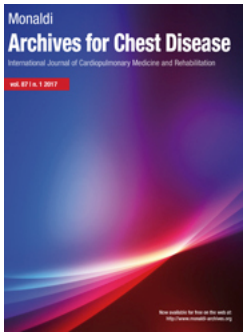

Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2026 [Online ahead of print]

To cite this Article:
Baby UR, Mathew NR, Adiody S. **Prevalence of liver function test derangements in adult tuberculosis patients initiated on a daily fixed combination regimen: a prospective study from Kerala, India**. Monaldi Arch Chest Dis doi: 10.4081/monaldi.2026.3715

Submitted: 5-9-2025
Accepted: 7-1-2026

Prevalence of liver function test derangements in adult tuberculosis patients initiated on a daily fixed combination regimen: a prospective study from Kerala, India

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Contributions: all the authors have contributed significantly, and agree with the content of the manuscript. Unni R Baby, Namita Rachel Mathew: conceptualization. Unni R Baby, Namita Rachel Mathew, Supriya Adiody: methodology. Unni R Baby: formal analysis, data curation, writing - original draft preparation, writing - review and editing. Supriya Adiody: validation. Namita Rachel Mathew: investigation. All the authors have read and approved the final version of the manuscript and agreed to be accountable to all aspects of work

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: the study protocol was approved by the Institutional Ethics Committee of the Jubilee Mission Medical College (IEC Study Ref no – 133/24/IEC/JMMC & RI).

Informed consent: written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article. The manuscript does not contain any individual person's data in any form.

Availability of data and materials: the data used to support the findings of this study are available from the corresponding author upon request

Acknowledgments: the authors express their gratitude to the patients and staff of the Respiratory Medicine Department of the Jubilee Mission Medical College.

Abstract

Anti-tuberculosis drug–induced hepatotoxicity is a major challenge in tuberculosis (TB) management, particularly in high-burden countries like India. Early liver function test (LFT) derangements during daily fixed-dose combination (FDC) therapy may reflect subclinical hepatocellular stress and guide timely intervention; however, evidence from Indian programmatic settings remains limited. To determine the prevalence, severity, demographic associations, biochemical trends, and clinical outcomes of early (two-week) LFT abnormalities in adult TB patients initiating daily FDC therapy under the National Tuberculosis Elimination Programme (NTEP). A prospective observational study was conducted among adults with newly diagnosed TB at a tertiary center in Kerala (January-June 2025). Baseline and two-week LFTs were compared using paired t-tests. Associations with demographic and clinical variables were assessed using Chi-square tests. LFT derangement was defined as per the WHO/NTEP criteria.

Among 146 participants, 41 (28.1%) developed LFT derangements at two weeks (95% CI: 20.9–36.4%). No significant associations were observed with age (χ^2=0.05, p=0.977), sex (χ^2=0.11, p=0.898), TB type (χ^2=0.00, p=1.000), or weight band (p>0.05). Mean alanine aminotransferase (ALT) increased from 26.6 to 58.1 IU/L (mean difference +31.5 IU/L; 95% CI: 25.8-37.2; p<0.001), and aspartate aminotransferase (AST) from 29.5 to 55.1 IU/L (+25.6 IU/L; 95% CI: 20.1-31.0; p<0.001). Total bilirubin rose from 0.63 to 0.83 mg/dL (+0.20 mg/dL; 95% CI: 0.09-0.31; p<0.01). Severity grading showed 65.9% Grade 1, 22.0% Grade 2, and 12.1% Grade 3 abnormalities; no Grade 4 hepatotoxicity occurred. Clinically, 29/41 (70.7%) patients continued therapy with monitoring, 8 (19.5%) required temporary interruption, 3 (7.3%) were successfully rechallenged, and 1 (2.4%) required permanent regimen modification. No patient developed jaundice, hepatic failure, or required hospitalization.

Early LFT derangements are common but predominantly mild and clinically manageable among adults initiating daily FDC ATT. Significant early rises in ALT and AST highlight the value of routine two-week monitoring. Structured early biochemical surveillance under NTEP may prevent severe outcomes and minimize treatment disruption.

Key words: anti-tuberculosis therapy, drug-induced hepatotoxicity, liver function tests, fixed-dose combination, tuberculosis.

Introduction

Tuberculosis (TB) continues to be a major global public health challenge, with over 10 million incident cases and 1.6 million deaths annually, and India contributing nearly one-quarter of the global burden [1,2]. In an effort to enhance treatment outcomes, prevent drug resistance, and improve adherence, the National Tuberculosis Elimination Programme (NTEP) has adopted daily fixed-dose combination (FDC) therapy as the standard regimen for drug-susceptible TB [3,4]. However, hepatotoxicity associated with first-line anti-tuberculosis therapy (ATT) remains a significant concern, often leading to treatment interruption, prolongation of therapy, and avoidable morbidity [5-7].

Reported incidences of ATT-induced liver injury (ATD-DILI) vary considerably across Indian and Asian populations, ranging from 5% to 30%, influenced by genetic, nutritional, environmental, and programmatic factors [8-11]. South and East Asian populations have a higher prevalence of NAT2 slow-acetylator and CYP2E1 risk alleles, which predispose individuals to isoniazid- and pyrazinamide-related hepatotoxicity [12-14]. Additional risk modifiers such as low body mass index (BMI), malnutrition, alcohol use, chronic viral hepatitis, and polypharmacy further increase susceptibility [15-17]. Early biochemical abnormalities frequently occur without clinical symptoms, making reliance on symptom-based detection unreliable [18,19].

Although baseline liver function tests (LFTs) are routinely recommended under NTEP, evidence supporting the timing, feasibility, and clinical utility of early two-week LFT monitoring in patients initiated on daily FDC regimens remains sparse in the Indian context [20]. Several Asian cohort studies have demonstrated that most biochemical abnormalities occur within the first 1–4 weeks of therapy and that early detection allows conservative management, thereby preventing severe outcomes [21-25]. Nonetheless, real-world Indian data describing early biochemical trends, clinical severity grading, and management outcomes following daily FDC initiation are limited.

This prospective observational study aimed to address these gaps by evaluating early (two-week) LFT alterations in adults started on daily FDC ATT at a tertiary care center in Kerala. Specifically, the study assessed the prevalence, severity grading, demographic associations, and clinical management outcomes of LFT derangements. By integrating biochemical data with treatment modifications and rechallenge patterns, the study provides practical insights that can inform risk-based clinical monitoring strategies and guide programmatic decision-making within NTEP.

Materials and Methods

This prospective observational study was conducted in the Department of Respiratory Medicine at a tertiary care centre in Kerala between January 28, 2025, and June 28, 2025, following approval from the institutional ethics committee. Participants included adults aged 18 years and above with newly diagnosed tuberculosis, confirmed through clinical assessment, radiological findings, or microbiological evidence, and comprising both pulmonary and extrapulmonary forms of the disease. All enrolled patients were initiated on daily fixed-dose combination therapy in accordance with the National Tuberculosis Elimination Programme (NTEP) guidelines. Patients with pre-existing acute or chronic liver disease, baseline transaminase levels exceeding twice the upper limit of normal, or suspected or confirmed drug-resistant tuberculosis were excluded from the study.

Demographic and clinical data, including age, sex, body weight, and tuberculosis classification, were systematically recorded. Baseline and two-week liver function tests (LFTs) were performed for all participants, and patients received counselling regarding the symptoms of potential hepatotoxicity prior to treatment initiation. Plasma specimens collected in green-top tubes were centrifuged immediately, ensuring a minimum sample volume of 1 mL. Liver enzyme levels were analyzed using an automated biochemistry analyzer.

Treatment followed standard NTEP recommendations, comprising a two-month intensive phase containing isoniazid, rifampicin, pyrazinamide, and ethambutol administered according to weight bands, followed by a four- to six-month continuation phase with isoniazid, rifampicin, and ethambutol. LFT derangement was defined in accordance with WHO and NTEP criteria as the presence of jaundice, an elevation of ALT or AST greater than five times the upper limit of normal in the absence of symptoms, greater than three times the upper limit of normal in the presence of symptoms, or a rise in serum total bilirubin exceeding twice the upper limit of normal.

Severity of LFT derangement was graded based on WHO/NTEP hepatotoxicity definitions. Grade 1 was defined as ALT or AST less than three times the upper limit of normal without symptoms. Grade 2 represented elevations three to five times the upper limit of normal, while Grade 3 indicated elevations greater than five times the upper limit of normal or total bilirubin levels exceeding twice the upper limit of normal. Grade 4 denoted clinical hepatitis, jaundice, or features suggestive of liver failure.

The sample size was calculated using previously reported proportions of liver enzyme dysfunction among patients receiving first-line anti-tuberculosis therapy [20], yielding a

minimum requirement of 147 participants at a 95% confidence level with a 20% relative allowable error. Data were collected using a standardized proforma and entered into Microsoft Excel, after which statistical analysis was performed using IBM SPSS Statistics version 25. Appropriate statistical tests were applied to assess associations between variables. Written informed consent was obtained from all participants in both English and the local language.

Statistical analysis

Data entry was performed in Microsoft Excel and statistical analysis was carried out using IBM SPSS Statistics version 25. Continuous variables such as ALT, AST, and bilirubin were expressed as mean ± standard deviation. Normality of continuous variables was assessed using the Shapiro–Wilk test. Baseline and two-week liver enzyme levels were compared using the paired t-test for normally distributed variables, and the Wilcoxon signed-rank test for non-normal distributions.

Categorical variables, including age group, sex, tuberculosis type (PTB/EPTB), and weight band, were summarized as frequencies and percentages. Associations between categorical variables and liver function test (LFT) derangement were analyzed using the Chi-square test or Fisher's exact test when appropriate. Chi-square values, degrees of freedom, and corresponding p-values were reported for all association tests. A p-value of <0.05 was considered statistically significant for all analyses.

Results

Among the 146 adult tuberculosis patients analyzed, 41 (28.1%) developed liver function test (LFT) derangements following the initiation of daily fixed-dose combination (FDC) anti-tuberculosis therapy (ATT). No statistically significant association was found between LFT derangement and age (Chi-square test, $\chi^2 = 0.05$, df = 2, $p = 0.977$), sex (Chi-square test, $\chi^2 = 0.11$, df = 1, $p = 0.898$), or tuberculosis type (Chi-square test, $\chi^2 = 0.00$, df = 1, $p = 1.000$) (Table 1) (Figure 1).

Mean ALT increased from 26.6 IU/L at baseline to 58.1 IU/L at two weeks (paired t-test, $p < 0.001$), and mean AST increased from 29.5 IU/L to 55.1 IU/L (paired t-test, $p < 0.001$). Total bilirubin rose from 0.63 to 0.83 mg/dL (paired t-test, $p < 0.01$), and direct bilirubin from 0.49 to 0.64 mg/dL (paired t-test, $p < 0.01$). These elevations were predominantly asymptomatic.

Among the 41 patients who developed LFT derangement, the severity distribution showed that 27 patients (65.9%) had Grade 1 abnormalities, 9 patients (22.0%) had Grade 2 changes, and

5 patients (12.1%) had Grade 3 derangement, while none exhibited Grade 4 toxicity. The majority of cases were therefore mild, and importantly, no patient progressed to clinical hepatitis or experienced severe Grade 4 hepatotoxicity.

Of the 41 patients with LFT derangement, 29 (70.7%) did not require any treatment modification and were able to continue their anti-tuberculosis therapy under DOTS with routine monitoring, underscoring the importance of structured follow-up within the DOTS system. Overall, most patients were managed conservatively without major adjustments to therapy. Among the remainder, 8 patients (19.5%) required temporary treatment interruption, 3 patients (7.3%) were successfully rechallenged after normalization of liver enzymes, and 1 patient (2.4%) required permanent modification with substitution of hepatotoxic drugs. Importantly, no cases progressed to clinical jaundice, hepatic failure, or hospitalization.

Among extrapulmonary tuberculosis cases, the most commonly involved sites were lymph nodes (15 cases), pleural tuberculosis (10 cases) and spinal tuberculosis (5 cases), with the remainder being abdominal, genitourinary, central nervous system, and joint tuberculosis cases.

A comparison of baseline and 2-week liver function test values showed a significant rise in aminotransferase levels following the initiation of daily FDC therapy. Mean ALT increased from 26.6 IU/L at baseline to 58.1 IU/L at two weeks, while mean AST rose from 29.5 IU/L to 55.1 IU/L. Total bilirubin increased from 0.63 mg/dL to 0.83 mg/dL, and direct bilirubin from 0.49 mg/dL to 0.64 mg/dL. All patients underwent baseline and 2-week LFT monitoring, and of the 146 cases evaluated, 105 (72%) maintained normal 2-week LFT values whereas 41 patients (28%) developed LFT derangements and were managed accordingly (Table 1).

When stratified by age, although derangement was distributed across all age groups, no clear linear trend was observed between advanced age and the incidence of hepatotoxicity (Chi-square test, $\chi^2 = 0.05$, df = 2, $p = 0.977$). The 18–40 years group showed 28.9% derangement (11/38 patients), the 40–60 years group showed 27.1% (16/59 patients), and the >60 years group showed 28.6% (14/49 patients) (Table 2).

Liver function test derangement was most frequent (32.7%) in patients with a weight band 55–69 kg, followed by 40–54 kg (29.7%), >70 kg (23.1%), and 25–39 kg (11.7%). However, these differences were not statistically significant (Chi-square test, $p > 0.05$) (Table 3).

Most cases involved elevated levels of asymptomatic aminotransferases. Among patients with deranged liver function tests, 23 had pulmonary tuberculosis and 18 had extrapulmonary tuberculosis, with no significant statistical association (Chi-square test, $p > 0.05$) (Figure 2).

Discussion

Anti-tuberculosis drug–induced hepatotoxicity remains one of the most important challenges in the management of tuberculosis, particularly in countries with a high disease burden such as India. Understanding the timing, pattern, and clinical significance of early liver function abnormalities is essential for optimizing treatment safety and strengthening programmatic decision-making under NTEP.

In this prospective cohort of 146 adults initiated on daily FDC ATT, early LFT derangements occurred in 28.1% of patients, aligning with previously reported rates from Indian and Asian settings, which range between 15% and 30% during the intensive phase of therapy [21-25]. The consistency across regions suggests that early hepatotoxicity is an expected occurrence in high-burden populations receiving isoniazid- and pyrazinamide-containing regimens.

We observed no significant association between LFT derangements and age, sex, or TB type. Similar findings have been reported in Indian and Chinese cohorts where demographic variables alone did not reliably predict early ATD-DILI [22,24,26]. This reinforces the need for universal—not selective—early biochemical monitoring, especially since clinical symptoms were absent in most patients.

Mean ALT and AST values more than doubled from baseline to two weeks, while bilirubin showed modest but significant increases. These patterns mirror those documented in large Chinese and South Asian cohorts where aminotransferase elevations typically precede symptomatic hepatitis and represent early biochemical stress markers [18,21,27]. Because all increases occurred within two weeks, the findings support the practice of scheduling early monitoring at 10–14 days, a time window that reliably captures the initial hepatic response to FDC initiation.

In our study, 65.9% of abnormalities were Grade 1, 22% Grade 2, and 12.1% Grade 3, with no Grade 4 hepatotoxicity. This severity distribution aligns with prospective studies from India, the Himalayan region, and Thailand, all of which describe predominantly mild early abnormalities with a smaller proportion of moderate-severe elevations [23-25]. The absence of severe hepatitis or liver failure underscores the effectiveness of early detection and timely intervention.

A key strength of this study is its detailed evaluation of clinical outcomes and management patterns following LFT derangement. Among the affected patients, 70.7% were able to continue ATT with close monitoring under DOTS, while 19.5% required temporary treatment interruption. A smaller proportion, 7.3%, underwent successful rechallenge after

normalization of liver enzymes, and only 2.4% required permanent modification of their regimen with substitution of hepatotoxic drugs. These outcomes closely mirror findings from South Indian and Chinese cohorts, where early biochemical monitoring allowed predominantly conservative management and effectively prevented progression to clinically significant DILI [24,27]. Importantly, none of the patients in our study developed jaundice, hepatic failure, or required hospitalization, underscoring the programmatic safety of early detection and structured follow-up.

Although LFT derangements were more frequent in the 55–69 kg group (32.7%), weight bands overall did not show statistically significant differences. Prior literature suggests that BMI and nutritional status, rather than weight alone, are stronger predictors of hepatotoxicity [15,28]. Similarly, pulmonary versus extrapulmonary disease had no impact on hepatotoxicity risk, consistent with earlier studies showing that hepatic vulnerability is driven more by host metabolic and genetic factors than by disease site [13,26].

Our findings demonstrate that routine early (two-week) LFT monitoring is both clinically valuable and programmatically feasible. Most district laboratories already conduct basic LFTs, and integration into DOTS follow-up visits requires minimal operational adjustments. Evidence from multiple Asian studies supports early monitoring as an effective strategy to limit treatment disruption, prevent severe DILI, and standardize decision-making on interruption and rechallenge [23-25]. These results support NTEP's movement toward structured biochemical surveillance, especially in the early phases of therapy (Figure 3).

The observed incidence likely reflects an interplay of factors prevalent in the Indian population, including NAT2 slow-acetylator genotypes, CYP2E1 variants, and continuous pyrazinamide exposure in daily regimens [12-14,29]. Nutritional challenges and underlying hepatic stress may further amplify risk, as reported in endemic regions [15,30].

Strengths and limitations

This study has several strengths, including its prospective design, uniform early liver function monitoring, and detailed characterization of biochemical patterns and clinical management outcomes within a real-world NTEP setting. The use of standardized WHO/NTEP criteria for grading hepatotoxicity and clearly defined algorithms for treatment modification further strengthen the reliability of the findings. However, certain limitations should be acknowledged: the single-center setting may limit broader generalizability, and the focus on early two-week changes does not capture late-onset hepatotoxicity. Additionally, genetic and nutritional

factors—which may influence individual susceptibility—were not assessed. Despite these modest limitations, the study provides valuable programmatically relevant insights into early ATT-related hepatotoxicity and supports the feasibility of structured early monitoring in routine practice.

Conclusions

In conclusion, early liver function abnormalities are relatively common during the initial phase of daily FDC anti-tuberculosis therapy, yet the majority are mild, asymptomatic, and manageable with careful monitoring. Routine baseline testing followed by structured early reassessment enables prompt identification and conservative management of hepatotoxicity, preventing treatment interruptions and minimizing the risk of severe outcomes. These findings underscore the practical value of integrating early biochemical surveillance into routine NTEP practice and highlight the importance of continued vigilance during the initial weeks of therapy to ensure both treatment safety and adherence.

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Table 1. Comparison of baseline and 2-week LFT values.

Parameter	Baseline (mean ± SD)	2-Week (mean ± SD)	Mean difference	p-value
ALT (IU/L)	26.6	58.1	+31.5	<0.001
AST (IU/L)	29.5	55.1	+25.6	<0.001
Total bilirubin (mg/dL)	0.63	0.83	+0.20	<0.01
Direct bilirubin (mg/dL)	0.49	0.64	+0.15	<0.01

Table 2. Association between age group and LFT derangement.

Age Group (years)	Normal LFT (n)	Deranged LFT (n)	Percentage deranged (%)
18–40	27	11	28.9%
40–60	43	16	27.1%
>60	35	14	28.6%
Total	105 (71.9%)	41 (28.1%)	—

Chi-square = 0.05, df = 2, p = 0.977.

Table 3. Association between weight band and LFT derangement

Weight Band (kg)	FDC Tablets per Day	Deranged LFT (n)	Total (n)	Percentage Deranged (%)
25–39	2	2	17	11.7%
40–54	3	19	64	29.7%
55–69	4	17	52	32.7%
>70	5	3	13	23.1%

Chi-square test: p > 0.05 (not significant).

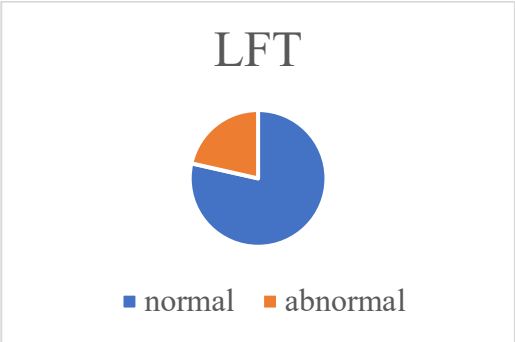

Figure 1. Prevalence of liver function test (LFT) derangement among tuberculosis patients (normal 71.9%, deranged 28.1%).

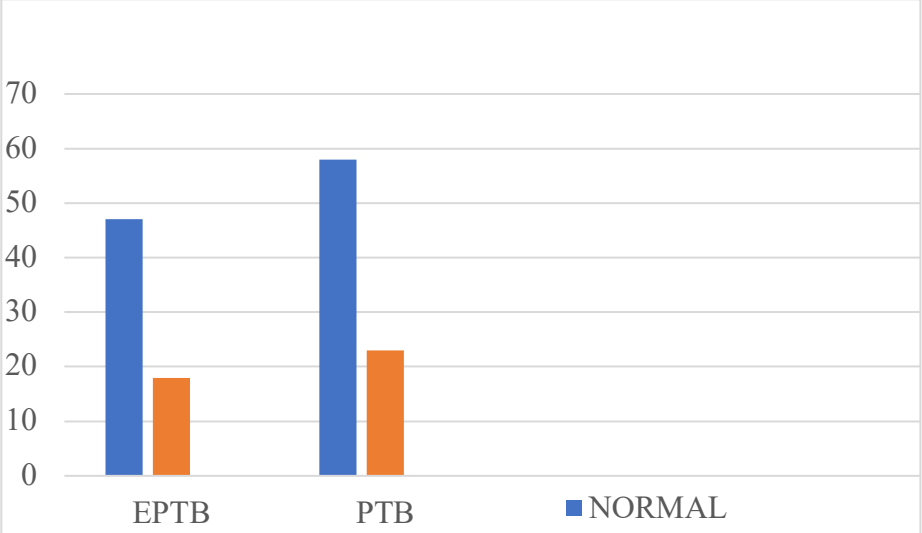

Figure 2. Association of LFT derangement with pulmonary vs. extrapulmonary tuberculosis (PTB: 23 cases; EPTB: 18 cases).

Figure 3. Flowchart of ATT monitoring.