

Impact of Non-Alcoholic Simple Fatty Liver Disease on Antituberculosis Drug-Induced Liver Injury

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Objective: To observe the effect of non-alcoholic simple fatty liver disease on drug-induced liver injury caused by tuberculosis.

Methods: We retrospectively analyzed the incidence, characteristics, and risk factors of antituberculosis drug-induced liver injury in 104 patients with initial treatment of tuberculosis complicated with non-alcoholic simple fatty liver disease. The patients were divided into two groups according to whether there was liver injury or not. The differences in age, gender, body mass index (BMI), cholesterol, and triglycerides were studied between the two groups.

Results: Among the 104 patients with initial treatment of tuberculosis complicated with non-alcoholic fatty liver disease, 24 (23%) patients developed a drug-induced liver injury. The remaining 80 (77%) patients did not develop drug-induced liver injury ($\chi^2 = 60.308$, $P < 0.05$). In the liver injury group, there were 20 cases of mild liver injury, two cases of moderate liver injury, two cases of severe liver injury, 22 cases of hepatocellular injury, two cases of cholestasis, and no cases of mixed liver injury. The time of abnormal liver function in antituberculosis treatment was 16.42 ± 9.18 days from the beginning of the antituberculosis treatment. There were no significant differences in gender, age, BMI, or triglyceride between the liver injury group and the non-liver injury group ($\chi^2 = 2.063$, $t = 0.179$, $t = 0.703$, $t = 1.12$, $P > 0.05$ in all), but there were significant differences in cholesterol ($t = 3.08$, $P < 0.05$). By logistic regression analysis, cholesterol was a high-risk factor for liver injury.

Conclusion: Non-alcoholic simple fatty liver disease may increase the risk of antituberculosis drug-induced liver injury.

Keywords: non-alcoholic simple fatty liver disease, antituberculosis drugs, drug-induced liver injury

Introduction

Drug-induced liver injury (DILI) is one of the most common side effects of antituberculosis drugs. In addition to the effects of the drugs themselves, the risk factors for antituberculosis DILI are not completely clear. Theoretically, advanced age, female gender, poor nutritional status/ hypoproteinemia, HIV infection, diabetes, alcoholism, basic liver disease, Pregnancy/3 months post-partum, extrapulmonary tuberculosis (especially abdominal tuberculosis) etc., are risk factors of antituberculosis DILI. Previous studies have suggested that chronic hepatitis B and chronic hepatitis C can increase the incidence of antituberculosis DILI. The risk of

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DILI in patients with viral hepatitis is three to five times higher than that of non-viral hepatitis.^{1–5} With the effective control of hepatitis B and the prevalence of obesity, non-alcoholic fatty liver disease (NAFLD) has become the largest chronic liver disease in China. Although many patients with tuberculosis have NAFLD, there are few studies on the effect of NAFLD on antituberculosis DILI. Therefore, this study mainly studied the influence of non-alcoholic simple fatty liver disease on DILI caused by tuberculosis.

Materials and Methods

I. The data of 104 patients with non-alcoholic simple fatty liver complicated with an initial treatment of tuberculosis in our hospital were collected from January 2019 to March 2021. This study was conducted in accordance with the Declaration of Helsinki, and approved by the ethics committee of Hangzhou Red Cross Hospital, and all patients had signed the informed consent.

II. The following information was recorded: age, gender, occupation, serum liver function (TBIL, ALT, AST, ALP, GGT), triglyceride, cholesterol, weight, and height. The observation time was eight weeks, and the time of abnormal liver function was recorded.

II. Inclusion criteria: (1) According to the Guidelines for Diagnosis and Treatment of Tuberculosis,⁶ all patients with initial treatment for tuberculosis received 2HRZE/4HR antituberculosis treatment. (2) The diagnostic criteria of DILI refer to the Guidelines for the Diagnosis and Treatment of Anti-tuberculous Drug-induced Liver Injury in 2019.⁷ (3) The diagnostic criteria of non-alcoholic simple fatty liver disease refer to the Guidelines for the Diagnosis and Treatment of Non-alcoholic Fatty Liver Disease in 2006.⁸ (4) NAFLD and normal liver function were diagnosed prior to antituberculosis treatment. (5) No prophylactic liver protective drugs were used. (6) Clinical data is complete. Exclusion criteria: (1) Patients who had tuberculosis combined with viral hepatitis A, B, C, D, E, autoimmune liver disease, genetic metabolic liver disease, etc. (2) Patients with a long history of alcohol consumption. (3) Patients whose basic liver function was abnormal.

IV. The type of liver injury was judged according to the Guidelines for Diagnosis and Treatment of Drug-induced Liver Injury in 2015.⁹ (1) Hepatocyte injury type: $ALT \geq 3 \times ULN$, and $R \geq 5$. (2) Cholestasis type: $ALP \geq 2 \times ULN$, and $R \leq 2$; (3) Mixed type: $ALT \geq 3 \times ULN$, $ALP \geq 2 \times ULN$, and $2 < R < 5$. $R = (ALT/ULN)/(ALP/ULN)$.

V. The degree of liver injury was classified as follows. Grade 1 (mild liver injury): a recoverable increase of serum ALT, ALP, or both, $TBIL < 2.5 ULN$. Grade 2 (moderate liver injury): elevated serum ALT, ALP, or both, $TBIL \geq 2.5 ULN$. Grade 3 (severe liver injury): elevated serum ALT, ALP, or both, $TBIL \geq 5 ULN$.

Statistical Analyses

Normally distributed variables were expressed as mean \pm SD and were compared using Student's *t*-test. Categorical variables were expressed in percentages and compared using the χ^2 test. Logistic regression was performed to test the association between indicators and liver injury. All P-values were two-tailed, and values less than 0.05 were considered statistically significant. Analyses were carried out using SPSS software (version 26.0).

Results

Basic Characteristics

1. A total of 104 patients with pulmonary tuberculosis complicated with NAFLD participated in the study, including 56 males and 48 females. The mean age was 56.41 ± 14.75 , with 64 farmers, 6 workers, 14 employees, and 20 other professions (retired/unemployed/not working). The mean BMI was $23.53 \pm 3.57 \text{ kg/m}^2$.

Characteristics of Liver Injury in Pulmonary Tuberculosis Complicated with NAFLD

There were 24 cases of pulmonary tuberculosis complicated with non-alcoholic simple fatty liver who suffered a liver injury, including 16 males and eight females. Of these cases, 20 had a mild liver injury, 2 had a moderate liver injury, and 2 had a severe liver injury. There were 22 cases of hepatocyte injury type, two cases of cholestasis type, and no cases of mixed type. The mean age was 57.08 ± 14.33 . The abnormal liver function was found in (16.42 ± 9.18) days during antituberculosis treatment (Table 1).

Comparison of Liver Injury Group and Non-Liver Injury Group of Pulmonary Tuberculosis Complicated with Non-Alcoholic Simple Fatty Liver Disease

There were 24 (23%) cases with liver injury and 80 (77%) cases without liver injury in pulmonary tuberculosis complicated with non-alcoholic simple fatty liver disease.

Table 1 Comparison of Liver Injury Group and Non-Liver Injury Group of Pulmonary Tuberculosis Complicated with Non-Alcoholic Simple Fatty Liver Disease (Mean \pm SD)

Group	Case (n, %)	Gender (Male/Female)	Age (Year)	BMI (kg/m ²)	Cholesterol (mmol/L)	Triglyceride (mmol/L)
Liver injury group	24 (23)	16/8	57.08 \pm 14.33	24.17 \pm 4.06	4.96 \pm 1.01	1.80 \pm 0.60
Non-liver injury group	80 (77)	40/40	56.21 \pm 15.04	23.33 \pm 3.44	4.13 \pm 0.74	1.55 \pm 0.70
t			0.179	0.703	3.08	1.12
χ^2		2.063				
p		0.151	0.859	0.486	0.003	0.267

There were no significant differences in gender, age, BMI, triglyceride between the liver injury group and the non-liver injury group ($\chi^2 = 2.063$, $t = 0.179$, $t = 0.703$, $t = 1.12$, $P > 0.05$ in all). The difference in cholesterol was statistically significant ($t = 3.08$, $P < 0.05$) (Table 2).

Table 2 Characteristics of Liver Injury in Pulmonary Tuberculosis Complicated with NAFLD

Basic Characteristics	Results
n	24
Gender (male/female)	16/8
Age (mean \pm SD, years)	57.08 \pm 14.33
Degree of liver injury	
Mild	20
Moderate	2
Severe	2
Types of liver injury	
Hepatocyte injury	22
Cholestasis type	2
Mixed	0
Time of abnormal liver function (mean \pm SD, days)	16.42 \pm 9.18

Analysis of Risk Factors of Liver Injury in Pulmonary Tuberculosis Complicated with Non-Alcoholic Simple Fatty Liver Disease

Logistic regression analysis found that among factors such as gender, age, BMI, triglycerides, and cholesterol, only cholesterol was a statistically significant high-risk factor (Table 3).

Discussion

China is a country with a large population of patients who have pulmonary tuberculosis, and many patients need anti-tuberculosis treatment. Drug-induced liver injury is one of the most common side effects of antituberculosis drugs, with the greatest harm. This harm manifests as transient transaminase elevation in light cases and liver failure in serious cases, even endangering life. Therefore, some patients need to stop antituberculosis treatment, thus affecting the therapeutic effect of tuberculosis medication. In addition to the hepatotoxicity of the drugs themselves, advanced age, alcoholism, and basic liver disease are high-risk factors for liver injury. There are many studies on the impact of chronic viral hepatitis on antituberculosis DILI.

Table 3 Analysis of Risk Factors of Liver Injury in Pulmonary Tuberculosis Complicated with Non-Alcoholic Simple Fatty Liver Disease

Factors	B	S.E	Wals	P	OR	95% CI for OR	
Gender	0.471	0.788	0.357	0.550	1.601	0.342	7.496
Age	-0.008	0.027	0.078	0.780	0.993	0.942	1.046
BMI	0.110	0.115	0.930	0.335	1.117	0.892	1.398
Triglyceride	-0.345	0.676	0.260	0.610	0.708	0.188	2.667
Cholesterol	1.441	0.626	5.308	0.021	4.226	1.240	14.405

Meta-analysis shows that both chronic hepatitis B and chronic hepatitis C may increase the risk of antituberculosis DILI.^{3,10,11} Patients with chronic hepatitis B co-infection receiving antituberculosis treatment are more prone to liver failure and progress to poor prognosis during antituberculosis treatment.⁵

Non-alcoholic fatty liver disease has become the most significant liver disease in China. However, there are relatively few studies on the influence of NAFLD on the incidence of antituberculosis DILI. Whether NAFLD will affect the incidence of antituberculosis DILI has not been confirmed. Mak et al used animal models to show that NAFLD does not increase the risk of liver injury induced by idiosyncratic drugs.¹² When evaluating many drugs, a pre-existing liver disease did not seem to be associated with an increased risk of idiosyncratic hepatotoxicity. However, an increasing number of studies have suggested that certain drugs can induce liver injury more frequently and more severely when exposed to pre-existing fatty liver disease. These drugs can also exacerbate pre-existing NAFLD and accelerate the transformation from steatosis to steatohepatitis.^{13,14} Compared with chronic hepatitis C, patients with NAFLD have a 4-fold higher risk of developing DILI.¹⁵ Cao et al showed that the incidence of DILI in patients with pulmonary tuberculosis complicated with NAFLD was 24.56%, which was significantly higher than that in patients with NAFLD.¹⁶ Fang et al reported that the incidence of antituberculosis DILI in patients with pulmonary tuberculosis complicated with fatty liver was 22%, significantly higher than 14.3% in patients without fatty liver.¹⁷ Xu et al believed that the incidence of antituberculosis DILI in patients with pulmonary tuberculosis complicated with fatty liver was 32.1%, and fatty liver is a high-risk factor for liver injury.¹⁸

In clinical practice, NAFLD can be divided into non-alcoholic simple fatty liver disease, non-alcoholic steatohepatitis, and steatohepatitis-associated cirrhosis. We chose non-alcoholic simple fatty liver as the study object to better accord with clinical practice and avoid the influence of basic liver function and liver protection drugs on the study. Our study found that the incidence of liver injury in the initial treatment of tuberculosis complicated with non-alcoholic simple fatty liver disease was 23%. This is significantly higher than 9.5–10.6% of antituberculosis DILI in China,¹⁹ but consistent with other domestic studies.^{16–18} This suggests that basic liver disease increases the risk of antituberculosis DILI. In the present study, the degree of liver injury was mostly mild liver injury, and the type of liver injury was more

common in hepatocyte types. The detection time of abnormal liver function in antituberculosis treatment was about two weeks. This was consistent with the relevant guidelines,^{7,9} indicating that most liver injuries could be controlled. Due to the limited observation time, it was not clear whether the liver injury would affect the antituberculosis efficacy. Our study suggested that age, gender, BMI, and triglyceride were not high-risk factors for antituberculosis DILI, but cholesterol was a high-risk factor for liver injury. Xu et al believed that dyslipidemia and being female were significantly correlated with DILI.²⁰ The increased risk of DILI in dyslipidemia may be explained by two mechanisms. First, malnutrition could slow drug clearance and subsequently lead to delayed drug elimination and higher drug plasma levels.²¹ Second, host factors, such as overnutrition and alcohol, may increase the pre-existing cellular oxidants of the host, modifying the drug-induced oxidative liver damage, resulting in steatosis, lipid peroxidation, and mitochondrial degeneration.²² Omaima et al believed that age, gender, alcohol consumption, and smoking status had no significant correlation with antituberculosis DILI.²³ Muzamil et al found that women were associated with an increased risk of antituberculosis DILI, while age and BMI did not significantly increase the risk of liver injury.^{24,25} Abbata et al believed that the risk factors for antituberculosis DILI included low body weight, HIV-combined infection, and alcohol consumption.²⁶ Therefore, the effect of influencing factors on the antituberculosis DILI was not determined from various studies and still excite controversy.

So far, the mechanism by which NAFLD increases liver injury with anti-tuberculosis drugs is unclear. It may be due to hepatic blood perfusion disorders, decreased hepatic blood flow, and decreased activity of liver metabolic enzymes, leading to slower drug clearance, prolonged biological half-life, and free drug concentration. Increased, thereby increasing the toxicity of the drug.

In summary, our study found that non-alcoholic simple fatty liver disease may increase the risk of antituberculosis DILI. However, there are some limitations. The sample size was small, and it was not possible to thoroughly observe whether antituberculosis treatment and prognosis were affected. There was no definite conclusion about the risk factors of antituberculosis DILI. Whether the non-alcoholic simple fatty liver disease impacts liver injury caused by antituberculosis drugs and other drugs has not yet been determined, and further studies are needed to better prevent and treat DILI.

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Disclosure

The authors report no conflicts of interest in this work.

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