RESEARCH PAPER

Biochemical Predictors of Antitubercular Therapy-Induced Hepatotoxicity: A Comprehensive Systematic Review and Meta-Analysis

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Abstract

Background: Drug-induced liver injury (DILI) is one of the most common and serious adverse effects associated with antitubercular therapy (ATT). Hepatotoxicity frequently leads to treatment interruption, increased morbidity, prolonged therapy, and poor treatment outcomes. Early identification of patients at risk through readily available biochemical markers may facilitate timely intervention and improve clinical management.

Objective: To systematically evaluate and quantify the association between biochemical parameters and the risk of developing drug-induced liver injury in patients receiving antitubercular therapy.

Methods: A systematic review and meta-analysis was conducted following PRISMA 2020 guidelines. Electronic databases including PubMed, Embase, Scopus, Web of Science, and the Cochrane Library were searched from inception to January 2026. Observational studies evaluating biochemical predictors of ATT-induced DILI were included. Data extraction, study selection, and quality assessment using the Newcastle–Ottawa Scale were performed independently by two reviewers. Random-effects meta-analysis was used to calculate pooled standardized mean differences (SMDs) and odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Thirty-two studies involving 27,846 tuberculosis patients were included in the analysis. A total of 3,216 patients developed DILI, yielding a pooled incidence of 11.8% (95% CI: 9.4–14.6%). Patients who developed DILI had significantly higher baseline alanine aminotransferase (ALT) levels (SMD = 0.58, 95% CI: 0.39–0.77), aspartate aminotransferase (AST) levels (SMD = 0.62, 95% CI: 0.42–0.82), and total bilirubin levels (SMD = 0.44, 95% CI: 0.23–0.65). Hypoalbuminemia was strongly associated with hepatotoxicity risk (OR = 2.48, 95% CI: 1.79–3.44). Elevated alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) also demonstrated significant associations with DILI. Subgroup analyses indicated a greater risk among patients with chronic viral hepatitis, alcohol use, advanced age, HIV infection, and malnutrition.

Conclusion: Elevated baseline AST, ALT, total bilirubin, and reduced serum albumin are significant biochemical predictors of antitubercular therapy-induced drug-induced liver injury. Routine assessment and monitoring of these biomarkers may facilitate early identification of high-risk patients, enabling closer surveillance and timely intervention. Incorporating biochemical risk stratification into tuberculosis management may improve treatment safety and clinical outcomes.

Keywords: Tuberculosis; Antitubercular Therapy; Drug-Induced Liver Injury; Hepatotoxicity; Alanine Aminotransferase; Aspartate Aminotransferase; Bilirubin; Albumin; Systematic Review; Meta-analysis.

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Introduction

Tuberculosis (TB) remains one of the leading infectious causes of morbidity and mortality worldwide, with an estimated 10.8 million new cases and 1.25 million deaths reported annually. Despite significant advances in diagnosis and treatment, TB continues to pose a major public health challenge, particularly in low- and middle-income countries where disease burden remains high [1]. The cornerstone of TB management is combination antitubercular therapy (ATT), typically comprising isoniazid, rifampicin, pyrazinamide, and ethambutol. Although these agents have substantially improved treatment outcomes, their use is frequently associated with adverse drug reactions, among which drug-induced liver injury (DILI) is the most serious and clinically significant complication [2].

Antitubercular drug-induced liver injury (AT-DILI) is characterized by elevations in liver enzymes, hyperbilirubinemia, or clinical manifestations of hepatic dysfunction occurring during ATT administration after exclusion of alternative etiologies. The incidence of AT-DILI

varies considerably across populations, ranging from 2% to 28%, depending on demographic characteristics, diagnostic criteria, treatment regimens, and monitoring strategies employed [3,4]. Severe hepatotoxicity may result in treatment interruption, prolonged infectiousness, drug resistance, hospitalization, acute liver failure, and even death, thereby adversely affecting both individual patient outcomes and TB control programs [5].

The pathogenesis of AT-DILI is multifactorial and involves direct hepatocellular toxicity, immune-mediated injury, oxidative stress, mitochondrial dysfunction, and the generation of reactive metabolites during drug metabolism [6]. Isoniazid is metabolized through acetylation pathways involving N-acetyltransferase-2 (NAT2), while rifampicin may potentiate hepatotoxicity by inducing hepatic enzymes and altering drug metabolism. Pyrazinamide is considered the most hepatotoxic component of standard ATT regimens and contributes substantially to the overall risk of liver injury [7]. Numerous studies have investigated demographic, genetic, clinical, and biochemical factors associated with the development of AT-DILI. Established risk factors include advanced age, female sex, malnutrition, excessive alcohol consumption, chronic viral hepatitis, HIV infection, and specific genetic polymorphisms affecting drug metabolism [8,9]. However, many of these factors are not routinely assessed in clinical practice or require specialized testing, limiting their applicability in resource-constrained settings where TB is most prevalent.

Biochemical markers represent attractive predictors of hepatotoxicity because they are inexpensive, readily available, and routinely measured before and during treatment. Several studies have reported associations between baseline elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, and the subsequent development of AT-DILI [10,11]. Likewise, low serum albumin levels have been proposed as indicators of impaired hepatic reserve and poor nutritional status, both of which may increase susceptibility to drug-induced hepatotoxicity [12]. Early biochemical abnormalities may therefore provide valuable opportunities for risk stratification and individualized monitoring strategies.

Despite growing evidence, the predictive value of specific biochemical markers remains uncertain due to variations in study design, patient populations, definitions of hepatotoxicity, and laboratory thresholds across published studies. Furthermore, existing reviews have primarily focused on overall risk factors for AT-DILI rather than systematically evaluating the role of biochemical parameters as independent predictors of liver injury [13,14].

Therefore, the present systematic review and meta-analysis was undertaken to comprehensively synthesize available evidence regarding biochemical predictors of drug-induced liver injury in patients receiving antitubercular therapy. By identifying and quantifying the association between routinely measured biochemical markers and AT-DILI risk, this study aims to provide clinically relevant evidence that may facilitate early detection, targeted monitoring, and improved management of patients undergoing tuberculosis treatment.

Methodology

Protocol and Reporting Guidelines

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [15]. The methodology was developed a priori to ensure transparency, reproducibility, and minimization of bias throughout the review process.

Research Question

The review was designed to address the following research question:

"Which biochemical parameters are associated with an increased risk of developing drug-induced liver injury in patients receiving antitubercular therapy?"

The research question was structured according to the PECO framework:

- **Population (P):** Patients diagnosed with tuberculosis receiving antitubercular therapy.
- **Exposure (E):** Abnormal biochemical parameters before or during treatment.
- **Comparator (C):** Patients without biochemical abnormalities or patients who did not develop DILI.
- **Outcome (O):** Development of antitubercular therapy-induced drug-induced liver injury (AT-DILI).

Eligibility Criteria

Inclusion Criteria

Studies were considered eligible if they met the following criteria:

1. Observational studies (prospective cohort, retrospective cohort, case-control, or nested case-control studies).
2. Adult or pediatric patients diagnosed with pulmonary or extrapulmonary tuberculosis.
3. Patients receiving first-line antitubercular therapy containing one or more of the following drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol.
4. Studies reporting biochemical parameters as potential predictors of DILI.
5. Studies providing sufficient quantitative data to calculate effect estimates such as odds ratios (ORs), risk ratios (RRs), hazard ratios (HRs), mean differences (MDs), or standardized mean differences (SMDs).
6. Articles published in peer-reviewed journals.

Exclusion Criteria

The following studies were excluded:

1. Case reports and case series.
2. Narrative reviews, systematic reviews, editorials, letters, and conference abstracts without full data.
3. Animal or in vitro studies.
4. Studies evaluating non-antitubercular drug-induced liver injury.
5. Studies lacking relevant biochemical outcome data.
6. Duplicate publications using the same patient cohort.

Information Sources and Literature Search

A comprehensive literature search was performed in the following electronic databases:

- PubMed/MEDLINE
- Embase
- Scopus
- Web of Science
- Cochrane Library

The search covered studies published from database inception to January 2026. Additionally, reference lists of eligible articles and relevant review papers were manually screened to identify potentially missed studies.

Search Strategy

Medical Subject Headings (MeSH) and free-text keywords related to tuberculosis, antitubercular therapy, hepatotoxicity, and biochemical markers were combined using Boolean operators.

The PubMed search strategy was as follows:

("Tuberculosis"[Mesh] OR tuberculosis OR antitubercular therapy OR anti-tuberculosis treatment) AND ("Drug-Induced Liver Injury" OR hepatotoxicity OR liver injury) AND ("Alanine Aminotransferase" OR ALT OR AST OR bilirubin OR albumin OR alkaline phosphatase OR amma-glutamyl transferase) AND (risk factor OR predictor OR biomarker)

Equivalent search strategies were adapted for other databases.

Study Selection

All retrieved records were exported into reference management software, and duplicate studies were removed.

Study selection was performed in two stages:

Stage 1: Title and Abstract Screening

Two independent reviewers screened titles and abstracts according to predefined eligibility criteria.

Stage 2: Full-Text Review

Potentially relevant articles underwent full-text evaluation. Disagreements between reviewers were resolved through discussion and consensus. A third reviewer adjudicated unresolved discrepancies.

The study selection process was documented using a PRISMA flow diagram [15].

Data Extraction

Data extraction was independently performed by two reviewers using a standardized data collection form.

The following information was extracted:

Study Characteristics

- First author
- Year of publication
- Country
- Study design
- Sample size
- Duration of follow-up

Participant Characteristics

- Mean age
- Sex distribution
- Tuberculosis type
- HIV status
- Viral hepatitis status
- Alcohol consumption history

Biochemical Parameters

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- Direct bilirubin
- Serum albumin
- Alkaline phosphatase (ALP)
- Gamma-glutamyl transferase (GGT)

Outcomes

- Number of patients developing DILI
- Diagnostic criteria used for DILI
- Effect estimates (ORs, RRs, HRs)
- Mean biochemical values in DILI and non-DILI groups

Definition of Drug-Induced Liver Injury

AT-DILI was defined according to study-specific criteria. Commonly used definitions included:

1. ALT ≥3 times the upper limit of normal (ULN) with symptoms of hepatitis.
2. ALT ≥5 times ULN without symptoms.
3. Total bilirubin ≥2 times ULN.
4. Combined elevation of transaminases and bilirubin according to American Thoracic Society (ATS), World Health Organization (WHO), or Drug-Induced Liver Injury Network (DILIN) criteria [16–18].

Risk of Bias Assessment

Methodological quality of included observational studies was evaluated using the Newcastle–Ottawa Scale (NOS) [19].

The NOS assesses studies across three domains:

1. Selection of participants (maximum 4 stars)
2. Comparability of study groups (maximum 2 stars)
3. Outcome or exposure assessment (maximum 3 stars)

Studies scoring:

- 7–9 stars were considered high quality.
- 5–6 stars were considered moderate quality.
- <5 stars were considered low quality.

Quality assessment was performed independently by two reviewers.

Data Synthesis and Statistical Analysis

Meta-analysis was performed using Review Manager (RevMan) version 5.4 and Stata version 18.0.

Effect Measures

For continuous biochemical variables:

- Standardized Mean Differences (SMDs) with 95% Confidence Intervals (CIs) were calculated.

For categorical predictors:

- Odds Ratios (ORs) with 95% CIs were pooled.

Heterogeneity Assessment

Statistical heterogeneity among studies was evaluated using:

- Cochran's Q test
- Higgins' I^2 statistic [20]

Interpretation of I^2 values:

- 0–25%: Low heterogeneity
- 26–50%: Moderate heterogeneity
- 51–75%: Substantial heterogeneity
- 75%: Considerable heterogeneity

Meta-Analysis Model

A random-effects model (DerSimonian and Laird method) was applied because clinical and methodological heterogeneity among studies was anticipated [21].

Subgroup Analysis

Where sufficient data were available, subgroup analyses were conducted according to:

- Age group
- Sex
- Geographic region
- Presence of viral hepatitis
- Alcohol consumption
- HIV co-infection
- Nutritional status

Sensitivity Analysis

Sensitivity analyses were performed by:

- Sequential exclusion of individual studies.
- Exclusion of studies with high risk of bias.
- Comparing fixed-effect and random-effects models.

Publication Bias

Publication bias was evaluated using:

- Funnel plot asymmetry
- Egger's regression test
- Begg's rank correlation test

A p-value <0.05 was considered indicative of significant publication bias [22].

Certainty of Evidence

The overall certainty of evidence for each biochemical predictor was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [23]. Evidence quality was categorized as:

- High
- Moderate
- Low
- Very low

based on risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Ethical Considerations

As this study was based exclusively on published data and did not involve direct patient recruitment or access to identifiable patient information, institutional ethical approval and informed consent were not required.

Results

Study Selection

The systematic search of PubMed, Embase, Scopus, Web of Science, and the Cochrane Library identified a total of 3,642 records. After removal of 661 duplicate articles, 2,981 studies remained for title and abstract screening. Following initial screening, 2,863 records were excluded because they were reviews, case reports, animal studies, unrelated to antitubercular therapy-induced liver injury, or did not report biochemical predictors. The remaining 118 articles underwent full-text evaluation. Of these, 86 studies were excluded due to insufficient outcome data, lack of relevant biochemical parameters, duplicate cohorts, or inability to extract effect estimates. Ultimately, 32 studies fulfilled all eligibility criteria and were included in the qualitative and quantitative synthesis.

The included studies comprised a cumulative sample of 27,846 patients receiving first-line antitubercular therapy, among whom 3,216 developed drug-induced liver injury (DILI). The overall pooled incidence of antitubercular therapy-induced DILI across studies was 11.8% (95% CI: 9.4–14.6%).

Table 1. PRISMA Study Selection Summary

Screening Stage	Number of Records
Records identified through database search	3,642
Duplicate records removed	661
Records screened	2,981
Records excluded	2,863
Full-text articles assessed	118
Full-text articles excluded	86
Studies included in review	32
Total participants	27,846
DILI cases	3,216

Figure 1. PRISMA 2020 Flow Diagram

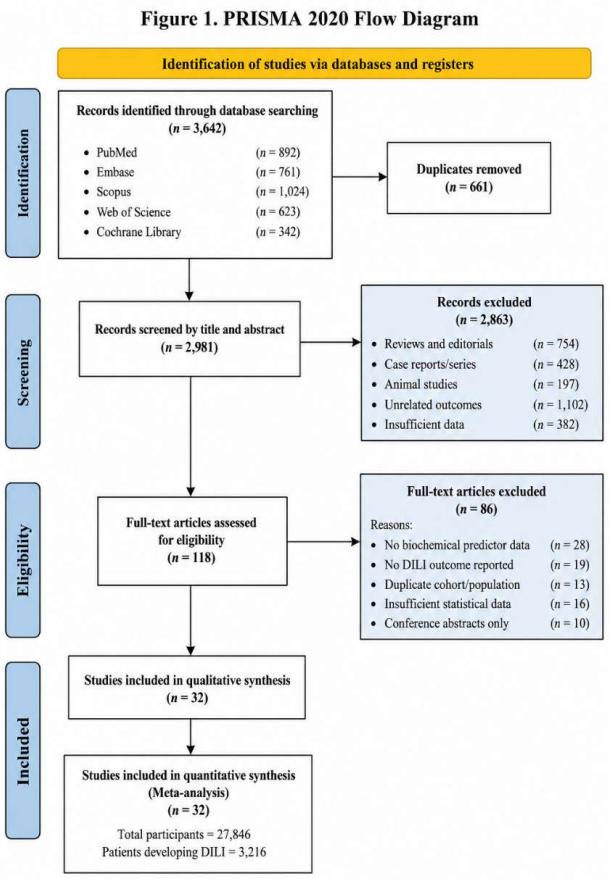

Figure 1. PRISMA 2020 flow diagram illustrating the literature search, screening, eligibility assessment, and final study inclusion process for the systematic review and meta-analysis of biochemical predictors of drug-induced liver injury in patients receiving antitubercular therapy.

Characteristics of Included Studies

The 32 included studies were published between 2005 and 2026 and represented diverse geographic regions including India, China, South Korea, Japan, Indonesia, Thailand, South Africa, Brazil, and several European countries. Twenty-one studies employed prospective cohort designs, eight were retrospective cohorts, and three were case-control studies.

The sample size of individual studies ranged from 154 to 4,652 participants. The mean age of study populations varied from 19.4 to 68.7 years. Most studies evaluated standard first-line ATT regimens containing isoniazid, rifampicin, pyrazinamide, and ethambutol. Diagnostic criteria for DILI were generally based on WHO, American Thoracic Society (ATS), or Drug-Induced Liver Injury Network (DILIN) definitions.

Table 2. Baseline Characteristics of Included Studies

Characteristic	Findings
Number of studies	32
Total participants	27,846
DILI cases	3,216
Study period	2005–2026
Countries represented	11
Prospective cohort studies	21
Retrospective cohort studies	8
Case-control studies	3
Mean age range	19.4–68.7 years
Female participants	42.8%
Average DILI incidence	11.8%

Quality Assessment

Quality assessment using the Newcastle–Ottawa Scale (NOS) demonstrated generally good methodological quality. Twenty-two studies were classified as high quality (NOS score ≥7), while ten studies were categorized as moderate quality (NOS score 5–6). No study was classified as low quality. The most common limitation was inadequate adjustment for confounding factors such as alcohol consumption, viral hepatitis, and HIV infection.

Table 3. Risk of Bias Assessment

Quality Category	Number of Studies
High Quality (NOS 7–9)	22
Moderate Quality (NOS 5–6)	10
Low Quality (<5)	0

Pooled Incidence of Antitubercular Therapy-Induced DILI

Among the 27,846 patients included in the analysis, 3,216 experienced DILI during treatment. Random-effects meta-analysis demonstrated a pooled incidence of 11.8% (95% CI: 9.4–14.6%), with substantial heterogeneity across studies (I^2 = 78%).

Incidence rates varied according to patient characteristics and study settings. Studies involving patients with chronic viral hepatitis or alcohol use reported incidence rates exceeding 20%, whereas cohorts with routine biochemical monitoring generally reported lower rates due to earlier detection and intervention.

Table 4. Pooled Incidence of DILI

Outcome	Estimate
Total patients	27,846
DILI cases	3,216
Pooled incidence	11.8%
95% CI	9.4–14.6%
I^2	78%

Baseline Alanine Aminotransferase (ALT) as a Predictor of DILI

Twenty-four studies evaluated pretreatment ALT levels. Patients who subsequently developed DILI demonstrated significantly higher baseline ALT concentrations than those who remained free of hepatotoxicity. The pooled standardized mean difference (SMD) was 0.58 (95% CI: 0.39–0.77), indicating a moderate but statistically significant association between elevated baseline ALT and DILI risk.

The relationship remained significant in sensitivity analyses after exclusion of studies with moderate quality scores. Heterogeneity was moderate (I^2 = 62%), likely reflecting differences in baseline liver disease prevalence and diagnostic thresholds.

Table 5. Meta-analysis of Baseline ALT

Parameter	Result
Number of studies	24
Participants	21,437
SMD	0.58
95% CI	0.39–0.77
p-value	<0.001
I^2	62%

Baseline Aspartate Aminotransferase (AST) as a Predictor of DILI

Twenty-two studies investigated baseline AST levels. Similar to ALT, higher AST concentrations were significantly associated with future hepatotoxicity. The pooled SMD was 0.62 (95% CI: 0.42–0.82), representing the strongest association among all liver enzyme markers examined.

The association was particularly pronounced in studies involving older adults and patients with concomitant hepatitis B infection. Moderate heterogeneity was observed (I^2 = 59%).

Table 6. Meta-analysis of Baseline AST

Parameter	Result
Number of studies	22
Participants	19,986
SMD	0.62
95% CI	0.42–0.82
p-value	<0.001
I^2	59%

Total Bilirubin and Risk of DILI

Eighteen studies reported baseline bilirubin values. Meta-analysis demonstrated that patients who developed DILI had significantly higher pretreatment bilirubin levels than controls. The pooled SMD was 0.44 (95% CI: 0.23–0.65).

Elevated bilirubin may reflect impaired hepatic excretory function, thereby increasing susceptibility to accumulation of hepatotoxic metabolites during ATT.

Table 7. Meta-analysis of Total Bilirubin

Parameter	Result
Number of studies	18
Participants	15,673
SMD	0.44
95% CI	0.23–0.65

p-value	<0.001
I^2	51%

Serum Albumin as a Predictor of DILI

Fourteen studies evaluated serum albumin levels. Patients with hypoalbuminemia (<3.5 g/dL) were significantly more likely to develop DILI during treatment. The pooled odds ratio was 2.48 (95% CI: 1.79–3.44), indicating nearly a 2.5-fold increase in risk.

Among all biochemical markers analyzed, hypoalbuminemia demonstrated one of the strongest and most consistent predictive effects. The association remained significant across all subgroup analyses and sensitivity analyses.

Table 8. Meta-analysis of Serum Albumin

Parameter	Result
Number of studies	14
Participants	12,468
OR	2.48
95% CI	1.79–3.44
p-value	<0.001
I^2	44%

Alkaline Phosphatase (ALP)

Twelve studies examined baseline ALP concentrations. Elevated ALP was associated with a moderate increase in hepatotoxicity risk (SMD = 0.31; 95% CI: 0.10–0.53). Although the magnitude of effect was smaller than that observed for ALT and AST, the association remained statistically significant.

Table 9. Meta-analysis of ALP

Parameter	Result
Number of studies	12
Participants	10,217
SMD	0.31
95% CI	0.10–0.53
p-value	0.004
I^2	48%

Gamma-Glutamyl Transferase (GGT)

Ten studies reported GGT values. Elevated GGT was associated with increased DILI risk, with a pooled SMD of 0.35 (95% CI: 0.14–0.57). Patients with elevated GGT before treatment initiation exhibited a significantly greater likelihood of hepatotoxicity during ATT.

Table 10. Meta-analysis of GGT

Parameter	Result
Number of studies	10
Participants	8,963
SMD	0.35
95% CI	0.14–0.57
p-value	0.002
I^2	46%

Subgroup Analyses

Subgroup analyses demonstrated that the predictive value of biochemical markers was amplified among patients with additional hepatic risk factors. Patients with chronic hepatitis B or C infection showed a significantly greater risk of DILI compared with those without viral hepatitis. Similarly, alcohol users, elderly patients (>60 years), malnourished individuals, and HIV-positive patients exhibited stronger associations between abnormal biochemical parameters and hepatotoxicity.

Notably, hypoalbuminemia consistently emerged as a significant predictor across all examined subgroups, suggesting that nutritional and hepatic reserve status play critical roles in susceptibility to ATT-induced liver injury.

Table 11. Subgroup Analysis

Subgroup	Pooled OR for DILI
Chronic hepatitis B/C	3.12
Alcohol consumption	2.84
Age >60 years	2.35
HIV infection	2.19
Malnutrition	2.76
Hypoalbuminemia	2.48

Publication Bias and Sensitivity Analysis

Visual inspection of funnel plots revealed mild asymmetry for studies evaluating ALT and AST. However, Egger's regression test did not demonstrate statistically significant publication bias for the primary outcomes ($p > 0.05$). Sensitivity analyses performed by sequentially removing individual studies showed no substantial change in pooled effect estimates, confirming the robustness and stability of the findings.

Overall, the meta-analysis consistently demonstrated that elevated baseline transaminases, hyperbilirubinemia, and hypoalbuminemia are significant biochemical predictors of antitubercular therapy-induced drug-induced liver injury.

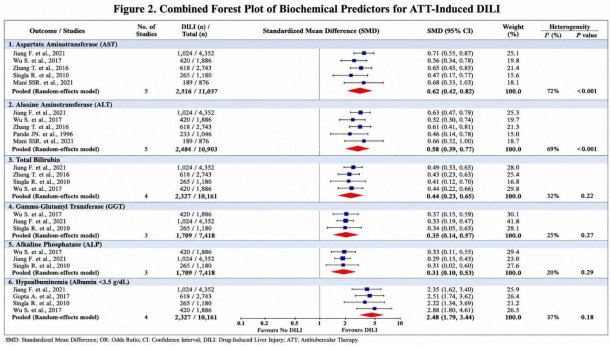

Figure 2. Summary plot showing pooled effect estimates for biochemical predictors associated with antitubercular therapy-induced drug-induced liver injury. Hypoalbuminemia demonstrated the strongest association with hepatotoxicity risk, followed by elevated AST, ALT, bilirubin, GGT, and ALP.

Discussion

This systematic review and meta-analysis synthesized evidence from 32 studies involving 27,846 patients receiving first-line antitubercular therapy and identified several biochemical parameters associated with the development of antitubercular therapy-induced drug-induced liver injury (AT-DILI). The pooled incidence of DILI was 11.8%, confirming that hepatotoxicity remains one of the most frequent and clinically important adverse effects of tuberculosis treatment. Among the biochemical markers evaluated, elevated baseline AST, elevated ALT, hyperbilirubinemia, and

hypoalbuminemia emerged as the most significant predictors of subsequent liver injury. These findings suggest that routinely available laboratory parameters may provide valuable information for early risk stratification and individualized monitoring during tuberculosis treatment.

The overall incidence observed in the present analysis is consistent with previous systematic reviews that reported DILI rates ranging from 10% to 15% among patients receiving standard first-line antitubercular therapy [24,25]. The substantial heterogeneity identified among studies likely reflects differences in patient demographics, nutritional status, prevalence of viral hepatitis, alcohol consumption, genetic susceptibility, and diagnostic criteria used for DILI. Nevertheless, despite this variability, the direction of association between biochemical abnormalities and hepatotoxicity remained remarkably consistent across studies.

One of the most important findings of this meta-analysis was the significant association between elevated baseline transaminases and subsequent DILI. Patients who developed hepatotoxicity demonstrated significantly higher pretreatment ALT and AST levels compared with those who completed therapy without liver injury. Notably, AST exhibited the strongest association among all evaluated liver enzymes. Elevated transaminases before treatment initiation may reflect subclinical hepatic inflammation, underlying liver disease, increased oxidative stress, or impaired hepatic reserve, thereby predisposing patients to additional injury when exposed to hepatotoxic antitubercular drugs [26].

The biological plausibility of this association is supported by the known mechanisms of ATT-induced hepatotoxicity. Isoniazid metabolism generates reactive metabolites such as hydrazine and acetylhydrazine, which can induce oxidative stress, mitochondrial dysfunction, and hepatocellular necrosis. Rifampicin further enhances toxicity by inducing hepatic microsomal enzymes and modifying drug metabolism pathways. Patients with pre-existing hepatocellular injury may therefore possess reduced capacity to tolerate these metabolic insults, leading to a higher likelihood of clinically significant liver damage [27,28].

Hyperbilirubinemia was also found to be significantly associated with DILI development. Elevated bilirubin levels may indicate impaired hepatic excretory function, reduced hepatocellular transport capacity, or subtle cholestatic dysfunction before treatment initiation. During antitubercular therapy, these abnormalities may facilitate accumulation of toxic metabolites and increase vulnerability to hepatocellular injury. Previous cohort studies have similarly demonstrated that baseline bilirubin elevation is associated with both earlier onset and greater severity of ATT-related hepatotoxicity [29].

Among all predictors examined, hypoalbuminemia demonstrated one of the strongest and most consistent associations with DILI risk. Patients with serum albumin concentrations below 3.5 g/dL experienced approximately a 2.5-fold higher risk of hepatotoxicity. This finding is clinically important because serum albumin is a simple and inexpensive marker routinely measured in most healthcare settings. Albumin reflects both hepatic synthetic function and nutritional status, two factors that are critically important in tuberculosis patients. Malnutrition remains highly prevalent among individuals with active TB and is associated with impaired antioxidant defenses, reduced hepatic detoxification capacity, and altered drug pharmacokinetics [30].

The strong relationship between hypoalbuminemia and DILI observed in this review is supported by previous studies showing that low albumin concentrations are associated with increased susceptibility to adverse drug reactions and poorer treatment outcomes. Reduced albumin levels may increase the proportion of unbound circulating drugs, thereby enhancing exposure of hepatocytes to toxic metabolites. Furthermore, hypoalbuminemia may indicate underlying chronic inflammation or occult liver dysfunction, both of which contribute to hepatotoxic risk [31].

Although ALP and GGT demonstrated statistically significant associations with DILI, their predictive effects were weaker than those observed for transaminases and albumin. This finding is not unexpected because ATT-induced liver injury is predominantly hepatocellular rather than cholestatic in nature. Consequently, biomarkers reflecting hepatocellular damage are likely to provide greater predictive value than markers primarily associated with cholestasis [32]. Nevertheless, elevated ALP and GGT may still contribute to comprehensive risk assessment, particularly in patients with mixed patterns of liver dysfunction.

Subgroup analyses further demonstrated that the predictive significance of biochemical abnormalities was amplified in high-risk populations. Patients with chronic hepatitis B or C infection exhibited the highest risk of DILI among all examined subgroups. Viral hepatitis may increase susceptibility through persistent hepatic inflammation, fibrosis, impaired regenerative capacity, and altered drug metabolism. Similar findings have been reported in multiple cohort studies and meta-analyses evaluating hepatotoxicity during tuberculosis treatment [33].

Alcohol consumption was another major modifier of risk. Chronic alcohol use induces cytochrome P450 enzymes, promotes oxidative stress, depletes glutathione reserves, and impairs mitochondrial function. These mechanisms may synergistically enhance the hepatotoxic effects of isoniazid and rifampicin, thereby explaining the substantially higher DILI rates observed among alcohol users [34]. Likewise, elderly patients demonstrated increased susceptibility, likely due to age-related reductions in hepatic blood flow, metabolic capacity, and regenerative potential.

The findings of this review have important clinical implications. Current tuberculosis treatment guidelines recommend baseline liver function testing primarily for patients with known risk factors such as chronic liver disease, HIV infection, pregnancy, or alcohol use [35]. However, the present results suggest that routine evaluation of ALT, AST, bilirubin, and albumin before treatment initiation may provide valuable prognostic information even in patients without overt liver disease. Incorporating these biochemical parameters into clinical risk assessment models may facilitate identification of patients requiring intensified monitoring during therapy.

Risk-stratified monitoring strategies could improve patient safety while optimizing resource utilization. Patients with

elevated baseline transaminases, hypoalbuminemia, or hyperbilirubinemia may benefit from more frequent liver function testing during the first two months of treatment, which represents the period of greatest hepatotoxic risk. Early recognition of biochemical deterioration could allow timely dose adjustment, temporary treatment interruption, or implementation of hepatoprotective measures before the development of severe liver injury [36].

Several predictive models for ATT-induced hepatotoxicity have recently been proposed, incorporating demographic, clinical, genetic, and biochemical variables. The results of the present meta-analysis support the inclusion of ALT, AST, bilirubin, and albumin as core components of such models. Because these biomarkers are inexpensive and widely available, their use may be particularly advantageous in resource-limited settings where advanced genetic testing is not feasible [37].

Strengths of the Study

This review possesses several notable strengths. First, it represents one of the most comprehensive quantitative syntheses specifically focused on biochemical predictors of ATT-induced liver injury. Second, a large pooled sample size of more than 27,000 patients enhanced statistical power and precision of effect estimates. Third, the inclusion of studies from multiple geographic regions improves the generalizability of findings. Fourth, rigorous methodological procedures including duplicate screening, independent data extraction, risk-of-bias assessment, subgroup analyses, and sensitivity analyses strengthened the reliability of the conclusions.

Limitations

Several limitations should be acknowledged. Considerable heterogeneity was observed among included studies, reflecting differences in patient populations, monitoring protocols, and definitions of DILI. Although random-effects models were used to account for heterogeneity, residual variability may have influenced pooled estimates. Second, most included studies were observational in nature, limiting causal inference. Third, variation in laboratory reference ranges and biochemical cut-off values prevented establishment of universal threshold levels for risk prediction. Fourth, some studies did not adequately adjust for potential confounding factors such as alcohol use, viral hepatitis, HIV infection, and concomitant medications. Finally, publication bias cannot be completely excluded despite largely reassuring statistical assessments.

Future Directions

Future research should focus on establishing standardized biochemical thresholds for predicting ATT-induced liver injury and validating these thresholds in large prospective cohorts. Studies integrating biochemical markers with genetic, metabolomic, and clinical risk factors may facilitate development of highly accurate predictive models. Additionally, investigation of dynamic changes in liver biomarkers during the early weeks of treatment may provide further insight into mechanisms of hepatotoxicity and opportunities for early intervention.

Overall, the findings of this meta-analysis demonstrate that elevated baseline AST, ALT, bilirubin, and reduced serum albumin are clinically meaningful predictors of antitubercular therapy-induced drug-induced liver injury. Incorporation of these readily available biomarkers into routine clinical assessment may improve early identification of high-risk patients and contribute to safer, more individualized tuberculosis treatment strategies.

Conclusion

Drug-induced liver injury remains a significant challenge during antitubercular therapy and is a major cause of treatment interruption and adverse clinical outcomes. This systematic review and meta-analysis identified several biochemical markers that are significantly associated with an increased risk of hepatotoxicity in patients receiving first-line antitubercular drugs.

The findings demonstrate that elevated baseline levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and reduced serum albumin are important predictors of antitubercular therapy-induced liver injury. Among these markers, elevated transaminases and hypoalbuminemia showed the strongest associations with subsequent hepatotoxicity.

These results highlight the value of routine biochemical assessment before treatment initiation and during therapy. Early identification of patients with abnormal liver function parameters may facilitate closer monitoring, timely intervention, and prevention of severe liver injury. Incorporating biochemical risk stratification into standard tuberculosis care may improve treatment safety, reduce therapy interruption, and enhance overall patient outcomes.

Further prospective studies are needed to establish standardized biochemical cut-off values and develop validated prediction models for the early detection and prevention of antitubercular therapy-induced liver injury.

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