by type, clinical structure of TB, the prevalence of the process, and destructive changes in the lungs.

The study of gender characteristics of the patients showed prevalence of men in both groups—in group 1: 270 (65.5%), in group 2: 376 (69.6%); women: 142 (34.5%) and 164 (30.4%) in group 1 and group 2, respectively. There were no significant differences between the groups. The analysis of the age structure of patients showed that the groups did not differ in age. The mean age of the patients at the time of admission was 39.3 ± 14.2 years in group 1 and 39.6 ± 13.3 years in group 2.

Distribution of the patients by social status showed that the majority of the patients in groups 1 and 2 were unemployed ($n=267$ [64.8%] and $n=379$ [70.2%], respectively). According to the social parameters, *i.e.*, unemployed, employed, homeless, and pensioners, there were no significant differences between the treatment groups ($p>0.05$). In group 1, a statistically significant 5.1% prevalence of students was observed compared with 2.6% in group 2 ($p=0.042$) (Table 1).

The analysis of the patients by case type is presented in Table 2. In group 1, the “New case” type was significantly predominant, *i.e.*, primary drug-resistant TB in 39.6% ($n=163$), and in group 2, it was 27.8% ($n=150$) ($p=0.0001$). In patients

of group 2, the “Failed treatment” type prevailed in 17.0% ($n=92$), and in group 1, it was 5.1% ($n=21$), with statistically significant prevalence ($p<0.0001$). In group 1, patients with “Recurrence” type were 26.2% ($n=108$), and in group 2, this type was observed in 20.2% ($n=109$) ($p=0.028$). In patients of group 2, compared with patients of group 1, the “Treatment after interruption” type was significantly more common, 13% ($n=70$) compared with 8% ($n=33$) ($p=0.0148$). There were no significant differences between the compared groups ($p>0.05$) regarding other types of patients.

All examined patients were diagnosed with a pulmonary form of TB. Table 3 shows the distribution of the patients diagnosed with TB. In both observation groups, infiltrative TB was most common, 75% ($n=309$) in group 1 and 68.1% ($n=368$) in group 2, but the number of patients with pulmonary infiltrative TB was significantly higher in group 1 compared with group 2 ($p=0.0208$). The most advanced form of TB, fibrous-cavernous TB, was most often observed in group 2 (22.6%, $n=122$), and in group 1, it was 11.9% ($n=49$), with statistically significant prevalence ($p<0.0001$). Miliary TB was observed only in group 1, which is 1.0% ($n=4$) ($p=0.0218$). The remaining clinical forms of TB in both groups showed no significant differences ($p>0.05$).

Before the start of therapy, acid-resistant mycobacteria (AR-MB) were detected in sputum in 68.9% ($n=284$) of the patients in group 1 and in 73.5% ($n=397$) of the patients in group 2 using bacterioscopy; no significant differences were observed between the groups ($p>0.05$). *MTB* were detected in 70.9% ($n=292$) of the patients in group 1 and in 73.1% ($n=395$) of the patients in group 2 using bacteriologic method; there were no significant differences between the groups ($p>0.05$).

The localization of the process in the lungs, established according to X-ray data, was as follows in group 1: unilateral process in 59.5% ($n=245$) and bilateral process in 40.5% ($n=167$) of patients. In group 2, bilateral process prevailed and was observed in 50.7% ($n=274$) of patients ($p=0.002$) (Fig. 3).

The X-ray examination showed destructive changes in the lungs in 78.2% ($n=322$) of the patients in group 1 and in 83.7% ($n=452$) of the patients in group 2, with statistically significant prevalence in group 2 ($p=0.033$).

Therefore, the characteristics of the compared groups showed that the multiple drug resistance affected the structure of clinical forms. This is confirmed by the prevalence of destructive forms of TB with a severe progressive course, as well as common and massive isolation of *MTB*. The abovementioned adverse factors could not but affect the efficacy of treatment of patients in the study groups. In general, the compared groups did not differ in gender, age, and social status.

TABLE 4. CHANGES IN BACTERIA ISOLATION IN SPUTUM USING BACTERIOSCOPY

Months	Group 1 ($n=284$)				Group 2 ($n=397$)				z	p
	n	p%	−95% CI	+95% CI	n	p%	−95% CI	+95% CI		
1–3	176	62.0	56.3	67.6	170	42.8	38.0	47.7	5.0	0.000*
4–6	212	74.6	69.6	79.7	210	52.9	48.0	57.8	6.0	0.000*
7–9	229	80.6	76.0	85.2	236	59.4	54.6	64.3	6.2	0.000*
10–12	233	82.0	77.6	86.5	245	61.7	56.9	66.5	6.1	0.000*

* $p<0.05$, statistically significant differences.

TABLE 5. CHANGES IN BACTERIA ISOLATION IN SPUTUM USING BACTERIOLOGICAL

Months	Group 1 (n=292)				Group 2 (n=395)				z	p
	n	p%	-95% CI	+95% CI	n	p%	-95% CI	+95% CI		
1-3	217	76.4	71.5	81.3	204	51.4	46.5	56.3	7.0	0.000*
4-6	236	83.1	78.7	87.5	225	56.7	51.8	61.5	7.9	0.000*
7-9	244	85.9	81.9	90.0	234	58.9	54.1	63.8	8.4	0.000*
10-12	246	86.6	82.7	90.6	239	60.2	55.4	65.0	8.3	0.000*

* $p < 0.05$, statistically significant differences.

Analysis of the efficacy of treatment of patients in different groups

A significant difference between the groups was observed in the types of patients, *i.e.*, “Recurrence” prevailed in the study group; “Failed treatment” prevailed in the control group. These differences can be explained by the fact that the Xpert MTB/RIF assay is mainly used for the diagnosis of TB, *i.e.*, at the beginning of treatment, and the Lowenstein-Jensen test is used for both diagnosis and monitoring of treatment, *i.e.*, monthly during the intensive phase and quarterly during the maintenance phase.

Patients of both groups received chemotherapy according to the standard scheme of category 4, according to the Order No. 19 of the Ministry of Health and Social Development of the Republic of Kazakhstan of August 22, 2014 “On approval of the Instructions for the Organization and Implementation of Preventive Measures for Tuberculosis”: Cm/Km/Am+Ofx(Lfx)+Eto (Pto)+Cs+Z+PAS; maintenance phase according to the scheme: Lfx (Ofx)+Pto(Eto)+Cs+PAS.^{28,32} The results of treatment of patients were assessed based on time and rate of the elimination of bacteria using bacterioscopy and bacteriological methods, healing of destructive changes in the lungs, and disease outcomes by the end of general course of chemotherapy.

The assessment of time to disappearance of mycobacteria in sputum using luminescent microscopy showed most rapid disappearance in group 1, where after 1-3 months of treatment, AR-MB did not manifest itself in 62% ($n=176$) of patients compared with 42.8% ($n=170$) in group 2 ($p=0.000$). In group 1, bacteria were not detected using bacterioscopy by the

end of the intensive phase of treatment in 82.0% of patients; this parameter is significantly higher than in patients of group 2. In this group, the conversion of sputum smears was achieved in 61.7% of cases ($p=0.000$) (Table 4).

According to inoculation results, the best results were observed in group 1 compared with group 2. In patients of group 1, sputum abacillation by the end of intensive phase of treatment was observed in 86.6% of cases, which is also significantly higher than in the patients of group 2, where sputum abacillation was observed in 60.2% of cases ($p=0.000$). After 3 months of treatment, *MTB* was not detected using bacteriological method in a large number of patients of group 1, 76.4%, and in 51.4% of patients in group 2 ($p=0.000$) (Table 5).

To assess the radiological changes, chest X-rays were performed every 2 months. Evaluation of changes in reparative processes was carried out in all patients at the same time (every 2 months after the start of treatment), according to the criterion of cavity closure.

During therapy, cavity closure in both groups was achieved by the 6th month in the same number of patients (7.8% and 6.4%, respectively); there were no significant differences between the compared groups ($p > 0.05$). At the end of the intensive phase of treatment, cavity closure was observed in 29.8% ($n=96$) of patients in group 1 and in 16.9% ($n=76$) of patients in group 2 ($p=0.000$). By the 24th month of treatment, the highest rate of cavity closure was achieved in 57.1% ($n=184$) of patients in group 1; and in group 2, it was 38.4% ($n=173$) ($p=0.000$), with statistically significant prevalence found in group 1 (Fig. 4).

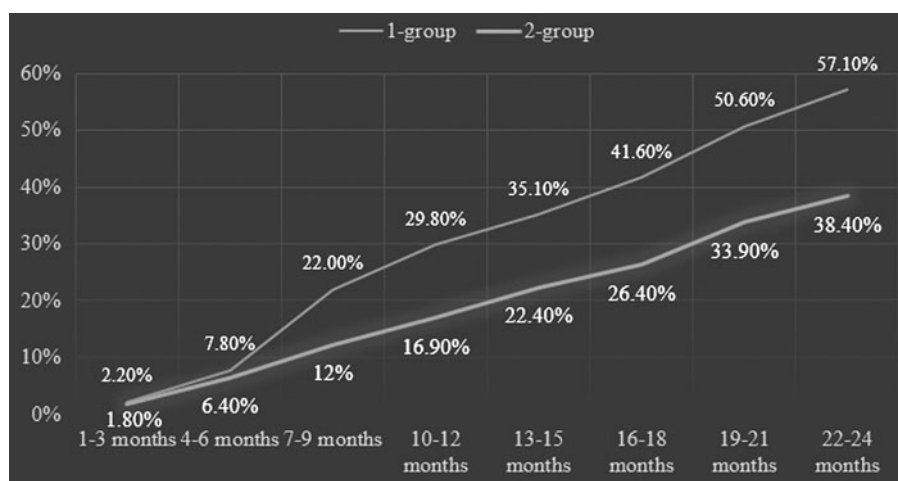


FIG. 4. Rates and terms of cavity closure.

TABLE 6. OUTCOMES OF TREATMENT

Case type	Group 1 (n=412)			Group 2 (n=540)			z	p
	n	p%	95% CI	n	p%	95% CI		
Successful treatment	304	73.79	68.83–78.75	266	49.26	43.24–55.28	8.034	0.000*
Failed treatment	30	7.28	0–16.6	91	16.85	9.14–24.56	4.651	0.000*
Noncompliance	36	8.74	0–17.99	91	16.85	9.14–24.56	3.810	0.000*
Transfer	5	1.21	0–10.82	9	1.67	0–10.06	0.597	0.551
Death	37	8.98	0–18.22	83	15.37	7.59–23.15	3.049	0.002*

* $p < 0.05$, statistically significant differences.

At the end of the treatment, each patient was familiarized with an outcome of treatment in accordance with the Order No. 19 of August 22, 2014 “On approval of the Instructions for the Organization and Implementation of Preventive Measures for Tuberculosis.” As the duration of treatment for patients with MDR-TB is at least 18 months, the outcomes of their treatment were assessed 2 years after registration (Table 6).

The treatment outcomes were as follows (Table 6). In group 1, the “Successful treatment” outcome (“cured” and “treatment completed”) significantly prevailed in 73.79% ($n=304$); in group 2, it was 49.26% ($n=266$) ($p=0.000$). In group 1, the “Failed treatment” outcome was less common in 7.28% ($n=30$); in group 2, it significantly prevailed in 16.85% ($n=91$) ($p=0.000$). In group 2, the “Noncompliance” outcome was observed in 16.85% ($n=91$) of patients versus 8.74% ($n=36$) ($p=0.000$); in group 2, the “Death” outcome prevailed and was 15.37% ($n=83$) versus 8.98% ($n=37$) in group 1 ($p=0.002$). There were no significant differences in the “Transfer” outcomes between the groups ($p > 0.05$).

The results of our studies are consistent with the data of Russian authors,^{33,34} who also proved that the early prescription of chemotherapy according to the GeneXpert MTB/RIF test, followed by correction according to the culture results on BACTEC MGIT 960, significantly improves the outcome in MDR-TB patients treatment both in terms of the rate of cessation of bacterial excretion and in the rate of closure of disruption, compared with the group where treatment was corrected only after receiving the culture result on liquid media, and they indicate that the use of test GeneXpert MTB/RIF significantly reduces the number of cases of chemotherapy correction or switching to another regimen.^{35–37}

Conclusion

TB has a risk of multiple drug resistance and is tested in the drug susceptibility tests of patients with MDR-TB as a result of timely diagnosis using the Xpert MTB/RIF rapid method in the clinical structure infiltrative pulmonary TB prevailed in 75% (in the control group, 68.2%, $p=0.019$) and a neglected clinical form—fibro-cavernous pulmonary TB occurred less often—in 11.9% (in the control group, 22.6%, $p < 0.000$), X-ray examination often revealed unilateral lesions in 59.5% (in the control group, 49.3%, $p=0.002$), and there was little decay of pulmonary tissue in 78.2% (in the control group, 83.7%, $p=0.033$).

Timely diagnosis of MDR-TB using the Xpert MTB/RIF assay increased the efficacy of anti-TB chemotherapy at early stages of treatment. After 3 months, bacteria were not isolated in 62.0% of patients in this group and in 42.8% of patients from the control group using bacterioscopy ($p=0.000$), and at the end of the intensive phase of treatment, in 82.0% of patients (61.7% in the control group, $p=0.000$); using inoculation, respectively, in 76.4% (51.4% in the control group, $p < 0.05$) and 86.6% (60.2% in the control group, $p < 0.000$); cavity closure was achieved by the end of the intensive phase of treatment in 29.8% of patients (16.9% in the control group, $p=0.000$) and at the end of treatment in 57.1% of patients (38.4% in the control group, $p=0.000$). As a result, the rate of the “Successful treatment” outcomes (“cured” and “treatment completed”) was significantly higher in patients diagnosed using the Xpert MTB/RIF assay, 73.8% versus 49.3% in group 2 ($p=0.000$).

Disclosure Statement

No competing financial interests exist.

Funding Information

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