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ANTITUBERCULOSIS THERAPY-INDUCED LIVER INJURY IN PATIENTS ON TREATMENT FOR TUBERCULOSIS

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Abstract

Objective:
To determine the frequency of antituberculosis therapy-induced liver injury (ATLI) in patients on treatment for tuberculosis.

Methods:
This descriptive research involved 176 individuals diagnosed with tuberculosis who received anti-tuberculosis therapy at the Department of Medicine, Nishtar Hospital, Multan, between August 2024 and February 2025. All participants received the standard first-line regimen consisting of Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol. Follow-up assessments were conducted at 2, 4, and 8 weeks post-treatment initiation, during which blood samples were collected to monitor changes in liver enzymes to determine the occurrence of ATLI.

Results:
In this study, 176 participants were included, with a mean age of 41.6 years (±13.4). Males comprised 61.9% (109 individuals) of the cohort, while females accounted for 38.1% (67 individuals). Regarding comorbidities, 14.2% (25 individuals) had diabetes, and 17.6% (31 individuals) had hypertension. The majority of tuberculosis cases were pulmonary (72.2%, 127 individuals), with the remaining 27.8% (49 individuals) presenting with extra-pulmonary tuberculosis. Of 176 patients, ATLI occurred in 26 (14.77%) patients.

Conclusion:
The prevalence of liver injury is high among patients on first-line anti-TB drug treatment. In the present study, the prevalence of ATLI was 14.7%.

INTRODUCTION:

Tuberculosis remains a significant infectious disease affecting much of the developing world, posing a considerable socioeconomic burden. In 2018, approximately 10 million new cases and 1.5 million fatalities were reported.[1] The prevalence of TB in Pakistan stands at around 398 cases per 100,000 people.[2] One complication of treatment is drug-induced liver injury (DILI), which can result from various factors such as genetic predisposition related to HLA types, metabolic differences, and the production of reactive free radicals.[3] Most anti-TB medications are lipid-soluble, and their elimination from the body depends on liver biotransformation processes. These involve specific phase I and phase II hepatic enzymes that convert these drugs into water-soluble forms, facilitating their excretion.[4] Isoniazid (INH), a primary drug used in treating tuberculosis, is frequently associated with hepatotoxicity, an adverse effect that becomes more pronounced when combined with other

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anti-TB medications.[5] Individuals classified as slow acetylators of INH are at a heightened risk of developing liver toxicity compared to those who are intermediate or fast acetylators.[6] Another important medication, Rifampicin, is also known to induce hepatitis, particularly in elderly patients, alcoholics, or those with chronic liver disease.[7] The manifestation of drug-induced liver injury (DILI) from tuberculosis treatments can vary widely, from elevated liver enzymes in the blood and acute hepatic damage to chronic hepatitis. In severe cases, it can lead to life-threatening acute liver failure requiring transplantation.[8]

Tuberculosis drug-induced liver injury (TB DILI) can lead to treatment failure, which may worsen drug resistance and ultimately jeopardize TB eradication efforts. Understanding the clinical features of TB DILI—such as when symptoms appear, how severe they become, early signs, and possible outcomes—is essential for timely detection and intervention. The purpose of this study was to assess how often liver injury occurs as a side effect of antituberculosis medications in patients undergoing TB treatment.

METHODS:

This descriptive research involved 176 individuals diagnosed with tuberculosis who received anti-tuberculosis therapy at the Department of Medicine, Nishtar Hospital, Multan, between August 2024 and February 2025. Eligible participants were those aged 18 to 65 years, of any gender, who were newly diagnosed with either pulmonary or extrapulmonary TB and prescribed first-line anti-tubercular treatment. Patients who were already on other hepatotoxic or antipsychotic medications, or who had been diagnosed with Hepatitis A, B, or C, and exhibited abnormal liver function tests before beginning anti-tuberculosis therapy, were excluded.

Baseline data encompassing age, gender, TB classification (pulmonary or extrapulmonary), and liver enzyme levels prior to antitubercular therapy (ALT in U/L, alkaline phosphatase in U/L, bilirubin in mg/dl, GGT in U/L) were recorded. All participants received the standard first-line regimen consisting of Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol. Follow-up assessments were conducted at 2, 4, and 8 weeks post-treatment initiation, during which blood samples were collected to monitor changes in liver enzymes. The diagnosis of antitubercular therapy-induced liver injury (ATLI) was based on specific criteria: (1) a rise in alanine aminotransferase (ALT) levels to at least five times the upper normal limit (ULN), (2) a twofold or greater increase in alkaline phosphatase (ALP) accompanied by a similar increase in γ-glutamyl transpeptidase (GGT) levels above the ULN, with no evidence of bone disease, and (3) at least a threefold increase in ALT alongside bilirubin levels exceeding twice the ULN. Patients diagnosed with ATLI were managed according to the protocols established by the local healthcare facility.

Data were analyzed using SPSS v. 25. Baseline & follow-up ALT, bilirubin, alkaline phosphatase, and GGT were presented as mean and standard deviation. Gender, diabetes mellitus, hypertension, type of tuberculosis, and ATLI (yes/no) were presented as frequencies and percentages.

RESULTS:

In this study, a total of 176 participants were included, with a mean age of 41.6 years (±13.4). Males comprised 61.9% (109 individuals) of the cohort, while females accounted for 38.1% (67 individuals). Regarding comorbidities, 14.2% (25 individuals) had diabetes and 17.6% (31 individuals) had hypertension. The majority of tuberculosis cases were pulmonary (72.2%, 127 individuals), with the remaining 27.8% (49 individuals) presenting with extra-pulmonary tuberculosis. Laboratory findings revealed a mean ALT level of 27.9 U/L (±8.9), a mean AST level of 30.2 U/L (±9.5), and a mean bilirubin concentration of 0.62 mg/dL (±0.28). The average gamma-glutamyl transferase (GGT) level was 46.2 U/L (±15.6) [Table 1].

Out of 176 patients, ATLI occurred in 26 (14.77%) patients (Figure 1).

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Table 1. Baseline Characteristics (N=176).

Age (Years)	41.6±13.4
Gender (%)	
Male	109 (61.9%)
Female	67 (38.1%)
Diabetes (%)	25 (14.2%)
Hypertension (%)	31 (17.6%)
Type of Tuberculosis (%)	
Pulmonary	127 (72.2%)
Extra-pulmonary	49 (27.8%)
ALT (U/L)	27.9±8.9
AST (U/L)	30.2±9.5
Bilirubin (mg/dL)	0.62±0.28
Gamma-Glutamyl Transferase (GGT) (U/L)	46.2±15.6

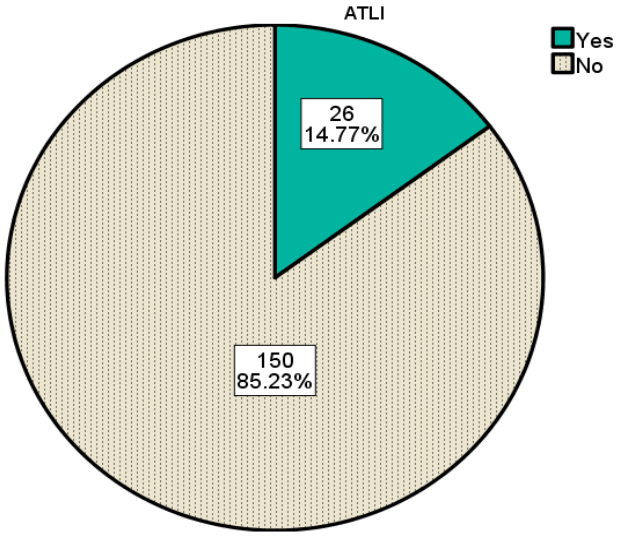

Figure 1. Frequency of ATLI.

DISCUSSION:

In this research, the occurrence rate of ATLI among participants on anti-tuberculosis medications was found to be 14.77%. This figure aligns closely with the 17% prevalence reported in a study conducted in Ethiopia, as well as the 15% noted in studies from Egypt and Nepal.[9-11] Nonetheless, our observed rate exceeds the 8% documented in a study from Southern Ethiopia, the 12.6% pooled prevalence from an Indian meta-analysis, and the 11.5% reported elsewhere.[12-14] Such disparities in ATLI prevalence may stem from variations in study methodologies, geographic regions, definitions of liver injury, and timing of liver enzyme assessments across studies. Genetic differences could also significantly influence these outcomes. Our investigation employed a prospective design, contrasting with many of the referenced studies that utilized retrospective approaches. Prospective cohort studies generally yield stronger evidence for causal links and reduce certain biases, as they enable clear establishment of temporality—demonstrating that exposure precedes the outcome—along with better control over data collection and minimized recall and selection biases.[15] Additionally, we adopted the latest criteria for diagnosing ATLI and used the International DILI Expert Working Group's standards to assess severity.[16]

In contrast, the occurrence of ATLI observed in our research was significantly lower than the figures documented in earlier studies, which reported rates ranging from 18% to 22% in mainland China.[17, 18]

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The clinical signs of liver injury triggered by anti-tuberculosis medications are varied and often non-specific, ranging from silent liver dysfunction to severe acute hepatitis, and potentially leading to liver failure. The primary mechanism behind drug-induced hepatotoxicity tends to involve hypersensitivity reactions, which can present with symptoms such as fever, rash, or an increase in eosinophils. In our research, the most frequently observed clinical features included fever, rash, tiredness, decreased appetite, and dark brown urine. While some patients exhibit overt symptoms, approximately 20% show elevated transaminase levels without any symptoms during standard anti-TB treatment. During therapy, it is important to discontinue the suspected offending drug and to limit the use of hepatoprotective agents to prevent worsening due to allergic reactions.[19, 20] Liver damage can be life-threatening if not diagnosed and managed promptly. Therefore, routine monitoring of liver function is recommended for all patients undergoing anti-TB treatment.

CONCLUSION:

The prevalence of liver injury is high among patients on first-line anti-TB drug treatment. In the present study, the prevalence of ATLI was 14.7%.

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