

Hepatitis C prevalence in a priority municipality for tuberculosis: single center study

Soroprevalência de hepatite C em município prioritário para tuberculose: estudo unicêntrico

Eliana Peresi-Lordelo, Aline Cintra Nemer Diório, Ana Carolina Munuera Pereira, Bruna Alves Martins, Bruno Kenji Kito, Fernando Nunes Gavioli Boni, Yara Felipe Bueno Crosciolli, Paulo José Mascarenhas Mazaro, João Guilherme Araujo Matarazo, Priscila Paulin

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Autor correspondente:

Nome: Eliana Peresi-Lordelo
E-mail: lordeloeliana@gmail.com Telefone
Formação: Doutora em Doença Tropicais pela Universidade Estadual Paulista – UNESP, Botucatu, SP, Brasil
Filiação: Universidade do Oeste Paulista – Unoeste, Presidente Prudente, SP, Brasil

Endereço: Universidade do Oeste Paulista - Unoeste
Rod. Raposo Tavares km 572, CEP 19067-175
Presidente Prudente - SP - Brasil

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Abstract:

Objective: Hepatitis C virus (HCV) infection could be a risk factor for the development of active tuberculosis (TB) and, despite the proven prevalence of tuberculosis/hepatitis C (TB/HCV) co-infection, there are still few studies addressing this relationship. The aim of the present study was to assess the prevalence of hepatitis C in patients with TB and its association with clinical and epidemiological data. **Methods:** Patients with TB (n=34), older than 18 years, of both genders, were studied. Anti-HCV antibodies were evaluated by ELISA and the clinical and epidemiological data were obtained from medical records. Analyses were performed using Fisher and Mann-Whitney tests ($p<0.05$). **Results:** Among the 34 TB patients assessed, 3 had anti-HCV antibodies demonstrating a seroprevalence of 8.82%. There was no association of TB/HCV with clinical and epidemiological data in the studied population. **Final Considerations:** Due to the association TB/HCV being a reality, the introduction of a routine screening for hepatitis C markers before antituberculosis treatment would be recommended for a better follow-up of patients and reduced risk of hepatotoxicity.

Keywords: Tuberculosis, Hepatitis C, prevalence.

Resumo:

Objetivo: A infecção pelo vírus da hepatite C (HCV) pode ser um fator de risco para o desenvolvimento da TB ativa e, apesar da comprovada prevalência de coinfeção tuberculose/hepatite C (TB/HCV), ainda existem poucos estudos que abordam esta relação. O objetivo do presente estudo foi avaliar a soroprevalência de hepatite C em pacientes com TB e sua associação com os dados clínico-epidemiológicos. **Métodos:** Foram estudados pacientes com TB (n=34), maiores de 18 anos, de ambos os sexos. Os anticorpos anti-HCV foram avaliados por ELISA e as características clínico-epidemiológicas através de levantamento de prontuários. As análises foram realizadas pelos testes de Fisher e de Mann-Whitney ($p<0,05$). **Resultados:** Dentre os 34 pacientes com TB avaliados, 3 apresentaram anticorpos anti-HCV, demonstrando uma soroprevalência de 8,82%. Não houve associação TB/HCV com os dados clínico-epidemiológicos da população estudada. **Considerações finais:** Devido à associação TB/HCV ser uma realidade, a introdução de uma triagem de rotina para a pesquisa de marcadores para a hepatite C antes do tratamento antituberculose seria recomendada para um melhor acompanhamento dos pacientes com TB.

Palavras-chave: Tuberculose, Hepatite C, prevalência.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* and it is estimated that a quarter of the global population is infected with the bacillus. The World Health Organization (WHO), in 1993, assessed TB as a public health emergency. Since then, this pathology has been treated as a morbidity of great magnitude. In 2019, in Brazil, 96,000 people had TB and 6,700 died, among which 1,800 had TB/HIV co-infection¹.

Transmission occurs through infectious particles of individuals with active disease that survive in the air, promoting contact of the bacillus with susceptible individuals². Thus, according to the virulence of the bacillus and the host's immune response, three outcomes are possible: eradication of the pathogen, latent infection, or active disease³.

After entering the airways, *M. tuberculosis*, an obligate intracellular pathogen, interacts with alveolar macrophages stimulating the innate immune response, which, through the presentation of antigens and the production of cytokines such as IL-12, will stimulate Th1 profile formation⁴. Granuloma is a complex and well-orchestrated mechanism between the innate and adaptive immune response, mainly the Th1 profile, sealing *M. tuberculosis* inside, present in the latent form of most infected individuals⁵.

Among individuals with the latent form, only a small proportion, between 5 and 15%, will develop active disease, however, this probability is much higher in people with risk factors, such as people living with HIV/Aids (PLWHA), undernourished, diabetic, smokers and alcohol consumers⁶. A study suggests that hepatitis C virus (HCV) infection may also be a risk factor for the development of active TB⁷. Other authors point out that both infections share the same type of vulnerable population, such as homeless people, deprived of liberty and PLWHA⁸⁻¹⁰. A recent meta-analysis study reported a worldwide prevalence of HCV infection in TB patients of 7%, with wide variation between the analyzed studies, between 2% and 27%¹¹.

Despite this evidence, there are still few studies that addressed the TB/HCV relation. To our knowledge, no studies that evaluated TB/HCV co-infection have been carried out in the city of Presidente Prudente, which is in the western region of São Paulo state/Brazil and is considered a priority municipality for TB control¹². Thus, the aim of the present study was to evaluate the prevalence of hepatitis C in patients with TB and its association with clinical and epidemiological data.

METHODS

DESIGN OF THE STUDY AND STUDY POPULATION

This is a primary, cross-sectional and prevalence study, in which TB patients treated at the Tisiology Outpatient Clinic of the “Prof^a Ana Cardoso Maia de Oliveira Lima” Ambulatory of the city of Presidente Prudente, São Paulo/Brazil were evaluated. The research was approved by the Research Ethics Committee (CAAE: 37457520.6.0000.5515) and is in accordance with the Helsinki Declaration of 1964.

The study included patients with TB of both sexes, over 18 years of age, treated during the period between 2017 and 2018, who were invited to participate in the study on the day of their medical appointment (convenience sample). Patients who belong to the penitentiary system were excluded due to ethical issues.

TB diagnosis was confirmed by demonstrating the presence of *M. tuberculosis* (smear and/or culture) and/or by clinical, laboratory and imaging tests compatible with active TB. Patients were treated with the Rifampicin (R), Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E) regimen. Clinical, laboratory and radiological data were obtained from medical records.

ANTI- HEPATITIS C ANTIBODIES PREVALENCE

The prevalence of anti-HCV antibodies was performed from plasma samples using the ELISA technique (Wiener). The samples initially reactive were repeated in duplicate and considered reactive if one or both duplicates were reactive, according to manufacturer's standards.

STATISTICAL ANALYSES

To assess the association between the clinical-epidemiological characteristics and the different groups of TB patients (with and without hepatitis C), the Fisher and Mann-Whitney tests were used ($p < 0.05$).

RESULTS

Among the 34 TB patients evaluated, 3 had anti-HCV antibodies (8.82%). Regarding gender, 28 were male, with 2 HCV(+), and 6 were female, with 1 HCV(+), there was no dif-

ference in this association ($p=0.4525$). The mean age of the TB/HCV(-) group was 46.74 (± 16.26) years and the TB/HCV(+) group was 58.67 (± 3.05) years, with no difference between the two groups ($p=0.1980$). The pulmonary form was predominant ($n=23$), with 2 TB/HCV(+), 6 pulmonary/extrapulmonary and 4 extrapulmonary, with 1 TB/HCV(+), with no difference between the groups ($p=0.4507$). As for the laboratory diagnosis, 18 patients with TB had positive smear microscopy, among which 1 TB/HCV(+), with no difference between the groups ($p=0.4507$). Most TB patients had symptoms, associated or not with fever, with no difference between the groups in relation to HCV ($p>0.9999$). Regarding the evaluation of radiological alterations, most of the findings were suggestive of TB, with no difference between the studied groups ($p>0.9999$) (Table 1). Only one patient was PLWHA, with no association with the diagnosis of HCV.

Table 1. Anti-HCV seroprevalence in relation to the clinical and epidemiological characteristics of tuberculosis (TB) patients.			
Variables	TB patients n (%)	TB/HCV patients n (%)	p
Age¹			
Years	46.74 (± 16.26)	58.67 (± 3.05)	0.1980
Sex			
Men	26	2	ref
Woman	5	1	0.4525
Type of TB			
Pulmonary TB	22	2	ref
Pulmonary and Extrapulmonary TB	4	0	0.4507
Extrapulmonary TB	2	1	0.4507
Not informed	2	0	-
Smear microscopy			
Negative	3	1	ref
Positive	17	1	0.3377
Not informed	11	1	-
Clinical signs			
No fever or other symptoms ²	1	0	>0.999
Other symptoms ² (no fever)	13	1	>0.9999
With fever and other symptoms ²	14	2	ref
Not informed	3	0	-
Imaging diagnosis			
Suggestive of TB	14	2	ref

Table 1. Anti-HCV seroprevalence in relation to the clinical and epidemiological characteristics of tuberculosis (TB) patients.

Variables	TB patients n (%)	TB/HCV patients n (%)	p
Cavitation	6	0	>0.9999
Not informed	11	1	-

¹Values presented as mean \pm standard deviation; ² Cough, fatigue, night sweats and weight loss.

DISCUSSION

The present study showed an 8.82% anti-HCV seroprevalence in patients with TB, finding similar to another study carried out in Brazil, which found a seroprevalence of 7.5%¹⁰. However, another national study found a higher prevalence of 20%¹³, while other authors showed a lower prevalence of 3.1%¹⁴. Different prevalences in the same country were also found in studies from Ethiopia, with a study demonstrating a high prevalence of 17.3%¹⁵, while other did not detect anti-HCV antibodies in TB patients¹⁶. Other authors have demonstrated a varied prevalence such as 0.9% in Iraq¹⁷ and 17.02% in Egypt¹⁸. Another study shows that individuals with HCV infection have a 1.51 higher risk of developing TB, compared to individuals not previously infected with the virus⁷. Different prevalences may be associated with the geographic difference and habits of the populations studied, as well as the types of tests used for diagnosis, such as the investigation of anti-HCV by ELISA or HCV RNA by molecular techniques.

The presence of active TB in individuals with HCV may be associated with immunomodulation promoted by the virus, which would facilitate the development of intracellular infections. Dendritic cells play a fundamental role in the immune defense system against *M. tuberculosis*, through the presentation of antigens, costimulatory activity and great capacity to produce cytokines with activity in the distinction cluster of TCD4+ lymphocytes⁵. A study has shown that dendritic cells originated *in vitro* from the peripheral blood of HCV patients have their antigen presentation function impaired¹⁹. TNF- α is an essential cytokine to stimulate macrophages in the production of nitric oxide and control of *M. tuberculosis*⁵. Studies show that the HCV core protein can bind to and inhibit the TNF- α receptor²⁰, suggesting that it could compromise the response of macrophages to the bacillus.

Despite this evidence, only one study has addressed immunological aspects of the immune response to the bacillus during TB/HCV co-infection. The authors found a decrease in IFN- γ -producing cells in response to mycobacterial antigens, showing that the Th1-mediated immune response is impaired in this population, suggesting an impairment of granuloma formation, the main defense against the bacillus²¹.

Anti-TB treatment lasts for six months. In the intensive phase, the first two months, the combination of RHZE drugs is used²². In the maintenance phase, the next four months, only the use of R and H is maintained. The doses are established according to the individual's weight range²³. Some of the anti-TB drugs induce hepatotoxicity, especially R and H, a fact that can be potentialized by viral coinfections, such as HCV. Due to the ability of the virus to remain chronically in the infected individual, the patient can progress, in about 70 to 80% of cases, to more severe forms, such as cirrhosis or hepatocellular carcinoma^{24,25}. Elevation of liver function markers during antituberculosis treatment is uncommon, therefore, a study suggests that patients with a history of TB/HCV association should be monitored to reduce the risk of hepatotoxicity induced by antituberculosis treatment¹⁸. In the present study, record of liver markers in the patients' charts was not found.

Regarding the characteristics of the population studied and the TB/HCV ratio, a national study showed an association with skin color, use of illicit drugs, alcohol abuse, history of incarceration, previous TB and PLWHA¹³. Other Brazilian authors found an association between PLWHA and injecting drug use¹⁴. A study in Ethiopia reported an association with alcohol abuse, female sex, PLWHA, and the presence of chronic disease¹⁵. The present study did not observe an association between TB/HCV and the clinical-epidemiological characteristics of the population studied. These results are probably due to the limitations of this study, which were the small number of patients and the single-center nature of the conducted work, as well as the lack of information in the medical records.

FINAL CONSIDERATIONS

Due to the association TB/HCV being a reality, the introduction of a routine screening for hepatitis C markers before antituberculosis treatment would be recommended for a better follow-up of patients and reduced risk of hepatotoxicity. Furthermore, future

studies are needed to address the assessment of different markers, such as serological and molecular markers for the virus, as well as immune response and liver function markers, to improve the understanding of the TB/HCV association and the pathological mechanisms associated.

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