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The predictors of pulmonary tuberculosis in Xpert MBT/Rif positive and resistant assay patients with diabetes mellitus

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Abstract

Background: One of the most important among risk factors for active tuberculosis development represents diabetes mellitus. The aim of the study was the assessment of the predictive factors for pulmonary tuberculosis in Xpert MBT/Rif resistant assay patients with diabetes mellitus.
Material and methods: A retrospective, selective, descriptive and case-control study was performed. Were enrolled 119 pulmonary drug resistant tuberculosis patients, diagnosed and hospitalized in the Municipal Clinical Hospital of Phthysiopneumology of Chisinau city in the period of 01.01.2013-01.01.2015. The patients were distributed in 2 groups: the 1st group – 34 MDR-TB patients with diabetes mellitus and the 2nd – 85 MDR-TB patients. Investigations were performed according to the National Clinical Protocol – 123.
Results: The biological characteristics of the pulmonary MDR-TB patients with diabetes mellitus were old age with associated diseases, which contributed to a lower treatment outcome. For MDR-TB groups were common social-economic vulnerability, late detection as symptomatic cases and a high treatment success rate.
Conclusions: Patients with MDR-TB and diabetes mellitus need an individualized approach for an early TB detection and prompt initiation of the adequate treatment regimen according of the susceptibility testing results.

Key words: tuberculosis, Xpert MBT/Rif, diabetes mellitus.

Introduction

Tuberculosis is one of the most important challenges for the health care system and was declared a global emergency in 1993 [45, 46, 47]. In 2017 were registered 9 million new cases globally. The Republic of Moldova ranked among 30 countries with the biggest burden of multidrug-resistant tuberculosis (MDR-TB), an estimated disease incidence of 101/100.000 [7]. Health indicators that evaluate the achievement of the sustainable development goals associated with tuberculosis are: HIV prevalence, diabetes prevalence, alcohol use disorders and tobacco smoking prevalence and health expenditure per capita. Diabetes mellitus is an important public health problem, one of four priority non-communicable diseases targeted by the development goals. Diabetes mellitus leads to complications and premature death. In the Republic of Moldova every 10th citizen suffers from disturbances of glucose metabolism and the indices are continuously rising. National capacity to prevent and control tuberculosis is reflected by the early case detection, especially of MDR-TB cases. The incidence of MDR-TB among new and relapsed cases was 19/100.000 and 64.6/100.000 among retreated cases. Patients with both types of diabetes mellitus represent one of the risk groups for tuberculosis and should be annually screened by the chest X-ray. The association of the diabetes mellitus and pulmonary tuberculosis usually occurs in patients where diabetes was the previous diagnosed disease [15]. If both, tuberculosis and diabetes mellitus are detected simultaneously, diabetes worsens the tuberculosis outcome. One half of patients with diabetes mellitus develop tuberculosis in the first three years after the exposure to the infection [5]. Factors associated with the increased risk for tuberculosis are: disturbances of the innate resistance, dysfunction of alveolar macrophages, low cellular immunity response to the specific and non-specific infections, and reduced capacity of the organism to produce antibodies, low levels of interferon gamma, microangyopathy (inclusive pulmonary) and micronutrient deficiency [35].

The first clinical signs of tuberculosis in patients with diabetes mellitus have a low specificity: increased weakness, decreased appetite, loss of the weight, and worsening of the diabetes symptoms [18]. The development of the chronic

forms of tuberculosis – fibro-cavernous type, occurs when the organism's defenses are depleted [29]. The evolution of tuberculosis in diabetes mellitus is unfavorable due to disturbances of glucose metabolism [35]. Late detection and late onset of the therapy, dietary errors and inadequate treatment represent the causes of the worsening of tuberculosis process under the specific treatment. In diabetic patients, blood sugar levels increase, diuresis and glucosuria increase, acidosis may appear, patients have the feeling of dry mouth, thirst, frequent urination and important weight loss [14, 15].

Antidiabetic therapy in tuberculosis patients should be individualized and depends on the patient's state, the tuberculosis extensibility and the severity of diabetes [27,40]. Each patient with diabetes mellitus must be hospitalized. First of all, it is necessary to compensate the metabolic disorders with a physiological diet and optimal doses of antidiabetic drugs. Anti-tuberculosis therapy should be administrated with caution due to high rate of adverse reactions [39].To prevent possible side effects patients must be strictly monitored.

Although, most of the diabetic patients are misdiagnosed regarding tuberculosis, several factors are involved: low specificity of the clinical signs and atypical radiological aspects. The relevant localization of the pulmonary tuberculosis is upper and posterior segments of the lungs: I, II, VI and X, while in diabetic patients tuberculosis is identified in segments III, IV and V. In patients with carbohydrate metabolism disorders predominate the inferior lobe involvement and may be revealed multiple cavities [18].

According to the WHO recommendation microbiological methods remain the golden standard for pulmonary tuberculosis diagnosis**.** Conventional microscopy for identification of acid-fast-bacilli is the first step in TB detection algorithm. The low sensibility of the conventional microscopy diminishes the detection efficiency of TB patients. The long duration of the culture methods delays TB diagnoses. WHO recommends using Xpert MTB/Rif assay in adults, children and persons living with HIV or other risk factors. Xpert MTB/Rif assay represents *in vitro* diagnostic medical device owned by Cepheid Company. Xpert MTB/Rif assay used with Cepheid Xpert MBT/Rif system is a semi-nested, quantitative, real-time polymerase chain reaction testing for the DNA detection of all *Mycobacterium tuberculosis (MBT) complex* species and rifampicin resistance mutations of the *rpoB* gene [23]. Several standard results must be known for appropriate interpretation of Xpert MBT/Rif system: 1. MTB detected & RIF resistance means that MTB target is present and mutation of *rpoB*gene is detected; 2. MTB detected & RIF susceptible means that MTB target is present and no mutation of *rpoB* gene has been detected; 3. MTB not detected – MTB target is not detected within the sample. Despite of clearly defined interpretations the test results must be always correlated with laboratory and clinical data of the investigated patient. Data established that sputum examination through Xpert MBT/Rif assay shows sensitivity among culture positive specimens in an average 97.3% and among smear positive patients – 99.5%. The specificity rate comparing with non-tuberculosis patients was 97.9% [31]. However negative result does not exclude active tuberculosis.

The aim of the study was the assessment of the predictive factors of pulmonary tuberculosis in Xpert MBT/Rif resistant assay patients with diabetes mellitus.

Material and methods

It was performed a retrospective, selective, descriptive and case-control study targeting peculiarities of pulmonary MDR-TB patients, diagnosed and hospitalized in the Municipal Clinical Hospital of Phthysiopneumology of Chisinau city in the period of 01.01.2014-01.01.2016, distributed in two groups. Including criteria in the 1st group: age > 18 years old; patients with pulmonary tuberculosis, established as a new case and diagnosed with diabetes mellitus before tuberculosis; positive and resistant Xpert MBT/Rif assay; including criteria in the 2nd group: age > 18 years old; patients with pulmonary tuberculosis established as a new case without associated diabetes mellitus; positive and resistant Xpert MBT/Rif assay. The total number of 119 cases was distributed in 2 groups: the 1st group (the 1st Group) included 34 patients and the second group (the 2nd Group) included 85 patients. Collection of primary material involved the extraction of data from medical record forms. The individual schedule included information about: anamnesis, clinical examination, results of radiological investigations (chest radiography, high resolution computer tomography), results of microbiological investigations (smear microscopy by Ziehl-Neelson coloration and culture on classic solid medium Lowenstein-Jensen or liquid medium). Investigations were performed according to the National Clinical Protocol – 123 Tuberculosis in adults. Statistical analysis methods used in the study were: comparative, synthesis and discriminant analysis. Mathematic and statistical assessment was carried out by checking the quantitative and qualitative features. Accumulated material was tabled in simple and complex groups. Statistical study was performed using Microsoft Excel XP soft. The predictibility value of each involved factor was calculated using two by two tables. Relative risk and confidence interval was calculated according to the established formula [7]. The interval of 1.2 to 1.6 was assessed as a low predictive factor, 1.6 to 2.4 – as a mild predictive factor, and more than 2.5 – as a high predictive factor.

Results

Assessing general, social and economical peculiarities it was established the statistical predominance of male *vs* female in both groups: 21 (61.8%) *vs* 13 (38.2%) in the 1st group and 61 (71.1%) *vs* 24 (28.3%) in the 2nd group. Comparing the groups it was established a moderate predomination of male in the 2nd group comparing with the 1st group, so male/female ratio=1.6/1 in the 1st group and 2.5/1 in the 2nd group. Assessing the patients according to the age groups it was established the statistical predominance of the young

patients (18-34 years) in the 2nd group 40 (47.1%) comparing with the 1st group 4 (11.8%) and older than 55 years in the 1st group 19 (55.8%) *vs* 15 (17.6%) in the 2nd group. Summing patients in two subgroups: under 44 and older than 44 years, it was identified a statistical difference between the predominance of patients less than 44 years in the 2nd group 52 (61.7%) *vs* 6 (17.6%) in the 1st group and older than 44 years in the 1st group 28 (82.3%) *vs* 25 (29.4%) patients in the 2nd group. Considering that old age represents the specific feature for the group with diabetes and MDR-TB it was assessed as a high risk factor for tuberculosis (OR=11,2 95% CI: 5.8-60). The data are presented in the table 1.

Table 1

Distribution in sex and age groups

Groups	Indices	MDR-TB&DM	MDR-TB	p
		n = 34 (P%)	n = 85 (P%)	
Sex	**Men**	21 (61.8%)	61 (71.1%)	>0.05
	Women	13 (38.2%)	24 (28.3%)	>0.05
18-44 years	**18-24**	0	12 (14.1%)	<0.05
	25-34	4 (11.8%)	28 (33.1%)	<0.05
	35-44	2 (5.8%)	12 (14.1%)	>0.05
>44 years	**45-54**	9 (26.5%)	10 (11.8%)	>0.05
	55-64	12 (35.2%)	12 (14.1%)	<0.05
	>65 years	7 (20.6%)	3 (3.5%)	<0.05

Among patients of both groups a similar distribution from rural and urban areas was established, however homeless were detected only in the 2nd group – 6 (7.1%) patients. Distribution of patients by economic groups was relevant. Due to the old age of the patients with TB-MDR and DM, employed persons statistically predominated in the 1st group 14 (41.2%) *vs* 21 (24.%) in the 2nd group. Socially vulnerable patients were more frequently registered in the TB-MDR group: 52 (61.7%) unemployed patients *vs* 8 (23%) in the 1st group. Low living conditions also predominated in the 2nd group 68 (80.1%) *vs* 21 (61.7%) in the 1st group due to high rate of unemployed patients. Retired patients predominated in the MDR-TB+DM group: 8 (23.5%) *vs* 8 (9.4%) in the 1st group; the same situation was determined for the persons with disabilities: 4 (11.8%) *vs* 7 (8.3%) patients, respectively (tab. 2).

Table 2

Main demographic, social and economical characteristics

Groups	Indices	MDR-TB&DM	MDR-TB	p
		n = 34 (P%)	n = 85 (P%)	
Demographic	Urban	17(50.1%)	41 (48.2%)	>0.05
	Rural	14(41.2%)	38 (44.7)	>0.05
	Homeless	0	6 (7.1%)	>0.05
Economic	Employed	14 (41.2%)	21 (24.7%)	>0.05
	Unemployed	8 (23.5%)	52 (61.7%)	<0.01
	Retired	8 (23.5%)	8 (9.4%)	>0.05
	Students	0	5 (5.9%)	>0.05
	Disease disability	4 (11.8%)	7 (8.3%)	>0.05
Life conditions	Low living conditions	21 (61.7%)	68 (80.1%)	<0.05

The social risk groups with epidemiological role were evaluated. Migrants constituted a similar part in both groups, ex-detained were identified only in the MDR-TB group (13 (15.3%) cases). Exposure to tuberculosis infection (TB contact) statistically predominated in the 1st group – 11 (52.9%) *vs* 25 (29.4%) in the 2nd group and was identified as a low risk factor (OR=1.1 CI 95% 0.5-2.7). All patients in the 1st group and half of the 2nd group had associated diseases. So, the co-morbitities were established as a high risk factor (OR=45; CI 95% 42-48) for developing tuberculosis. In 15 (44.1%) patients of the 1st group diabetes mellitus was diagnosed at the same time as tuberculosis. Regarding the harmful habits, active tobacco smoking and alcohol drinking statistically prevailed in the 2nd group. Tobacco smokers were 63 (74.1%) in the 1st group *vs* 13 (39.2%) in the 2nd group and alcohol abusers were 38 (44.7%) in the 1st group *vs* 7 (20.6%) cases in the 2nd group (tab. 3).

Table 3

Distribution in risk groups

High risk groups	Indices	MDR-TB&DM	MDR-TB	p
		n = 34 (P%)	n = 85 (P%)	
High risk groups	Migrants	6 (17.6%)	16 (18.8%)	>0.05
	Ex-detained	0	13 (15.3%)	<0.05
	TB contact	11(52.9%)	25 (29.4%)	<0.01
	HIV infection	1 (2.9%)	2(2.6%)	>0.05
	Associated diseases	34 (100%)	36 (42.4%)	<0.05
	Psychiatric disorders	1 (2.9%)	8(9.4%)	>0,05
Associated harmful habits	Tobacco smoking	13 (39.2%)	63 (74.1%)	<0.001
	Alcohol abusers	7 (20.6%)	38 (44.7%)	<0.05

By studing the civil status it was identified a statistical higher rate of married patients in the 1st group: 16 (47.1%) *vs* 15 (17.6%) patients in the 2nd group and of the divorced and widowed persons: 10 (29.4%) *vs* 22 (7.1%), respectively. Single persons predominated in the 2nd group due to young age of most of the patients. When assessing the educational level it was established that one half of both groups graduated general school. The incomplete general educational level was more frequently identified in the patients from the 2nd group: 24 (28.2%) *vs* 6 (17.6%) in the 1st group. Higher education level was established in a limited number of cases in both groups. No statistical differences were established between the groups of tuberculosis patients (tab. 4).

Table 4

Main social characteristics

Status	Indices	MDR-TB&DM	MDR-TB	P
		n = 34 (P%)	n = 85 (P%)	
Marital	Single	8 (23.5%)	48 (56.5%)	<0.01
	Married	16 (47.1%)	15 (17.6%)	<0.001
	Divorced/widowed	10 (29.4%)	22 (7.1%)	<0.05

Education	Primary/illiteracy	2 (5.7%)	8 (9.4%)	>0.05
	Incomplete secondary	6 (17.6%)	24 (28.2%)	>0.05
	General	16 (47.1%)	34 (40.1%)	>0.05
	Professional	6 (16.6%)	17 (20%)	>0.05
	Superior	4 (11.7%)	2 (2.4%)	>0.05

Studying case-management it was identified that most of the patients from the 1st group comparing with the 2nd group were detected by high risk group screening, as recommended by the national protocol: 22 (64.1%) *vs* 13 (15.3%), respectively. As to symptomatic cases the patients were detected more often in the 2nd group: 60 (70.6%) *vs* 12 (35.3%) in the 1st group. By direct addressing were detected 12 (14.2%) patients in the 2nd group. Microscopic smear positive results were established in more than two thirds of patients of both groups: 22 (64.1%) in the 1st group and 61 (71.6%) in the 2nd group. Positive culture results were 24 (70.6%) patients in the 1st group and 76 (89.4%) in the 1st group. Positive results of Xpert MTB/Rif assay were more frequently identified in patients from the 2nd group: 76 (89.4%) *vs* 26 (76.5%) in the 1st group (tab. 5).

Table 5

Case-finding detection, microbiological characteristics and treatment outcomes

Characteristics	Indices	MDR-TB&DM	MDR-TB	p
		n = 34 (P%)	n = 85 (P%)	
Case-finding	Detected as symptomatic case	12 (35.3%)	60 (70.6%)	<0.001
	Detected by active screening	22 (64.1%)	13 (15.3%)	<0.001
	Direct addressing to the specialized hospital	0	12 (14.2%)	<0.05
Microbiological positive results	Microscopy	22 (64.1%)	61 (71.6%)	>0.05
	Culture	24 (70.6%)	64 (75.3%)	>0.05
	Xpert MTB/Rif	26 (76.5%)	76 (89.4%)	>0.05

When identifying the radiological characteristics of pulmonary tuberculosis patients it was established lung parenchymal destruction in both groups: 25 (73.6%) in the 1st group and 61 (71.7%) cases in the 2nd group. Disseminated opacities were established at a similar rate in patients of both groups: 21 (61.7%) in the 1st group and 58 (68.2%) in the 2nd group. Both lungs were affected more frequently in patients of the 1st group: 24 (70.6%) *vs* 49 (57.6%) in the 2nd group, but the statistical threshold was not achieved. More than three affected segments had 65 (76.5%) patients in the 2nd group and 22 (64.7%) in the 1st group. Radiologic evolution under the specific treatment with second line antituberculosis drugs assessed as partial resorption was determined in a similar proportion in both groups: 28 (82.3%) in the 1st group and 76 (89.4%) in the 2nd group. Lung infiltrates progression was established in higher proportion in the 1st group: 7 (20.6%) *vs* 6 (7.1%) in the 2nd group, which contributed to the high rate of died patients. Although infiltrative TB form was diagnosed in the majority of patients, the severest forms such as disseminated TB and fibro-cavernous TB were diagnosed more frequently in the 1st group: 6 (17.6%) *vs* 9 (10.6%) in the 2nd group. Data are exposed in the table 6.

Table 6

Case-management characteristics and imagistic features

Characteristics	Indices	MDR-TB&DM	MDR-TB	p
		n = 34 (P%)	n = 85 (P%)	
Imagistic	Destruction	25 (73.6%)	61 (71.7%)	>0.05
	Dissemination	21 (61.7%)	58 (68.2%)	>0.05
	Both lungs	24 (70.6%)	49 (57.6%)	>0.05
	Extensive TB	22 (64.7%)	65 (76.5%)	>0.05
	Partial resorption	28 (82.3%)	67 (78.8%)	>0.05
	Progression	7 (20.6%)	6 (7.1%)	>0.05
Clinical radiological forms	Infiltrative	28 (82.3%)	76 (89.4%)	>0.05
	Disseminated	4 (11.7%)	8 (9.4%)	>0.05
	Fibro-cavernous	2 (5.9%)	1 (1.2%)	>0.05

Treatment outcome was assessed using the standardized indices. The success rate was lower than recommended by WHO (85%) in both groups. The lowest success rate was registered in the 1st group: 20 (58.8%) *vs* the 2nd group 66 (77.6%). Poor outcomes predominated in the 1st group: 14 (41.2%) *vs* the 2nd group 11 (12.9%). The highest rate of died patients was identified in the 1st group: 6 (17.5%) comparing with the 2nd group 3 (3.5%) (tab. 7).

Table 7

Treatment outcome types

Outcome	MDR-TB&DM	MDR-TB	p
	n = 34 (P%)	n = 85 (P%)	
Successfully treated	20 (58.8%)	66 (77.6%)	<0.05
Died	6 (17.5%)	3 (3.5%)	>0.05
Lost to follow-up	5 (14.7%)	8 (9.4%)	>0.05
Failure	3 (8.8%)	5 (5.8%)	>0.05

Considering all above exposed data it was established that the most relevant general and biological characteristics of the pulmonary MDR-TB patients associated with diabetes mellitus were old age and comorbid state. They were more frequently divorced or widowed and were detected by active screening according to the national recommendations (tab. 8).

The most relevant social-economic characteristics of the pulmonary MDR-TB patients were economical disadvantaged state, low living conditions, single civil state and life history of imprisonment. They were more frequently detec-

Table 8

Odds Ratio assessing factors associated with diabetes mellitus and MDR-TB in patients with Xpert MBT/Rif resistant results

Factors	Odds Ratio
Old age (more than 55)	11.2 (95% CI: 5.8-60), p<0.001
Comorbid state	45 (95% CI: 42-48), p<0.001
Detected by active screening	11.2 (95% CI:11.7-11.4),p<0.05
Divorced or widowed	1. (95% CI: 1.16-1.3), p<0.05

ted as to symptomatic cases and were directly addressedto the specialised hospital. Despite the low social-economic state and late detection associated with the passive way of detection they had a high treatment success, demonstrating the strong impact on the disease outcome of the diabetes mellitus (tab. 9).

Table 9

Odds Ratio assessing factors associated with MDR-TB in patients with Xpert MBT/Rif resistant results

Factors	Relative Risk
History of imprisonment	5.6 (95% CI: 5.3-5.9), p<0.05
Economicaly disadvantaged state (unemployment)	5.12 (95% CI: 2.9-13.6), p<0.001
Low living conditions	2.5 (95% CI: 1.5-3.8), p<0.001
Single-civil state	3.9 (95% CI: 3.7-4.1), p<0.01
Detected as symptomatic case	4.2 (95% CI: 4.1-4.3), p<0.001
Detected by addressing to the specialized hospital	5.3 (95% CI: 4.9-5.7), p<0.05
Successfully treated	1.3 (95% CI: 1.25-1.37), p<0.05

Discussion

Association of tuberculosis and diabetes represents an epidemiological challenge and important problem for the health system in the Republic of Moldova. It was established that the tuberculosis prevalence rate among patients with diabetes is 1.8–9.5 times higher than in the general population [48].

In the Republic of Moldova 12.3% of the population have diabetes or reduced tolerance to glucose and 409 patients died due to diabetic complications in 2015 [7]. Since the tuberculosis incidence in the Republic of Moldova slowly decreased, the rate of MDR-TB increased. MDR-TB represents another serious threat to the global disease control. In clinical study was established a strong association between the risk factors and MDR-TB. There are several risk factors which increase the risk for MDR-TB in patients with diabetes: previous treatment, young age, HIV associated infection, smoking, alcohol and other substances abuse [14]. Some clinical studies denoted a high rate (10-23%) of MDR-TB among patients with diabetes [15, 20, 40, 42]. Other cited factors were: HIV co-infection, age older than 45, overweight, and male sex [13, 20].

If tuberculosis is detected earlier a more favorable outcome can be achieved. A severe course of tuberculosis with a tendency to the rapid progression and lung parenchyma destruction occurs mainly in patients with untreated diabetes mellitus or in late detected tuberculosis [6].

Our study demonstrated a strong influence of diabetes on tuberculosis outcome. Obtained results were similar to other studies, which determined a high rate of failure and death among patients with tuberculosis and diabetes [5, 10, 24, 29, 38]. Poor treatment outcomes could be explained by the co-morbidities such as diabetes, HIV infection, and social determinants of health (unemployment, educational level, income distribution, social vulnerability, health services accessibility) [10]. Nowadays, in the Republic of Moldova the global prevalence of tuberculosis among patients with diabetes is high and reflects the general epidemiological situation.

Conclusions

The treatment success rate among patients with drug resistant tuberculosis and diabetes was low due to following contributing factors: old age and comorbid state.

More frequently patients with drug resistant tuberculosis and diabetes were detected by active screening and had a civil unfavorable state (divorced and widowed), associated with old age.

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