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OUTCOME OF LIVER FUNCTIONS IN NEWLY DIAGNOSED PATIENTS OF TUBERCULOSIS ON ANTI TUBERCULAR TREATMENT

Respiratory Medicine

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ABSTRACT

Background: Anti-tubercular treatment (ATT) plays a key role in managing tuberculosis but it can have negative effects on the liver. Drug-induced liver damage is a frequent problem that causes poor compliance to treatment and it frequently prompts physicians to modify treatment. **Objective:** To assess changes in liver function among newly diagnosed tuberculosis patients initiated on standard anti-tubercular therapy (ATT) under the National Tuberculosis Elimination Programme (NTEP), and to explore their clinical profiles along with potential risk factors associated with drug-induced hepatotoxicity. **Material:** A prospective observational study was carried out over 18 months at a tertiary care hospital. A total of 150 newly diagnosed tuberculosis patients with normal baseline liver function tests (LFTs) were enrolled and followed after the initiation of anti-tubercular therapy (ATT). Patients were monitored at regular intervals through clinical evaluation and serial LFTs. Hepatotoxicity was assessed based on standard criteria, and follow-up evaluations, as well as drug reintroduction protocols, were conducted in accordance with established guidelines. **Results:** Of 150 patients, 18 (12%) developed ATT induced heapatotoxicity during follow-up. Among them, 17 (94.4%) showed symptoms such as anorexia, abdominal pain , nausea and vomiting. Hepatotoxicity appeared predominantly within the first 15 days of therapy. First line ATT was temporarily withheld, and modified treatment regimens were administered. First-line drugs were successfully reintroduced in 16 (85.7%) patients following normalization of liver function tests. Significant associations were found with female gender , hypoalbuminemia and low BMI. **Conclusion:** During anti-tubercular therapy, liver function must be regularly monitored, especially in high-risk individuals. In the management of tuberculosis, early identification of hepatotoxicity and treatment regimen change can greatly enhance clinical results and lessen the burden of drug-induced liver impairment.

KEYWORDS

INTRODUCTION

Tuberculosis (TB) has always been a significant health challenge worldwide, ranking as number one cause of death from single infectious agent , except for 3 years when it was replaced by COVID 19 , Tb causes almost double the mortality in comparison to HIV/AIDS(1) In India the incidence rate of TB is 195 per 100,000 people in 2023[2]. Furthermore, the disease was responsible for 22 deaths per lac population in the country during the same period.[2] The persistence of high TB incidence and mortality rates in India can be attributed to multiple factors, including delayed diagnosis, inadequate healthcare access, treatment non-adherence, and the emergence of drug-resistant TB strains[3]. Socioeconomic determinants such as poverty, malnutrition, and overcrowding further exacerbate the spread of the disease. Despite the availability of highly effective anti-tuberculosis treatment, challenges in case detection and management continue to hinder complete disease eradication[4].Efforts to control TB in India have involved large-scale programs, including the Revised National Tuberculosis Control Programme (RNTCP), which was later restructured as the National Tuberculosis Elimination Program (NTEP)[5].The standard first-line anti-tubercular therapy (ATT)—comprising Isoniazid (H), Rifampicin (R), Ethambutol (E), and Pyrazinamide (Z)—is highly effective in treating tuberculosis. However, these drugs are also associated with a known risk of hepatotoxicity[6]. The incidence of ATT-induced hepatotoxicity varies across populations, with studies reporting higher rates in Asian countries (ranging from 3% to 28%) compared to Western populations[7]. Interestingly, not all patients on the same anti-tubercular regimen develop hepatotoxicity, suggesting that individual, host-related factors play a significant role. Clinical risk factors associated with increased susceptibility include female gender, low body mass index (BMI), malnutrition, pre-existing liver conditions, abnormal baseline liver function tests, and co-infections such as HIV. Among these, nutritional status is especially important, as deficiencies can impair liver metabolism and increase vulnerability to drug-induced toxicity[8]. Genetic factors also contribute—particularly polymorphisms in the N-acetyltransferase 2 (NAT2) gene, which influence Isoniazid metabolism. Individuals who are slow acetylators tend to accumulate toxic metabolites more readily, placing them at greater risk for liver injury[9]. Regular liver function tests (LFTs), particularly in high-risk individuals, can help identify hepatotoxicity before it progresses to significant liver damage. When abnormalities in LFTs are detected, timely adjustments to the treatment regimen—such as temporarily stopping therapy, modifying dosages, or substituting specific drugs—may be necessary. Incorporating personalized approaches, such as pharmacogenetic screening and close clinical surveillance, holds promise for improving both the safety and effectiveness of TB treatment[10].Despite numerous studies on ATT-induced hepatotoxicity, it remains difficult to predict which patients will develop drug-induced liver injury (DILI) before treatment begins[11]. The complex interplay of genetic, metabolic, and clinical factors makes early identification of at-risk individuals particularly challenging. As a result, liver function abnormalities are often the first indicators, with diagnosis occurring only after damage has begun. This study aims to address this gap by examining the prevalence of ATT-induced hepatotoxicity, identifying associated clinical risk factors, and evaluating the effectiveness of modified ATT regimens in managing patients who develop liver-related complications.

MATERIALS AND METHODS

A prospective observational follow-up study was conducted over 18 months (July 2023 to January 2025) at the Department of Respiratory Medicine, Heritage Institute of Medical Sciences, Varanasi. A total of 150 newly diagnosed tuberculosis patients (both pulmonary and extrapulmonary), initiated on first-line ATT under NTEP, were enrolled after obtaining informed consent. Patients with pre-existing liver dysfunction, MDR-TB, or those taking hepatotoxic drugs other than ATT were excluded.Baseline LFTs were performed prior to starting ATT and LFT after 1 week was performed in all patients.Those developing hepatotoxicity (defined as ≥3 times elevation in ALT/AST with symptoms or ≥5 times without symptoms, or bilirubin ≥2.5 mg/dL) were switched to a modified ATT regimen and followed up weekly. Symptoms suggestive of hepatitis (anorexia, nausea, vomiting, abdominal pain, jaundice) were explained to all patients for early reporting.Reintroduction of ATT drugs was done stepwise once liver enzymes normalized (≤2 times the upper limit of normal). The number of drugs successfully reintroduced and time to LFT normalization were recorded. Risk factors such as age, sex, BMI, albumin level, comorbidities, and type of TB were analyzed.

RESULT

A total of 150 newly diagnosed TB patients were included, with 94 men (62.7%) and 56 women (37.3%). Of these, 92 (61.3%) had pulmonary TB and 58 (38.7%) had extrapulmonary TB. The mean age was 43 ± 16.8 years. Nutritionally, 67 patients (44.7%) were

underweight, 66 (44%) had normal BMI, 15 (10%) were overweight, and 2 (1.3%) were obese. Baseline mean serum albumin was 3.6 ± 0.7 g/dL, with liver enzymes ALT 28.4 ± 6.2 U/L, AST 30.1 ± 7.5 U/L, and bilirubin 1.04 ± 0.09 mg/dL.ATT-induced hepatotoxicity occurred in 18 patients (12.0%), with 17 (94.4%) symptomatic and 1 (5.6%) asymptomatic. The most common symptoms were nausea/vomiting (83.3%), anorexia (61.1%), and abdominal pain (61.1%). Hepatotoxicity developed early: 55.6% within the first week, 33.3% by the second week, and 11.1% after two weeks. The mean age of affected patients was 39 ± 15.9 years.Hepatotoxicity incidence was similar in pulmonary (12.0%) and extrapulmonary TB (12.1%) (p = 0.999), but female sex was significantly associated (66.7% vs. 33.3%, p = 0.008). Underweight status (50%, p = 0.048) and hypoalbuminemia (77.8% vs. 31.8%, p < 0.001) were also significantly linked to hepatotoxicity. No associations were found with diabetes (p = 0.982) or alcohol use (p = 0.927).Drug reintroduction was successful in 16 of 18 cases (88.9%) after liver enzyme normalization. One patient could not tolerate pyrazinamide, and another could not tolerate isoniazid. Full ATT was resumed within 4 weeks in 6 patients (23.5%), within 5 weeks in 7 (41.2%), and within 6 weeks in 3 (17.6%). Two patients (11.8%) could not resume therapy due to persistent liver dysfunction.

Table 1 : Characterstics of Study Population (n = 150)

PARAMETERS	No. of Patients	Percentage (%)
EPIDEMIOLOGICAL DATA		
Type Of TB		
Pulmonary	92	61.3
Extrapulmonary	58	38.7
Gender		
Male	94	62.7
Female	56	37.3
Mean Age group (years)	43 ± 16.8	
BMI		
Underweight (<18.5)	67	44.7
Normal (18.5–24.9)	66	44.0
Overweight (25–29.9)	15	10.0
Obese (≥30)	2	1.3
Alcohalism	24	16.0
CO MORBIDITIES		
DIABETES	33	22.0
HYPERTENSION	25	16.7
LABORATORY PARAMETERS		
Albumin <3.5 g/dL	56	37.3
Mean Albumin levels (g/dl)	3.6 ± 0.7	
Mean AST levels(U/L)	30.1 ± 7.5	
Mean ALT levels(U/L)	28.4 ± 6.2	
Mean Bilirubin levels(mg/dl)	1.04 ± 0.09	

Table 2 : Characterstics of Patients With Hepatotoxixity (n = 18)

Category	No. of Patients	Percentage (%)
TB TYPE		
Pulmonary	11	61.1
Extrapulmonary	7	38.9
GENDER		
Female	12	66.7
Male	6	33.3
BMI		
Underweight (<18.5)	9	50
Normal (18.5–24.9)	7	38.9
Overweight (25.0–29.9)	2	11.1
Obese (≥30.0)	0	0
Serum Albumin <3.5 g/dL	14	77.8
Diabetes Mellitus	4	22.2
Alcohalism	3	16.7
Symptomatic	17	94.4
Nausea/Vomiting	15	83.3
Anorexia	11	61.1
Abdominal Pain	11	61.1
Time to Onset of Hepatotoxicity		
1 Week	10	55.6
2 Weeks	6	33.3
>2 Weeks	2	11.1
Reintroduction of ATT Drugs		
All 4 Drugs	16	88.9
Only 3 Drugs	2	11.1
Shift to Normal Regimen		
In 4 Weeks	6	33.3
In 5 Weeks	7	38.9
In 6 Weeks	3	16.7
Not Shifted	2	11.1

Table 3 Risk Factors For ATT Induced Hepatitis

Risk Factor	p-value
Gender	0.008
BMI (Undernutrition)	0.048
Hypoalbuminemia (Serum Albumin <3.5 g/dL)	<0.001

DISCUSSION

Our study assessed the incidence and risk factors of ATT induced hepatotoxicity in newly diagnosed TB patients. The incidence of hepatotoxicity was 12%, consistent with previous Indian studies reporting rates between 8% and 13%. Most cases emerged within the first two weeks of ATT initiation, underscoring the need for early liver function monitoring during this critical period. Latief et al.[12] also observed early onset of hepatotoxicity within two weeks of therapy.A statistically significant association was observed between ATT-induced hepatotoxicity and female gender (p = 0.008), low body mass index (BMI <18.5 kg/m²) (p = 0.048), and hypoalbuminemia (serum albumin <3.5 g/dL) (p < 0.001) in line with findings by Puri et al.[13] and Molla et al.[14] . These findings align with existing evidence that suggests compromised nutritional status and diminished hepatic reserves may heighten the risk of drug-induced liver injury. In contrast, variables such as age, type of TB (pulmonary vs. extrapulmonary), alcohol use, and diabetes mellitus were not significantly associated with hepatotoxicity, which may be attributed to limited subgroup sizes in this study. Most patients (94.4%) with ATT-induced hepatotoxicity were symptomatic, mainly with gastrointestinal complaints and elevated transaminases. Reintroduction of first-line drugs was successful in 88.9% of cases, supporting the safety of monitored re-challenge. This study highlights the need for close monitoring of high-risk groups—especially females, undernourished patients, and those with hypoalbuminemia—to enable early detection and effective management of hepatotoxicity during TB treatment.

Limitations

This single-center study may limit the generalizability of findings to other populations or clinical settings. Although the sample size was adequate for primary objectives, it may not have captured rare adverse events or uncommon risk factors. Potential confounders—such as undiagnosed comorbidities, nutritional deficiencies, or concurrent hepatotoxic medications—may not have been fully accounted for. Follow-up bias is possible due to reliance on patient adherence to scheduled visits and lab monitoring. Additionally, the study did not assess genetic susceptibility; future research incorporating pharmacogenomic data could enhance understanding of individual risk for ATT-induced hepatotoxicity.

CONCLUSION

This study highlights liver-related outcomes in newly diagnosed tuberculosis patients on anti-tubercular therapy (ATT), emphasizing the importance of routine liver function monitoring, especially early in treatment. Female gender, low BMI (<18.5 kg/m²), and hypoalbuminemia emerged as key risk factors, underscoring the need for personalized risk assessment. The findings also demonstrate successful reintroduction of first-line ATT post-hepatotoxicity, supporting practical clinical management. Regular biochemical monitoring and nutritional assessment could enhance safety, improve outcomes, and strengthen TB control efforts.

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