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Patterns of Drug-Induced Liver Injury Among Patients Receiving First-Line Anti- Tuberculosis Therapy at a National Referral Centre in Sri Lanka: A Prospective Observational Study

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Abstract

Background

Drug-induced liver injury (DILI) represents a significant complication of anti-tuberculosis therapy (ATT). There is limited evidence on its biochemical patterns and clinical outcomes in Sri Lanka. This study aimed to characterise the biochemical patterns, clinical features, and outcomes of ATT-associated DILI.

Methods

A prospective observational study was conducted at the National Hospital for Respiratory Diseases, Welisara, Sri Lanka, from January to June 2026. Adults who developed DILI while receiving first-line ATT were consecutively recruited and prospectively followed. Biochemical injury patterns were classified using the R-ratio calculated from alanine aminotransferase and alkaline phosphatase measurements obtained at initial DILI diagnosis. Clinical characteristics, treatment modifications and outcomes were analysed.

Results

Forty-six patients were included (mean age 58.7 ± 14.8 years; 71.7% male). Mixed-pattern injury was most prevalent (60.9%), followed by hepatocellular (26.1%) and cholestatic (13.0%) patterns. The most frequently reported symptoms were nausea (89.1%), vomiting (69.6%), and fatigue (67.4%). Jaundice was observed in 15.2% of patients and occurred significantly more often in those with cholestatic injury ($p = 0.026$). No statistically significant associations were found between biochemical patterns and demographic or clinical characteristics. Modification of ATT was necessary in 73.9% of cases, and 93.5% underwent drug rechallenge. Full recovery was achieved in 65.2% of patients, partial recovery in 28.3%, and mortality was 4.3%.

Conclusions

Mixed-pattern liver injury predominated in this prospective Sri Lankan cohort, in contrast to the hepatocellular predominance reported in several international studies. ATT-associated DILI frequently required treatment modification, illustrating the importance of early recognition, biochemical monitoring and careful drug reintroduction.

Introduction

Tuberculosis (TB) is still a major global public health challenge, particularly in low- and middle-income countries. Standard first-line anti-tuberculosis therapy (ATT), comprising isoniazid, rifampicin, pyrazinamide and ethambutol, is highly effective in treating drug-susceptible TB. However, drug-induced

liver injury (DILI) is an important complication of treatment, particularly associated with isoniazid, rifampicin and pyrazinamide. DILI may require treatment interruption, regimen modification, or prolonged monitoring, affecting treatment continuity and clinical outcomes [1].

Anti-tuberculosis DILI presents with a range of clinical and biochemical abnormalities, from asymptomatic elevations in liver enzymes to clinically significant hepatitis and, in rare cases, acute liver failure. Biochemical classification of DILI includes hepatocellular, cholestatic, and mixed patterns, determined by the R-ratio calculated from alanine aminotransferase (ALT) and alkaline phosphatase (ALP) concentrations relative to their respective upper limits of normal [2]. Characterising these patterns facilitates understanding of the heterogeneity of liver injury and its association with clinical manifestations and treatment outcomes.

Previous research has largely focused on the incidence and risk factors of ATT-associated DILI. Factors including advanced age, alcohol consumption, pre-existing liver disease, and baseline biochemical abnormalities have been evaluated in relation to liver injury development [3, 4]. However, less emphasis has been placed on the distribution of biochemical injury patterns and their associated clinical characteristics and outcomes. Differences in patient populations, diagnostic criteria, and timing of biochemical assessment may account for the variability in reported patterns across studies.

Although Sri Lanka has been previously studied ATT-associated hepatotoxicity, including at Chest Hospital, Welisara [3], there is limited local evidence specifically characterising hepatocellular, cholestatic, and mixed patterns of liver injury. A prospective evaluation of these biochemical patterns, alongside clinical manifestations and outcomes, may offer valuable insights into the presentation and management of ATT-associated DILI in routine clinical practice.

Therefore, this study aimed to determine the distribution of hepatocellular, cholestatic, and mixed DILI patterns among patients receiving first-line ATT at the National Hospital for Respiratory Diseases, Welisara, Sri Lanka, and to evaluate associated demographic characteristics, clinical manifestations, biochemical profiles, and clinical outcomes.

Methods

Study design and setting

A prospective observational study was conducted at the National Hospital for Respiratory Diseases (NHRD), Welisara, Sri Lanka, a national referral centre for tuberculosis and respiratory diseases. Adult patients who developed drug-induced liver injury (DILI) while receiving first-line anti-tuberculosis therapy (ATT) were consecutively recruited between 1 January and 30 June 2026. Participants were prospectively followed to assess clinical manifestations, treatment modifications, drug rechallenge, and clinical outcomes. A total of 47 records were initially identified during the study period. Following data verification, one duplicate record was removed, leaving 46 unique patients who were included in the final analysis.

Study population and sampling

Adult patients aged ≥ 18 years who developed drug-induced liver injury (DILI) while receiving first-line anti-tuberculosis therapy (ATT), comprising isoniazid, rifampicin, pyrazinamide and ethambutol, were eligible for inclusion. Patients with documented pre-existing chronic liver disease, acute or chronic viral hepatitis, concomitant hepatotoxic medications unrelated to ATT that could independently explain liver injury, or incomplete clinical or biochemical information required for injury-pattern classification were excluded.

Eligible patients were consecutively recruited during the study period. The minimum required sample size was calculated using the single-proportion formula, assuming an expected proportion of 50%, a 95% confidence level and 15% absolute precision, yielding a minimum sample size of 43 patients. All eligible patients were recruited, and none declined participation. No patients were excluded, except for removing one duplicate record.

Data collection

Data were prospectively collected using a structured data collection form through direct patient assessment, review of clinical records and laboratory investigations. Information contained demographic characteristics, body weight, type of tuberculosis, comorbidities, smoking and alcohol-use status, anti-tuberculosis treatment regimen and duration of treatment before the development of DILI.

Clinical manifestations, including nausea, vomiting, fatigue, abdominal pain and jaundice, were recorded at the time of DILI diagnosis. Biochemical parameters included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and total bilirubin. ALT and ALP measurements obtained from the same blood sample at initial DILI diagnosis were used to classify the biochemical pattern of liver injury. Baseline liver function tests and other relevant investigations were recorded when available.

Participants were prospectively followed to document modifications to anti-tuberculosis therapy, subsequent drug rechallenge and clinical outcomes. Liver function tests were repeated during follow-up to assess biochemical recovery from DILI. Follow-up continued until 12 August 2026.

Definition and classification of DILI

Drug-induced liver injury (DILI) was defined using prespecified biochemical criteria as the presence of at least one of the following: alanine aminotransferase (ALT) ≥ 3 times the upper limit of normal (ULN) with symptoms; ALT ≥ 5 times ULN without symptoms; alkaline phosphatase (ALP) ≥ 2 times ULN accompanied by elevated gamma-glutamyl transferase (GGT); or ALT ≥ 3 times ULN with total bilirubin ≥ 2 times ULN.

The biochemical pattern of liver injury was classified using the R-ratio, calculated from ALT and ALP concentrations obtained from the same blood sample at initial DILI diagnosis:

R = (ALT / ALT ULN) / (ALP / ALP ULN)

Hepatocellular injury was defined as R ≥ 5, cholestatic injury as R ≤ 2, and mixed injury as 2 < R < 5.

The laboratory upper reference limits were ALT 40 U/L, AST 40 U/L, ALP 120 U/L, GGT 55 U/L and total bilirubin 1.2 mg/dL, consistent with the reference values used at NHRD Welisara.

Clinical and biochemical outcomes were assessed during prospective follow-up using serial liver function tests. Full recovery was defined as normalisation of liver function tests, while partial recovery was defined as biochemical improvement without complete normalisation by the end of follow-up. Failure to recover from DILI was defined as the absence of meaningful biochemical improvement during follow-up. Death was recorded as a separate clinical outcome

Statistical analysis

Data were analysed using IBM SPSS Statistics version 31.0. Categorical variables were summarised as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate.

Demographic characteristics, comorbidities, clinical manifestations and biochemical parameters were compared across the hepatocellular, mixed and cholestatic DILI groups. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the Kruskal–Wallis test when distributions were non-normally distributed.

Missing data were handled using available-case analysis without imputation. Symptom-onset dates were available for 19 of the 46 participants (41.3%); therefore, time to symptom onset was analysed only among these patients. All 46 participants had the biochemical measurements required for DILI pattern classification.

All statistical tests were two-sided, with $p < 0.05$ considered statistically significant. Multivariable regression analysis was not performed because of the small sample size and the limited number of patients in the cholestatic group.

Ethical considerations

The Ethics Review Committee of the Faculty of Medicine, University of Kelaniya, Sri Lanka, approved the study (Approval No. P/248/12/2025). Written informed consent was obtained from all participants before enrolment. The study was conducted in accordance with the principles of the Declaration of Helsinki. Patient confidentiality was maintained throughout the study, and all data were anonymised

before analysis. No additional investigations or interventions were performed solely for research purposes.

Results

Patient characteristics

A total of 46 patients who developed drug-induced liver injury (DILI) while receiving first-line anti-tuberculosis therapy were prospectively recruited and included in the final analysis. The mean age was 58.7 ± 14.8 years, and 33 (71.7%) patients were male. The mean body weight was 44.9 ± 11.2 kg.

Pulmonary tuberculosis was diagnosed in 34 (73.9%) patients, extrapulmonary tuberculosis in 10 (21.7%), and both pulmonary and extrapulmonary tuberculosis in 2 (4.3%). Diabetes mellitus was present in 12 (26.1%) patients, while 11 (23.9%) had cardiovascular disease. Eight (17.4%) patients were current smokers, 17 (37.0%) were former smokers, and 14 (30.4%) reported current alcohol consumption.

All patients received first-line anti-tuberculosis therapy, including isoniazid, rifampicin, pyrazinamide, and ethambutol, at the time of DILI development. All 46 participants completed the planned follow-up, with no loss to follow-up. Data were complete for all variables except symptom-onset dates, which were available for 19 participants (41.3%).

Distribution of DILI patterns

Among the 46 patients with anti-tuberculosis drug-induced liver injury, mixed-pattern injury was the most frequently observed biochemical pattern, occurring in 28 (60.9%) patients. Hepatocellular injury was identified in 12 (26.1%) patients, while cholestatic injury was observed in 6 (13.0%) patients. Table 1 presents the distribution of biochemical injury patterns.

Table 1
Distribution of biochemical patterns of anti-tuberculosis drug-induced liver injury (n = 46)

DILI pattern	Number (n)	Percentage (%)
Mixed	28	60.9
Hepatocellular	12	26.1
Cholestatic	6	13.0
Total	46	100.0

Clinical manifestations and time to onset of DILI

Nausea was the most frequently reported clinical manifestation, occurring in 41 (89.1%) patients, followed by vomiting in 32 (69.6%), fatigue in 31 (67.4%), abdominal pain in 19 (41.3%) and jaundice in 7 (15.2%) (Table 2).

Jaundice differed significantly across the three biochemical injury patterns (exact p = 0.026). Jaundice occurred in 3 of 6 (50.0%) patients with cholestatic injury and 4 of 28 (14.3%) with mixed injury, while none of the 12 patients with hepatocellular injury had jaundice.

Among the 19 patients with available symptom-onset dates, the median interval from initiation of anti-tuberculosis therapy to symptom onset was 10 days (IQR 6.5–21 days), ranging from 1 to 34 days.

Table 2
Clinical manifestations of DILI (n = 46)

Clinical manifestation	n (%)
Nausea	41 (89.1)
Vomiting	32 (69.6)
Fatigue	31 (67.4)
Abdominal pain	19 (41.3)
Jaundice	7 (15.2)

Biochemical characteristics according to DILI pattern

The biochemical profiles differed across the three patterns of drug-induced liver injury (Table 3). The overall median alanine aminotransferase (ALT) concentration was 149 U/L (IQR 129–169.5), while the median aspartate aminotransferase (AST) concentration was 130.5 U/L (IQR 100–221.5).

ALT concentrations differed notably across the three injury patterns (p < 0.001), with the highest median concentration observed in the hepatocellular group (189.5 U/L), followed by the mixed (149 U/L) and cholestatic (77 U/L) groups.

Alkaline phosphatase (ALP) concentrations also differed significantly between groups (p < 0.001), with the highest median in the cholestatic group (255 U/L), followed by the mixed group (106.5 U/L) and the hepatocellular group (91.5 U/L). Gamma-glutamyl transferase (GGT) concentrations differed significantly across injury patterns (p = 0.022), with the highest median concentration in the cholestatic group.

In contrast, AST (p = 0.089) and total bilirubin (p = 0.292) concentrations did not differ significantly (Table 3).

Table 3
Biochemical parameters according to DILI pattern

Parameter	Overall (n = 46)	Hepatocellular (n = 12)	Mixed (n = 28)	Cholestatic (n = 6)	p-value
AST (U/L)	130.5 (100–221.5)	176 (126–340.8)	126.5 (90–194.3)	99.5 (35.8–163.3)	0.089
ALT (U/L)	149 (129–169.5)	189.5 (150–238.8)	149 (129–156.8)	77 (29.5–123)	< 0.001
ALP (U/L)	109.5 (92.5–146)	91.5 (57–112.5)	106.5 (100–124.8)	255 (245.5–284)	< 0.001
GGT (U/L)	79.5 (53.8–106)	55 (21–79.8)	86 (59.8–108.8)	105.5 (84–157)	0.022
Bilirubin (mg/dL)	1.0 (0.6–1.9)	0.85 (0.55–2.15)	0.90 (0.58–1.83)	1.50 (1.43–2.25)	0.292

Patient-related factors associated with DILI patterns

Demographic characteristics and selected clinical factors were compared across the hepatocellular, mixed and cholestatic DILI groups. No statistically significant differences were observed in age (p = 0.297), body weight (p = 0.454) or sex distribution (p = 0.158) between the three biochemical injury patterns.

Similarly, the distribution of pulmonary tuberculosis (p = 0.394), diabetes mellitus (p = 0.703), cardiovascular disease (p = 0.335), smoking status (p = 0.796) and alcohol consumption (p = 0.931) did not differ notably across the three groups.

None of the evaluated demographic or clinical characteristics demonstrated a statistically significant association with biochemical DILI pattern in this cohort.

Treatment modifications, rechallenge and clinical outcomes

Following the development of drug-induced liver injury, anti-tuberculosis therapy was modified in 34 (73.9%) patients. Rechallenge with anti-tuberculosis drugs was subsequently undertaken in 43 (93.5%) patients.

During prospective follow-up, 30 (65.2%) patients achieved full biochemical recovery, while 13 (28.3%) demonstrated partial biochemical recovery. One patient (2.2%) failed to recover from DILI, and two patients (4.3%) died during follow-up.

Table 4 presents the distribution of treatment modifications, rechallenge, and clinical outcomes.

Table 4
Treatment modifications and clinical outcomes (n = 46)

Variable	n (%)
Treatment management	
ATT modified	34 (73.9)
ATT rechallenge performed	43 (93.5)
Clinical outcomes	
Full recovery	30 (65.2)
Partial recovery	13 (28.3)
Failure to recover from DILI	1 (2.2)
Death	2 (4.3)

Discussion

This prospective observational study characterised the biochemical patterns, clinical manifestations and treatment results of drug-induced liver injury (DILI) among patients receiving first-line anti-tuberculosis therapy at a national referral centre in Sri Lanka. The principal finding was the predominance of mixed-pattern liver injury (60.9%), followed by hepatocellular (26.1%) and cholestatic (13.0%) injury. Gastrointestinal and constitutional symptoms were common, while jaundice was more frequent among patients with cholestatic injury. DILI also frequently necessitated modification of anti-tuberculosis therapy, highlighting its clinical consequences for tuberculosis management.

The predominance of mixed-pattern liver injury contrasts with findings from several international studies. Zhang et al. [5], in a retrospective study involving 567 patients in China, reported hepatocellular injury as the predominant pattern (71.4%), while mixed and cholestatic patterns accounted for 14.8% and 13.8%, respectively. Similarly, Jiang et al. [4] reported hepatocellular injury in 86.5% of 170 patients with DILI, compared with mixed injury in only 8.8%. Differences in study populations, case selection, diagnostic definitions, and timing of biochemical assessment may explain these variations. Previous Sri Lankan research by Senaratne et al. [3], conducted at Chest Hospital, Welisara, primarily investigated the incidence, risk factors and management of anti-tuberculosis drug-induced hepatitis. Our study expands the available local evidence by prospectively characterising biochemical injury patterns, clinical manifestations and subsequent outcomes.

Nausea, vomiting and fatigue were the most frequently reported symptoms, whereas jaundice occurred in only 15.2% of patients. Jaundice was significantly more frequent among patients with cholestatic injury (50.0%) than those with mixed injury (14.3%) or hepatocellular injury (0%; $p = 0.026$). Zhang et al. [5] also reported differences in clinical presentation across biochemical injury patterns. These findings

show that clinical manifestations may vary according to the biochemical pattern of liver injury. The relatively low frequency of jaundice in this cohort illustrates the importance of biochemical assessment in patients developing nonspecific symptoms during anti-tuberculosis treatment. Previous research has also demonstrated the clinical importance of identifying patients at risk of more severe anti-tuberculosis DILI [6].

No statistically significant associations were identified between biochemical injury pattern and age, sex, body weight, diabetes mellitus, cardiovascular disease, smoking or alcohol consumption. Previous studies have investigated several of these characteristics as potential risk factors for developing DILI [3, 4]. A systematic review and meta-analysis by Zhang et al. [7] identified alcohol consumption as a risk factor for anti-tuberculosis DILI. However, the current analysis examined differences in biochemical patterns among patients who had already developed DILI, rather than factors associated with the initial development of liver injury. Therefore, interpret the absence of statistically significant associations cautiously.

DILI had important consequences for tuberculosis treatment, with 73.9% of patients requiring modification of anti-tuberculosis therapy and 93.5% undergoing drug rechallenge. During prospective follow-up, 65.2% of patients achieved full biochemical recovery, while 28.3% achieved partial biochemical recovery. Two deaths occurred during follow-up, although direct attribution to DILI could not be established. Management recommendations emphasise appropriately interrupting hepatotoxic drugs, biochemical monitoring, and careful reintroduction of treatment [1, 8]. Sharma et al. [9], in a randomised trial involving 175 patients, evaluated different drug-reintroduction regimens following anti-tuberculosis treatment-induced hepatotoxicity, further demonstrating the clinical importance of structured rechallenge strategies.

An important strength of this study was its prospective design, with consecutive recruitment and follow-up of patients who developed DILI during first-line anti-tuberculosis therapy. The use of predefined diagnostic criteria and standardised R-ratio classification strengthened the consistency of biochemical assessment. In particular, ALT and ALP measurements obtained from the same blood sample at initial DILI diagnosis were used for R-ratio calculation, ensuring time consistency. Prospective documentation of clinical manifestations, treatment modifications, rechallenge and biochemical recovery provided a comprehensive description of DILI in routine clinical practice. Nevertheless, the single-centre design and relatively small sample size, particularly the limited number of patients with cholestatic injury, may restrict generalisability and statistical power. Furthermore, symptom-onset dates were available for only 19 patients, limiting assessment of the timing of clinical presentation. Larger prospective multicentre studies are needed to confirm the recorded distribution of biochemical injury patterns and investigate potential contributing factors.

Conclusion

Mixed-pattern liver injury was the predominant biochemical presentation of anti-tuberculosis drug-induced liver injury in this prospective Sri Lankan cohort, in contrast to the hepatocellular predominance reported in several international studies. Gastrointestinal and constitutional symptoms were common, while jaundice was more frequently observed among patients with cholestatic injury. DILI frequently necessitated modification of anti-tuberculosis therapy and subsequent drug rechallenge, illustrating the importance of early recognition, biochemical monitoring and careful drug reintroduction. These data contribute to the limited evidence on biochemical patterns and clinical outcomes of anti-tuberculosis DILI in Sri Lanka and warrant confirmation through larger prospective multicentre studies.

Abbreviations

ALP
Alkaline phosphatase
ALT
Alanine aminotransferase
AST
Aspartate aminotransferase
ATT
Anti-tuberculosis therapy
DILI
Drug-induced liver injury
GGT
Gamma-glutamyl transferase
IQR
Interquartile range
NHRD
National Hospital for Respiratory Diseases
SD
Standard deviation
TB
Tuberculosis
ULN

Upper limit of normal

Declarations

Ethics approval and consent to participate

The Ethics Review Committee of the Faculty of Medicine, University of Kelaniya, Sri Lanka, approved the study (Approval No. P/248/12/2025). Written informed consent was obtained from all participants before enrolment. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Kriya Badugei Kasun Tharaka Maduranga conceived and designed the study, led patient recruitment and prospective follow-up, collected and analysed the data, interpreted the findings, and drafted the manuscript. U. V. Jayasingha, Piumi Ellangage, and H.I. M. Dissanayaka assisted with patient recruitment, clinical data collection, interpretation of findings, and critical revision of the manuscript. Eshanth Perera provided scientific guidance and supervision, helped interpret the findings, and critically revised the manuscript. All authors read and approved the final manuscript.

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Data Availability

The corresponding author can provide the datasets generated and analysed during the current study upon reasonable request, subject to applicable ethical and institutional requirements.

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