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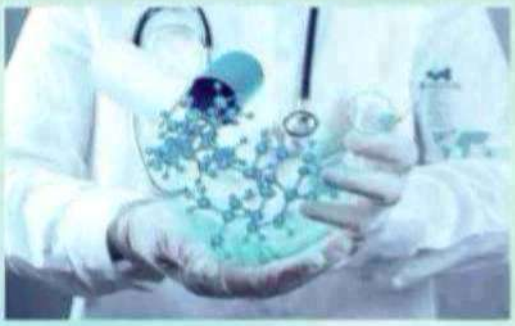

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COMPARATIVE ASSESSMENT OF THE INITIAL STATE OF LIVER FIBROSIS IN TUBERCULOSIS AND CHRONIC VIRAL HEPATITIS COINFECTION

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✓ ***Resume***

Coinfection with tuberculosis (TB) and chronic viral hepatitis (CVH) is a serious problem leading to the rapid progression of liver disease. The study aimed to comparatively evaluate the degree of liver fibrosis in patients with TB and CVH coinfection versus patients with CVH only, prior to the initiation of anti-tuberculosis therapy. The study included 59 coinfected patients (main group) and 30 patients with only CVH (control group). The degree of liver fibrosis was assessed using the non-invasive "FibroTest/FibroMax" method according to the METAVIR scale. The results revealed significantly more pronounced liver fibrosis in coinfected patients: advanced fibrosis stages (F3-F4) were significantly more common in this group compared to the control group (p<0.01). In conclusion, the presence of TB infection acts as an independent factor that accelerates liver fibrogenesis against the background of chronic viral hepatitis.

This necessitates a thorough assessment of the liver status in coinfected patients before starting treatment

Keywords: tuberculosis, chronic viral hepatitis, coinfection, liver fibrosis, FibroTest, comparative analysis

СРАВНИТЕЛЬНАЯ ОЦЕНКА ИСХОДНОГО СОСТОЯНИЯ ФИБРОЗА ПЕЧЕНИ ПРИ КОИНФЕКЦИИ ТУБЕРКУЛЕЗОМ И ХРОНИЧЕСКИМ ВИРУСНЫМ ГЕПАТИТОМ

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✓ ***Резюме***

Коинфекция туберкулеза (ТБ) и хронического вирусного гепатита (ХВГ) является серьезной проблемой, ведущей к быстрому прогрессированию заболеваний печени. Цель исследования – провести сравнительное изучение степени фиброза печени у пациентов с коинфекцией ТБ и ХВГ и у пациентов только с ХВГ до начала противотуберкулезной терапии. В исследовании приняли участие 59 пациентов с коинфекцией (основная группа) и 30 пациентов только с ХВГ (контрольная группа). Степень фиброза печени оценивали с помощью неинвазивного метода "ФиброТест/ФиброМакс" по шкале METAVIR. Результаты показали более выраженный фиброз печени у коинфицированных пациентов: тяжелые стадии фиброза (F3-F4) в этой группе встречались значительно чаще, чем в контрольной группе (p<0.01). В заключение, наличие туберкулезной инфекции является независимым фактором, усиливающим фиброгенез печени на фоне хронического вирусного гепатита. Это диктует необходимость тщательной оценки состояния печени у коинфицированных пациентов перед началом лечения

Ключевые слова: туберкулез, хронический вирусный гепатит, коинфекция, фиброз печени, ФиброТест, сравнительный анализ, METAVIR

SIL VA SURUNKALI VIRUSLI GEPATIT KOINFEKTSIYASIDA JIGAR FIBROZINING DASTLABKI HOLATINI QIYOSIY BAHOLASH

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✓ ***Resume***

Sil (TB) va surunkali virusli gepatit (SVG) koinfeksiyasi jigar kasalliklarining tez rivojlanishiga olib keluvchi jiddiy muammodir. Tadqiqotning maqsadi TB va SVG koinfeksiyasi bo‘lgan bemorlar hamda faqat SVG bilan kasallangan bemorlarda silga qarshi davolash boshlangunga qadar jigar fibrozi darajasini qiyosiy o‘rganishdan iborat. Tadqiqotda 59 nafar koinfeksiyali (asosiy guruh) va 30 nafar faqat SVG mavjud bo‘lgan (nazorat guruhi) bemorlar ishtirok etdi. Jigar fibrozi darajasi noinvaziv "FibroTest/FibroMax" usuli yordamida METAVIR shkalasi bo‘yicha baholandi. Natijalar koinfeksiyali bemorlarda jigar fibrozining yaqqolroq namoyon bo‘lishini ko‘rsatdi: ushbu guruhda og‘ir fibroz (F3-F4) darajalari nazorat guruhiga nisbatan sezilarli darajada ko‘p uchradi ($p<0.01$). Xulosa qilib aytganda, sil infeksiyasining mavjudligi surunkali virusli gepatit fonida jigar fibrogenezini kuchaytiruvchi mustaqil omil bo‘lib xizmat qiladi. Bu esa koinfeksiyali bemorlarni davolashni boshlashdan oldin jigar holatini chuqur baholash zarurligini taqozo etadi

Kalit so‘zlar: sil, surunkali virusli gepatit, koinfeksiya, jigar fibrozi, FibroTest, qiyosiy tahlil

Relevance

On a global scale, tuberculosis (TB) and chronic viral hepatitis (CVH), particularly hepatitis B (CHB) and C (CHC), are among the most widespread infectious diseases posing a significant threat to public health. The World Health Organization, in its 2024 Global Reports (1, 2), emphasizes that these two infections cause high rates of morbidity and mortality globally, placing a substantial burden on healthcare systems. At the intersection of these two pandemics lies the problem of TB/CVH coinfection, which constitutes a distinct clinical challenge. Choi, J. C., & Ihm, J. S. (3) in their study investigated the clinical characteristics of patients with TB and chronic hepatitis B coinfection, noting that this condition leads to an atypical disease course and requires complex treatment approaches. The relevance of this issue for our region is reflected in the research conducted by Umarova, A. A., & Alimov, A. V. (4). They found that in an endemic region, the course of chronic hepatitis B in patients with pulmonary tuberculosis has unique features and exacerbates liver damage.

Liver fibrosis is a universal pathological process in chronic liver diseases, the progression of which ultimately leads to cirrhosis and its life-threatening complications, as emphasized by Schuppan, D., & Afdhal, N. H. (6) in their influential review. The primary mechanism of fibrosis development in chronic viral hepatitis is the persistent inflammation caused by the virus. For instance, Mihm, S. (7) demonstrated in his work that the hepatitis C virus stimulates the production of potent profibrotic cytokines like transforming growth factor-beta (TGF-β) in the liver. TB infection, in turn, induces a systemic inflammatory response affecting the entire body. A systematic review by Hussain, R., et al. (8) shows that high levels of tumor necrosis factor-alpha (TNF-α) and other inflammatory mediators characteristic of TB can activate hepatic stellate cells and intensify fibrogenesis. Thus, the simultaneous impact of both infections can deliver a "double-hit" to the liver tissue, creating a foundation for more rapid fibrosis progression.

Accurate assessment of the fibrosis stage is crucial for determining treatment strategy and prognosis. For many years, liver biopsy has been the "gold standard,"

invasiveness, risk of complications, and sampling errors. Therefore, as highlighted in the review by Rockey, D. C., & Bissell, D. M. (5), non-invasive methods are becoming increasingly important in

clinical practice. In this regard, methods based on serum biomarkers, such as FibroTest, hold a special place. Meta-analyses conducted by Poynard, T., et al. (10) have proven the high diagnostic value of FibroTest in various chronic liver diseases.

Many studies are dedicated to the hepatotoxicity of anti-tuberculosis drugs. The official statement from the American Thoracic Society, led by Saukkonen, J. J. (11), as well as the work of Ivanova D.A., et al. (12), have thoroughly examined the risk factors and patterns of drug-induced liver injury caused by these medications. However, the initial state of the liver in coinfected patients before the start of treatment—specifically, how TB infection itself affects fibrosis in the context of CVH—remains insufficiently studied. This is critical for accurately assessing the risk and individualizing treatment before initiating anti-TB therapy.

The aim of the study: To conduct a comparative assessment of the degree of liver fibrosis in a group of patients with TB and CVH coinfection versus a group of patients with CVH only, before the initiation of anti-tuberculosis therapy.

Materials and methods

Study Design and Patient Population: This single-center, prospective, comparative study was conducted at the Republican Specialized Scientific and Practical Medical Center of Phthisiology and Pulmonology. A total of 89 patients were enrolled and divided into two groups:

1. Main Group (Coinfection): 59 patients diagnosed with pulmonary tuberculosis and chronic viral hepatitis (B and/or C).
2. Control Group (Monoinfection): 30 patients diagnosed only with chronic viral hepatitis (B and/or C), without tuberculosis.
3. Inclusion Criteria:
4. Age from 18 to 65 years.
5. For the main group: Bacteriologically or molecularly (GeneXpert MTB/RIF) confirmed pulmonary TB AND positive markers for HBsAg or Anti-HCV.
6. For the control group: Positive HBsAg or Anti-HCV markers for more than 6 months and the absence of any signs of tuberculosis.
7. Written informed consent to participate in the study.

Exclusion Criteria:

- HIV infection.
- Regular alcohol consumption (>30 g/day for men, >20 g/day for women).
- History of other liver diseases (e.g., autoimmune hepatitis, Wilson's disease).
- Decompensated liver cirrhosis (Child-Pugh class B and C).
- Severe cardiovascular, renal, or endocrine diseases.
- Pregnancy and lactation.
- Patients who had already started anti-tuberculosis or antiviral treatment.

Fibrosis Assessment: The degree of liver fibrosis in all patients was determined using the "FibroTest/FibroMax" non-invasive diagnostic system developed by BioPredictive (France). The levels of 6 biochemical markers (alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, gamma-glutamyl transpeptidase, total bilirubin, ALT) were measured in the venous blood serum. The results were analyzed using a special mathematical algorithm that accounted for the patient's age and gender. The results were presented on the METAVIR scale from F0 to F4 (F0 - no fibrosis, F1 - mild, F2 - moderate, F3 - severe, F4 - cirrhosis).

Clinical and Laboratory Tests: Complete blood count, liver function tests (ALT, AST, ALP, total protein), viral hepatitis markers (HBsAg, HBeAg, Anti-HCV, viral load by PCR), coagulogram.

Ethical Considerations: The study was approved by the local ethics committee and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Statistical Analysis: statistical analysis was performed using the SPSS 22.0 software package. Quantitative data between groups were compared using Student's t-test or the Mann-Whitney U test.

Qualitative data were compared using the chi-square (χ^2) test. Results were considered statistically significant at $p<0.05$.

Results and discussions

There were no statistically significant differences in the age and gender distribution between the two patient groups ($p>0.05$), indicating that the groups were comparable for baseline analysis (Table 1).

Table 1

General Characteristics of the Patients

Characteristic	Main Group (Coinfection, n=59)	Control Group (Monoinfection, n=30)	p
Mean Age, years	41.2 ± 10.8	43.5 ± 11.4	>0.05
Gender, male/female (%)	38/21 (64.4%/35.6%)	18/12 (60.0%/40.0%)	>0.05
CHB, n (%)	22 (37.3%)	13 (43.3%)	>0.05
CHC, n (%)	37 (62.7%)	17 (56.7%)	>0.05

Analysis of the distribution of liver fibrosis stages according to the METAVIR scale revealed stark differences between the two groups (Table 2).

Table 2

Distribution of Liver Fibrosis Stages in the Groups (FibroTest)

Fibrosis Stage (METAVIR)	Main Group (Coinfection, n=59)	Control Group (Monoinfection, n=30)
F0-F1 (No/Mild Fibrosis)	14 (23.7%)	18 (60.0%)
F2 (Moderate Fibrosis)	20 (33.9%)	8 (26.7%)
F3 (Severe Fibrosis)	16 (27.1%)	3 (10.0%)
F4 (Cirrhosis)	9 (15.3%)	1 (3.3%)
F3-F4 (Severe Fibrosis/Cirrhosis), Total	25 (42.4%)	4 (13.3%)

The results showed that the majority of patients in the control group (60.0%) had no or mild fibrosis. In contrast, this figure was only 23.7% among coinfected patients.

The most significant finding was observed in the advanced stages of fibrosis (F3) and cirrhosis (F4). In the main group, 42.4% of patients had severe fibrosis or cirrhosis, whereas in the control group, this figure was only 13.3%. This difference is highly statistically significant ($\chi^2=8.91$; $p<0.01$). The mean fibrosis score was also significantly higher in the coinfection group.

The results of this study fully confirm our initial hypothesis: patients with TB and CVH coinfection have a significantly higher degree of liver fibrosis before the start of treatment compared to patients with only viral hepatitis. The fact that cases of severe fibrosis and cirrhosis (F3-F4) were more than three times more frequent in the main group compared to the control group indicates that TB infection is an independent factor that powerfully exacerbates liver fibrogenesis.

This phenomenon can be explained by several pathogenetic mechanisms. Firstly, according to the "double-hit" theory, the chronic inflammation caused by CVH is compounded by the potent systemic inflammatory response due to the TB infection. The high levels of TNF-α, IL-6, and other cytokines characteristic of TB can strongly stimulate hepatic stellate cells, dramatically accelerating collagen synthesis and fibrosis progression. Secondly, conditions such as TB intoxication, hypoxia, and cachexia reduce the liver's metabolic and regenerative capacity, making it more vulnerable to the damaging effects of the viral infection.

Our findings are consistent with the work of other authors. For instance, several studies have shown a higher risk of liver cirrhosis and its complications (e.g., hepatocellular carcinoma) in coinfected patients. However, most studies have focused on the hepatotoxicity of anti-tuberculosis treatment. The uniqueness of our study is that we assessed the initial state before any treatment. This

means that coinfected patients already have significant liver damage before starting anti-TB therapy, placing them in an extremely high-risk group for additional drug-induced liver injury.

The clinical significance of this study is substantial. It once again confirms the importance of screening every TB patient for CVH markers and, conversely, screening patients under care for CVH for tuberculosis. If coinfection is detected, it should become standard practice to determine the degree of liver fibrosis using non-invasive methods like FibroTest before starting anti-TB treatment. In patients with advanced fibrosis (F3-F4), anti-TB therapy should be administered using individualized regimens with the least hepatotoxic drugs, under constant hepatoprotective cover, and with extremely careful monitoring of liver function.

Conclusion

Coinfection with tuberculosis and chronic viral hepatitis is characterized by a significantly more severe degree of liver fibrosis compared to chronic viral hepatitis alone. Cases of severe fibrosis (F3) and cirrhosis (F4) are 3.2 times more common in coinfected patients than in those with monoinfection.

The presence of tuberculosis infection is an independent and significant risk factor that accelerates liver fibrogenesis in the context of chronic viral hepatitis.

It is necessary to conduct a mandatory assessment of the liver fibrosis stage using non-invasive methods in coinfected patients before starting anti-tuberculosis treatment, to manage them as a high-risk group, and to individualize their treatment strategy.

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