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Original Article

Frequency of Anti-tuberculosis Treatment Induced Hepatitis in Patients Taking Standard Anti-Tuberculosis Treatment

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Abstract

Objective: To determine the frequency of ATT induced hepatitis in patients taking Standard ATT presenting in a tertiary care hospital of Lahore, Pakistan.

Methods: This cross sectional study was undertaken at the Department of Medicine, Gulab Devi Teaching Hospital, Lahore from 12th February 2025 to 11th April 2025. Data from 80 adult patients meeting inclusion criteria were collected after verbal consent. Baseline assessments included liver enzyme tests, abdominal ultrasound, and screening for HBV, HCV, and HIV to exclude existing liver disease. Demographic and clinical details were recorded, and patients were followed up weekly at Gulab Devi Hospital, Lahore. Data were examined utilizing SPSS version 25.

Results: The average age of the patients was 35.61±12.17 years. Out of the total of 80 patients that were examined, 14 patients (17.5%) presented with ATT-induced hepatitis as one of the complications of the treatment. Alternatively, 66 patients (82.5%) presented with no hepatic complications of the therapy. The findings indicate a strong correlation between age and ATT-induced hepatitis ($p = 0.035$) and patients ≥ 35 years old were at higher risk of developing hepatic side effects. Hepatitis developed in 19.6% of men and 14.7% of women ($p = 0.572$), indicating no gender difference. Hepatitis developed in 12.1% of overweight patients and 25.0% of obese patients ($p = 0.544$). Hepatitis was more frequently observed in treated patients for ≤ 30 days (21.8%) than those treated for 31–45 days (8.0%), although the variation was not significant ($p = 0.132$).

Conclusion: The study found that 17.5% of patients on anti-tuberculosis treatment developed hepatitis, highlighting a notable risk of hepatotoxicity. Adults aged ≥ 35 may require closer liver function monitoring during therapy.

Keywords: Mycobacterium tuberculosis, ATT induced hepatitis, Rifampicin, Rifabutin

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Introduction

Tuberculosis (TB) is an infectious, long-standing disease produced by Mycobacterium tuberculosis. It has been known to be a most deadly infectious illness for centuries. Even with vast improvements in the field of medicine, TB is still a dangerous worldwide health concern.[1,2] It is still considered one of the deadliest infections transmitted by a single causative agent.[3] It is most burdened by this disease in developing countries, where Pakistan ranks number 7 of countries with the most prevalent TB. Pakistan's incidence rate is 275 cases per 100,000 population.[4] Drug-induced hepatitis due to anti-tuberculosis drugs (AT-DIH) is a common and possibly serious side effect during treatment for tuberculosis. Evidence suggests that a number of factors—advanced age, smoking, alcohol use, and oxidative stress—can play a role in the development of AT-DIH.[5] In addition to the disease, management is further complicated by the adverse effects of anti-tubercular therapy (ATT) especially its hepatotoxicity.[3]

In one study, hepatic impairment was observed in 19.67% of ATT patients[3]. The complications are observed more often in developing regions,[6] where baseline liver disease is also more common. This is problematic for the management of ATT-induced liver toxicity in countries like Pakistan that already have a high burden of

liver disease. The hepatotoxicity commonly presents with increased liver enzymes and may lead to the suspension or stopping of therapy, putting at risk the success of tuberculosis treatment.[4] Currently, the main drugs for the treatment of tuberculosis are isoniazid, rifampin, pyrazinamide, and ethambutol. Of these drugs, all except ethambutol are associated with hepatotoxic effects. The prevalence of hepatotoxicity and other adverse effects related to them is variable, occurring in about 3% to 28% of the patients.[7]

Of these, Pyrazinamide is the most hepatotoxic with an incidence of liver injury at around 9%, then Isoniazid at 3%, and Rifampicin at around 1%.[8] While Rifampicin is not too highly hepatotoxic, it very markedly potentiates the hepatotoxicity of other drugs, specifically Isoniazid. Ethambutol, on the contrary, is commonly described as hepatoprotective or "liver- friendly.[9]" When these drugs are administered concomitantly—particularly during the intensive phase of treatment for TB—the risk of hepatotoxicity is additive. International reports have documented ATT-induced liver damage in 5% to 31% of patients, while studies from Pakistan show a relatively lower incidence, which varies between 5% and 11%.[10,11]

A notable adverse effect of first-line ATT is drug-induced hepatitis, which can result in the discontinuation of treatment, greater morbidity, and even death due to liver failure.[12] Prompt recognition of risk factors and periodic liver function monitoring can facilitate earlier detection of hepatotoxicity, with better outcomes and fewer complications. A Lahore study revealed that 72.7% of cases of ATT-induced hepatitis developed early in the course of treatment.[3] Hepatotoxicity was seen more frequently in advanced pulmonary TB (16.66%) patients than in those with minimal (7.14%) or moderately advanced (2.17%) disease.[13] Elderly patients, especially those above the age of 35 years, were at increased risk. In a study conducted by Memon et al.[1] of Liaquat University, Jamshoro, an 11% incidence of hepatitis, usually with jaundice, abdominal pain, nausea, and vomiting, was reported. In the majority of instances (8%), the illness cleared within six weeks, whereas 3% had severe complications 2% developed hepatic encephalopathy, 1% became chronic hepatitis, and 1% died.[1] A cross-sectional study conducted by Sana et al. (2017) at Sheikh Zayed Medical College, Rahim Yar Khan, evaluated 150 TB patients on ATT and detected hepatotoxicity in 17 cases (11.33%).[14] Retrospective cross-sectional study by Gezahegn et al.[15] within a healthcare institution showed that 13.8% of the patients got hepatitis due to anti-tuberculosis drug treatment.[15]

Methods

Between 12th February 2025 to 11th April 2025 the cross-sectional study was conducted at Gulab Devi Teaching Hospital, Lahore, Department of Medicine. With a cross-sectional sample size calculation formula, a sample of 80 was calculated on a 5% level of significance, 95% confidence interval, and an expected proportion of 11.33% of ATT-induced hepatitis among TB patients with a margin of error of 7%. The research included 80 tuberculosis patients aged 16-60 years of both sexes who were undergoing ATT therapy for a minimum of 1 month and gave verbal consent. Non-probability consecutive sampling was applied to select the patients. The information of each participant was recorded on a structured proforma that recorded demographic information like age, sex, weight, height, and BMI. All patients were subjected to baseline investigations, such as liver function tests, ultrasonography (USG) of the abdomen, and viral serology for hepatitis B, C, and HIV, before enrollment to rule out any underlying liver disease. Following eligibility confirmation, patients were observed on a weekly basis at Lahore's Gulab Devi Hospital laboratory. On follow-up, clinical signs like abdominal discomfort, loss of appetite, and ATT- induced hepatitis symptoms were checked and documented.

Statistical analysis was conducted using SPSS software (version 25, IBM Corp., Armonk, NY, USA). Descriptive and inferential analysis was conducted on all variables. Categorical variables such as gender and ATT-induced hepatitis were represented in the form of frequency and percentages, while quantitative variables such as age were represented in the form of mean ± SD. Effect modifiers such as age, BMI categories, gender, and duration of ATT were controlled by stratification. The poststratification chi- square test was used. A p-value ≤0.05 was considered significant.

Results

Of the total 80 patients who were studied, 14 patients (17.5%) had ATT-induced hepatitis as a complication of their treatment. On the other hand, 66 patients (82.5%) did not have any hepatic complications of the therapy (Table-1).

Table 1: *Frequency of ATT induced hepatitis in patients taking standard ATT.*

ATT induced hepatitis	Number	Percentage
Present	14	17.5
Absent	66	82.5
Total	80	100.0

The data show a statistically significant relationship between age and incidence of ATT- induced hepatitis ($\chi^2 = 8.602$, $p = 0.035$), revealing that age ≥ 35 years can be implicated in susceptibility to hepatic adverse

effects in routine anti-tuberculosis therapy (Table-2).

Table 2: *Frequency of ATT induced hepatitis in different age groups.*

Age	ATT induced hepatitis		Total	P value/ x^2
	Present	Absent		
≤19	-	5(100%)	5(100%)	
20-34	3(8.1%)	34(91.9%)	37(100%)	P=0.035
35-49	9(34.6%)	17(65.4%)	26(100%)	x^2=8.602
50-60	2(16.7%)	10(83.3%)	12(100%)	
Total	14(17.5%)	66(82.5%)	80(100%)	
Mean±SD		**35.61±12.17**		

Table-3 shows the number of ATT-induced hepatitis in male and female patients. Out of the males, 9 (19.6%) developed ATT-induced hepatitis, whereas 37 (80.4%) did not. Compare this with 5 females (14.7%) having hepatitis, and 29 (85.3%) of them being unaffected (p=0.572).

Table 3: *Frequency of ATT induced hepatitis among males and females*

Gender	ATT induced hepatitis		Total	P value / x^2
	Present	Absent		
Male	9(19.6%)	37(80.4%)	46(100%)	P=0.572
Female	5(14.7%)	29(85.3%)	34(100%)	x^2= 0.32
Total	14(17.5%)	66(82.5%)	80(100%)	

Table-4 illustrates that out of the 39 patients with normal BMI, 8 (20.5%) developed ATT-induced hepatitis whereas 31 (79.5%) did not. Out of the overweight group (n = 33), a reduced number was noted, with 4 patients (12.1%) developing hepatitis and 29 (87.9%) being unaffected. Comparatively, the obese group (n = 8) had the highest rate of ATT- induced hepatitis, where 2 patients (25.0%) were affected and 6 (75.0%) were unaffected (p=0.544).

Table 4: *Frequency of ATT induced hepatitis with regard to BMI categories*

BMI (Kg/m^2)	ATT induced hepatitis		Total	P value/ x^2
	Present	Absent		
Normal	8(20.5%)	31(79.5%)	39(100%)	P=0.544
Over weight	4(12.1%)	29(87.9%)	33(100%)	x^2=1.218
Obese	2(25.0%)	6(75.0%)	8(100%)	
Total	14(17.5%)	66(82.5%)	80(100%)	
Mean ± SD			**22.96 ± 3.19**	

Normal (18.5 to < 23.0); Overweight (23.0-27.4); Obese (>27.4)

Table-5 examines the incidence of ATT-induced hepatitis in terms of anti-tuberculosis treatment (ATT) duration, expressed in days. In the ≤30 days category, 12 out of 55 patients (21.8%) experienced ATT- induced hepatitis, while 43 patients (78.2%) did not. Conversely, in the 31–45 days category, 2 out of 25 patients (8.0%) were affected by hepatitis, while 23 patients (92.0%) were not. Even though there was a greater percentage of cases of hepatitis in the group with lower treatment duration (≤30 days), the difference wasn't statistically significant (p = 0.132).

Table 5: *Frequency of ATT induced hepatitis with regard to ATT duration (days)*

Duration (days)	ATT induced hepatitis		Total	P value /x^2
	Present	Absent		
≤ 30	12(21.8%)	43(78.2%)	55(100%)	P=0.132
31-45	2(8.0%)	23(92.0%)	25(100%)	x^2=2.273
Total	14(17.5%)	66(82.5%)	80(100%)	
Mean ± SD			**23.31±11.52**	

Figure-I shows the prevalence of tuberculosis types in the study group of 80 patients. The most prevalent type was pulmonary tuberculosis, occurring in 59 patients (73.8%), reflecting the general predominance of pulmonary involvement in TB cases. There were 15 patients (18.8%) with extrapulmonary tuberculosis, which is the second most common type. Both tuberculous meningitis and miliary tuberculosis were seen in 3 patients each (3.8%), suggesting that these presentations were comparatively uncommon in the study population. In general, the findings show that pulmonary TB continues to be the most common clinical presentation, with extrapulmonary and disseminated presentations being less common.

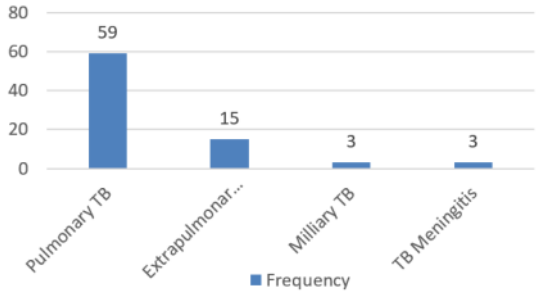

Figure I: *Frequency of tuberculosis types*

Discussion

The extensive prevalence of tuberculosis around the globe makes it a social and financial issue, particularly for developing nations, and the administration of anti-tuberculous drugs is an optimistic solution to this condition. Nonetheless, some of the concerns related to its administration must be assessed well, particularly

ATT-induced liver damage and predisposing factors contributing to this hepatotoxicity.[16] In this study, 17.5% of patients undergoing anti- tuberculosis therapy (ATT) developed drug-induced hepatitis. This incidence aligns with the higher end of global estimates, which range from 2% to 28%, and is particularly comparable to rates reported in Asian populations, including India and Pakistan.[17]

In northern Ethiopia, 13.8% incidence of anti- tuberculosis drug-induced hepatitis was reported among patients which is consistent with our findings.[15] A systematic review and meta-analysis in India documented a pooled incidence of 12.6% for anti- tuberculosis drug-induced liver injury (ATDILI) in adult patients.[18] In contrast, in Wuhan, China, 3.77% of inpatient patients were found to have developed anti- tuberculosis drug-induced hepatotoxicity in a retrospective analysis.[19] Two studies conducted by Steele et al., and Abera et al., in Ethiopia revealed an ATDH incidence of 8.9% and 8.1%, respectively.[8,20]

One large cohort study of 4,652 Chinese adult patients with tuberculosis reported an ATDILI incidence of 5.4%.[21] The differences in the global incidence of anti-TB drug-induced hepatotoxicity can be explained by differences in patients' characteristics, drug use without selection, and definition criteria of hepatotoxicity and TB prevalence.[22] The increased prevalence reported in this study could be due to differences at the regional level, patient populations, treatment regimens, or monitoring strategies. These observations reinforce the need for close monitoring of liver function during ATT to allow early detection and management of hepatotoxicity.

In our study, the majority of patients were diagnosed with pulmonary tuberculosis, accounting for 56 (73.7%) cases. This was followed by extrapulmonary tuberculosis in 15 (18.7%) patients, while miliary TB and TB meningitis were each identified in 3 (3.8%) cases. Earlier research has found that pulmonary tuberculosis is the most common indication of starting anti-tuberculous therapy (ATT), which agrees with the findings in the current study.[16,23] The current study established a statistically significant correlation between advance age and the risk of anti-tuberculosis treatment (ATT)-induced hepatitis, with those 35 years and above being more susceptible ($p = 0.035$). This result is in agreement with Liu et al,[5] who found that various factors—older age, smoking, alcohol consumption, and oxidative stress — contribute to the development of anti- tuberculosis drug-induced hepatitis (AT-DIH). The elevated risk in older patients probably reflects diminished liver capacity for regeneration and diminished metabolic activity, increasing susceptibility to toxic metabolites of such drugs as isoniazid and rifampicin.

Conclusion

Present study results indicate that ATT-induced hepatitis was seen in 17.5% of patients on regular anti- tuberculosis treatment. This indicates that while most patients can tolerate ATT, a considerable number are at risk of hepatotoxicity. Additionally, these findings indicate that adults ≥ 35 years, might be at higher risk and would be better monitored for liver function during treatment. Thus, monitoring of liver function on a regular basis is important throughout the treatment period to facilitate early detection and control of hepatic complications, maintaining patient safety and continuation of effective therapy.

Ethical Approval: The IRB/EC approved this study via letter no. AAMC/IRB/EA09.2025 dated February 10, 2025.

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Authors' Contribution

AF: Conception.

FM, FAK: Design of the work.

ARP, HAR, NS: Data acquisition, analysis, or interpretation.

FM, ARP, FAK, NS: Draft the work.

AF, HAR: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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