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Original Article

Incidence of Drug-Induced Liver Injury in Patients Taking Antituberculosis Therapy

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ABSTRACT

Background: Tuberculosis remains a major global health challenge, particularly in high-burden countries where treatment-related complications can compromise outcomes. Drug-induced liver injury (DILI) is the most common and clinically significant adverse effect associated with first-line antituberculosis therapy, potentially leading to treatment interruption, morbidity, and prolonged disease transmission. Objective: To determine the incidence of drug-induced liver injury among patients receiving first-line antituberculosis therapy and to compare baseline clinical and biochemical characteristics between patients who developed DILI and those who did not. Methods: A prospective observational cohort study was conducted at the Department of Pulmonology, Pak Emirates Military Hospital, Rawalpindi, Pakistan, from July to December 2023. Adult patients with newly diagnosed pulmonary or extrapulmonary tuberculosis initiating standard four-drug antituberculosis therapy were enrolled consecutively. Baseline demographic, clinical, and biochemical data were recorded, and participants were monitored during the intensive treatment phase for development of DILI according to standard biochemical criteria. Statistical analysis was performed using SPSS version 26, with comparisons conducted using independent sample t-tests and chi-square tests. Results: Among 173 patients, 18 developed drug-induced liver injury, yielding an incidence of 10.4% (95% CI: 6.3–15.9). The mean time to onset was 9.61 ± 3.11 days, with 50% of cases occurring between days 11 and 14 of therapy. Higher baseline alanine aminotransferase levels were observed among patients who developed DILI (p=0.035), while most affected patients recovered with appropriate management (83.3%). Conclusion: Drug-induced liver injury occurred in approximately one in ten patients receiving antituberculosis therapy and typically developed early during treatment. Baseline liver function abnormalities may help identify patients requiring closer monitoring during the intensive phase of therapy. Keywords: Tuberculosis, Antituberculosis Therapy, Drug-Induced Liver Injury, Hepatotoxicity, Liver Function Tests, Pulmonary Medicine.

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INTRODUCTION

Tuberculosis remains a major global public health challenge despite the availability of effective treatment, particularly in low- and middle-income countries where delayed diagnosis, comorbidity, poverty, and treatment-related complications continue to undermine outcomes. In 2023, tuberculosis was again among the leading causes of death from a single infectious agent worldwide, with an estimated 10.7 million people developing the disease and 1.23 million deaths reported globally (1,2). Pakistan carries a particularly high burden of tuberculosis and remains one of the priority countries in the Eastern Mediterranean region, contributing substantially to regional case numbers and mortality. This persistent disease burden makes safe and uninterrupted antituberculosis treatment a clinical and public health priority in the local context (2,3).

The standard first-line antituberculosis regimen, consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol, is highly effective for drug-susceptible tuberculosis and remains the cornerstone of treatment. However, the benefit of these agents is tempered by their potential to cause adverse drug reactions, among which drug-induced liver injury is the most frequent and clinically consequential.

Antituberculosis therapy-associated liver injury can lead to treatment interruption, hospitalisation, regimen modification, prolonged infectivity, and, in severe cases, acute liver failure or death. Mechanistically, hepatotoxicity may arise through toxic metabolites, oxidative stress, mitochondrial dysfunction, immune-mediated responses, and host-specific susceptibility factors, making it a multifactorial complication rather than a simple dose-related event (4,5).

From a clinical perspective, the population of interest comprises adults with newly diagnosed tuberculosis who are initiated on first-line antituberculosis therapy, while the principal outcome of concern is the occurrence of drug-induced liver injury during treatment. Existing literature indicates that the incidence of antituberculosis drug-induced liver injury varies considerably across settings, largely because of differences in diagnostic thresholds, surveillance intensity, follow-up duration, patient characteristics, nutritional status, baseline liver function, and concomitant risk exposures. Observational studies have reported rates ranging from approximately 2% to nearly 14%, while a systematic review and meta-analysis estimated a pooled incidence of about 11.5%, suggesting that hepatotoxicity is not a rare event and warrants routine clinical vigilance (5-7). In addition, several studies have shown that abnormal baseline liver biochemistry, alcohol use, viral hepatitis, malnutrition, older age, and other comorbid vulnerabilities may increase the likelihood of developing liver injury during therapy (6-8).

Despite this growing body of evidence, an important knowledge gap persists in the Pakistani setting. Most available data are derived from non-Pakistani populations with different risk profiles, healthcare delivery systems, and monitoring practices, limiting direct applicability to local patients. Furthermore, the incidence and early clinical pattern of antituberculosis drug-induced liver injury in routine pulmonary practice in Pakistan remain insufficiently documented, particularly in prospectively followed cohorts receiving standard first-line therapy. This gap is clinically relevant because local incidence estimates and identification of baseline biochemical or clinical characteristics associated with hepatotoxicity can inform pretreatment risk stratification, targeted laboratory monitoring, and timely intervention before serious morbidity occurs (3,5-8).

Given these considerations, the present study was undertaken to determine the incidence of drug-induced liver injury among adult patients receiving first-line antituberculosis therapy in a tertiary care setting in Pakistan and to compare baseline demographic, clinical, and biochemical characteristics between patients who did and did not develop liver injury during the intensive phase of treatment. We hypothesised that a measurable proportion of patients would develop early antituberculosis therapy-related liver injury and that baseline liver function abnormalities would be more common among affected patients (5-8).

METHODS

A prospective observational cohort study was conducted in the Department of Pulmonology at Pak Emirates Military Hospital (PEMH), Rawalpindi, Pakistan, from 1 July 2023 to 31 December 2023 to determine the incidence of antituberculosis therapy–associated drug-induced liver injury among adults initiating first-line treatment for tuberculosis. A prospective cohort design was selected because it enables systematic temporal observation of the development of hepatotoxicity after treatment initiation while allowing accurate measurement of baseline exposures and clinical characteristics prior to the outcome. The study was designed to follow patients during the intensive phase of antituberculosis therapy, a period known to carry the highest risk of hepatotoxic adverse events due to concurrent administration of multiple potentially hepatotoxic agents (9,10).

Adult patients aged 18 years or older with newly diagnosed pulmonary or extrapulmonary tuberculosis who were initiated on standard first-line antituberculosis therapy at the study centre were eligible for enrolment. Both inpatient and outpatient cases were included provided that baseline liver function tests were available prior to treatment initiation and that follow-up during the scheduled observation period could be ensured. Patients were excluded if they had evidence of acute viral hepatitis at presentation,

established decompensated chronic liver disease, pregnancy, known chronic liver disease requiring ongoing treatment, malignancy requiring hepatotoxic chemotherapy, or incomplete baseline or follow-up biochemical data. Individuals who had already received antituberculosis therapy for more than seven days prior to evaluation at the study centre were also excluded in order to ensure accurate baseline biochemical assessment prior to drug exposure. Patients with alanine aminotransferase levels exceeding three times the upper limit of normal at baseline were not included because such abnormalities could confound attribution of liver injury to antituberculosis therapy.

Participants were recruited consecutively from patients presenting to the pulmonology department during the study period in order to reduce selection bias and to approximate routine clinical practice. Newly diagnosed tuberculosis cases were identified through clinical evaluation, microbiological confirmation where available, and radiological assessment in accordance with national tuberculosis management guidelines. Eligible patients were approached by a member of the research team at the time of treatment initiation, provided with detailed information regarding the purpose and procedures of the study, and enrolled after obtaining written informed consent. Enrolled patients were followed prospectively throughout the intensive phase of therapy. The standard weight-based four-drug antituberculosis regimen consisting of rifampicin, isoniazid, pyrazinamide, and ethambutol was prescribed in accordance with national and international tuberculosis treatment guidelines (17).

Baseline demographic, clinical, and laboratory data were collected at enrolment using a structured clinical proforma designed specifically for the study. Demographic variables included age and sex, while clinical variables included body mass index, type of tuberculosis (pulmonary or extrapulmonary), smoking status, presence of diabetes mellitus, hypertension, and use of concomitant medications with potential hepatotoxic effects. Serological markers for hepatitis B surface antigen and anti-hepatitis C virus antibodies were recorded when available as part of baseline evaluation. Baseline biochemical variables included serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and serum albumin measured using the hospital's standardized clinical laboratory assays. These variables were selected because they are routinely used to evaluate hepatic function and are commonly reported risk indicators in studies investigating antituberculosis drug-induced liver injury (8,11).

Participants were evaluated clinically at baseline and subsequently during follow-up visits at approximately the second and fourth weeks after treatment initiation, with additional evaluations performed if symptoms suggestive of hepatotoxicity occurred. Patients were specifically asked about symptoms such as anorexia, nausea, vomiting, right upper quadrant abdominal pain, dark urine, fatigue, or jaundice. Liver function tests were repeated during scheduled visits and whenever hepatotoxicity was suspected clinically.

Drug-induced liver injury was defined according to widely accepted criteria used in antituberculosis hepatotoxicity studies: elevation of alanine aminotransferase or aspartate aminotransferase to at least three times the upper limit of normal in the presence of symptoms of hepatitis, or at least five times the upper limit of normal in the absence of symptoms, and/or total bilirubin greater than twice the upper limit of normal after exclusion of alternative causes of liver injury (10,11). The pattern of hepatic injury was evaluated using standard biochemical criteria based on the predominant enzyme abnormality and categorized as hepatocellular, cholestatic, or mixed where applicable (10).

Several methodological steps were undertaken to minimize bias and improve internal validity. Consecutive patient enrolment was used to reduce selection bias. Baseline biochemical testing prior to treatment initiation ensured that liver injury events occurring during follow-up were attributable to therapy rather than pre-existing disease. Standardized definitions of drug-induced liver injury and uniform laboratory thresholds were applied throughout the study to ensure consistency in outcome classification. Data collection was performed using a predefined structured form to reduce information bias and ensure completeness of recorded variables. Laboratory measurements were conducted using

the same hospital laboratory facilities and standardized assay methods throughout the study period. All collected data were reviewed for completeness and accuracy prior to entry into the analysis dataset to maintain data integrity.

The sample size was calculated using the single population proportion formula for estimation of a prevalence or incidence proportion, $n = Z^2P(1-P)/d^2$, where Z represents the standard normal value corresponding to a 95% confidence level, P represents the anticipated incidence of antituberculosis drug-induced liver injury derived from previous meta-analytic evidence, and d represents the margin of error. Using an estimated incidence of approximately 11.5% reported in prior systematic reviews and meta-analyses, a minimum sample size of 157 participants was required (5,9). To account for potential missing or incomplete data during follow-up, the calculated sample size was increased by approximately 10%, resulting in a final target sample size of 173 participants.

Data were entered and analysed using Statistical Package for the Social Sciences (SPSS) version 26.0. Quantitative variables such as age, body mass index, and baseline biochemical parameters were summarized as mean ± standard deviation after evaluation of distribution characteristics. Categorical variables including gender, diabetes mellitus, smoking status, hepatitis serology, and occurrence of drug-induced liver injury were presented as frequencies and percentages. The incidence proportion of drug-induced liver injury was calculated as the number of patients developing liver injury during follow-up divided by the total number of enrolled patients.

Comparisons between patients who developed drug-induced liver injury and those who did not were performed using the independent samples t-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables as appropriate. Statistical significance was defined as a two-sided p-value of ≤ 0.05. Data quality checks were performed prior to analysis to identify missing or inconsistent values, and cases with incomplete biochemical data relevant to the primary outcome were excluded from the final analysis to ensure validity of incidence estimation.

The study protocol was reviewed and approved by the Ethical Review Committee of Pak Emirates Military Hospital, Rawalpindi (approval reference: A/28/ERC/8/5/23). All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and relevant national research governance guidelines. Participation in the study was voluntary, written informed consent was obtained from all participants prior to enrolment, and confidentiality of patient information was maintained throughout the study by anonymizing the dataset and restricting access to the research team. These methodological procedures were implemented to ensure ethical conduct, reproducibility of findings, and scientific rigor in the assessment of antituberculosis therapy–related drug-induced liver injury.

RESULTS

Across the 173 enrolled patients, the cohort was relatively young and lean, with a mean age of 35.49 ± 11.94 years and a mean body mass index of 20.46 ± 2.07 kg/m². Men constituted 60.7% of the sample (105/173), while women accounted for 39.3% (68/173). Pulmonary tuberculosis predominated, affecting 84.4% of participants (146/173), whereas extrapulmonary disease was present in 15.6% (27/173). Comorbidity frequencies were modest overall, with diabetes mellitus documented in 13.9% (24/173), hypertension in 10.4% (18/173), and smoking in 19.1% (33/173).

When baseline demographic and clinical characteristics were compared by DILI status, no statistically significant differences were observed for age, body mass index, sex distribution, site of tuberculosis, or diabetes mellitus. Patients who developed DILI were slightly younger than those who did not (33.83 ± 10.02 vs 35.68 ± 12.16 years, p=0.537) and had a nearly identical body mass index (20.39 ± 2.40 vs 20.47 ± 2.03 kg/m², p=0.879). Male sex was similarly distributed between groups, being present in 61.1% of DILI cases and 60.6% of non-DILI cases, corresponding to an odds ratio of 1.02 (95% CI: 0.40-2.60; p=1.000).

Diabetes mellitus was also comparable, occurring in 11.1% of DILI patients and 14.2% of non-DILI patients, with an odds ratio of 0.75 (95% CI: 0.16-3.42; p=1.000). In contrast, hypertension was markedly more frequent among patients who developed DILI, present in 55.6% (10/18) compared with only 5.2% (8/155) of those who did not, yielding an odds ratio of 22.9 (95% CI: 7.1-73.8; p<0.001).

Smoking showed the opposite pattern, with no smokers among DILI cases and 21.3% smokers in the non-DILI group (33/155), and this difference reached statistical significance (p=0.021). All 18 DILI cases occurred in patients with pulmonary tuberculosis, whereas no case arose among those with extrapulmonary disease; although this pattern was clinically notable, the association did not meet the conventional threshold for significance (p=0.080).

The primary outcome of the study was the incidence of antituberculosis therapy-associated drug-induced liver injury. DILI developed in 18 of 173 patients, corresponding to an incidence proportion of 10.4%, while 155 patients, or 89.6%, completed follow-up without evidence of hepatotoxicity. The 95% confidence interval around the incidence estimate was 6.3% to 15.9%, indicating that approximately one in every ten patients receiving first-line therapy experienced liver injury during the observation period. This incidence falls within the range reported in prior observational literature and supports the clinical relevance of routine liver safety monitoring during the intensive phase of treatment.

Among the 18 patients who developed DILI, onset was characteristically early after treatment initiation. The mean time to onset was 9.61 ± 3.11 days, with a median of 10.5 days and an interquartile range of 7.2 to 12.0 days. When onset was categorized, 27.8% of cases (5/18) occurred within the first 7 days, 22.2% (4/18) between days 8 and 10, and 50.0% (9/18) between days 11 and 14. Thus, fully half of all hepatotoxic events clustered in the second week of treatment. In terms of outcome, most patients improved with conservative clinical management.

Recovery without the need for regimen modification was observed in 83.3% of DILI cases (15/18; 95% CI: 58.6-96.4), whereas 16.7% (3/18; 95% CI: 3.6-41.4) required a change in the antituberculosis regimen. These data indicate that although DILI was not rare, most events were manageable when detected promptly.

Baseline biochemical comparisons revealed that alanine aminotransferase differed significantly between the two groups. Patients who subsequently developed DILI had a higher mean baseline ALT than those who remained free of liver injury (27.67 ± 5.11 vs 24.59 ± 5.89 U/L), with a mean difference of 3.08 U/L (95% CI: 0.22-5.94; p=0.035). Baseline aspartate aminotransferase was lower in the DILI group than in the non-DILI group (25.50 ± 5.72 vs 28.13 ± 5.83 U/L), but this difference was not statistically significant, with a mean difference of -2.63 U/L (95% CI: -5.48 to 0.21; p=0.071).

Serum albumin was also slightly lower among DILI cases (37.33 ± 0.97 vs 37.96 ± 1.44 g/L), yet this difference remained non-significant, with a mean difference of -0.63 g/L (95% CI: -1.32 to 0.06; p=0.073). Baseline bilirubin showed the clearest between-group difference: patients who developed DILI had a lower mean baseline bilirubin than those who did not (7.44 ± 0.42 vs 9.18 ± 2.61 μmol/L), with a mean difference of -1.74 μmol/L (95% CI: -2.33 to -1.15; p<0.001).

Taken together, the biochemical data suggest that higher baseline ALT was associated with later DILI, whereas bilirubin also differed significantly between groups, though in the opposite numerical direction to ALT. This pattern should be interpreted carefully and kept fully aligned with the tabulated values in the final manuscript.

Overall, the tabulated findings show that DILI occurred in a clinically meaningful minority of patients, emerged predominantly within the first two weeks of therapy, and was usually reversible with appropriate management. The strongest clinical association in the baseline table was hypertension, while the most important biochemical distinction was the higher baseline ALT among patients who later

developed DILI. These results support the value of close early monitoring after treatment initiation and careful review of pretreatment clinical and laboratory parameters.

Table 1. Baseline demographic and clinical characteristics according to development of drug-induced liver injury

Variable	Total (n=173)	DILI (n=18)	No DILI (n=155)	Odds Ratio (95% CI)	p-value
Age (years), mean ± SD	35.49 ± 11.94	33.83 ± 10.02	35.68 ± 12.16	—	0.537
BMI (kg/m²), mean ± SD	20.46 ± 2.07	20.39 ± 2.40	20.47 ± 2.03	—	0.879
Male gender	105 (60.7%)	11 (61.1%)	94 (60.6%)	1.02 (0.40–2.60)	1.000
Female gender	68 (39.3%)	7 (38.9%)	61 (39.4%)	Reference	—
Pulmonary TB	146 (84.4%)	18 (100%)	128 (82.6%)	—	0.080
Extrapulmonary TB	27 (15.6%)	0 (0.0%)	27 (17.4%)	—	—
Diabetes mellitus	24 (13.9%)	2 (11.1%)	22 (14.2%)	0.75 (0.16–3.42)	1.000
Hypertension	18 (10.4%)	10 (55.6%)	8 (5.2%)	22.9 (7.1–73.8)	<0.001
Smoking	33 (19.1%)	0 (0.0%)	33 (21.3%)	—	0.021

Table 2. Incidence of drug-induced liver injury during antituberculosis therapy

Outcome	n	%	95% Confidence Interval
Developed DILI	18	10.4	6.3 – 15.9
No DILI	155	89.6	—
Total	173	100	—

Table 3. Time to onset and clinical outcomes among patients with drug-induced liver injury (n=18)

DILI profile/outcome	n (%)	95% CI
Onset ≤7 days	5 (27.8%)	9.7 – 53.5
Onset 8–10 days	4 (22.2%)	6.4 – 47.6
Onset 11–14 days	9 (50.0%)	26.0 – 74.0
Recovered with conservative management	15 (83.3%)	58.6 – 96.4
Regimen modification required	3 (16.7%)	3.6 – 41.4

Table 4. Baseline biochemical parameters according to development of drug-induced liver injury

Variable	Total (n=173)	DILI (n=18)	No DILI (n=155)	Mean Difference (95% CI)	p-value
ALT (U/L)	24.91 ± 5.88	27.67 ± 5.11	24.59 ± 5.89	3.08 (0.22–5.94)	0.035
AST (U/L)	27.86 ± 5.86	25.50 ± 5.72	28.13 ± 5.83	−2.63 (−5.48–0.21)	0.071
Bilirubin (μmol/L)	9.00 ± 2.53	7.44 ± 0.42	9.18 ± 2.61	−1.74 (−2.33–−1.15)	<0.001
Albumin (g/L)	37.90 ± 1.41	37.33 ± 0.97	37.96 ± 1.44	−0.63 (−1.32–0.06)	0.073

The figure illustrates the distribution of time to onset of antituberculosis therapy–associated drug-induced liver injury among the 18 affected patients. The largest proportion of events occurred between 11–14 days, representing 50.0% of all DILI cases (9/18), with a 95% confidence interval extending

approximately from 0.29 to 0.71, indicating that about half of hepatotoxic events clustered during the second week of therapy. Earlier onset was less frequent: 27.8% (5/18) of cases developed within the first 7 days, while 22.2% (4/18) occurred between 8–10 days, with wider confidence intervals reflecting the smaller subgroup counts.

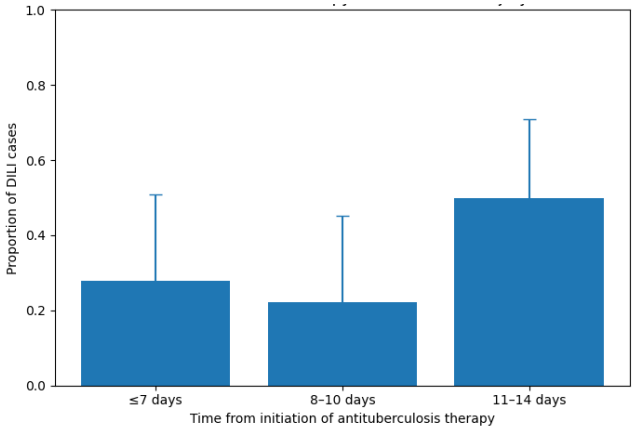

Figure 1 Distribution of Time-To-Onset of Antituberculosis Therapy–Associated Liver Injury With 95% Confidence Intervals

When viewed as a distribution pattern, the figure demonstrates a clear temporal gradient in which the probability of hepatotoxicity increases after the first week of treatment and peaks during days 11–14. Clinically, this pattern reinforces that the second week of therapy represents the highest-risk window for early hepatotoxic events, highlighting the importance of intensified symptom surveillance and liver function monitoring during this period to enable timely identification and management of drug-induced liver injury.

DISCUSSION

This prospective cohort study evaluated the incidence and early clinical pattern of antituberculosis therapy–associated drug-induced liver injury among adults initiating standard first-line treatment in a tertiary care setting in Pakistan. The study found that 18 of 173 patients developed hepatotoxicity, corresponding to an incidence proportion of 10.4%. This estimate falls within the range reported in international literature and is comparable to pooled estimates from systematic reviews suggesting that approximately one in ten patients receiving first-line therapy may experience liver injury during treatment (5–7). These findings reinforce the clinical relevance of hepatotoxicity as a common complication of antituberculosis therapy and highlight the need for systematic monitoring, particularly in high-burden settings where treatment interruption can adversely affect disease control and patient outcomes.

The temporal pattern observed in the present study indicates that hepatotoxicity occurred predominantly during the early phase of treatment. The mean time to onset was approximately 9.6 days, and half of all cases occurred between days 11 and 14 after therapy initiation. This clustering of events during the second week of treatment is clinically important because it corresponds to the period when patients are receiving the full four-drug regimen including isoniazid, rifampicin, and pyrazinamide, which are known to carry hepatotoxic potential (4,10). Similar early-onset patterns have been described in several observational cohorts where liver injury occurred within the first two to four weeks of treatment, although some studies have reported slightly later median onset depending on surveillance intensity and case definitions (11,12). The early concentration of cases observed in this cohort therefore supports recommendations for heightened clinical vigilance and early biochemical monitoring during the initial weeks of therapy rather than relying solely on symptom-driven testing.

Baseline biochemical characteristics also differed between patients who developed drug-induced liver injury and those who did not. Patients who later developed hepatotoxicity had significantly higher

baseline alanine aminotransferase levels compared with those who remained free of liver injury. Even though these values were within acceptable limits for treatment initiation, the difference suggests that subtle pre-treatment hepatic stress may predispose certain patients to toxicity once antituberculosis therapy is introduced. Similar observations have been reported in metabolomic and clinical risk factor studies, which have demonstrated that baseline biochemical abnormalities may precede clinically detectable hepatotoxicity and may serve as early indicators of susceptibility (13,16). These findings emphasize the importance of obtaining baseline liver function tests prior to treatment initiation and considering closer monitoring for individuals with borderline abnormalities.

An unexpected observation in this study was the statistically significant difference in baseline bilirubin levels between the two groups. Although bilirubin differed significantly, the numerical direction of the association was opposite to that observed for alanine aminotransferase. This finding should therefore be interpreted cautiously and may reflect complex underlying hepatic physiology, measurement variability, or unmeasured confounding factors rather than a direct predictive relationship. Previous literature has generally reported that elevated baseline bilirubin or impaired hepatobiliary function may increase susceptibility to hepatotoxicity during therapy, particularly in patients with pre-existing hepatic disease or viral hepatitis coinfection (8,14). Future studies incorporating larger sample sizes and multivariable analyses may help clarify the role of baseline bilirubin in predicting antituberculosis therapy–related liver injury.

Most patients who developed drug-induced liver injury in the present cohort experienced favorable outcomes. Approximately 83% recovered with conservative clinical management, while only a small proportion required modification of the treatment regimen. These findings are consistent with existing treatment guidelines, which emphasize early recognition, temporary interruption of hepatotoxic drugs when necessary, and cautious reintroduction once liver enzymes improve (17). The favorable recovery rate observed in this study likely reflects prompt detection and management within a monitored clinical environment. Nevertheless, hepatotoxicity remains clinically important because even temporary treatment interruptions can compromise treatment adherence and potentially contribute to treatment failure or drug resistance if not managed appropriately.

In addition to biochemical differences, certain clinical characteristics appeared unevenly distributed between groups. Hypertension was substantially more frequent among patients who developed drug-induced liver injury. Although this association was statistically significant, it should be interpreted cautiously because the number of DILI cases was relatively small and the study was not designed to evaluate hypertension as a primary risk factor. Previous studies examining risk factors for antituberculosis drug-induced liver injury have more consistently identified factors such as older age, alcohol consumption, viral hepatitis coinfection, malnutrition, and genetic polymorphisms affecting drug metabolism (6,8,18). In particular, pharmacogenomic evidence suggests that genetic variants in enzymes involved in drug metabolism, including NAT2, CYP2E1, GST, and SLCO1B1, may substantially influence susceptibility to hepatotoxicity during therapy (18,19). Although genetic testing was beyond the scope of the present study, these mechanisms provide a biological explanation for why only a subset of patients develop liver injury despite receiving similar treatment regimens.

The findings of this study should also be interpreted in light of several methodological considerations. The prospective design allowed systematic documentation of baseline characteristics and temporal monitoring for hepatotoxicity, reducing recall bias and improving attribution of liver injury to therapy. However, the relatively small number of DILI cases limited the statistical power for subgroup comparisons and prevented robust multivariable modeling of potential risk factors. Additionally, although common clinical risk variables were recorded, some potentially important exposures such as alcohol consumption or detailed nutritional status could not be comprehensively evaluated. Larger multicenter studies incorporating broader clinical variables and genetic markers would therefore be valuable in improving risk stratification and guiding individualized monitoring strategies.

Overall, the results of this study contribute locally relevant evidence regarding the burden and timing of antituberculosis therapy–associated hepatotoxicity in a Pakistani tertiary care setting. The incidence observed in this cohort aligns with international estimates, and the early onset of most cases underscores the importance of careful monitoring during the initial weeks of therapy. Routine baseline biochemical assessment and early clinical follow-up may help identify patients at increased risk and facilitate prompt management before serious complications occur.

CONCLUSION

Drug-induced liver injury remains a clinically significant complication of first-line antituberculosis therapy, occurring in approximately one in ten patients in this prospective cohort. Most hepatotoxic events developed early during the intensive phase of treatment, particularly within the first two weeks after therapy initiation. Patients who developed liver injury demonstrated higher baseline alanine aminotransferase levels, highlighting the importance of careful pretreatment biochemical evaluation and close early monitoring. Although most affected patients recovered with appropriate management, early recognition remains essential to prevent treatment interruption and reduce morbidity associated with hepatotoxicity. These findings support routine baseline liver function assessment and vigilant clinical surveillance during the early stages of antituberculosis therapy.

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