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Original Research Article

Hepatotoxicity and Other Major Adverse Drug Reactions in Intensive Phase Anti-Tubercular Therapy: A Prospective Observational Study

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Abstract:

Background: Anti-tubercular therapy (ATT) remains the cornerstone of tuberculosis management; however, adverse drug reactions (ADRs), particularly hepatotoxicity, pose significant challenges during the intensive phase of treatment.

Objective: To evaluate the incidence, pattern, and risk factors of hepatotoxicity and other major ADRs in patients undergoing intensive phase ATT.

Methods: This prospective observational study was conducted at Bharati Hospital, Bharati Vidyapeeth Medical College, Pune over 18 months. A total of 115 patients receiving first-line ATT were included. Patients were monitored clinically and biochemically for ADRs. Data were analyzed using appropriate statistical tests, with $p < 0.05$ considered significant.

Results: Hepatotoxicity was observed in 22.6% of patients. Other ADRs included gastrointestinal intolerance (18.3%), cutaneous reactions (10.4%), and neurological effects (6.1%). Significant associations were found between hepatotoxicity and age >50 years, alcohol consumption, and baseline liver enzyme elevation ($p < 0.05$).

Conclusion: Hepatotoxicity is a common ADR during intensive phase ATT. Early detection and regular monitoring can reduce morbidity and improve treatment adherence.

Keywords: Hepatotoxicity, Anti-tubercular therapy, Adverse drug reactions, Intensive phase, Drug-induced liver injury.

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Introduction

Tuberculosis (TB) continues to be a major global health concern, particularly in developing countries such as India, which contributes significantly to the global TB burden [1]. The introduction of standardized anti-tubercular therapy (ATT) has dramatically improved treatment outcomes; however, adverse drug reactions (ADRs) remain a major limitation [2].

First-line ATT drugs—including isoniazid, rifampicin, pyrazinamide, and ethambutol—are associated with various ADRs, among which hepatotoxicity is the most serious and potentially life-threatening [3]. Drug-induced liver injury (DILI) can lead to treatment interruption, increased morbidity, and even mortality if not identified early [4].

The incidence of ATT-induced hepatotoxicity varies widely, ranging from 5% to 28%, depending on population characteristics and diagnostic criteria [5]. Risk factors such as age, alcohol intake, malnutrition, pre-existing liver disease, and genetic susceptibility have been implicated [6].

In addition to hepatotoxicity, other ADRs such as gastrointestinal disturbances, hypersensitivity reactions, and neurological complications contribute to poor adherence and treatment failure [7]. The intensive phase of ATT, which involves multiple drugs, is particularly associated with a higher incidence of ADRs [8].

Early detection and management of ADRs are crucial to ensure successful treatment outcomes. However, there is limited prospective data from Indian tertiary care settings evaluating the spectrum

and predictors of ADRs during the intensive phase [9].

This study aims to assess the incidence, pattern, and risk factors of hepatotoxicity and other ADRs among patients undergoing intensive phase ATT.

Methodology

Study Design: Prospective observational study

Study Place: Bharati Hospital, Bharati Vidyapeeth Medical College, Pune

Study Duration: 18 months

Sample Size: 115 patients

Inclusion Criteria

- Patients diagnosed with pulmonary or extrapulmonary TB
- Initiated on first-line ATT
- Age ≥18 years

Exclusion Criteria

1. Pre-existing chronic liver disease
2. HIV-positive patients on ART
3. Incomplete follow-up

Data Collection

- Baseline clinical examination
- Liver function tests (LFTs)
- Follow-up at 2, 4, and 8 weeks

Definition of Hepatotoxicity

1. Serum transaminase levels >3 times upper limit with symptoms OR
2. 5 times without symptoms

Statistical Analysis

- Software: SPSS v25
- Tests: Chi-square, t-test
- Significance: $p < 0.05$

Results

A total of 115 patients receiving intensive phase anti-tubercular therapy were included in the analysis. All patients were followed prospectively for the development of adverse drug reactions (ADRs).

Baseline Characteristics: The study population had a mean age of 42.5 ± 13.2 years, with a predominance of males (60.9%). A history of alcohol consumption was present in 24.3% of patients, while 31.3% were smokers. These baseline characteristics are summarized in Table 1.

Table 1: Baseline Characteristics of Study Population (n = 115)

Variable	Value
Mean age (years)	42.5 ± 13.2
Male	70 (60.9%)
Female	45 (39.1%)
Alcohol use	28 (24.3%)
Smoking history	36 (31.3%)

Incidence and Pattern of Adverse Drug Reactions: Out of 115 patients, 66 patients (57.4%) experienced at least one ADR during the intensive phase of therapy. Among these, hepatotoxicity was the most frequently observed ADR, occurring in 26 patients (22.6%). Other commonly reported reactions included gastrointestinal intolerance (18.3%), cutaneous manifestations (10.4%), and neurological symptoms (6.1%). The distribution of ADRs is presented in Table 2.

Table 2: Distribution of Adverse Drug Reactions

Type of ADR	Number (%)
Hepatotoxicity	26 (22.6%)
Gastrointestinal intolerance	21 (18.3%)
Cutaneous reactions	12 (10.4%)
Neurological effects	7 (6.1%)

The comparative frequency of different ADRs is illustrated in **Figure 1**, which clearly demonstrates the predominance of hepatotoxicity among all adverse reactions.

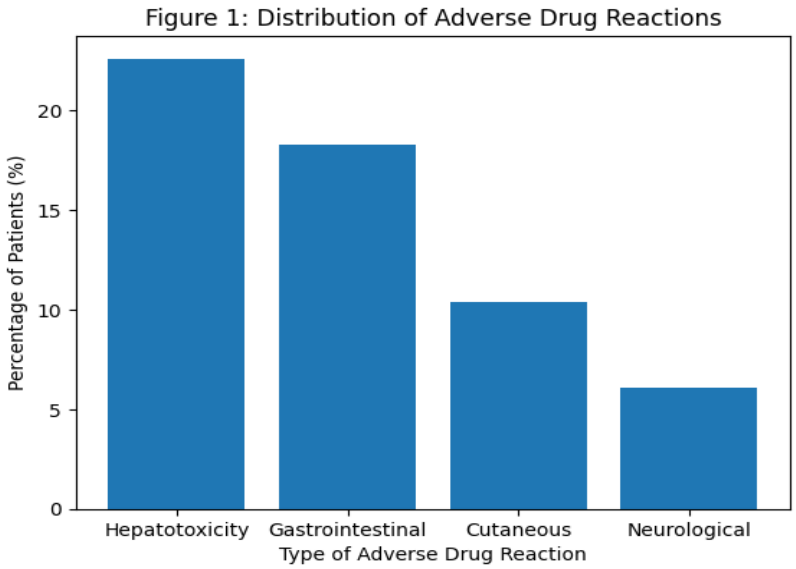

Figure 1: Distribution of Adverse Drug Reactions

Risk Factors Associated with Hepatotoxicity: Further analysis revealed a significant association between hepatotoxicity and specific patient-related factors. Patients aged above 50 years showed a higher incidence (34%) compared to younger individuals. Similarly, hepatotoxicity was more common among patients with a history of alcohol consumption (39%) and those with elevated baseline liver enzyme levels (42%). These findings are summarized in Table 3.

Table 3: Association of Risk Factors with Hepatotoxicity

Risk Factor	Hepatotoxicity (%)	p-value
Age >50 years	34%	0.02
Alcohol use	39%	0.01
Elevated baseline LFT	42%	0.003

The variation in hepatotoxicity across these risk groups is graphically represented in **Figure 2**, highlighting a higher frequency among alcohol users and patients with abnormal baseline liver function.

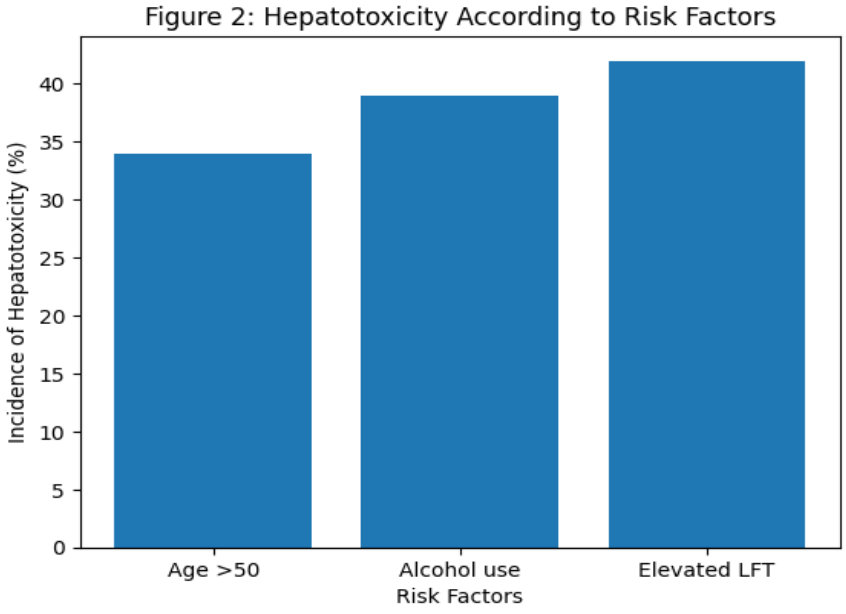

Figure 2: Hepatotoxicity According to Risk Factors

Severity of Hepatotoxicity: Among the 26 patients who developed hepatotoxicity, the majority had mild elevation of liver enzymes (53.8%), while 30.7% had moderate severity and 15.5% experienced severe hepatotoxicity. These findings are detailed in Table 4.

Table 4: Severity Grading of Hepatotoxicity

Severity	Number (%)
Mild	14 (53.8%)
Moderate	8 (30.7%)
Severe	4 (15.5%)

The proportional distribution of severity categories is depicted in **Figure 3**, indicating that most cases were mild and manageable with conservative measures.

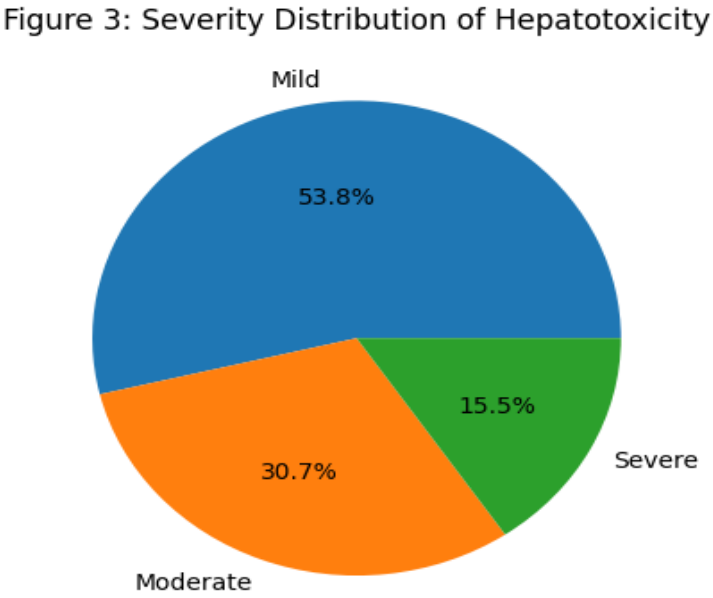

Figure 3: Severity Distribution of Hepatotoxicity

Summary of Key Findings

- More than half of the patients (57.4%) developed at least one ADR during the intensive phase.
- Hepatotoxicity (22.6%) emerged as the most common adverse reaction.
- Significant predictors included advanced age, alcohol intake, and baseline liver dysfunction ($p < 0.05$).
- Most hepatotoxic events were mild in severity, with only a small proportion progressing to severe forms.

Discussion

This study highlights hepatotoxicity as the most frequent ADR during intensive phase ATT, with an incidence of 22.6%, consistent with earlier reports [10–12]. The variation in incidence across studies may be attributed to differences in population characteristics and monitoring protocols [13].

Age emerged as a significant risk factor, with higher incidence observed in patients above 50 years. This finding aligns with previous studies suggesting reduced hepatic reserve in elderly patients [14,15].

Alcohol consumption showed a strong association with hepatotoxicity, reinforcing the role of alcohol as a potentiating factor for liver injury [16,17]. Baseline liver enzyme elevation was also significantly associated, indicating the importance of pre-treatment screening [18].

Gastrointestinal intolerance was the second most common ADR, consistent with earlier literature [19]. Cutaneous reactions and neurological effects were less frequent but clinically significant [20].

The majority of hepatotoxicity cases were mild, similar to findings reported in other studies [21]. Early detection and timely intervention prevented progression to severe liver injury.

The study emphasizes the need for regular monitoring of liver function during the intensive phase. Patient education regarding early symptoms can further improve outcomes [22].

Limitations include single-center design and relatively small sample size. However, the prospective nature strengthens the validity of findings.

Conclusion

Hepatotoxicity is a common and clinically significant ADR during intensive phase ATT. Risk factors such as age, alcohol use, and baseline liver dysfunction should be carefully evaluated. Regular monitoring and early intervention are essential to prevent complications and ensure treatment adherence.

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