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ASSESSMENT OF TUBERCULOSIS RELAPSES DURING THE NEW CORONAVIRUS INFECTION PANDEMIC

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ABSTRACT. With the pandemic of a new coronavirus infection, the relevance of tuberculosis as a disease is not diminished. Against the backdrop of the pandemic, deaths from TB are predicted to increase for a number of reasons, one of them being an increase in early and late relapses, which are important in the epidemiology of TB. This is due to the fact that relapses of respiratory TB are much more severe and characterized by more severe clinical and radiological manifestations of the disease compared to the newly detected process. The causes of relapses remain poorly understood. During the study, the outpatient records of 122 patients who were observed in SPB PTD 8 during 2013–2022 were studied. The social status of the patients varied, allowing them to be divided into three groups: homeless persons, other socially maladapted persons with registration in the Central District, and socially adapted persons. The socially adapted comprised 44% and the socially disadapted 66%, including homeless people, who comprised 59% of all socially adapted and 33% of all those surveyed. The incarceration rate was 25%. There was a significant aggravation in the structure of diagnoses after relapse, with a shift towards forms of tuberculosis prone to progression and generalization, with a predominance of destructive forms and increase in drug resistance. Almost absent among relapses was a favourable form such as focal tuberculosis, which was in second place in the structure of diagnoses before relapse. Disseminated tuberculosis occupied this place in the structure of post relapse diagnoses. Among relapses in individuals who had had a new coronavirus infection, early relapses predominated. The leading place in structure of concomitant pathology in investigated patients with relapses belonged to diseases of cardiovascular system and chronic nonspecific lung diseases.

KEY WORDS: tuberculosis; tuberculosis relapses; new coronavirus infection; homeless persons.

ОЦЕНКА РЕЦИДИВОВ ТУБЕРКУЛЕЗА В УСЛОВИЯХ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ

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РЕЗЮМЕ. В условиях пандемии новой коронавирусной инфекции актуальность туберкулеза как заболевания не снижается. На фоне пандемии прогнозируется рост смертности от туберкулеза в силу ряда причин, одной из которых является рост числа ранних и поздних рецидивов, имеющих важное значение в эпидемиологии туберкулеза. Обусловлено это тем, что рецидивы туберкулеза органов дыхания протекают значительно тяжелее и характеризуются более тяжелыми клинико-рентгенологическими проявлениями заболевания по сравнению со впервые выявленным процессом. Причины рецидивов остаются недостаточно изученными. В ходе исследования были проанализированы амбулаторные карты 122 пациентов, наблюдавшихся в СПб ГБУЗ ПТД № 8 в течение 2013–2022 гг. Социальный статус пациентов был различен, что позволило разделить их на три потока: лица без определенного места жительства (БОМЖ), другие социально дезадаптированные лица, имеющие регистрацию в Центральном районе, и социально адаптированные лица. Социально адаптированные составили 44%, социально дезадаптированные — 66%, включая лиц БОМЖ, составлявших 59% от всех социально дезадаптированных и 33% от общего числа всех обследованных. В местах лишения свободы находилось 25% пациентов. Отмечалось значительное утяжеление структуры диагнозов после рецидива, со сдвигом в сторону склонных к прогрессированию и генерализации форм туберкулеза, с преобладанием деструктивных форм и ростом лекарственной устойчивости. Среди рецидивов практически отсутствовала такая благоприятная форма, как очаговый туберкулез, находившийся на втором месте в структуре диагнозов до рецидива. Данное место в структуре пострецидивных диагнозов занял диссеминированный туберкулез. Среди рецидивов у лиц, перенесших новую коронавирусную инфекцию, преобладали ранние рецидивы. Ведущее место в структуре сопутствующей патологии у обследованных больных с рецидивами принадлежало заболеваниям сердечно-сосудистой системы и хроническим неспецифическим заболеваниям легких.

КЛЮЧЕВЫЕ СЛОВА: туберкулез; рецидивы туберкулеза; новая коронавирусная инфекция; лица БОМЖ.

INTRODUCTION

The most significant epidemic of the beginning of the XXI century, which erupted in 2020 and continues to this day, is associated with the spread of the SARS-CoV-2 virus, which causes a new coronavirus infection, has not made less relevant the oldest chronic infectious disease, which has coexisted with humanity for millennia, but namely tuberculosis. The World Health Organization (WHO) documents emphasize: "Tuberculosis is preventable and curable. About 85% of people who develop TB disease can be successfully treated with a 4/6-month drug regimen; treatment has the added benefit of curtailing onward transmission of infection" [13]. However, the COVID-19 pandemic may reverse the progress achieved in the fight against tuberculosis [5]. WHO estimates that 10.6 million people worldwide fell ill with tuberculosis in 2021, an increase of 4,5% from 2020, and 1,6 million people died from tuberculosis (including 187,000 among HIV positive people). The burden of drug-resistant tuberculosis also increased by 3% between 2020 and 2021. This is the first time in many years an increase has been reported in the number of people falling ill with TB, including drug-resistant tuberculosis, as noted in a WHO press release dated October 2022 [35]. There is growing evidence that tuberculosis is closely associated with unfavorable outcomes from COVID-19, including an approximately two- to three-fold increase in patient mortality, as well as a 25% decrease in recovery rates [2, 22, 24, 29, 36].

According to mathematical modeling, the forecast for the period from 2020 to 2025 is that, as a direct impact of the COVID-19 pandemic, the incidence of tuberculosis could increase by more than 1 million new cases per year, and mortality by 1,4 million people [28, 34].

Tuberculosis has long been one of the top ten leading causes of death worldwide and is the third leading cause of death among women in the Russian Federation aged 25–34 years [18, 27, 33]. In our time, the new coronavirus COVID-19 infection, being in first place among the causes of mortality from infectious diseases, has pushed tuberculosis to second place in this list [3]. Against the backdrop of the pandemic, deaths from TB are predicted to increase for a number of reasons. These include the following:

- delayed detection due to low patient attendance because of anti-epidemic measures against COVID-19 [26];
- temporary conversion of TB healthcare facilities into COVID-19 hospitals;
- refusal of patients with suspected and confirmed tuberculosis to contact phthisiatricians due to fear of a new coronavirus infection;
- activation (relapses) of tuberculosis infection in persons who have had tuberculosis or have latent tuberculosis infection [19];
- the challenge of diagnosing TB infection, since the diagnosis of tuberculosis, verified under normal conditions only in 80% of cases, can be even more difficult during a pandemic period [7, 31, 32];
- widespread use of immunosuppressive therapy in the treatment of new coronavirus infection, which leads to reactivation of tuberculosis;
- the difficulty detecting tuberculosis due to massive lung lesions during COVID-19, masking the initial manifestations of tuberculosis; in turn, latent or active tuberculosis may be a risk factor for SARS-CoV-2 infection [23]; according to foreign researchers, in approximately 20% of cases, COVID-19 occurred in patients with post-tuberculosis changes detected by X-ray [30].

The combination of COVID-19 and tuberculosis is registered in 0,3–8,3% of cases worldwide, more often in high tuberculosis burden countries (China and India) [19].

Since both new coronavirus infection and tuberculosis are infectious diseases characterized primarily by damage to the respiratory system, they can cause its dysfunction. The cellular immune response to *Mycobacterium tuberculosis* and SARS-CoV-2 is also similar, one of the important characteristics of which is the predominance of specific phagocytes and CD4+ T-lymphocytes. Chronic stimulation with SARS-CoV-2 virus antigens can cause T cell exhaustion in a person with a pre-existing tuberculosis infection, active or latent [25].

The latest version of the temporary guidelines Ministry of Health of the Russian Federation on the prevention, diagnosis and treatment of COVID-19 noted: “The consequences of infection with COVID-19 in patients with tuberculosis are not completely clear. There are scientific publications that the presence of tuberculosis infection, including latent, aggravates the course of COVID-19 <...> Tuberculosis can occur before, simultaneously or after COVID-19” [4].

Relapses in tuberculosis are important in the epidemiology of this chronic infectious disease. The causes of relapse remain poorly understood. The views of different researchers regarding the influence of certain factors on the development of relapse vary. A number of authors give priority to concomitant diseases in the reactivation of tuberculosis, others prefer the presence of large residual changes in the lungs [10, 12, 21]. And finally, many clinicians pay attention to the inferiority of the main course of chemotherapy for the first disease, believing that relapses of pulmonary tuberculosis more often occur in patients who received inadequate initial treatment [8]. However, the possibility of reinfection as a result of exogenous superinfection and the development of a new tuberculosis episode remains unexplored. Currently, clinical and social risk factors for pulmonary tuberculosis recurrence are being actively studied. Reactivation of tuberculosis is 1,8 times more likely to occur in disadvantaged groups and 2 times more often in patients suffering from chronic alcoholism [17]. The most significant risk factors for the occurrence of relapses of tuberculosis are: destructive forms of tuberculosis, inadequate therapy, late detection of the disease, males, concomitant pathology (HIV infection), incarceration [11].

The concept of relapse of pulmonary tuberculosis was officially formulated at the VII All-Union Congress of Phthisiologists (1966). The need to adopt this term arose in connection with the widespread use of specific chemotherapy and surgical treatment methods and caused by them loss of one of the characteristic features of tuberculosis — the undulation of the course, as well as with the emergence of the concept of “clinical recovery” [1]. In Russian literature,

the definition of "early" (up to five years after removing from the register) and "late" relapses were given in the works of V.L. Einis (1954) and A.E. Rabukhin (1957) [16, 20]. Until the mid-1990s, the leading role in the pathogenesis of secondary tuberculosis was assigned to endogenous reactivation of old foci (mainly in the lungs and lymph nodes) [1].

Relapses of respiratory TB are much more severe and are characterized by more severe clinical and radiological manifestations of the disease, reflected by severe or moderate intoxication syndrome, more often become chronic and lead to higher mortality compared to the newly detected process. Treatment of this category of persons turns out to be longer, more expensive and less effective [8]. Patients with relapses of pulmonary tuberculosis pose a great epidemic risk due to the massive bacterial excretion.

AIM

The aim of the present study an assessment of the X-ray picture of patients with relapses of tuberculosis in the work of a radiologist at the TB dispensary in a metropolis in the context of a new coronavirus infection.

MATERIALS AND METHODS

During the study, outpatient records (form No. 025/y) of 122 patients with relapses of tuberculosis, who were observed in St. Petersburg State Budgetary Institution of Health "TB Dispensary № 8" during 2013–2022, were examined. (selectively, part of the flow attributable to the work area of one radiologist), of which 84 were men and 38 women aged from 18 to 70 years. Among the patients there were both those who did not have COVID-19 (both before and during the pandemic) — 97 people (79,5%), and those who were sick with the new coronavirus infection — 25 people (20,5%).

The received information was entered into an electronic database using the software Microsoft Office Excel 2016. The work analyzed qualitative characteristics, which were presented in the form of absolute numbers (n) and extensive indicators (%). When performing interval assessments of extensive indicators, the 95% confidence interval (95% CI) was calculated using the Wilson method. Statistical processing of the results was carried out using analytical software IBM SPSS Statistics (version 20.0) for Windows. The reliability of differences between qualitative dichotomous characteristics in dependent samples was assessed when constructing contingency tables using the McNemar's test; a critical value of the significance level of $p \leq 0,05$ was used.

RESULTS AND ITS DISCUSSION

When analyzing the data obtained, the social status of the patients was first examined. The social status of the patients varied, allowing them to be divided into three groups: homeless persons, other socially maladapted persons with registration in the Central District, and socially adapted persons. The socially adapted comprised 44% and the socially disadapted 66%, including homeless people, who made up 59% of all socially maladjusted people and 33% of the total number of all those surveyed. The incarceration rate was 25% (80% of them were homeless people), and during the initial examination, half of the patients mentioned presence in a place of deprivation of liberty (which was reflected in the outpatient record), for the rest it was clarified later, by taking an anamnesis by a radiologist [6].

83% of those surveyed (including homeless people living with cohabitants or relatives, as well as renting housing), had permanent accommodation (own or rented) while 17% did not have any housing and lived in a night shelter and in shelters (only homeless persons). 65% had a permanent job. Those unemployed due to dismissal not on their own volition (enterprise bankruptcy, including during a pandemic) or layoffs were classified as socially maladapted, even if the earnings of their spouse or parents allowed them to lead an acceptable way of life and not to lack food. The number of pensioners was 10% (non-working pensioners — 2%), disabled people — 5% (disability in all cases was not related to tuberculosis). Among the patients with relapses were persons under the age of 25 years who had suffered forms of primary tuberculosis in adolescence (primary tuberculosis complex — 1 person, tuberculosis of the intrathoracic lymph nodes, complicated by foci of dropout into the lung tissue — 2 persons) and were removed from the register. All of these individuals developed infiltrative tuberculosis during relapse.

The majority of patients (97%) suffered from pulmonary tuberculosis, generalized tuberculo-

sis was found in 2% of cases, and one patient had extrapulmonary tuberculosis. All patients underwent a complex examination, including radiological examination, in particular chest X-ray and computed tomography of the chest organs (chest CT). In the examined groups, early relapses predominated, accounting for 82% of cases, while in the group of homeless people they amounted to 100%. The structure of clinical forms after relapses in the groups surveyed is presented in Figures 1 and 2.

As can be seen from Figure 1, among the diagnoses of patients with newly diagnosed tuberculosis, infiltrative tuberculosis had the largest share — 51%, focal tuberculosis was in second place (16%), tuberculosis of the intrathoracic lymph nodes and disseminated tuberculosis were in third place (9 and 8%, respectively). Destruction was observed in 44% of cases. After the cure, the residual changes of various types (fibrous, fibrous-focal, bullous-dystrophic, the presence of calcifications in the lung tissue and lymph nodes, pleuropneumosclerosis, pleural calcification) and extent (from one or two segments to a lobe or several lobes with unilateral or bilateral lung lesions) persisted.

Structure of diagnoses after relapses was as follows. As before, infiltrative tuberculosis, whose share was 65%, was in first place in the diagnosis structure. In second place was disseminated tuberculosis (17%), in third place was generalized tuberculosis (8%), and focal tuberculosis was found in 2% of cases. Destructive forms accounted for 70% of all those surveyed. Caseous pneumonia, cirrhotic tuberculosis and cavernous tuberculosis were not noted either as a primary

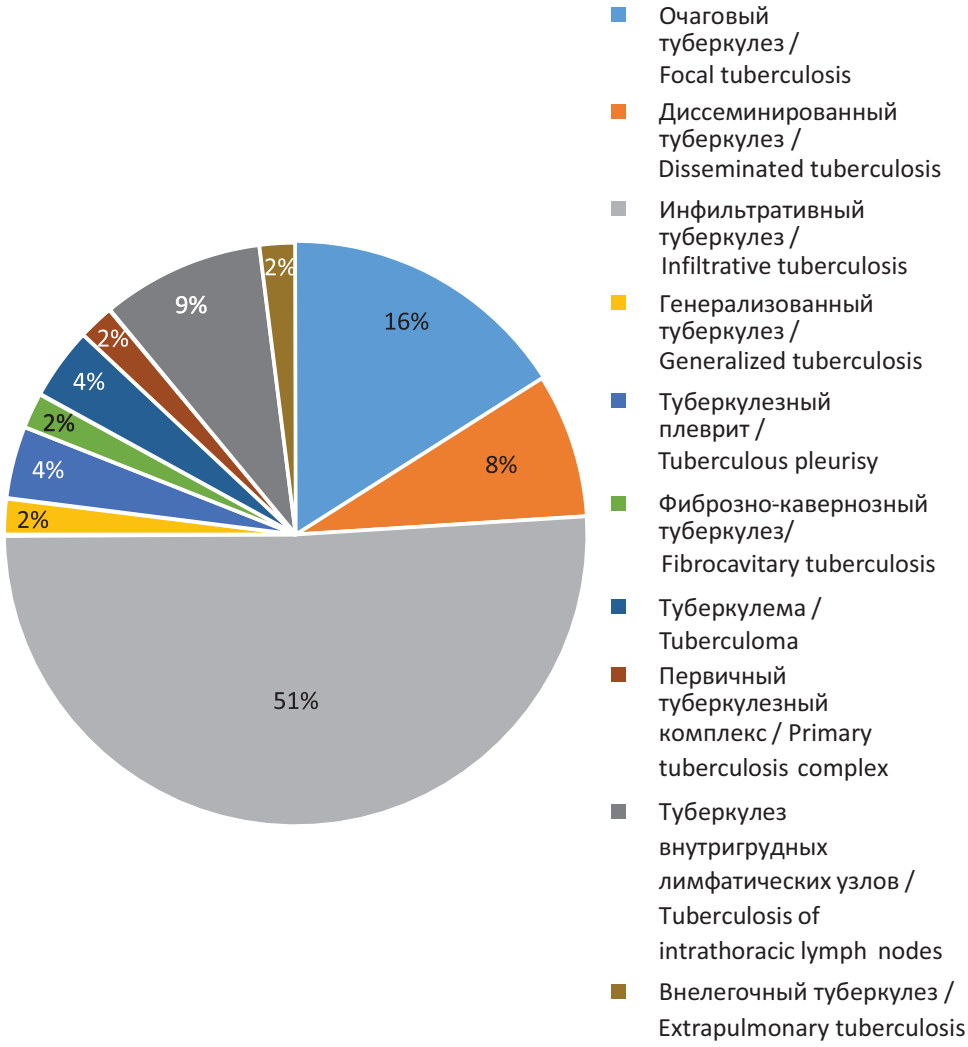

Fig. 1. Structure of diagnoses of newly diagnosed tuberculosis

Рис. 1. Структура диагнозов при впервые выявленном туберкулезном процессе

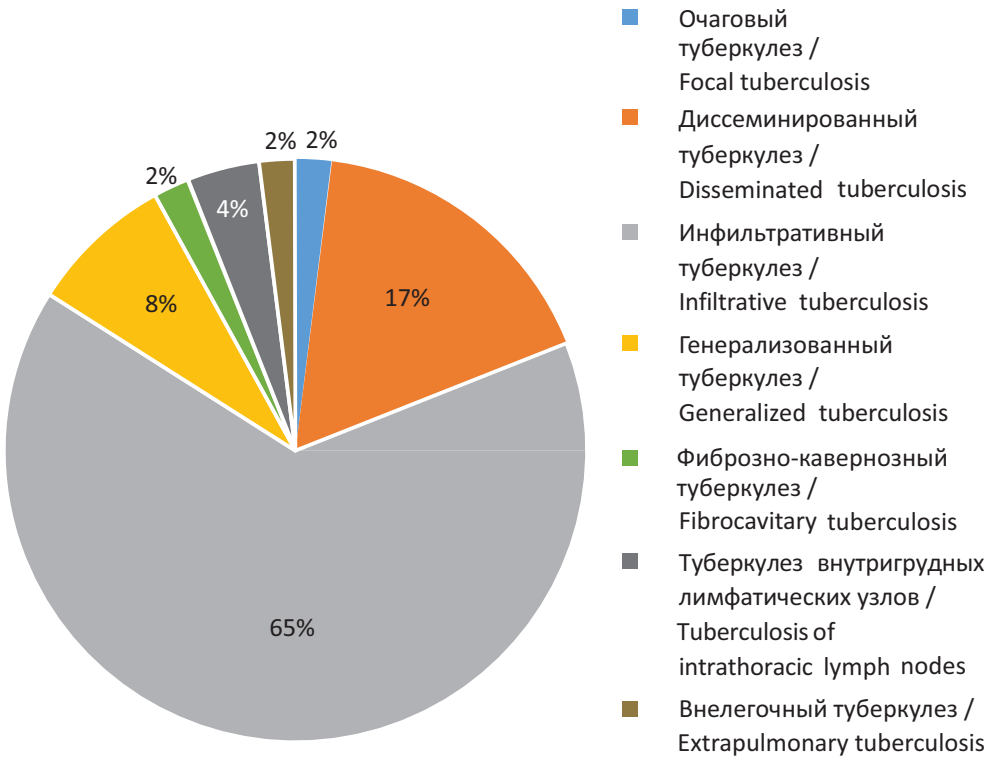

Fig. 2. Structure of diagnoses after relapses of tuberculosis

Рис. 2. Структура диагнозов при рецидиве

diagnosis or as a recurrence. In one person, a relapse of disseminated tuberculosis with decay and excretion of bacilli was diagnosed post-mortem (heroin-dependent, HIV-positive, without antiretroviral therapy (ART)); upon relapse, a diagnosis of generalized tuberculosis was established.

In 65% of patients, when the primary diagnosis was made, a limited TB process was detected within one lobe of the lung, a widespread process was detected in the remaining 35%, while 80% of them had unilateral localization, 20% had bilateral lung lesion. During relapse, the prevalence of the process in patients, as a rule, increased both due to the appearance of foci of dropout in the affected or opposite lung, and due to the development of disseminated and generalized forms. In the case of relapses, a limited TB process within one lobe of the lung was detected in 25% of patients, a widespread process was detected in 75%, while 60% of them had unilateral localization, and 40% had bilateral lung damage. The X-ray picture was characterized by the presence of exudative or productive foci, dissemination, infiltration of lung tissue with focal, limited or subtotal darkening syndromes, the presence of a decay cavity or cavities, cavity formation, a decrease in the volume of part of the lung, mediastinal widening, and signs of unilateral hydrothorax.

Drug resistance at primary diagnosis was determined in 24% of patients (multiple drug resistance (MDR)) — 18%, broad drug resistance (BDR) — 6%), and after relapse — in 29% (MDR — 17%, BDR — 12%).

Table 1 shows the distribution of the frequency of *M. tuberculosis* isolation with BDR in patients before and after relapse of tuberculosis.

In patients with tuberculosis, strains of *M. tuberculosis* with BDR were detected in 5.7% (95% CI 2.8–11.4) of cases before relapse and in 11.5% (95% CI 6.9–18.3) of cases after relapse of the disease. To assess the impact of the development of TB relapse on the frequency of *M. tuberculosis* isolation with BDR, two hypotheses were formulated: H_0 — TB relapse does not significantly affect the frequency *M. tuberculosis* of isolation with BDR, H_1 — TB relapse significantly affects the frequency of *M. tuberculosis* isolation with BDR. When calculating the McNemar test, the value of the statistic χ^2=7.0 exceeded the critical value of 3.8 for a given number of degrees of freedom

Table 2

Distribution of the frequency of *M. tuberculosis* isolation with broad drug resistance (BDR) in patients depending on the development of tuberculosis relapse

Таблица 1

Распределение частоты выделения *M. tuberculosis* с широкой лекарственной устойчивостью у пациентов в зависимости от развития рецидива туберкулеза

		After the tuberculosis relapse / После рецидива туберкулеза		
		Presence of BDR (n) / Наличие ШЛУ (n)	**Absence of BDR (n) / Отсутствие ШЛУ (n)**	**Total / Всего**
Before the tuberculosis relapse / До рецидива туберкулеза	Presence of BDR (n) / наличие ШЛУ (n)	7	0	7
	Absence of BDR (n) / отсутствие ШЛУ (n)	7	108	115
	Total / Всего	14	108	122

df=1, significance level p=0.009. This allows us to accept hypothesis H_1 and conclude that there is a statistically significant increase in the frequency of *M. tuberculosis* isolation with BDR in patients after relapse of tuberculosis.

Structure of diagnoses of concomitant pathology. One of the important factors contributing to the development of relapse of respiratory TB is concomitant pathology [1]. The leading place in the structure of concomitant pathology in the investigated patients with relapses belonged to diseases of the cardiovascular system and chronic nonspecific lung diseases (51 and 49%, respectively; in the group of socially adapted patients these values were equal to 66 and 78%, respectively, and in the group of maladapted individuals they were 20 and 48%). Moreover, these socially disadapted persons had concomitant pathology that was absent in socially adapted patients (viral hepatitis — 10%, drug addiction — 5%, alcoholism — 8%). HIV infection was observed in 5%. Of the HIV-positive patients with recurrent tuberculosis, none received ART regularly; There was no ART in 25% of people with HIV. Patients with a combination of HIV infection and tuberculosis are observed in a special center to care for such persons, and therefore they less often come to the attention of the TB dispensary.

Of all patients, 20.5% (25 people) suffered a new coronavirus infection, among them socially adapted ones prevailed (88%). A larger proportion of socially adapted individuals was associated with a more attentive attitude to their health and independent access to PCR testing; in socially maladjusted individuals, the disease was detected after hospitalization with 25–50% lung damage and above. All patients who had a new coronavirus infection were examined, including a computed tomography scan of the chest, of which 65% were hospitalized. Lung lesions after coronavirus infection were distributed as follows: the absence of signs of viral pneumonia on chest CT was noted in 12% of patients, a characteristic picture of areas of compaction of the lung tissue by type “ground-glass opacity” and interstitial changes, occupying up to 25% of the lung tissue, was observed in 46% patients, damage to 25–50% of lung tissue — in 34%, damage to 50–75% of lung tissue — in 8% of patients. Lesions of more than 75% were not found among the examined group. Early relapses were predominated among those who had a new coronavirus infection (earlier than 5 years after removing from register at the TB dispensary) — 78%. There were 24% of patients with late relapses, all of them were socially adapted, 83% of them were women who went to the tuberculosis dispensary on their own, concerned that the new coronavirus infection would affect their health. Large residual changes were occured only in 35% of all individuals who had a relapse after suffering a new coronavirus infection, the rest had small residual changes. In the structure of diagnoses after relapses, infiltrative tuberculosis prevailed (80% had infiltrative tuberculosis, 16% had focal tuberculosis, 4% had generalized tuberculosis).

According to the results of the study, it turned out that there was a significant aggravation in the structure of diagnoses after relapses, with a shift towards forms of tuberculosis that are prone to progression and generalization, with a predominance of destructive forms. The share among diagnoses during relapses of such a favourable form such as focal tuberculosis was minimal (2%), although it was in second place in the structure of primary diagnoses (16%). In the structure of diagnoses after relapses, disseminated tuberculosis took second place. Diagnoses that were not among the primary ones (before relapse) appeared, such as generalized and fibrocavitary tuberculosis. This corresponds to studies data showing that the clinical picture of relapses of pulmonary tuberculosis is much more severe than with newly detected processes [15]. There is an aggravation in the structure of diagnoses due to an increase in drug-resistant forms after relapse. It is noteworthy that among the cases reviewed, 2% were patients who developed a relapse after surgery. This confirms the prevailing opinion in national phthisiology that resection operations are a highly effective method of treatment in case of limited and local pulmonary tuberculosis, [14]. An alarming fact is that among the patients with relapses there were people under the age of 25 years, cured of primary tuberculosis in adolescence, who developed forms of secondary tuberculosis during relapse. All these persons were classified as socially maladapted and came from families with a low general culture and a difficult social and living status, which confirms the role of social and epidemiological disadvantage in their families in the development of the unfavorable course of tuberculosis [9]. With a new coronavirus infection, relapses developed both in the presence and absence of viral damage to the lung tissue, determined by chest CT scan. Identification of relapses in people who have had a new coronavirus infection was often associated with personal responsibility and concern for their own health in socially adapted patients, while socially maladjusted people who were diagnosed with tuberculosis were examined in a hospital during hospitalization for a new coronavirus infection in moderate and severe condition.

CONCLUSION

Thus, the combination of tuberculosis and new coronavirus infection poses certain difficulties at the outpatient stage of TB service in relation to identifying relapses in people with cured tuberculosis. The heavier structure of diagnoses during relapse of tuberculosis, the prone to generalized forms, forms with decay of lung tissue, resistance to anti-tuberculosis drugs, and the development of fibrocavitary tuberculosis becomes even more relevant against the background of a new coronavirus infection as an aggravating factor. Active preventive examination of persons with cured tuberculosis who have suffered a new coronavirus infection is necessary to exclude relapses of tuberculosis infection in them, with the joint work of the polyclinic and the anti-tuberculosis dispensary.

ADDITIONAL INFORMATION

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