Stela KULCIŢKAIA¹, Vasile POPA²,
Igor IVANES¹, Alina PREPELIŢA³
¹Pneumology and allergology discipline, Department of Internal
Medicine *Nicolae Testemitanu* PI State University
of Medicine and Pharmacy
²PMSI Municipal Clinical Hospital of Phthisiopneumology
³PMSI Clinical Hospital for Infectious Diseases Toma Ciorbă

ASPECTS OF CO-INFECTION WITH VIRAL HEPATITIS IN TUBERCULOSIS PATIENTS

Summary

This study focuses on the impact of viral hepatitis (VH) co-infection on patients with tuberculosis (TB), specifically regarding liver impairment and treatment outcomes. The research is a descriptive, retrospective analysis of patients diagnosed with pulmonary TB and VH, who were hospitalized for treatment from 2019 to 2021. A comparison was made between the parameters of the study group (91 patients with pulmonary TB and VH) and the control group (113 patients with pulmonary TB but no VH). The odds ratio (OR) was calculated to determine the probability of developing TB in the presence of risk factors, with a 95% confidence interval (CI) used to assess precision. Data analysis was performed using Microsoft Office 2007 Excel. The study revealed a significant predominance of males in patients with pulmonary TB and VH, with the most common age range being between 30 and 50 years. Infiltrative pulmonary TB was the most frequent diagnosis, and microbiological confirmation of TB remained a challenge. The occurrence of complications was notably high in patients with pulmonary TB and VH. The study also observed a high rate of retreatment and cases of death among patients with TB and VH as treatment outcomes. Overall, the research provides valuable insights into the severity, progression, and treatment response of TB patients with co-existing viral hepatitis.

Keywords: *tuberculosis, viral hepatitis, treatment*

Rezumat

Aspectele coinfecţiei cu hepatite virale la pacienţii cu tuberculoză

Acest studiu se concentrează asupra impactului coinfecţiei cu hepatită virală (HV) asupra pacienţilor cu tuberculoză (TB), în special în ceea ce priveşte afectarea ficatului şi rezultatele tratamentului. Cercetarea este o analiză descriptivă, retrospectivă a pacienţilor diagnosticaţi cu TB pulmonară şi HV, care au fost spitalizaţi pentru tratament în perioada 2019-2021. Parametrii grupului de studiu (91 de pacienţi cu TB pulmonar şi HV) au fost comparaţi cu cei ai grupului de control (113 pacienţi cu TB pulmonar, dar fără HV). Raportul probabilităţilor (RP) a fost calculat pentru a determina potenţialitatea dezvoltării TB în prezenţa factorilor de risc, cu un interval de încredere de 95% (IC) utilizat pentru a evalua precizia. Analiza datelor a fost realizată folosind Microsoft Office 2007 Excel. Rezultatele studiului au indicat o predominanţă semnificativă a sexului masculin în rândul pacienţilor cu TB pulmonară şi HV, cea mai frecventă grupă de vârstă fiind între 30 şi 50 de ani. TB pulmonară infiltrativă a fost cel mai frecvent diagnostic, iar confirmarea microbiologică a TB a rămas o provocare. Incidenţa complicaţiilor a fost semnificativ de mare la pacienţii cu TB pulmonar şi HV. Studiul a evidenţiat, de asemenea, o rată ridicată de retratament şi cazuri de deces la pacienţii cu TB şi HV ca rezultate ale tratamentului. În ansamblu, cercetarea furnizează perspective valoroase asupra severităţii, evoluţiei şi răspunsului la tratament al pacienţilor cu TB şi hepatită virală concomitentă.

Cuvinte-cheie: *tuberculoză, hepatită virală, tratament*

Резюме

Аспекты сопутствующей инфекции вирусными гепатитами у больных туберкулёзом

Данное исследование сосредоточено на изучении влияния сопутствующей инфекции вирусным гепатитом (ВГ) на пациентов с туберкулезом (ТБ), в частности на повреждение печени и результаты лечения. Исследование является описательным, ретроспективным анализом пациентов, у которых был диагностирован легочный ТБ и ВГ, и которые госпитализировались для лечения в период с 2019 по 2021 годы. Было проведено сравнение параметров группы исследования (91 пациент с легочным ТБ и ВГ) с параметрами контрольной группы (113 пациентов с легочным ТБ без ВГ). Отношение вероятностей (ОВ) было рассчитано для определения вероятности развития ТБ при наличии факторов риска, с использованием 95% доверительного интервала (ДИ) для оценки точности. Обработка данных была выполнена с использованием Microsoft Office 2007 Excel. Исследование выявило значительное преобладание мужчин среди пациентов с легочным ТБ и ВГ, наиболее распространенный возрастной диапазон составляет от 30 до 50 лет. Наиболее часто устанавливаемым диагнозом является инфильтративный легочный ТБ, и микробиологическое подтверждение ТБ остается сложной задачей. Частота осложнений у пациентов с легочным ТБ и ВГ оказалась высокой. Также было отмечено высокое количество случаев рецидива и летальных исходов среди пациентов с ТБ и ВГ после завершения лечения. В целом, данное исследование предоставляет ценные сведения о тяжести, динамике и результативности лечения пациентов с туберкулезом в сочетании с вирусным гепатитом.

Ключевые слова: *туберкулез, вирусный гепатит, лечение*

Introduction

Tuberculosis remains a significant medical and social problem, characterized by its widespread prevalence, increasing number of patients, high disability and mortality rates, as well as the toxicity of antituberculosis therapy. Among the common comorbidities observed in tuberculosis (TB) patients, liver damage has been frequently noted [1, 4]. Viral hepatitis in TB patients can elevate the risk of hepatotoxicity, thereby impacting the effectiveness of antituberculosis treatment.

Standard therapy for active TB is associated with several notable side effects, with drug-induced liver injury (DILI) being the most severe, carrying a mortality rate of up to 5% [7, 11]. The incidence of DILI resulting from antituberculosis treatment has been reported variably, ranging between 2% and 28%. Factors such as HLA phenotype and ethnicity have been identified as influencers of an individual's risk for a hepatotoxic drug reaction [5]. The clinical presentation of DILI ranges from transient mild elevation of liver enzymes to fulminant liver failure. Typically, DILI is defined as an increase in serum alanine transaminase (ALT) levels greater than 3 or 5 times the upper limit of normal, with or without symptoms of acute hepatitis, respectively [10]. Understanding the mutual influence of two infections, namely pulmonary TB and viral hepatitis, is of great interest due to their frequent co-occurrence and the liver's crucial role in immune response, detoxification, and the metabolism of anti-tuberculosis drugs. Persistent viral infections can introduce changes in homeostasis, metabolic and immune reactions, leading to new qualitative characteristics of tuberculosis [2, 13].

In recent years, there has been an increase in co-infections involving various viruses. According to the World Health Organization (WHO), approximately 240 million people worldwide are chronically infected with hepatitis B virus (HBV) [20, 21]. The estimated global prevalence of hepatitis C virus (HCV) infection is around 3%, with 170 million individuals being chronic carriers. European countries report a prevalence of HCV in the general population ranging from 0.5% to 2%. Effective therapies exist for both HBV and HCV, particularly when diagnosed before advanced liver disease occurs. Early detection and treatment are crucial for minimizing the health burden associated with chronic HBV and HCV infections [12, 13]. Viral hepatitis, particularly those transmitted parenterally, poses a significant public health challenge for the Republic of Moldova, characterized by high morbidity, mortality, and disability rates due to chronic infection. In the Republic of Moldova, approximately 30,000 cases of chronic hepatitis B virus infection and 3,000 cases of liver cirrhosis caused by the same etiology are reported. Moreover, individuals infected with the hepatitis B virus have a high potential for coinfection with the hepatitis D virus. In our country, around 15,000 people are registered with chronic hepatitis C virus infection and approximately 2,500 with liver cirrhosis caused by this virus. Statistical data from 2019 in the Republic of Moldova show a total of 3,523 new cases of viral hepatitis, including 733 (20.8%) cases of acute viral hepatitis and 2,790 (79.2%) cases of chronic forms.

According to international institutions, the Republic of Moldova ranks first in the world for mortality from cirrhosis of the liver, with 71.2 deaths per 100,000 population [12].

Patients with HBV and/or HCV who develop TB are at a higher risk of both pulmonary and extra-pulmonary tuberculosis. Extra-pulmonary forms, especially tuberculous peritonitis, and disseminated tuberculosis, are more common in those with viral hepatitis. Additionally, the bacterium responsible for tuberculosis is more virulent, and the risk of developing multidrug-resistant tuberculosis is elevated [12].

Viral hepatitis exhibits a higher incidence in risk groups, including individuals with social factors associated with TB such as HIV infection, alcoholism, smoking, and drug use [22]. These comorbidities contribute to liver damage and can increase the hepatotoxicity of antituberculosis drugs, potentially affecting the successful treatment of TB patients [1, 11].

Directives aimed at reducing the burden of TB in the Republic of Moldova are established within the National Tuberculosis Control Program (PNCT) for the years 2021-2025, the World Health Organization Strategy "End TB" for the years 2015-2035, and other national and international documents in the field [16, 18].

The COVID-19 pandemic caused by the "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) has had a significant impact on public health services worldwide due to its rapid global spread, severe disease presentation, high mortality rate (resulting in 4 million deaths), and the strain it places on healthcare systems. The impact of COVID-19 on TB services has been extensively described, with most countries experiencing a reduction in the number of diagnosed and managed TB cases due to limited access, delayed diagnosis of advanced forms, and overwhelmed health services. According to data from the WHO, TB cases decreased by 18% between 2019 and 2020, from 7.1 to 5.8 million cases. Furthermore, there is a projected 20% increase in TB deaths over the next five years as a result of the COVID-19 pandemic [3, 14].

In recent years, despite declining epidemiological indicators such as TB incidence and mortality in the Republic of Moldova, treatment success remains problematic [16, 18]. This **study aims** to analyze the evolution of pulmonary tuberculosis in patients with viral hepatitis.

Materials and Methods. To investigate the structure, features, and clinical manifestations of patients with pulmonary tuberculosis under current epidemiological and socioeconomic conditions, with the goal of improving effective tactics for detection, evidence-based treatment, and monitoring, we

analyzed 91 cases of patients diagnosed with pulmonary tuberculosis and viral hepatitis.

This paper presents a retrospective observational descriptive study conducted between January 1, 2019, and December 31, 2021, on hospitalized patients diagnosed with pulmonary tuberculosis (confirmed and unconfirmed bacteriologically) and viral hepatitis who were admitted for treatment at the Public Medical-Sanitary Institution Municipal Clinical Hospital Phthisiopneumology mun. Chisinau during the years 2019-2021.

The analysis of primary data involved calculating the simple arithmetic mean using the formula, which represents the average value obtained by summing the individual values in a homogeneous community and dividing it by the total number of cases studied [28].

Statistical processing was performed by calculating the odds ratio (OR) or probability ratio (PR). OR was calculated for qualitative parameters, considering them as risk factors for TB. A control group of 113 patients with pulmonary TB but without viral hepatitis was used to determine the OR for the probability of developing TB in the presence of a risk factor. The 95% confidence interval (CI) was used to estimate the precision of the OR, where a larger CI indicates a lower level of precision, while a smaller CI indicates higher precision. An OR is considered statistically true if the CI does not include 1. An OR of 1 implies that the exposure does not affect the odds of the outcome, an OR greater than 1 suggests that the exposure is associated with higher odds of the outcome, and an OR less than 1 indicates that the exposure is associated with lower odds of the outcome. OR calculations were performed using Microsoft Office 2007 Excel software.

Results and Discussion

In this study, we examined the gender affiliation of the 91 patients included, finding that a majority of them were male (79%), while only a small percentage were female (21%). The main group consisted mostly of men, with a male-to-female ratio of 4.1:1. By calculating the odds ratio (OR) for the epidemiological association force, we determined that the risk of men with TB and HV was 3.105 times higher compared to females, indicating an increased risk for males in developing TB when viral hepatitis is present.

The literature indicates a concerning trend of tuberculosis "rejuvenation" in recent decades, with young and active individuals becoming affected by the disease. We analyzed the age of the patients in the study and found that those between 30 and 50 years old predominated, indicating that they were young and capable of working. This age group also

had a higher prevalence of risk factors for both TB and viral hepatitis, such as drug use, alcohol abuse, smoking, and detention. Calculating the odds ratio (OR) in different age groups, we observed that the risk of exposure was lower in those below 50 years old (OR = 0.4, 95% CI = 0.21-0.83) and higher in those above 51 years old (OR = 2.38, 95% CI = 1.2-4.7) compared to patients without viral hepatitis.

The place of residence is known to influence the frequency of various diseases, including tuberculosis. We analyzed the domicile of the patients and found that those living in the city had a higher likelihood of having both TB and HV compared to those in the suburbs. However, after calculating the odds ratio (OR) for the epidemiological association force, we determined that the risk was not statistically significant, as the confidence interval included 1 (OR = 0.5, 95% CI = 0.33-1.064). Therefore, the association between domicile and the presence of TB and HV was not supported by statistical evidence.

Social status plays a crucial role in determining the risk group for tuberculosis, as it reflects the level of immunocompetence. Officially employed individuals are more likely to have a stable immunocompetent status due to better material resources for adequate nutrition. Among the patients included in the study, only 30% were officially employed, while the majority had unsatisfactory material income or were retired or disabled. Calculating the odds ratio (OR), we found that the risk was 3.734 times higher in unemployed patients diagnosed with TB and HV compared to those with employee status (95% CI = 1.48-9.39).

In terms of clinical forms of tuberculosis, infiltrative pulmonary TB was the most frequently diagnosed among patients with viral hepatitis as a comorbidity, followed by fibro-cavitary TB, tuberculous pleurisy, disseminated TB, and nodular pulmonary TB. These findings align with the known frequency of clinical forms of TB diagnosed in adults. The type of TB case is epidemiologically significant, as re-treatment cases pose an increased risk of transmitting the infection and developing mycobacterial resistance. New cases of pulmonary TB reflect the quality of medical service and indicate the detection and adherence of patients to treatment. In our study, new TB cases accounted for the majority (62%) of the cases, followed by TB recurrence (20%), cases "lost from surveillance" (6.6%), and therapeutic failure (3.3%).

Radiological examination plays a crucial role in assessing the extent and phase of the inflammatory process in lung pathology. Among patients with pulmonary TB and viral hepatitis, an extended process involving three or more lung segments was observed in the majority (76%) of cases, while limited pulmo-

nary localization (1-2 lung segments) was present in a smaller percentage (24%). Unilateral involvement was more common (91%) than bilateral involvement (9%). The presence of destruction and dissemination components indicated advanced and late-detected cases, highlighting potential deficiencies in the detection and adherence to treatment.

Complications were observed in patients with TB and HV, with respiratory failure being the most common (39.6%), followed by hemoptysis (19.8%), pleurisy (8.8%), and spontaneous pneumothorax (3.3%). These complications further emphasize the severity and impact of these dual infections on the patients.

The study confirmed that TB is an infectious and contagious disease caused by *Mycobacterium tuberculosis*. It is transmitted aerogenously, primarily from infectious pulmonary TB patients to susceptible individuals. The risk of developing active tuberculosis in infected individuals is approximately 10% throughout their lives. Several risk factors contribute to the development of the disease. Among the patients with TB and HV, 91% had established risk factors for TB. After calculating the odds ratio (OR), we concluded that the risk was 2.296 times higher in the groups of people belonging to the risk groups for TB compared to those who did not belong to the risk groups.

Contact with other pulmonary TB patients is a significant risk factor for TB transmission. In our study, 64% of the patients had obvious contact with other TB patients, with occasional contact reported in 43% of cases and permanent contact in 21% of cases, mainly within the family or household.

Migration is another notable risk factor for TB, as it involves changes in living and working conditions that can lead to immunodeficiency. Among the patients included in the study, 36% reported being migrants, having worked in the Russian Federation for various durations. The odds ratio (OR) for migrants developing TB and HV was 2.524 times higher compared to non-migrants (95% CI = 1.37-4.64).

Detention is recognized as a risk factor for TB due to overcrowding, inadequate infection control, psycho-emotional stress, poor nutrition, substance abuse, and smoking. In our study, 46.2% of the patients had a history of detention, which significantly increased their risk of developing TB and HV. The odds ratio (OR) for TB patients with a history of detention was 7.94 times higher compared to those without a history of detention (95% CI = 3.76-16.762).

Drug use (UD) is also known to cause significant immunodeficiency, increasing the risk of developing TB. Among the patients with TB and HV, 15.4% reported drug use, and the odds ratio (OR) for drug

users developing TB and HV was 20.3 times higher compared to non-drug users (95% CI = 2.6-15.804).

Smoking is a prevalent risk factor for various diseases, including TB. In our study, 96.7% of the patients diagnosed with TB and HV were smokers. The odds ratio (OR) for smokers developing TB and HV was 5.929 times higher compared to non-smokers (95% CI = 1.69-20.73).

Alcohol abuse is also considered a significant risk factor for TB, as it leads to immunodeficiency. Among the patients in our study, 55% reported occasional or abusive alcohol use. The odds ratio (OR) for alcohol abusers developing TB and HV was 3.087 times higher compared to non-abusers (95% CI = 1.726-5.521).

The study aimed to analyze the association between tuberculosis (TB) and viral hepatitis (HV) in a group of patients. The gender affiliation of the patients was assessed, with a higher prevalence of men (79%) compared to women (21%). The risk of men with TB and HV was found to be 3.105 times higher compared to females. The age analysis revealed a predominance of young people (30-50 years) among the patients, who are also more likely to have other risk factors such as drug use, alcohol abuse, smoking, and detention. The risk of TB and HV was found to be higher in patients above 51 years of age compared to those below 50 years. The domicile analysis showed a higher likelihood of TB and HV in patients living in the city compared to those in the suburbs, although the statistical significance was not established. The social status analysis revealed that the risk of TB and HV was 3.734 times higher in unemployed patients compared to those who were employed. Among the clinical forms of TB, infiltrative pulmonary TB was the most frequently diagnosed. The type of case analysis showed that new TB cases were more common than recurrent cases. Radiological examination revealed extended pulmonary TB in the majority of cases. Complications such as respiratory failure, hemoptysis, pleurisy, and spontaneous pneumothorax were also observed. The study further examined various risk factors for TB, including contact with TB patients, migration, detention, drug use, smoking, alcohol abuse, living conditions, and nutrition. The risk of TB and HV was found to be higher in patients with these risk factors. Microbiological confirmation of TB was achieved in a majority of cases, and the presence of comorbidities was observed in the majority of patients. The study highlighted the importance of active detection of TB in patients with risk factors. The sequence of diagnosis revealed that TB often developed in patients with known HV, and vice versa. The etiology of HV was predominantly HCV, followed by HBV and HV B+D.

Antiviral therapy was administered to a small number of patients. Liver damage, based on transaminase levels, was observed in a significant proportion of patients. Clinical manifestations included signs of intoxication and broncho-pulmonary syndrome. The study assessed the severity of liver damage and general condition at hospitalization, finding a range of severity levels. Adverse reactions to antituberculosis treatment were observed in a significant number of patients, predominantly gastrointestinal intolerance. Treatment modifications were made in cases of severe side effects and increased transaminase levels.

The final results of treatment in patients with TB and HV were as follows: Treatment completed - 26 (28.6%), Cured - 37 (39.6%), Lost from surveillance - 12 (13.2%), Death - 15 (16.5%).

Conclusions

Among patients with pulmonary tuberculosis (TB) and viral hepatitis (VH), there is a significant predominance of male gender, and the most common age range is between 30 and 50 years. In terms of clinical forms, infiltrative pulmonary TB was the most frequently diagnosed form among patients with viral hepatitis as a comorbidity. However, microbiological confirmation of TB remains a challenge and is often insufficient.

The frequency of complications is high in patients with pulmonary TB and VH, with respiratory failure, hemoptysis, pleurisy, and spontaneous pneumothorax being the most common complications. Risk factors for TB were identified in 82 (90%) cases of patients with the established diagnosis of tuberculosis and viral hepatitis, with TB contact being the most significant risk factor. Social factors such as migration, detention, alcohol abuse, smoking, and drug use were frequently observed among the patients included in the study.

Passive detection of TB was the predominant method, and pneumonia was the most common "mask" for TB. In approximately half of the cases, pulmonary TB developed in patients who already had a known diagnosis of viral hepatitis, while in the other half, viral hepatitis was diagnosed after the establishment of pulmonary TB. Hepatitis C virus (HCV) was the most commonly diagnosed virus, and it was associated with more severe and unfavorable liver damage compared to other viruses. Additionally, there were cases of co-infection with multiple viruses in some patients.

Treatment regimens varied among patients, with one-third receiving the standard regimen while the rest received individual or empirical treatment based on the sensitivity of the contact source. The administration of antituberculosis drugs to patients with VH comorbidity often resulted in various side effects. Regarding the final treatment outcomes in patients with TB and VH, 26 (28.6%) completed the treatment, 37 (39.6%) were healed, 12 (13.2%) were lost from surveillance, and 15 (16.5%) died.

Analyzing the odds ratio (OR), we found that drug use posed the highest risk among patients with TB and VH, with an OR of 20.3 (95% CI: 2.6-15.804). Other high-risk factors, in descending order, included "masked" TB (OR: 14.23, 95% CI: 7.15-28.32), smoking (OR: 7.94, 95% CI: 3.76-16.762), social status (employment) (OR: 3.734, 95% CI: 1.48-9.39), history of detention (OR: 3.36, 95% CI: 1,716-6,551), and male gender (OR: 3.105, 95% CI: 1.64-5.86). Alcohol abuse and living conditions carried a similar risk (OR: 3,087, 95% CI: 1,726-5,521). Comparatively smaller but statistically significant risks were observed in situations such as belonging to risk groups, migration, and age less than 50 years.

Statistically insignificant risks (OR < 1) were observed in situations where the confidence interval (CI) included 1. These situations included city residence (OR: 0.5, 95% CI: 0.33-1.064), age up to 50 years (OR: 0.4, 95% CI: 0.21-0.83), and power supply (OR: 1,201, 95% CI: 0.68-2,099).

Declaration about the conflict of interest. The authors declare that they have no conflict of interest.

Bibliography

1. Amir F. Khan et al. *Co-infection with hepatitis B in tuberculosis patients on anti-tuberculosis treatment and the final outcome*. Cureus. 2021 Apr; 13(4): e14433. Published online 2021 Apr 12. doi: 10.7759/cureus.14433.
2. Araujo-Mariz et al. *Serological markers of hepatitis B and C in patients with HIV/AIDS and active tuberculosis*. J Med Virol. 2016;88(6):996–1002.
3. Alyaquobi F. et al. *Country-specific lockdown measures in response to the COVID-19 pandemic and its impact on tuberculosis control: a global study*. J Bras Pneumol. 2022;48(2):e20220087. doi: 10.36416/1806-3756/e20220087.
3. Al-Khazraji A., Alkhawam H., Garrido B. *Hepatitis B virus reactivation in an inactive carrier of chronic HBV after the initiation of treatment for tuberculosis*. J Investig Med. 2016, 64:939. 10.1136/jim-2016-000120.56.
4. Behzadifar M., Heydarvand S., Behzadifar M., Bragazzi NL. *Prevalence of hepatitis C virus in tuberculosis patients: a systematic review and meta- analysis*. Ethiop J Health Sci. 2019;29(1):945–56.
5. Bao Y., Ma X., Rasmussen TP, Zhong X-B. *Genetic Variations associated with antituberculosis drug-induced liver injury*. Curr Pharmacol Rep. 2018;4(3): 171–81.
6. Chen L., Bao D., Gu L., Gu Y., Zhou L., Gao Z. et al. *Co-infection with hepatitis B virus among tuberculosis patients is associated with poor outcomes during antituberculosis treatment*. BMC Infect Dis. 2018;18(1):295.
7. Fisher K., Vuppalanchi R., Saxena R. *Drug-induced liver injury*. Arch Pathol Lab Med. 2015;139(7):876–87.

8. Feleke BE, Feleke TE, Adane WG, Girma A. *Impacts of hepatitis B and hepatitis C co-infection with tuberculosis, a prospective cohort study.* Virol J. 2020, 17:113. 10.1186/s12985-020-01385-z.

9. Lui GCY, Wong NS, Wong RYK et al. *Antiviral therapy for hepatitis B prevents liver injury in patients with tuberculosis and hepatitis B coinfection.* Clin Infect Dis. 2020, 70:660-6. 10.1093/cid/ciz241.

10. Mo P., Zhu Q., Teter C., Yang R., Deng L., Yan Y. et al. *Prevalence, drug- induced hepatotoxicity, and mortality among patients multi-infected with HIV, tuberculosis, and hepatitis virus.* Int J Infect Dis. 2014;28:95–100.

11. Mosedale M., Watkins PB. *Drug-induced liver injury: advances in mechanistic understanding that will inform risk management.* Clin Pharmacol Ther. 2017; 101(4):469–80.

12. De Oliveira et al. *High incidence of tuberculosis in patients treated for hepatitis C chronic infection.* Braz J Infect Dis. 2016;20(2):205–9.

13. Pedrosa M., Nogales S., Vergara M., Miquel M., Casas M., Dalmau B. *Reactivation of peritoneal and pleural tuberculosis during hepatitis C treatment with direct-acting antivirals.* Gastroenterol Hepatol. 2019;42(3): 174–5.

14. Rodrigues I., Aguiar A., Migliori GB, Duarte R. *Impact of the COVID-19 pandemic on tuberculosis services.* Pulmonology. 2022 May-Jun; 28(3):210-219. doi: 10.1016/j.pulmoe.2022.01.015.

15. Teschke R. *Hepatotoxicity: molecular mechanisms and pathophysiology.* Switzerland: Multidisciplinary Digital Publishing Institute; 2019.

16. World Health Organization. Global tuberculosis report 2022. Geneva. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022.

17. Global Tuberculosis Report 2020. Geneva: World Health Organization; 2020. https://www.who.int/teams/global-tuberculosis-programme/data.

18. Global strategy and targets for tuberculosis prevention, care and control after 2015 (Res. WHA67.1). In: Sixty-seventh World Health Assembly, Geneva, 19–24 May 2014. https://apps.who.int/iris/handle/10665/162760.

19. World Health Organization. The End TB Strategy- 2015.

20. World Health Organization. What is Hepatitis? Switzerland. Geneva. 2019.

21. World Health Organization.. Hepatitis B. 2021. http://who.int/news-room/fact-sheets/detail/ hepatitis- b.

22. Protocolul Clinic Naţional -123 "Tuberculoza la adult". 05.03.2020.

Autor corespondent:

Stela Kulcitkaia, conferenţiar universitar, Disciplina de pneumologie şi alergologie, Departamentul Medicină Internă, IP USMF *Nicolae Testemiţanu* tel. 069319109 e-mail: stela.kulcitkaia@usmf.md