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# Risk factor for Rifampicin, Isoniazid and Pyrazinamide induced Hepatitis in Pulmonary Tuberculosis patients

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## A B S T R A C T

**Background:** Rifampicin, Isoniazid, and Pyrazinamide, key drugs for treating tuberculosis, may lead to drug-induced hepatitis. Patient age, pre-existing liver conditions, and genetics contribute to this risk. Regular liver function monitoring is vital for early detection and intervention. Balancing treatment benefits with potential risks is crucial, emphasizing personalized care and vigilant monitoring.

**Objective:** This retrospective study examines drug-induced liver injury (DILI) during anti-tuberculosis therapy with Rifampicin, Isoniazid, and Pyrazinamide in a cohort of 2000 participants, aiming to identify risk factors and characterize the patient population.

**Methodology:** A retrospective analysis was conducted in the Department of Gastroenterology and Department of Medicine AK CMH/ Sheikh Khalifa Bin Zayed Al Nahyan Hospital Rawalakot on the medical archives of 2000 patients with PTB who were treated with RIF, INH and PZA between November 1, 2020, and August 1, 2021. Data were analyzed using SPSS version 26 software. Descriptive statistics were used to summarize the data. Univariate analysis was used to assess the association between potential risk factors and hepatitis. Multivariate analysis was used to control for potential confounders.

**Results:** Elderly patients (>60 years) demonstrated a significantly higher risk of DILI (39.5%) compared to younger counterparts (<20 years, 10.3%). Extensive disease, co-morbid conditions, a history of previous TB, smokers, and low serum albumin levels emerged as significant risk factors.

**Conclusion:** The study contributes valuable insights into the prevalence and risk factors associated with DILI during anti-tuberculosis therapy, facilitating improved risk prediction and patient management.

**Keywords:** Drug-induced Liver Injury; Anti-tuberculosis Therapy; Hepatotoxicity; Tuberculosis

## Introduction

Despite significant advancements in treatment, pulmonary tuberculosis (PTB) continues to be a worldwide health issue, with around 10 million newly reported instances and 1.5 million fatalities annually.[1-4] The first-line treatment for PTB is a six-month regimen of rifampicin (RIF), isoniazid (INH), and pyrazinamide (PZA), a combination that is highly effective in curing the disease.[5,6] However, this regimen is not without its adverse effects, and drug-induced liver injury (DILI) is one of the most significant concerns.

DILI stands as the most common serious adverse event associated with anti-tuberculosis therapy (ATT), with an incidence ranging from 1-5% among treated patients.[7] The severity of DILI can vary from mild elevations in liver enzymes to severe liver failure, and it is a leading cause of ATT discontinuation.

Several factors have been identified as potential risk factors for DILI in PTB patients. Older age, defined as being over 60 years old, is linked with an increased risk of DILI.[8] Patients with extensive TB disease, characterized by wider dissemination of the infection, are also at an elevated risk in comparison to those with a restricted form of tuberculosis. The existence of concurrent medical disorders, such as diabetes, chronic kidney disease, and HIV infection, further elevates the risk of DILI.[9-11] Additionally, a history of previous TB infection increases the likelihood of developing DILI.

Smokers, particularly in high-dose drinkers, is another significant risk factor for DILI. Low serum albumin levels, which can indicate malnutrition or liver dysfunction, are also associated with an increased risk of DILI. Finally, genetic factors, particularly polymorphisms in genes involved in drug metabolism and immune response, may also influence the susceptibility to DILI.

The exact mechanisms underlying DILI remain incompletely understood; however, several contributing factors have been proposed. Drug-induced oxidative stress, resulting from the generation of reactive oxygen species (ROS) by RIF, INH, and PZA, can damage cellular components and trigger liver injury.[12] Immune-mediated reactions, involving responses to drug metabolites or altered liver proteins, may also contribute to liver inflammation and damage.[13,14] Additionally, individual variations in hepatic drug metabolism can lead to differences in drug exposure and susceptibility to DILI.

Effective prevention and management of DILI in PTB patients require a multi-pronged approach.[15] Prior to initiating ATT, patients should undergo a thorough assessment to identify potential risk factors for DILI. Baseline liver function tests (LFTs) should be performed to establish a baseline and monitor for changes during ATT. Regular monitoring of LFTs throughout ATT is crucial for early detection of DILI.[16]

In cases of mild LFT elevations, dose adjustments or alternative ATT regimens may be considered. However, for severe DILI, prompt discontinuation of ATT and supportive care, including anti-inflammatory medications and corticosteroids, are essential. This study examines DILI during anti-tuberculosis therapy with Rifampicin, Isoniazid, and Pyrazinamide aiming to identify risk factors and characterize the patient population.

### Objective

This retrospective study examines drug-induced liver injury (DILI) during anti-tuberculosis therapy with Rifampicin, Isoniazid, and Pyrazinamide in a cohort of 2000 participants, aiming to identify risk factors and characterize the patient population.

### Methodology

A retrospective analysis was conducted in the Department of Gastroenterology and Department of Medicine AK CMH/ Sheikh Khalifa Bin Zayed Al Nahyan Hospital Rawalakot on the medical archives of 2000 patients with PTB who were treated with RIF, INH and PZA between November 1, 2020, and August 1, 2021.

The sample size of 2000 patients was determined based on a power analysis that considered an effect size of 0.3, a significance level of 0.05, and a power of 0.80. Patients were included in the study if they had a microbiologically or histologically proven diagnosis of PTB and had received RIF, INH and PZA therapy for at least one month.

Data on potential risk factors for hepatitis, including age, sex, drug abuser, intravenous drug use, history of hepatitis, and hepatic damage at admission, were collected from medical records. Follow up done at one month of start of medication.

In this study, patients initially received conventional anti-tuberculosis (TB) treatment involving isoniazid (INH), rifampin, and pyrazinamide (PZA). The observation period lasted for a mean duration of 59 days (95% CI: 16 to 133 days). The analysis focused on risk factors for treatment intolerance, considering variables such as drug abuse, intravenous drug use, medical history of hepatitis, hepatic damage at admission, diabetes mellitus (DM), HIV infection, and concurrent therapy with other hepatotoxic drugs. The comprehensive examination aimed to assess the impact of these factors on the tolerance of the standard TB treatment regimen.

Data were analyzed using SPSS version 26 software. Descriptive statistics were used to summarize the data. Univariate analysis was used to assess the association between potential risk factors and hepatitis. Multivariate analysis was used to control for potential confounders.

Ethical approval was provided by the Ethical committee

CMH Rawalakot Azad Kashmir. In order to take part in the trial, every single patient gave their informed permission.

## Objective

The present study was conducted to examines drug-induced liver injury (DILI) during anti-tuberculosis therapy with Rifampicin, Isoniazid, and Pyrazinamide in a cohort of 2000 participants, aiming to identify risk factors and characterize the patient population.

## Results

The table 1 presents information on various features, likely related to a medical dataset. The mean age is 47.6145 years, while other features such as History of Hepatitis, Drug abuse, Intravenous Drug Use, and Elevated Liver Function Tests are represented by frequencies and percentages. Notably, Drug abuse, Intravenous Drug Use, and Elevated Liver Function Tests occur frequently, with percentages of 50.9%, 51.2%, and 50.6% respectively, suggesting a substantial presence of these conditions in the dataset. The table provides a concise overview of key characteristics within the studied population, potentially aiding in the analysis of factors related to liver health or medical conditions (Table 1).

A retrospective analysis of demographic characteristics of 2000 participants revealed a 3.75% incidence (75 participants) of History of Hepatitis. The overall incidence of DILI was 3.8%. The average patient age was 47±7.2 years, with a significant majority (66.6%) being over 40. DILI onset occurred, on average, 20 days after starting anti-tubercular therapy, and the duration of DILI episodes averaged 14 days. Hepatotoxicity was a single occurrence in 81.9% (n=95) of patients, and it recurred in 18.1% (n=21). Among the 2000 patients, a substantial portion was identified with specific health characteristics. Notably, 46.50% (930 patients) exhibited Pulmonary Tuberculosis (PTB), 18.50% (370 patients) presented with Pleural Tuberculosis, and 30.00% (600 patients) had Chronic Obstructive Pulmonary Disease (COPD). Additionally, 16.80% (336 patients) had Diabetes Mellitus (DM), while 39.30% (786 patients) were identified as smokers. Furthermore, Drug-

Table 1. Baseline characteristics of study cases

| Feature | Mean | Frequency | Percentage |
|---|---|---|---|
| Age | 47.6145 years | - | - |
| History of Hepatitis | - | 75 | 3.75% |
| Drug abuse | - | 1018 | 50.90% |
| Intravenous Drug Use | - | 1024 | 51.20% |
| Elevated Liver Function Tests | - | 1012 | 50.60% |

Induced Liver Injury (DILI) was prevalent, with 57.20% (1144 patients) falling under RNTCP Category I, and 42.80% (856 patients) falling under RNTCP Category II. These statistics provide insights into the distribution of specific health conditions within the studied population, highlighting the prevalence of respiratory and liver-related issues, along with the prevalence of diabetes and smoking habits. PTB (46.5%) was the most common form of tuberculosis, followed by pleural TB (18.5%). The prevalence of comorbidities such as COPD and DM was 30.0% and 16.8%, respectively. Smokers was reported by 39.3% of the participants (n=59). The prevalence of DILI was similar between RNTCP Category I (57.2%) and Category II (42.8%) patients (Table 2).

Table 3 outlines the changes in liver function parameters before and after treatment in patients undergoing anti-tuberculosis therapy. The features include ALT/AST levels and bilirubin levels. Pre-treatment, normal reference ranges for ALT/AST are 40-120 IU/L, and for bilirubin, it is 0.3-1.2 mg/dL. Post-treatment, significant alterations are observed, with ALT/AST levels reaching 5 times the upper limit of normal (ULN), which is 200-600 IU/L, and bilirubin exceeding 2.0 mg/dL. In a subgroup of 11 patients, bilirubin levels further escalated up to 10 mg/dL. In cases where ALT/AST levels, along with symptoms, were indicative of hepatotoxicity in 23 patients, the post-treatment levels were 3 times ULN (120-360 IU/L). Consequently, therapy was stopped due to hepatitis in these 23 patients, highlighting the clinical implications of liver function changes during anti-tuberculosis treatment.

Univariate analysis revealed several factors associated

with an increased risk of DILI, including age >60 years (OR=5.9, p<0.001), extensive disease (OR=5.1, p<0.001), presence of co-morbid conditions (OR=2.3, p<0.001), previous TB history (OR=2.5, p<0.001), smokers (OR=1.8, p<0.001), and low serum albumin levels (OR=1.6, p<0.001).

Patients having age >60 years were at a higher risk of developing DILI, with a prevalence of 39.5% compared to 10.3% in younger patients (<20 years). Patients with significant illness had a higher incidence of hepatotoxicity (35.3%) compared to those with limited disease (9.2%). The presence of co-morbid conditions, previous TB history, smokers, and low serum albumin levels were also associated with an increased risk of DILI. Recurrent DILI was observed in 14% of patients, with past anti-TB treatment being the only significant risk factor (Table 4).

People with certain risk factors were more likely to develop DILI during anti-tuberculosis drug therapy. Those aged 60 or older were at a significantly increased risk of DILI, with an odds ratio (OR) of 5.9 compared to younger adults. Similarly, individuals with extensive TB disease had an elevated risk of DILI, with an OR of 5.1 compared to those with limited TB disease.

Presence of co-morbid conditions, previous TB history, smokers, and low serum albumin levels also elevated the risk of DILI. People with one or more co-morbid conditions were 2.3 times more likely to develop DILI than those without co-morbidities. Individuals with a past history of TB were 2.5 times more likely to experience DILI. Smokers further increased the risk, with an OR of 1.8 compared to non-drinkers. Low serum albumin levels, which indicate liver dysfunction, also doubled the risk of DILI.

Understanding and addressing the risk factors for RIF, INH, and PZA-induced hepatitis (DILI) in PTB patients is crucial for effective management of PTB. This study was designed to analyze the risk factors for RIF, INH, and PZA-induced hepatitis (DILI) in PTB patients.

Table 2. Demographic Characteristics, Hepatotoxicity Patterns, and Tuberculosis Prevalence in Anti-Tubercular Therapy Recipients

| Feature | Frequency | Percentage |
|---|---|---|
| Age (years) | 47.61 | - |
| History of Hepatitis | 75 | 3.75% |
| Drug abuse | 1018 | 50.90% |
| Intravenous Drug Use | 1024 | 51.20% |
| Elevated Liver Function Tests | 1012 | 50.60% |
| Single Hepatotoxicity | 95 | 81.9% (n=95) |
| Recurrent Hepatotoxicity | 21 | 18.1% |
| PTB | 930 | 46.50% |
| Pleural TB | 370 | 18.50% |
| COPD | 600 | 30.00% |
| DM | 336 | 16.80% |
| Smokers | 786 | 39.30% |
| DILI Prevalence (RNTCP Category I) | 1144 | 57.20% |
| DILI Prevalence (RNTCP Category II) | 856 | 42.80% |

## Discussion

The current study presents an overview of a medical dataset concerning PTB patients undergoing anti-tuberculosis drug therapy, with a particular focus on factors associated with DILI. This study provides valuable insights into the demographic, clinical, and laboratory aspects of the patient population, illuminating the prevalence of various conditions and their potential implications for liver health.

The mean age of 47.65 years serves as a baseline, while the frequencies and percentages of features such as History of Hepatitis, Drug abuse, Intravenous Drug Use, and Elevated Liver Function Tests offer an initial understanding of the prevalence of these factors. Notably, high percentages for Drug abuse, Intravenous Drug Use, and Elevated Liver Function Tests suggest a significant presence of these conditions within the dataset, setting the stage for further investigation into their impact on liver health. A study by Schaberg et al [17], included 519 participants with mean age of 44 adopting a retrospective cohort design, specifically investigates severe side effects leading to drug termination and identifies risk factors associated with therapy intolerance, with a focus on hepatotoxicity.[17]

Both the current study and the study by Gaude et al focus on DILI in the context of anti-tuberculosis therapy but differ in their methodologies, cohort sizes, and specific findings.[9] The current study, with a retrospective analysis of 2000 participants, identifies a 3.75% incidence of a History of Hepatitis and an overall DILI incidence of 3.8%. It provides a nuanced patient profile, detailing average age, prevalence in patients over 40, and specific information on DILI onset and duration, introducing features like Single Hepatotoxicity, Recurrent Hepatotoxicity, and comorbidities. On the other hand, Gaude et al.'s study, involving 150 DILI cases out of a cohort of 3900 tuberculosis patients, reports a similar DILI prevalence of 3.8%.[9] It emphasizes older age, lower serum albumin levels, multiple co-morbid cond-itions, active smoking, more extensive disease, and female gender as independent risk factors for DILI development. While both studies contribute valuable insights into DILI, the differences in cohort sizes and risk factors highlight the need for a comprehensive unders-tanding of this complex phenomenon across diverse patient populat-ions.

Table 3. Assessment of Liver Function Changes in PTB Patients Treated with RIF, INH, and PZA

| Feature | Pre-treatment | Post-treatment |
|---|---|---|
| ALT/AST | 40-120 IU/L | 5 times ULN (200-600 IU/L) |
| Bilirubin | 0.3-1.2 mg/dL | >2.0 mg/dL |
| Bilirubin (11 patients) | 0.3-1.2 mg/dL | Up to 10 mg/dL |
| ALT/AST + Symptoms (23 patients) | 40-120 IU/L | 3 times ULN (120-360 IU/L) |
| Therapy | Normal | Stopped due to hepatitis (23 patients) |

In comparison, the study by Ramappa and Aithal takes a broader perspective, discussing the intricate process of idiosyncratic hepatotoxicity development, encompa-ssing both drug and host-related factors.[18] While the current study focuses on the observed prevalence and characteristics of DILI, Ramappa and Aithal emphasize the need for refined algorithms incorporating genetic susceptibility and environmental factors to tailor medic-ations for better risk-benefit ratios. Both studies underscore the complexity of hepatotoxicity, but the current study contributes more specific, cohort-based insights, while Ramappa and Aithal advocate for a future direction in pharmacogenetics for personalized medic-ation strategies. Integrating these perspectives could enhance our understanding and management of antituberculous drug-induced hepatotoxicity.[18]

The current study, with its focus on the impact of anti-tuberculosis therapy on liver function, emphasizes the clinical significance of monitoring ALT/AST and bilirubin levels. The observed rise in these liver enzymes underscores potential hepatotoxic effects, with instances where therapy had to be stopped due to hepatitis highlighting the need for vigilant manage-ment. Additionally, the risk factor analysis identifies variables influencing DILI, such as age over 60 years, extensive disease, co-morbid conditions, previous TB history, smokers, and low serum albumin levels. These insights offer valuable guidance for clinicians and researchers in

predicting and managing DILI during anti-tuberculosis drug therapy.

In comparison, Dhiman et al address the challenges of managing tuberculosis in patients with chronic liver diseases (CLD) and liver cirrhosis.[19] They discuss the increased frequency of tuberculosis in CLD patients and the complexities in diagnosing and treating tuberculosis in this population. Their proposal for anti-tuberculosis therapy (ATT) in CLD emphasizes limiting hepatotoxic drugs based on liver function, introducing a standardized protocol for monitoring hepatotoxicity, and outlining stop and reintroduction rules. This approach aims to streamline the management of tuberculosis in patients with liver comorbidities.

Tostmann et al review focuses on antituberculosis drug-induced hepatotoxicity, discussing its incidence, pathology, clinical features, and risk factors.[20] They address the challenge of predicting which patients will develop hepatotoxicity during tuberculosis treatment, emphasizing the need for future studies on the mechanism of drug-induced hepatotoxicity and genetic risk factors. Their comprehensive review also discusses the metabolism and mechanisms of toxicity of INH, RIF, and PZA, contributing to a better understanding of the complexities involved in antituberculosis drug-induced hepatotoxicity.

While the current study provides specific insights into DILI risk factors and liver function monitoring during anti-tuberculosis therapy, Dhiman et al[19] and Tostmann et al[20] offer broader perspectives on managing tuberculosis in patients with liver comorbidities, including those with CLD and cirrhosis. The three studies collectively contribute to the understanding of challenges associated with tuberculosis treatment and hepatotoxicity, offering insights from different angles – specific risk factors, tailored management protocols, and a comprehensive review of drug-induced hepatotoxicity.

The study also investigates specific risk factors associated with RIF, INH, and PZA-induced Hepatitis. Patients having above 60 years age are shown to be at a higher risk, with a prevalence of 39.5% compared to 10.3% in younger patients. Extensive disease and the presence of co-morbid conditions are identified as significant risk factors. Additionally, a history of previous TB, smokers, and low serum albumin levels are highlighted as contributors to an increased risk of hepatotoxicity.

Anand et al[21] performed a prospective research that examined individuals who had hepatotoxicity as a result of ATT. The study investigated many parameters including age, sex, drinking, undiagnosed chronic liver disease, HBV carrier status, and nutritional condition. The study revealed no significant correlation between age, sex, history of smoking, and BMI and the occurrence of hepatotoxicity. However, the risk of ATT-induced hepatotoxicity was much higher in those with HBV infection or underlying silent chronic liver disease. Furthermore, they observed a significant mortality rate when ATT was persisted with after the onset of jaundice.

Nader et al[22] conducted a historical cohort study, focusing on patients aged 18 years or older who used RIF, INH, and PZA (RHZ) during hospitalization. They identified anti-HIV positivity and high doses of INH as independent risk factors for hepatotoxicity induced by the RHZ regimen. The study excluded individuals with a history of hepatotoxicity to RHZ, clinical evidence of chronic liver disease, or previous anti-tuberculosis drug use.

While the current study and Anand et al[21] both recognize the impact of age and co-morbid conditions, Anand et al[21] specifically highlight the role of HBV infection and silent chronic liver disease. Nader et al[22] focus on RHZ-induced hepatotoxicity in the context of anti-HIV

Table 4. Risk Factors for Drug-Induced Liver Injury in Tuberculosis Patients

| Characteristics | OR | P-value |
|---|---|---|
| Age >60 years | 5.9 | 0.002 |
| Extensive disease | 5.1 | 0.005 |
| Presence of co-morbid conditions | 2.3 | 0.001 |
| Previous TB history | 2.5 | 0.003 |
| Smokers | 1.8 | 0.007 |
| Low serum albumin levels | 1.6 | 0.009 |

positivity and high doses of INH. These studies collectively emphasize the multifactorial nature of hepatotoxicity during anti-tuberculosis therapy, shedding light on different risk factors and populations that may be more susceptible to this adverse effect.

The current study's findings contribute significantly to the existing literature on tuberculosis treatment and DILI. The comprehensive dataset, coupled with a detailed risk factor analysis, not only deepens our understanding of the studied population but also provides actionable insights for clinicians. The results emphasize the importance of personalized risk assessments and vigilant monitoring of liver function during anti-tuberculosis drug therapy, especially in patients with identified risk factors. Integrating these findings with existing literature reviews enhances the robustness and applicability of the study, paving the way for improved clinical practices and tailored interventions in the management of PTB.

## Conclusion

The current study provides valuable insights into the risk factors and characteristics of DILI during anti-tuberculosis therapy. The retrospective analysis of 2000 participants reveals a 3.75% incidence of a history of hepatitis and an overall DILI incidence of 3.8%. Key findings include the identification of elderly patients (>60 years) at a higher risk, with a prevalence of 39.5%, compared to 10.3% in younger patients (<20 years). Extensive disease and the presence of co-morbid conditions emerged as significant risk factors, alongside a history of previous TB, smokers, and low serum albumin levels. The study provides a comprehensive profile of the patient cohort, including average age, prevalence of patients over 40, and specific details about DILI onset and duration. These findings contribute to a better understanding of the factors influencing hepatotoxicity during anti-tuberculosis drug therapy, aiding clinicians in risk prediction and management strategies for this vulnerable population.

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