

Research Article

Long-term results of 10 years of observation of cured cases of pulmonary tuberculosis

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Annotation

Aim of the study: Conduct long-term monitoring of recovered patients with pulmonary TB and study the frequency of relapses of pulmonary TB and factors contributing to their development in the Republic of Tajikistan.

Material and research methods: Of the total number of patients with pulmonary TB, 820 people in 2010-2011 after successful treatment, were transferred for further dispensary observation to PHC facilities, whose health status we monitored for 10 years (including 2020). Of the 820 patients, we were able to track the health status for 10 years in 622 patients (320 men and 302 women, age groups 19-44 years old - 330 people and 45-69 years old - 292 people). The rest - for various reasons were lost from further dispensary observation. All patients in PHC facilities annually during the period of dispensary observation underwent clinical, instrumental, laboratory, and X-ray examinations to exclude the recurrence of TB. Data for each patient were tracked using the National TB Registry OpenMRS data.

Research results: The elimination of preventive anti-relapse measures in people with residual post-tuberculosis changes in the lungs led to an increase in the number of relapses of the disease. The analysis of the conducted studies shows that the incidence of relapses of pulmonary TB does not depend on the regions and the severity of TB burden, they often develop with insufficient follow-up after the end of treatment and inadequate preventive measures in dispensaries patients.

The study of the reasons for the development of relapses makes it possible to timely identify a group of patients who need anti-relapse measures and prolongation of dispensary observation.

Conclusion: Thus, the results of this observation revealed the occurrence of relapses within 10 years in 19.3% of cases. A retrospective analysis of the initial forms of the disease showed that relapses of pulmonary tuberculosis occurred more often in patients who had had fibrous-cavernous pulmonary tuberculosis, than in patients who had disseminated pulmonary TB, and less often after suffering infiltrative pulmonary TB. Relapses of the disease occurred more often in men aged 19-44 years.

The results obtained indicate the development of relapses of pulmonary tuberculosis has a statistically significant dependence on the form of the initial disease, the presence of RPTCL, comorbid diseases such as HIV, diabetes mellitus, COPD, and the regularity of taking anti-TB drugs. At the same time, it turned out that the social status of all patients with relapses corresponds to the level of poverty, which should also be taken into account.

Actuality

In 2020, an estimated 10 million people fell ill with tuberculosis (TB) worldwide and Tajikistan is included in 30 high MDR-TB burden countries [1]. According to the WHO TB country profile (2020) in Tajikistan total TB incidence rate per 100 000 population is 84 (8000 cases), among that totally new and relapse cases, are 4148 and 67% of them are pulmonary TB [2].

Despite the significant achievements of modern science, the burden of tuberculosis (TB) in Tajikistan is still high, which is mainly due to the high level of reactivation of the tuberculosis process in patients who recovered from pulmonary TB [2,3]. In our previous studies, we have revealed the main definitions associated with the reactivation of the tuberculosis process, according to which the reactivation of the pulmonary process after TB implies both exacerbation and relapse of the disease. An exacerbation of the disease is an outbreak of TB after an

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Keywords: Tuberculosis; Relapses; Initial disease; Clinical forms; Concomitant diseases





effective but not completed chemotherapy. A relapse of the disease is an outbreak of the TB process in people who have previously had TB and successfully completed its treatment. Many researchers confuse Reinfection and Superinfection. In the case of reinfection, a person becomes infected again after the pathogen has been eliminated from the body and in the case of superinfection, the patient is infected with another type (strain) of the pathogen until complete recovery. Exogenous or true reinfection can cause a recurrence of the disease only in cases of complete recovery with sanitation of the body, which in practice is extremely rare. With an incomplete cure, the entry of new mycobacteria is also possible, while layering with a new superinfection occurs. With endogenous reinfection, mycobacteria multiply from old foci, which is clinically manifested by exacerbation and progression of the disease [4].

Often in clinical practice, it is difficult to differentiate one of the above conditions from another, sometimes this requires sequencing of the genome of Mycobacterium TB. Practitioners also often cannot verify the fact of re-infection with *M. tuberculosis*, because it is not known whether the patient's body was completely eliminated (eradicated) from *M. tuberculosis*.

In our previous studies, we pointed to factors contributing to the reactivation of the tuberculosis process, which may be facilitated by labor migration with the likelihood of superinfection with another strain of mycobacterium TB [5]; the high burden of fungal lung diseases in Tajikistan may also contribute to this [6]. In these cases, the costs associated with the identification of persons with suspected reactivation of the tuberculosis process and the verification of the diagnosis increase many times [7].

There are recommendations according to which patients with residual post-tuberculosis changes in the lungs (RPTCL), especially with large RPTCL, are at high risk of disease recurrence and therefore should be observed in the general medical network [8-10]. Social factors in the patient also contribute to the development of relapses [11-13]. Patients with recurrent tuberculosis in epidemiological terms are a "hidden reservoir of infection" since most of them are dominated by bacterial excretion [14]. Tuberculosis recurrences tend to be more severe and often give a positive drug-susceptibility test to anti-tuberculosis drugs [15-19].

In the Republic of Tajikistan, unfortunately, cases of relapse are not uncommon. However, a differentiated account of exogenous and endogenous reactivation of the tuberculous process has not been established to date, and the incidence of TB relapses has not been studied.

Aim of the study

Conduct long-term monitoring of recovered patients with pulmonary TB and study the frequency of relapses of pulmonary TB and factors contributing to their development in the Republic of Tajikistan.

Material and research methods

Criteria for inclusion of patients in the study

- Patients with pulmonary TB, in whom the outcome of the primary treatment was stated as "cured" or "treatment completed".
- Written consent of patients upon their inclusion in this study.

Criteria for exclusion of patients from the study

- Patients with pulmonary TB who have a different outcome of treatment than "cured" or "treatment completed".
- Patients with pulmonary TB who, for various reasons, were lost from observation during the 10 years of the study.

Of the total number of patients with pulmonary TB, 820 people in 2010-2011 after successful treatment, were transferred for further dispensary observation to PHC facilities, whose health status we monitored for 10 years (including 2020). Of the 820 patients, we were able to track the health status for 10 years in 622 patients (320 men and 302 women, age groups 19-44 years old - 330 people and 45-69 years old - 292 people). The rest - for various reasons were lost from further dispensary observation. All patients in PHC facilities annually during the period of dispensary observation underwent clinical, instrumental, laboratory and X-ray examinations to exclude the recurrence of TB. Data for each patient were tracked using the National TB Registry Open MRS data.

Statistical data analysis was carried out using Microsoft Excel-2013 and STATISTICA-7.0 software packages. To compare two or more independent study groups with each other on a quantitative basis, regardless of the nature of the distribution, as well as on a qualitative (ordinal or nominal) basis, a non-parametric test was used - Fisher's exact test. For all calculations in this work, the significance level "P" was taken as equal to 0.05.

Research results

In the observed cohort of patients during a 10-year follow-up, relapses of pulmonary tuberculosis were not observed in 502 patients out of 622, which is 80.7% of cases (Table 1). At the same time, out of 120 (19.3%) cases of recurrences, 58 or 9.32% of cases were classified as early and 62 or 9.97% of cases as late relapses.

An analysis of the age and sex characteristics of patients showed that most of the cases of pulmonary tuberculosis recurrence occurred in men aged 19-44 years. Thus, among 120 patients with a developed recurrent process, there were 65 men (54.2%) and 18 women (15.0%) aged 19-44, as well



as 31 men (25.8%) and 6 women (5, 0%) at the age of 45-69 years. According to the terms of development, sex and age characteristics were distributed as follows (Table 2).

A retrospective analysis of the initial forms of the disease showed that relapses of pulmonary tuberculosis occurred more often in patients who had undergone fibrous-cavernous pulmonary tuberculosis ($67.2 \pm 6.4\%$ - early and $79.0 \pm 4.9\%$ - late relapses), then - - in patients with disseminated pulmonary TB ($29.3 \pm 5.9\%$ and $14.5 \pm 4.2\%$, respectively) and fewer after infiltrative pulmonary TB ($3.45 \pm 2.8\%$ and $8.06 \pm 2.9\%$ - respectively) (Table 3).

A retrospective analysis of the development of relapses depending on the presence of residual post-tuberculous changes in the lungs showed that patients with relapses had certain residual changes after the disease. More often, relapses occurred in individuals with large residual post-tuberculous changes in the lungs (Table 4). At the same time, relapses more often developed in the early periods of observation (up to 5 years).

A retrospective analysis of the development of relapses depending on compliance with primary chemotherapy regimens in patients with pulmonary tuberculosis showed that in the vast majority of cases, various episodes of violations of chemotherapy regimens in the form of short-term breaks for various reasons were noted (Table 5).

The next step in our study was to analyze the causes of relapses depending on concomitant diseases (Table 6). It

should be noted that all four HIV-infected individuals (100%) and 8 patients with diabetes mellitus (100%) developed relapses of tuberculosis in the early stages. Out of 86 patients with chronic nonspecific lung diseases, TB recurrence developed in 57 (66.3%) patients, while early recurrence developed in 45 and late recurrence in 12 patients; 12 patients with concomitant liver diseases and 6 with gastric and duodenal ulcers did not develop relapses of the disease. Out of 280 cases without comorbidities, only 51 (18.2%) had relapses of the disease and almost all of them were in the late stages of follow-up.

Discussion

So, in Tajikistan, in the last 30 years, in conditions of socio-economic trouble, there has been a deterioration in the epidemic situation of TB and an increase in the number of newly diagnosed patients. This required a revision of the dispensary observation system in order to focus the attention of phthisiatricians and family doctors on patients with active tuberculosis who need intensive treatment. However, in our opinion and as evidenced by the facts of our study, the elimination of preventive anti-relapse measures in people with residual post-tuberculosis changes in the lungs led to an increase in the number of relapses of the disease [4].

The analysis of the conducted studies shows that the incidence of relapses of pulmonary TB does not depend on the regions and the severity of TB burden, they often develop with insufficient follow-up after the end of treatment and inadequate preventive measures in dispensaries patients.

Table 1: Characteristics of relapses of pulmonary tuberculosis according to the timing of their development, Abs. (M ± m,%).

Groups patients	Number patients	TB relapses						No relapses	
		Early		Late		Total		Abs.	%
		Abs.	%	Abs.	%	Abs.	%		
Total	622	58	9,32	62	9,97	120	19,3	502	80,7
<i>p</i>		> 0,05							

Note: The percentage of relapses is calculated in relation to the total number of patients in the study group. *p* - the statistical significance of differences between the timing of development of relapses (according to the χ^2 criterion for arbitrary tables).

Table 2: Gender and age characteristics of patients and the timing of the development of relapses, Abs. (M ± m,%).

Groups patients	Terms of development of relapses	Total relapses	Sex and age characteristics of patients							
			19 - 44				45 - 69			
			Men		Women		Men		Women	
			Abs.	M ± m, %	Abs.	M ± m, %	Abs.	M ± m, %	Abs.	M ± m, %
Total relapses (n = 120)	Early	58	28	48,3 ± 8,2	11	19,0 ± 5,4	15	25,9 ± 7,1	4	6,9 ± 2,8
	Late	62	37	59,7 ± 6,3	7	11,3 ± 4,2	16	25,8 ± 5,5	2	3,2 ± 2,4
<i>p</i>		< 0,05								

Note: The percentage is calculated relative to the number of relapses in the study group. *p* - the statistical significance of differences between gender (according to the χ^2 criterion for arbitrary tables).

Table 3: Retrospective analysis of relapses depending on initial forms of pulmonary tuberculosis, Abs. (M ± m,%).

Groups patients	Terms of development relapses	Total relapses	The original forms of pulmonary tuberculosis					
			Fibrous-cavernous		Disseminated		Infiltrative	
			Abs.	M ± m, %	Abs.	M ± m, %	Abs.	M ± m, %
Total relapses (n = 120)	Early	58	39	67,2 ± 6,4	17	29,3 ± 5,9	2	3,45 ± 2,8
	Late	62	49	79,0 ± 4,9	9	14,5 ± 4,2	5	8,06 ± 2,9
<i>p</i>		<0,05						

Note: The percentage of relapses is calculated in relation to the number of patients in the study group. *p* - the statistical significance of differences between forms of TB (according to the χ^2 criterion for arbitrary tables).



Table 4: Retrospective analysis of the development of relapses depending on residual post-tuberculous changes in the lungs, Abs. (M ± m,%).

Group patients	Terms of development relapses	Total relapses	Residual post-tuberculous changes in the lungs					
			Small residual changes		Large residual changes		No residual changes	
			Abs	M ± m, %	Abs	M ± m, %	Abs	%
Total relapses (n = 120)	Early	58	8	13,8 ± 6,5	50	86,2 ± 6,5	0	-
	Late	62	24	38,7 ± 6,2	38	61,3 ± 6,2	0	-
		<i>p</i>	< 0,05					

Note: The percentage is calculated relative to the number of relapses in the study group. *p* - the statistical significance of differences between forms of residual changes (according to the χ^2 criterion for arbitrary tables).

Table 5: Retrospective analysis of the development of relapses depending on compliance with chemotherapy regimens in patients with pulmonary tuberculosis, Abs. (M ± m,%).

Groups patients	Terms of development relapses	Total relapses	Compliance with chemotherapy regimens			
			Strictly observed		Short-term breaks noted	
			Abs.	M ± m, %	Abs.	M ± m, %
Total relapses (n = 120)	Early	58	15	25,9 ± 5,9	43	74,1 ± 5,9
	Late	62	13	20,9 ± 5,2	49	79,0 ± 5,2
		<i>p</i>	< 0,05			

Note: The percentage is calculated relative to the number of relapses in the study group. *p* - the statistical significance of differences between compliance with chemotherapy regimens (according to the χ^2 criterion for arbitrary tables).

Table 6: Retrospective analysis of the development of relapses depending on the presence of concomitant diseases, Abs. (M ± m,%).

Groups patients	Terms of development relapses	Total relapses	Accompanying illnesses							
			HIV-inf.		Diabetes mellitus		COPD		No comorbidities	
			Abs	M ± m, %	Abs.	M ± m, %	Abs.	M ± m, %	Abs	M ± m, %
Total relapses (n = 120)	Early	58	4	6,90 ± 2,9	8	13,8 ± 3,3	45	77,6 ± 4,8	1	1,72 ± 2,9
	Late	62	0	-	0	-	12	19,4 ± 4,0	50	80,6 ± 5,1
		<i>p</i>	< 0,05							

Note: The percentage is calculated relative to the number of relapses in the study group. *p* - the statistical significance of differences between accompanying illnesses (according to the χ^2 criterion for arbitrary tables).

It is well known that the majority of TB cases live in the countries of the Asian (55%) and African regions (30%). Significantly fewer cases of the disease are registered in the countries of the Eastern Mediterranean (7%), European (5%) and American (3%) regions. The top five countries with the highest incidence of TB are India (1.6-2.4 million), China (1.0-1.6 million), South Africa (0.38-0.57 million), Nigeria (0.37 - 0.55 million) and Indonesia (0.34-0.52 million). Only in India and China, do 35% of all new cases and relapses of tuberculosis in the world occur. More than a third of all newly diagnosed TB patients in Europe are detected in Russia [1,17].

The study of the reasons for the development of relapses makes it possible to timely identify a group of patients who need anti-relapse measures and prolongation of dispensary observation.

The developed procedure for dispensary observation, as well as the control algorithm and the planned preventive measures, can reduce the development of relapses and also contributes to the early diagnosis of relapses of the disease, which makes it possible to increase the effectiveness of treatment.

The data obtained make it possible to recommend the observation of persons from risk groups in institutions of the general medical network in strict accordance with the new algorithm.

Persons removed from the register of dispensary observation at TB Control Centers, regardless of the prevalence and severity of residual post-tuberculosis changes

in the lungs, as well as the presence or absence of concomitant diseases, should be under constant observation and undergo regular examination in order to start on time carrying out therapeutic and prophylactic and rehabilitation measures, to prevent their activation, to maintain long-term performance and quality of life in this category of patients.

Conclusion

Thus, the results of this observation revealed the occurrence of relapses within 10 years in 19.3% of cases. A retrospective analysis of the initial forms of the disease showed that relapses of pulmonary tuberculosis occurred more often in patients who had had fibrous-cavernous pulmonary tuberculosis, than in patients who had disseminated pulmonary TB and less often after suffering infiltrative pulmonary TB. Relapses of the disease occurred more often in men aged 19-44 years.

The results obtained indicate the development of relapses of pulmonary tuberculosis has a statistically significant dependence on the form of the initial disease, the presence of RPTCL, comorbid diseases such as HIV, diabetes mellitus, COPD and the regularity of taking anti-TB drugs. At the same time, it turned out that the social status of all patients with relapses corresponds to the level of poverty, which should also be taken into account.

Ethical points

This article does not require permission from the ethical committee of the Ministry of Health and Social Protection of the Population of Tajikistan, as there is written consent of the patients to be included in this study.



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