Original Article
DOI: https://doi.org/10.70749/ijbr.v3i6.1595

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Frequency of Hepatotoxicity in Pulmonary Tuberculosis Patients Taking Anti-Tuberculous Therapy

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ARTICLE INFO

Keywords: Hepatotoxicity, Pulmonary Tuberculosis, Anti-Tuberculous Therapy, Drug-Induced Liver Injury, TB Treatment,

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Declaration
Authors' Contribution
All authors equally contributed to the study and approved the final manuscript

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History
Received: 04-05-2025 Revised: 27-05-2025
Accepted: 05-06-2025 Published: 11-06-2025

ABSTRACT

Background: Anti-tuberculous therapy (ATT), while effective in treating pulmonary tuberculosis, carries the risk of hepatotoxicity due to drugs such as isoniazid, rifampicin, and pyrazinamide. **Objective:** To determine the frequency of hepatotoxicity among patients with newly diagnosed pulmonary tuberculosis receiving standard ATT during the intensive phase. **Methods:** This cross-sectional study was conducted at the Department of Pulmonology, Allama Iqbal Medical College / Jinnah Hospital, Lahore. A total of 112 patients aged 18–75 years with newly diagnosed pulmonary tuberculosis on ATT for at least one month were enrolled using non-probability consecutive sampling. Patients with a history of liver disease, prior tuberculosis, alcohol use, hakeem medications, or drug hypersensitivity were excluded. Liver function tests (ALT, AST, ALP, bilirubin) were performed fortnightly. **Results:** Among 112 patients, 9 (8.0%) developed ATT-induced hepatotoxicity. Most cases were observed within 4 to 6 weeks of treatment. A significant association was found between hepatotoxicity and age over 50 years ($p = 0.04$) and smoking history ($p = 0.01$). Other factors such as gender, residence, weight, and income level did not show statistically significant associations. ALT was elevated in all affected cases, followed by raised AST, ALP, and bilirubin levels. Most patients recovered with dose modification; one required hospitalization. **Conclusion:** It is concluded that hepatotoxicity is a notable adverse effect during the intensive phase of anti-tuberculous therapy, with smoking and older age emerging as significant risk factors.

INTRODUCTION

Tuberculosis (TB) in humans is caused by Mycobacterium tuberculosis, a bacterial species in the Mycobacterium tuberculosis complex which is a genus made up of nine different bacteria [1]. Globally, the rate of new TB cases (per 100,000 persons) has gone down, from 144.12 in 1990 to 97.56 in 2019, an average decrease of 1.28 percent each year. On the other hand, the number of extensively drug-resistant and multi-drug-resistant TB cases has been going up [2]. The gold standard test for TB diagnosis is mycobacterial culture and it may find as little as 10 bacilli per milliliter [3]. Because acid-fast bacilli (AFB) smear microscopy has a detection threshold of 5,000 bacilli/ml and is much lower in cost, it is commonly used for diagnosis [4]. The Mycobacterium tuberculosis/rifampicin (MTB/RIF) assay detects as little as 136 bacilli/ml and is able to spot the presence of rifampicin resistance [5].

The typical therapy for tuberculosis is anti-tuberculous therapy (ATT) which can result in the liver being injured, sometimes seriously enough for the therapy to be stopped [6]. In this situation, researchers found that out of those taking anti-tuberculosis medicine, 7.9% of pulmonary tuberculosis patients had hepatotoxicity 6. Another study reported that hepatotoxicity from ATT happened in 14% of cases [7]. A study found that 20.3% of patients with pulmonary tuberculosis experienced hepatotoxicity while receiving anti-tuberculous therapy (ATT) [8]. One article reported that anti-tuberculous drugs (ATT) might have caused hepatotoxicity in up to 36.8% of pulmonary tuberculosis patients [9].

If ATT-related toxicity in the liver is not handled early, it may be fatal. Many people in Pakistan have tuberculosis which is why so many cases of ATT are treated. Hence, measuring the impact of this serious ATT complication locally is important. The study aims to measure the number of pulmonary tuberculosis patients who experience hepatotoxicity when using anti-tuberculous therapy (ATT).

Objectives

To determine the frequency of hepatotoxicity in pulmonary tuberculosis patients taking anti-tuberculous therapy (ATT).

METHODOLOGY

This cross-sectional study was conducted at Department

of Pulmonology, Allama Iqbal Medical College / Jinnah Hospital, Lahore from Jan 2025- April 2025. Non-probability consecutive sampling technique was used for data collection. A sample size be calculated using WHO sample size calculator taking:

- Confidence interval = 95%
- Absolute precision = 5%
- Expected frequency of hepatotoxicity in pulmonary tuberculosis patients taking ATT = 7.9% [6]
  Calculated sample size is 112.

Inclusion criteria

- Age 18-75 years.
- Male and female gender.
- Newly diagnosed cases of pulmonary tuberculosis taking ATT during intensive phase (as per operational definition) for at least 1 month.

Exclusion criteria

1. Those with previous history of tuberculosis, assessed by review of previous medical records.
2. History of chronic liver disease, assessed by review of previous medical records.
3. History of alcohol use, assessed by review of previous medical records.
4. History of hakeem medication, assessed by review of previous medical records.
5. History of hypersensitivity to ATT, assessed by review of previous medical records.

Data Collection

Following approval from the College of Physicians and Surgeons Pakistan (CPSP) and informed consent from each participant, data collection was initiated in the pulmonology outpatient department. Demographic and baseline clinical information including age (in years), gender, weight (in kilograms), baseline liver function tests (serum bilirubin, AST, ALT, ALP), education status (illiterate vs. school education or above), area of residence (urban vs. rural), monthly income (< PKR 80,000 or ≥ PKR 80,000), and smoking history were recorded using a structured proforma. Participants were then initiated on standard ATT, and provided education regarding the clinical symptoms of hepatotoxicity. A contact number was shared for immediate reporting of symptoms. Additionally, liver function tests were repeated every two weeks during the intensive phase to detect evidence of hepatotoxicity, as per the study's operational definition. In cases where hepatotoxicity was identified, standard clinical protocols were followed for management in accordance with national guidelines. Confidentiality of all patient data was strictly maintained, and no personal identifiers were used.

Data Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 20. Numerical variables such as age, body weight, and liver enzyme levels were summarized as means ± standard deviations. Categorical variables, including gender, education level, residence, income category, smoking status, and occurrence of hepatotoxicity, were expressed as frequencies and percentages. The primary outcome frequency of ATT-induced hepatotoxicity was calculated and then stratified by potential effect modifiers, including age group, sex, body weight, and smoking history. Post-stratification, the chi-square test or Fisher's exact test was applied where appropriate to assess statistical significance. A p-value ≤ 0.05 was considered statistically significant for all analyses.

RESULTS

Data were collected from 112 patients. The mean age of the study participants was 42.6 ± 14.2 years, and the average weight was 58.1 ± 9.7 kg. Males made up 56.3% of the cohort, while females accounted for 43.8%. Most patients were educated (59.8%) and lived in rural areas (60.7%). The majority had a monthly income below PKR 80,000 (66.1%), and 31.3% of participants were smokers.

Table 1

Baseline Characteristics of Study Participants (n = 112)

Variable	Value
Age (years, Mean ± SD)	42.6 ± 14.2
Weight (kg, Mean ± SD)	58.1 ± 9.7
Gender	
– Male	63 (56.3%)
– Female	49 (43.8%)
Education	
– Illiterate	45 (40.2%)
– School or above	67 (59.8%)
Residence	
– Rural	68 (60.7%)
– Urban	44 (39.3%)
Monthly Income	
– < PKR 80,000	74 (66.1%)
– ≥ PKR 80,000	38 (33.9%)
Smoking Status	
– Smokers	35 (31.3%)
– Non-Smokers	77 (68.7%)
Hepatotoxicity Status	
– Present	9 (8.0%)
– Absent	103 (92.0%)

Hepatotoxicity was more common in patients older than 50 years (55.6% vs. 27.2%, p = 0.04) and those with a history of smoking (66.7% vs. 28.2%, p = 0.01). Other variables such as male gender, low body weight, rural residence, and low income were more frequent among patients with hepatotoxicity but did not reach statistical significance.

Table 2

Stratification of Hepatotoxicity by Demographic Variables

Variable	Hepatotoxicity Present (n=9)	Hepatotoxicity Absent (n=103)	p-value
Age > 50 years	5	28	0.04
Gender (Male)	6	57	0.51
Weight < 55 kg	4	29	0.32
Smoking History	6	29	0.01
Rural Residence	6	62	0.71
Low Income (<80,000 PKR)	7	67	0.47

Among patients who developed hepatotoxicity, raised ALT was observed in all cases (100%), making it the most consistent biochemical marker, followed by raised AST in 88.9% of cases. ALP and bilirubin levels were elevated in 66.7% and 55.6% of patients, respectively, indicating a predominantly hepatocellular pattern of liver injury. The onset of hepatotoxicity varied, with the majority of cases occurring within 4 to 6 weeks of initiating anti-tuberculous therapy. Specifically, 33.3% of patients developed hepatotoxicity at both 4 and 6 weeks, while

earlier onset at 2 weeks was noted in 22.2%, and 11.1% developed symptoms by 8 weeks.

Table 3
Liver Enzyme Abnormalities and Onset Time of Hepatotoxicity in Patients Receiving ATT

Parameter	Category	Frequency (n)	Percentage (%)
Liver Enzyme Abnormalities	Raised ALT	9	100.0
	Raised AST	8	88.9
	Raised ALP	6	66.7
	Raised Bilirubin	5	55.6
Onset Time of Hepatotoxicity	2 weeks	2	22.2
	4 weeks	3	33.3
	6 weeks	3	33.3
	8 weeks	1	11.1

Among the nine patients who developed hepatotoxicity, the majority (44.4%) recovered with simple dose adjustments. In 22.2% of cases, the offending drugs had to be discontinued, while another 22.2% required switching to an alternative regimen. Only one patient (11.1%) experienced severe hepatotoxicity necessitating hospitalization.

Table 4
Outcome of Hepatotoxicity Cases (n = 9)

Outcome	Frequency (n=9)	Percentage (%)
Resolved with dose adjustment	4	44.4
Required drug discontinuation	2	22.2
Switched to alternative regimen	2	22.2
Hospitalization required	1	11.1

DISCUSSION

The aim of this research was to see how often hepatotoxicity develops in patients treated with anti-tuberculous drugs (ATT) for newly identified pulmonary tuberculosis during the intensive phase. According to our results, 8.0% of all patients experienced ATT-induced hepatotoxicity, a number that is within the range reported in the literature (5% to 15%) for various types of populations, threshold tests and surveillance rules. The incidence found in this study is very similar to the 7.9 percent reported by other regional studies which suggests that standard first-line TB drugs may lead to liver toxicity, especially from isoniazid, rifampicin and pyrazinamide [11-13]. They have been found to trigger damage to liver cells through increasing oxidative stress which also leads to an elevation in liver enzymes. Higher levels of alanine transaminase and aspartate transaminase in affected patients further indicate a possible injury to liver cells (hepatocellular injury).

The analysis found that older people (greater than 50 years) and those with a history of smoking had a higher probability of developing hepatotoxicity. Findings like these go well with research suggesting age and changes in the liver can increase the risk of liver injury from drugs [14-15]. The presence of smoking which is modifiable, is believed to raise the intensity of oxidative effects in the liver and to alter the way cytochrome P450 responds to anti-tuberculous drugs, causing them to be more toxic.

Even though results here failed to link gender, weight, place of residence and low income with hepatotoxicity, research suggests that they can increase the risk by resulting in malnutrition and fewer visits to healthcare. Because of the small sample included and the strong exclusion of subjects with hepatic conditions, the results show no major link. Liver damage most often occurred in the first four to six weeks of starting treatment, hence it is very important to regularly check the liver function during this early period. Most people received prompt management because their condition was detected early and the management could involve altering the dose or halting treatment temporarily. There was just one patient hospitalized and no case of acute liver failure was seen.

These results back up what has been found in past studies [16-17]. As an example, Moudgil et al. noted that 6.6 percent of similar patients from Pakistan experienced hepatotoxicity and they concluded that age and nutritional health influenced this rate. Based on the results of Shakya and colleagues, 10.5 percent of cases they observed were associated with alcohol use or HIV, so those cases were excluded here to avoid confusion. Vashisht and the other researchers found that 13.1 percent of Indians experienced drug-induced liver injury which is different from our finding because they studied a group where existing liver disease was not excluded [18]. This study was effective because it followed a prospective design and societal feature and regularly checked patients' biochemical values during intensive treatment which revealed both apparent and silent liver complications. Still, this study was performed at only one center, included a small number of people and lacks any genetics or biochemistry that would show who would be more vulnerable. More research that includes larger numbers of patients and looks at pharmacogenetic data may give more insights into risk stratification for hepatotoxicity.

CONCLUSION

It is concluded that anti-tuberculous therapy during the intensive phase is associated with a measurable risk of hepatotoxicity, with an observed frequency of 8.0 percent in this study population. Older age and smoking history were significantly associated with an increased risk of developing hepatotoxicity. These findings emphasize the importance of baseline assessment, patient education, and regular liver function monitoring particularly during the first six weeks of treatment to enable timely detection and management. Implementing targeted surveillance for high-risk individuals may improve treatment outcomes and reduce the burden of drug-induced liver injury among patients receiving anti-tuberculous therapy.

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