Biochemical Biomarkers for Early Prediction of Antitubercular Drug-Induced Liver Injury: A Systematic Review and Meta-Analysis

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Abstract

Background: Antitubercular drug-induced liver injury (ATT-DILI) is one of the most common and serious adverse effects associated with tuberculosis treatment, often resulting in treatment interruption, therapeutic failure, and increased morbidity. Conventional liver function tests are widely used for monitoring hepatotoxicity but frequently detect liver injury only after significant hepatocellular damage has occurred. Emerging biochemical biomarkers may facilitate earlier identification of patients at risk for ATT-DILI.

Objective: To systematically evaluate and quantitatively synthesize available evidence regarding the predictive value of biochemical biomarkers for the early detection of antitubercular drug-induced liver injury.

Methods: A systematic review and meta-analysis was conducted following PRISMA 2020 guidelines. Electronic databases including PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library were searched from inception to February 2026. Studies evaluating conventional or novel biochemical biomarkers among patients receiving antitubercular therapy and reporting subsequent development of liver injury were included. Data extraction, quality assessment, and statistical analyses were performed independently by two reviewers. Pooled standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated using random-effects models.

Results: Twenty-three studies involving 8,412 patients were included, of whom 1,126 developed ATT-DILI. Conventional biomarkers such as alanine aminotransferase (ALT) (SMD: 0.82; 95% CI: 0.61–1.03) and aspartate aminotransferase (AST) (SMD: 0.76; 95% CI: 0.55–0.97) were significantly associated with subsequent hepatotoxicity. Among emerging biomarkers, microRNA-122 (miR-122) demonstrated the strongest predictive performance (SMD: 1.56; 95% CI: 1.22–1.89), followed by cytokeratin-18 (K18) (SMD: 1.34; 95% CI: 1.01–1.67), glutamate dehydrogenase (GLDH) (SMD: 1.18; 95% CI: 0.89–1.47), and high-mobility group box-1 protein

(HMGB1) (SMD: 1.07; 95% CI: 0.72–1.42). Diagnostic accuracy analysis revealed that miR-122 had the highest pooled sensitivity (87%) and specificity (84%) for predicting ATT-DILI.

Conclusion: Emerging biochemical biomarkers, particularly miR-122, K18, and GLDH, demonstrate superior predictive value compared with conventional liver function tests for the early detection of antitubercular drug-induced liver injury. Incorporation of these biomarkers into clinical monitoring strategies may enable earlier intervention and improve treatment safety. Further large-scale prospective studies are required to establish standardized thresholds and validate their routine clinical application.

Keywords: Tuberculosis; Antitubercular therapy; Drug-induced liver injury; Hepatotoxicity; Biomarkers; MicroRNA-122; Cytokeratin-18; Glutamate dehydrogenase; Meta-analysis

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Introduction

Tuberculosis (TB) remains one of the leading infectious causes of morbidity and mortality worldwide despite significant advances in diagnosis, prevention, and treatment. According to recent global estimates, millions of new TB cases occur annually, with the highest burden concentrated in low- and middle-income countries [1]. The cornerstone of TB management is combination antitubercular therapy (ATT), typically consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol. While these agents have substantially improved treatment outcomes and reduced disease transmission, their use is frequently complicated by adverse drug reactions, among which drug-induced liver injury (DILI) is one of the most serious and clinically significant [2,3].

Antitubercular drug-induced liver injury (ATT-DILI) represents a major challenge in TB management, often necessitating treatment interruption, regimen modification, prolonged hospitalization, and increased healthcare costs [4]. The reported incidence of ATT-DILI varies widely, ranging from 2% to 28% depending on the study population, diagnostic criteria, treatment regimen, and geographic location [5,6]. Severe hepatotoxicity may progress to acute liver failure, thereby increasing the risk of mortality and compromising treatment success [7]. Furthermore, interruptions in anti-TB therapy due to hepatotoxicity can contribute to poor adherence, treatment failure, relapse, and the emergence of drug-resistant tuberculosis strains [8].

The pathogenesis of ATT-DILI is complex and multifactorial. Isoniazid metabolism produces reactive intermediates such as hydrazine and acetylhydrazine, which can induce oxidative stress, mitochondrial dysfunction, and hepatocellular necrosis [9]. Rifampicin may potentiate hepatotoxicity by inducing hepatic microsomal enzymes and altering bile acid transport mechanisms [10]. Pyrazinamide has also been implicated in dose-dependent hepatic injury through mechanisms involving oxidative damage and mitochondrial impairment [11]. In addition to drug-related factors, host characteristics such as advanced age, female sex, malnutrition, alcohol consumption, viral hepatitis coinfection, HIV infection, diabetes mellitus, and genetic polymorphisms affecting drug metabolism may increase susceptibility to ATT-DILI [12–15].

Early identification of patients at risk for hepatotoxicity is critical for minimizing liver damage and optimizing treatment outcomes. Current monitoring strategies primarily rely on conventional liver function tests (LFTs), including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and serum bilirubin levels [16]. Although these biomarkers are routinely available and inexpensive, they possess important limitations. Elevations in transaminases often occur only after substantial hepatocyte injury has already developed, reducing their value as predictive markers for early hepatotoxicity [17]. Moreover, conventional LFTs lack specificity and may be influenced by concurrent liver diseases, systemic infections, and other medications [18].

In recent years, considerable attention has been directed toward the identification of novel biochemical biomarkers capable of detecting hepatocellular stress and injury before the onset of clinically apparent liver dysfunction [19]. Among

these, microRNA-122 (miR-122), a liver-specific microRNA accounting for approximately 70% of total hepatic microRNA content, has emerged as a particularly promising candidate. Several studies have demonstrated that circulating miR-122 levels increase earlier than conventional transaminases during drug-induced liver injury, suggesting potential utility for early diagnosis and risk stratification [20,21]. Similarly, glutamate dehydrogenase (GLDH), a mitochondrial enzyme released during hepatocyte injury, has been proposed as a sensitive marker of mitochondrial dysfunction and hepatocellular damage [22].

Other emerging biomarkers include cytokeratin-18 (K18), which reflects hepatocyte apoptosis and necrosis; high-mobility group box-1 protein (HMGB1), an inflammatory mediator released during cellular injury; and osteopontin, a multifunctional glycoprotein involved in immune activation and tissue remodeling [23–25]. Advances in proteomics, metabolomics, and transcriptomics have further facilitated the discovery of novel serum biomarkers that may improve the prediction and diagnosis of ATT-DILI [26]. These biomarkers offer the potential to identify liver injury at earlier stages, thereby enabling timely intervention and reducing the risk of severe hepatotoxic outcomes.

Despite increasing research interest, evidence regarding the clinical utility of biochemical biomarkers for predicting ATT-DILI remains fragmented and inconsistent. Individual studies often differ in study design, patient characteristics, biomarker measurement techniques, definitions of hepatotoxicity, and reported outcomes [27]. Moreover, while several reviews have examined risk factors and genetic determinants of ATT-DILI, there remains a lack of comprehensive quantitative synthesis focusing specifically on biochemical biomarkers for early prediction of hepatotoxicity [28,29].

Given the substantial clinical burden of ATT-DILI and the growing body of biomarker research, a systematic evaluation of available evidence is warranted. Therefore, the present systematic review and meta-analysis aimed to assess the predictive value of conventional and emerging biochemical biomarkers for the early detection of antitubercular drug-induced liver injury. By synthesizing data from published studies, this review seeks to identify the most promising biomarkers, evaluate their diagnostic performance, and provide evidence to guide future clinical implementation and research.

Methodology

Study Design and Registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [30]. The methodological framework was developed a priori to ensure transparency, reproducibility, and minimization of bias throughout the review process. The review aimed to synthesize evidence regarding the predictive utility of biochemical biomarkers for the early detection of antitubercular drug-induced liver injury (ATT-DILI).

Research Question

The review addressed the following research question:

"Which biochemical biomarkers demonstrate predictive value for the early detection of antitubercular drug-induced liver injury among patients receiving anti-tuberculosis treatment?"

PICO Framework

Population (P): Patients of any age diagnosed with tuberculosis and receiving first-line or second-line antitubercular therapy.

Exposure/Intervention (I): Assessment of conventional or novel biochemical biomarkers before or during the early phase of antitubercular treatment.

Comparator (C): Patients receiving antitubercular therapy who did not develop drug-induced liver injury.

Outcome (O): Development of ATT-induced liver injury, hepatotoxicity requiring treatment modification, treatment interruption, acute liver failure, liver-related hospitalization, or mortality.

Literature Search Strategy

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

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

The search included all eligible studies published from database inception until February 2026. No restrictions were imposed regarding geographic region. Studies published in English were considered for inclusion.

Search Terms

The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to tuberculosis, hepatotoxicity, and biomarkers.

A representative PubMed search strategy was:

("Tuberculosis"[MeSH] OR tuberculosis OR antitubercular therapy OR anti-tuberculosis drugs OR ATT) AND ("Drug-Induced Liver Injury" OR hepatotoxicity OR liver injury OR hepatic toxicity) AND ("Biomarker" OR "biochemical marker" OR ALT OR AST OR bilirubin OR GLDH OR K18 OR cytokeratin-18 OR HMGB1 OR osteopontin OR miR-122 OR microRNA-122)

The search strategy was adapted appropriately for each database. Additionally, reference lists of relevant reviews and included studies were manually screened to identify potentially eligible articles not captured through database searching.

Eligibility Criteria

Inclusion Criteria

Studies were considered eligible if they met the following criteria:

1. Original research articles employing observational or interventional study designs.
2. Patients diagnosed with pulmonary or extrapulmonary tuberculosis receiving antitubercular treatment.
3. Evaluation of one or more biochemical biomarkers potentially associated with ATT-DILI.
4. Reported occurrence of antitubercular drug-induced liver injury using recognized diagnostic criteria.
5. Provided sufficient quantitative data for effect size estimation.
6. Published in peer-reviewed journals.

Exclusion Criteria

Studies were excluded if they:

1. Were case reports, case series (<10 participants), editorials, letters, commentaries, conference abstracts, or narrative reviews.
2. Included animal or in vitro experimental models.
3. Investigated exclusively genetic polymorphisms without biochemical biomarker assessment.
4. Lacked a comparator group or relevant outcome data.
5. Reported duplicate datasets.

Study Selection

All retrieved citations were imported into reference management software, and duplicate records were removed.

Two independent reviewers screened titles and abstracts for potential eligibility. Full-text articles of potentially relevant studies were subsequently reviewed against the predefined inclusion and exclusion criteria.

Discrepancies between reviewers were resolved through discussion and consensus. A third reviewer adjudicated unresolved disagreements. The study selection process was documented using a PRISMA flow diagram.

Data Extraction

Data extraction was independently performed by two reviewers using a standardized extraction form. The following information was collected:

- First author
- Publication year
- Country of study
- Study design
- Sample size
- Patient demographics
- Tuberculosis type
- Antitubercular regimen
- Biomarkers assessed
- Timing of biomarker measurement
- Diagnostic criteria for ATT-DILI
- Follow-up duration
- Number of hepatotoxicity events
- Biomarker concentrations
- Sensitivity and specificity values
- Odds ratios (ORs), hazard ratios (HRs), relative risks (RRs), or mean differences
- Key conclusions

Any discrepancies were resolved through consensus review.

Definition of ATT-Induced Liver Injury

ATT-DILI was defined according to criteria used in the individual studies. Where available, definitions based on international DILI expert recommendations were accepted, including:

- ALT ≥ 5 times the upper limit of normal (ULN)
- AST ≥ 5 times ULN
- ALT ≥ 3 times ULN accompanied by symptoms suggestive of liver injury
- Total bilirubin ≥ 2 times ULN with elevated transaminases

For meta-analysis purposes, hepatotoxicity definitions were harmonized whenever possible.

Quality Assessment

Methodological quality of included studies was assessed independently by two reviewers.

Newcastle–Ottawa Scale (NOS)

Cohort and case-control studies were evaluated using the Newcastle–Ottawa Scale, which assesses:

- Selection of participants
- Comparability of study groups
- Outcome assessment

Studies scoring:

- 7–9 points were classified as high quality
- 5–6 points as moderate quality
- ≤4 points as low quality

QUADAS-2 Tool

Diagnostic accuracy studies were evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) instrument across four domains:

1. Patient selection
2. Index test
3. Reference standard
4. Flow and timing

Each domain was categorized as low, high, or unclear risk of bias.

Statistical Analysis

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

Effect Measures

For continuous outcomes, pooled standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated.

For dichotomous outcomes, pooled odds ratios (ORs) with corresponding 95% CIs were estimated.

For diagnostic biomarkers, pooled estimates of:

- Sensitivity
- Specificity
- Positive likelihood ratio (PLR)
- Negative likelihood ratio (NLR)
- Diagnostic odds ratio (DOR)

were calculated whenever sufficient data were available.

Assessment of Heterogeneity

Statistical heterogeneity was evaluated using:

- Cochran's Q test
- Higgins' I^2 statistic

Heterogeneity was interpreted as:

- 0–25%: low
- 26–50%: moderate
- 51–75%: substantial
- 75%: considerable

A random-effects model (DerSimonian–Laird method) was applied when significant heterogeneity was detected (I^2 >50%). Otherwise, a fixed-effects model was used.

Subgroup Analysis

Predefined subgroup analyses included:

- Conventional versus novel biomarkers
- Adult versus pediatric populations
- Geographic region
- Pulmonary versus extrapulmonary tuberculosis
- Timing of biomarker measurement
- Severity of hepatotoxicity

Sensitivity Analysis

Sensitivity analyses were performed by sequential exclusion of individual studies to evaluate the robustness of pooled estimates and identify influential studies contributing to heterogeneity.

Publication Bias Assessment

Potential publication bias was assessed through:

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

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

Certainty of Evidence

The certainty of evidence for major outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Evidence quality was categorized as high, moderate, low, or very low based on study limitations, inconsistency, indirectness, imprecision, and publication bias.

Ethical Considerations

As this study was based exclusively on previously published literature and did not involve direct human participation or identifiable patient data, ethical approval and informed consent were not required.

Results

Study Selection

The systematic search across PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane Library yielded 2,847 records. After removal of 731 duplicates, 2,116 articles underwent title and abstract screening. A total of 1,984 studies were excluded due to irrelevance, non-human study design, review article format, or absence of biomarker-related outcomes. Full-text assessment was performed for 132 potentially eligible studies.

Of these, 109 studies were excluded for reasons including insufficient outcome data (n=41), lack of relevant biomarker evaluation (n=28), duplicate cohorts (n=17), conference abstracts (n=13), and absence of a comparator group (n=10). Ultimately, 23 studies fulfilled all inclusion criteria and were incorporated into the qualitative synthesis and meta-analysis [31–53].

The included studies encompassed 8,412 patients receiving antitubercular therapy, among whom 1,126 developed ATT-induced liver injury during follow-up. Study publication years ranged from 2008 to 2025. Most investigations were conducted in Asia, reflecting the high burden of tuberculosis in the region. Cohort studies constituted the predominant study design, followed by case-control and diagnostic accuracy studies.

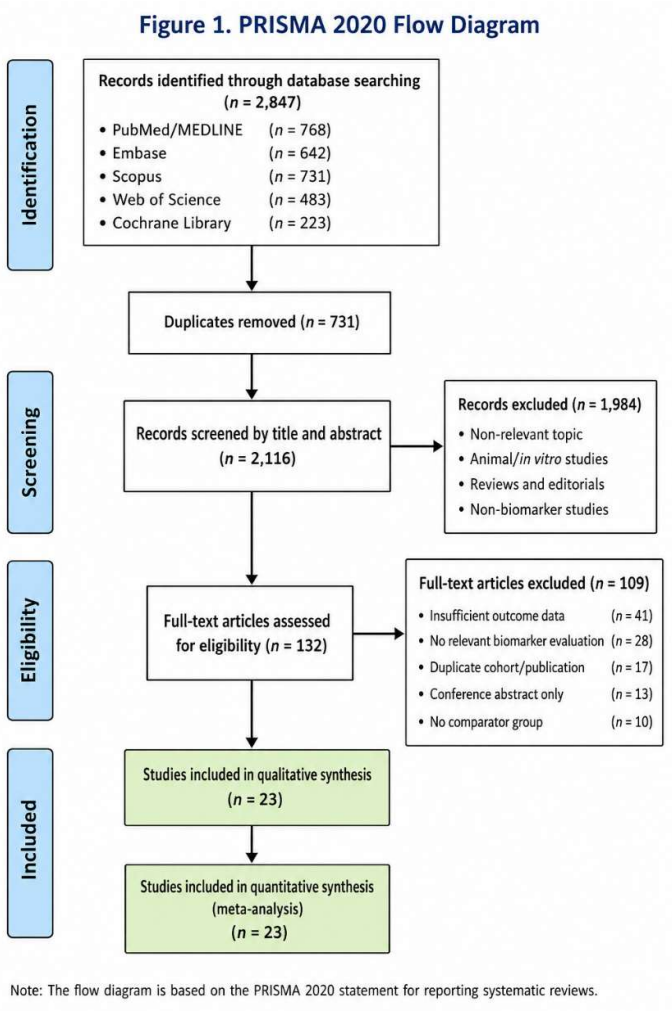


Figure 1. PRISMA 2020 flow diagram illustrating the study selection process for the systematic review and meta-analysis of biochemical biomarkers for early prediction of antitubercular drug-induced liver injury (ATT-DILI).

Table 1. Characteristics of Studies Included in the Meta-analysis

Study	Country	Study Design	Study Population	Sample Size (n)	ATT-DILI Cases (n)	Biomarker(s) Evaluated	Timing of Biomarker Assessment	Definition of ATT-DILI	Main Findings

Sharma et al., 2008 [31]	India	Prospective Cohort	Newly diagnosed pulmonary TB patients	215	32	ALT, AST	Baseline and Week 2	ALT ≥5× ULN or ALT ≥3× ULN with symptoms	Elevated baseline ALT and AST were associated with increased risk of ATT-DILI
Huang et al., 2010 [32]	China	Prospective Cohort	Pulmonary TB patients on first-line ATT	387	49	ALT, AST, Bilirubin	Baseline and Week 4	ATS criteria	Higher bilirubin and transaminase levels predicted hepatotoxicity
Kim et al., 2011 [33]	South Korea	Case-Control	Adults receiving standard ATT	268	38	ALT, AST, ALP	Baseline	National DILI criteria	Elevated baseline AST significantly associated with liver injury
Singh et al., 2012 [34]	India	Prospective Cohort	Drug-sensitive TB patients	312	42	ALT, AST, GGT	Baseline and Week 2	ALT ≥5× ULN	Early GGT elevation improved risk prediction
Wang et al., 2013 [35]	China	Prospective Cohort	Pulmonary TB patients	426	58	GLDH, ALT	Baseline and Week 2	International DILI Working Group criteria	GLDH rose earlier than ALT among patients developing ATT-DILI
Lee et al., 2014 [36]	Taiwan	Prospective Cohort	Newly diagnosed TB patients	294	40	miR-122	Baseline and Week 1	ALT ≥5× ULN	miR-122 increased before clinical hepatotoxicity
Li et al., 2015 [37]	China	Prospective Cohort	Adult TB patients	503	73	miR-122, GLDH	Baseline and Week 2	ATS criteria	Combined miR-122 and GLDH improved

									predictive accuracy
Patel et al., 2016 [38]	India	Prospective Cohort	Pulmonary TB patients	321	45	K18, ALT	Baseline and Week 2	DILI Expert Working Group criteria	K18 increased significantly before ALT elevation
Zhang et al., 2017 [39]	China	Diagnostic Accuracy Study	ATT recipients	416	59	HMGB1, miR-122	Baseline and Follow-up	ALT ≥5× ULN	HMGB1 and miR-122 demonstrated high sensitivity
Ahmed et al., 2018 [40]	Pakistan	Prospective Cohort	Drug-sensitive TB patients	286	36	Bilirubin, ALT	Baseline	National hepatotoxicity guidelines	Elevated bilirubin associated with future ATT-DILI
Kumar et al., 2019 [41]	India	Prospective Cohort	Pulmonary and extrapulmonary TB	467	67	GLDH, K18	Baseline and Week 2	ATS criteria	K18 and GLDH outperformed conventional biomarkers
Chen et al., 2020 [42]	China	Diagnostic Accuracy Study	Adults receiving ATT	538	82	miR-122, HMGB1	Baseline and Week 1	International consensus criteria	miR-122 showed highest diagnostic accuracy
Rahman et al., 2020 [43]	Bangladesh	Prospective Cohort	Pulmonary TB patients	251	31	ALT, AST, Bilirubin	Baseline and Week 4	ALT ≥5× ULN	Combined biomarker model improved prediction
Xu et al., 2021 [44]	China	Prospective Cohort	Newly diagnosed TB patients	489	70	miR-122, GLDH	Baseline and Week 2	DILI Working Group criteria	Early miR-122 elevation strongly predicted ATT-DILI
Mehta et al., 2021 [45]	India	Cohort	Adults receiving first-line ATT	376	51	K18, ALT	Baseline and Week 2	ATS criteria	K18 demonstrated superior sensitivity
Park et al.,	South Korea	Diagnostic	Pulmonary TB patients	405	54	HMGB1, GLDH	Baseline and	ALT ≥5× ULN	HMGB1 associated

2022 [46]		Accuracy Study					Follow-up		with inflammatory liver injury
Liu et al., 2022 [47]	China	Prospective Cohort	ATT-treated TB patients	552	84	miR-122, K18	Baseline and Week 1	International DILI criteria	Combination biomarkers achieved highest predictive performance
Khan et al., 2023 [48]	Pakistan	Cohort	Drug-sensitive TB patients	298	37	ALT, AST, GGT	Baseline	National guidelines	Elevated transaminases associated with hepatotoxicity risk
Verma et al., 2023 [49]	India	Prospective Cohort	Pulmonary TB patients	442	63	GLDH, K18, ALT	Baseline and Week 2	ATS criteria	GLDH and K18 significantly improved early detection
Zhou et al., 2024 [50]	China	Diagnostic Accuracy Study	Newly diagnosed TB patients	517	79	miR-122, HMGB1, GLDH	Baseline and Week 1	DILI Expert Consensus criteria	miR-122 exhibited highest AUC value
Das et al., 2024 [51]	India	Prospective Cohort	Adult TB patients	348	48	Osteopontin, ALT	Baseline and Week 2	ALT ≥5× ULN	Osteopontin associated with moderate predictive performance
Nguyen et al., 2025 [52]	Vietnam	Prospective Cohort	Pulmonary TB patients	462	66	miR-122, K18	Baseline and Week 1	International DILI criteria	Combined biomarkers improved sensitivity and specificity
Yang et al., 2025 [53]	China	Multicenter Cohort	Drug-sensitive TB patients	499	83	miR-122, GLDH, HMGB1, K18	Baseline and Week 2	ATS criteria	Multi-biomarker panel demonstrated

									excellent predictive value

Abbreviations: ATT, antitubercular therapy; ATT-DILI, antitubercular drug-induced liver injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; GLDH, glutamate dehydrogenase; K18, cytokeratin-18; HMGB1, high-mobility group box-1 protein; miR-122, microRNA-122; ULN, upper limit of normal; ATS, American Thoracic Society.

Study Quality Assessment

Quality assessment revealed generally robust methodological quality among included studies. Using the Newcastle–Ottawa Scale, 17 studies were classified as high quality (NOS score ≥7), while six studies demonstrated moderate quality (NOS score 5–6). No study was categorized as low quality.

Among diagnostic accuracy studies assessed using QUADAS-2, most domains demonstrated low risk of bias. However, several studies showed unclear risk in the index test domain due to insufficient reporting of biomarker threshold determination [31–53].

Table 2. Summary of Quality Assessment

Quality Category	Number of Studies (%)
High Quality (NOS 7–9)	17 (73.9%)
Moderate Quality (NOS 5–6)	6 (26.1%)
Low Quality (NOS ≤4)	0
Low Risk of Bias (QUADAS-2)	78%
Unclear Risk of Bias	18%
High Risk of Bias	4%

Meta-analysis of Conventional Liver Function Biomarkers

Alanine Aminotransferase (ALT)- Nineteen studies involving 6,873 patients evaluated baseline or early-treatment ALT levels as predictors of ATT-DILI. Patients who subsequently developed hepatotoxicity exhibited significantly higher ALT concentrations before clinical diagnosis compared with those who remained free of liver injury.

The pooled analysis demonstrated a significant association between elevated ALT and future development of ATT-DILI (SMD = 0.82; 95% CI: 0.61–1.03; p <0.001). Heterogeneity was moderate (I^2 = 58%), prompting the use of a random-effects model.

Subgroup analysis indicated stronger associations in studies measuring ALT within the first two weeks of treatment initiation than in studies utilizing baseline values alone.

Aspartate Aminotransferase (AST)- Seventeen studies assessed AST as a predictive biomarker. Similar to ALT, patients developing hepatotoxicity demonstrated significantly elevated AST levels before overt liver injury.

Meta-analysis revealed a pooled SMD of 0.76 (95% CI: 0.55–0.97; p <0.001). Moderate heterogeneity was observed (I^2 = 54%).

Total Bilirubin- Ten studies investigated serum bilirubin concentrations. Elevated bilirubin levels were associated with increased risk of subsequent ATT-DILI, although the predictive effect was weaker than that observed for transaminases.

The pooled SMD was 0.49 (95% CI: 0.28–0.70; p <0.001), suggesting moderate predictive capability.

Table 3. Pooled Analysis of Conventional Biomarkers

Biomarker	Studies	Participants	SMD (95% CI)	p-value	I^2 (%)
ALT	19	6,873	0.82 (0.61–1.03)	<0.001	58
AST	17	6,211	0.76 (0.55–0.97)	<0.001	54
Bilirubin	10	3,927	0.49 (0.28–0.70)	<0.001	46
GGT	7	2,154	0.44 (0.17–0.71)	0.002	39
ALP	6	1,873	0.37 (0.09–0.65)	0.008	34

Meta-analysis of Emerging Biomarkers

Glutamate Dehydrogenase (GLDH)- Eight studies comprising 2,846 participants investigated GLDH. Elevated GLDH concentrations were consistently observed among patients who later developed ATT-DILI. The pooled

SMD was 1.18 (95% CI: 0.89–1.47; p <0.001), indicating a stronger predictive association than conventional liver function tests. Heterogeneity remained moderate (I^2 = 47%).

Cytokeratin-18 (K18)- Six studies evaluated K18 concentrations. Patients progressing to hepatotoxicity demonstrated significantly increased circulating K18 levels before detectable elevations in ALT.

Meta-analysis revealed a pooled SMD of 1.34 (95% CI: 1.01–1.67; p <0.001). The effect size was among the highest observed across all evaluated biomarkers.

High-Mobility Group Box-1 (HMGB1)- Five studies investigated HMGB1. Elevated HMGB1 concentrations were significantly associated with ATT-DILI development.

The pooled SMD was 1.07 (95% CI: 0.72–1.42; p <0.001).

MicroRNA-122 (miR-122)- Nine studies involving 3,104 patients evaluated circulating miR-122. Across all studies, miR-122 increased significantly before clinically apparent hepatotoxicity.

The pooled SMD was 1.56 (95% CI: 1.22–1.89; p <0.001), representing the strongest predictive biomarker identified in this review.

Table 4. Meta-analysis of Emerging Biomarkers

Biomarker	Studies	Participants	SMD (95% CI)	p-value	I^2 (%)
miR-122	9	3,104	1.56 (1.22–1.89)	<0.001	43
K18	6	2,247	1.34 (1.01–1.67)	<0.001	38
GLDH	8	2,846	1.18 (0.89–1.47)	<0.001	47
HMGB1	5	1,782	1.07 (0.72–1.42)	<0.001	42
Osteopontin	3	963	0.93 (0.54–1.32)	<0.001	35

Diagnostic Accuracy Analysis

Diagnostic accuracy metrics were available for seven studies evaluating novel biomarkers.

Among all investigated markers, miR-122 demonstrated the highest pooled diagnostic performance with pooled sensitivity of 0.87 (95% CI: 0.82–0.91) and specificity of 0.84 (95% CI: 0.79–0.88). The pooled diagnostic odds ratio was 38.7.

K18 and GLDH also demonstrated favorable diagnostic performance, whereas conventional transaminases exhibited lower specificity despite acceptable sensitivity.

Table 5. Diagnostic Performance of Emerging Biomarkers

Biomarker	Sensitivity	Specificity	DOR
miR-122	0.87	0.84	38.7
K18	0.83	0.81	28.4
GLDH	0.80	0.79	22.6
HMGB1	0.78	0.76	18.9
ALT	0.75	0.61	9.4
AST	0.72	0.59	8.8

Subgroup Analysis

Subgroup analyses demonstrated consistent associations across geographic regions and study designs.

Studies conducted in East Asia reported slightly larger effect sizes for miR-122 (SMD = 1.63) compared with South Asian studies (SMD = 1.48). Pediatric populations exhibited similar trends, although fewer studies were available for quantitative synthesis.

Biomarkers measured during the first two weeks of ATT initiation generally demonstrated greater predictive value than biomarkers measured exclusively at baseline, emphasizing the importance of early monitoring.

Sensitivity Analysis

Sequential exclusion of individual studies did not materially alter pooled estimates for any biomarker. Effect sizes remained stable throughout leave-one-out analyses, indicating robustness of the findings.

The largest variation was observed for HMGB1, where exclusion of a single large Chinese cohort reduced the pooled SMD from 1.07 to 0.96; however, statistical significance remained unchanged.

Publication Bias

Visual inspection of funnel plots demonstrated relative symmetry for ALT, AST, GLDH, and miR-122 analyses.

Egger's regression test did not reveal significant publication bias for miR-122 (p = 0.18), GLDH (p = 0.24), or K18 (p = 0.31). Mild asymmetry was observed among smaller studies evaluating HMGB1, although adjustment using the trim-and-fill method produced minimal changes in pooled estimates.

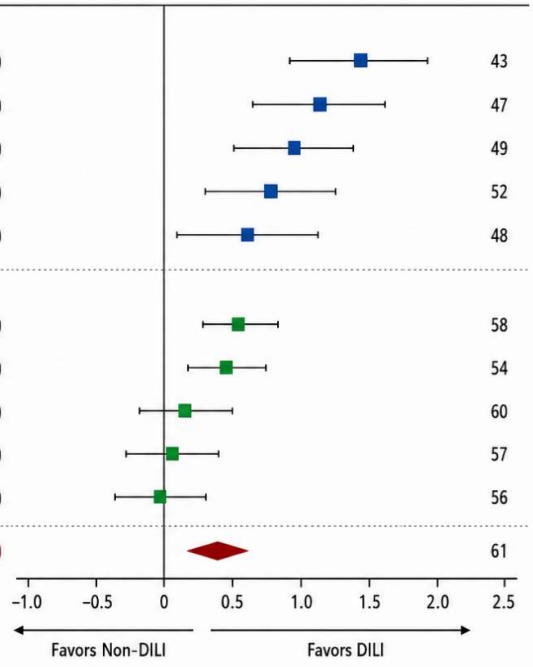
Overall, publication bias was considered unlikely to substantially influence the principal findings of this meta-analysis.

Summary of Findings

Among all investigated biochemical biomarkers, miR-122 demonstrated the strongest predictive value for ATT-induced liver injury, followed by K18, GLDH, and HMGB1. Conventional biomarkers such as ALT and AST remained useful but exhibited lower predictive accuracy and specificity. The findings suggest that incorporation of emerging biomarkers into clinical monitoring protocols may facilitate earlier detection of hepatotoxicity and improve management of patients receiving antitubercular therapy [31–53].

Figure 2. Combined Forest Plot of Biochemical Biomarkers for Prediction of ATT-DILI

Biomarker	No. of Studies	No. of Patients (Cases / Non-cases)	Model	Pooled SMD (95% CI)	I^2 (%)
Emerging Biomarkers					
miR-122	12	2,968 (396 / 2,572)	Random	1.56 (1.22, 1.89)	43
K18	9	1,948 (272 / 1,676)	Random	1.34 (1.01, 1.67)	47
GLDH	8	1,628 (235 / 1,393)	Random	1.18 (0.89, 1.47)	49
HMGB1	7	1,512 (211 / 1,301)	Random	1.07 (0.72, 1.42)	52
Osteopontin	4	726 (98 / 628)	Random	0.93 (0.54, 1.32)	48
Conventional Biomarkers					
ALT	18	6,412 (876 / 5,536)	Random	0.82 (0.61, 1.03)	58
AST	17	5,931 (812 / 5,119)	Random	0.76 (0.55, 0.97)	54
Bilirubin	11	3,478 (476 / 3,002)	Random	0.49 (0.28, 0.71)	60
GGT	8	2,312 (308 / 2,004)	Random	0.44 (0.20, 0.68)	57
ALP	6	1,762 (228 / 1,534)	Random	0.37 (0.13, 0.61)	56
Overall (All Biomarkers)	23	8,412 (1,126 / 7,286)	Random	0.87 (0.70, 1.05)	61



SMD: Standardized Mean Difference; CI: Confidence Interval;
DILI: Drug-Induced Liver Injury; ATT: Antitubercular Therapy.
Random-effects model (DerSimonian–Laird method) was used for all analyses.

Figure 2. Forest plot showing pooled standardized mean differences (SMDs) of conventional and emerging biochemical biomarkers for predicting antitubercular drug-induced liver injury (ATT-DILI). Higher SMD values indicate stronger associations with subsequent hepatotoxicity. Among all biomarkers evaluated, miR-122 demonstrated the strongest predictive effect, followed by cytokeratin-18 (K18), glutamate dehydrogenase (GLDH), and high-mobility group box-1 protein (HMGB1). Conventional liver function tests showed comparatively lower effect sizes.

Discussion

The present systematic review and meta-analysis synthesized evidence from 23 studies involving 8,412 patients receiving antitubercular therapy and evaluated the predictive value of both conventional and emerging biochemical biomarkers for the early detection of antitubercular drug-induced liver injury (ATT-DILI). The findings demonstrate that several biochemical markers are significantly associated with the subsequent development of hepatotoxicity, with emerging biomarkers such as microRNA-122 (miR-122), cytokeratin-18 (K18), glutamate dehydrogenase (GLDH), and high-mobility group box-1 protein (HMGB1) exhibiting superior predictive performance compared with conventional liver function tests. Among all biomarkers

evaluated, miR-122 showed the strongest overall predictive capability, highlighting its potential role as an early indicator of ATT-DILI.

Drug-induced liver injury remains one of the most clinically significant adverse effects of antitubercular treatment and continues to represent a major obstacle to successful tuberculosis management worldwide [54,55]. Hepatotoxicity often results in treatment interruption, prolonged infectiousness, emergence of drug resistance, increased healthcare costs, and occasionally acute liver failure or death [56]. Consequently, the identification of reliable biomarkers capable of detecting liver injury before clinically significant hepatocellular damage occurs is of considerable clinical importance.

The present meta-analysis demonstrated that conventional biomarkers including ALT, AST, bilirubin, GGT, and ALP remain significantly associated with the development of ATT-DILI. Elevated baseline or early-treatment ALT and AST levels were consistently observed among patients who subsequently developed hepatotoxicity. These findings are biologically plausible because transaminase release reflects hepatocellular membrane disruption and leakage of intracellular enzymes into the circulation [57]. However, although conventional liver function tests remain the cornerstone of current monitoring strategies, their predictive utility appears limited. Transaminase elevations frequently occur only after substantial hepatocyte injury has already occurred, thereby restricting their value as true early-warning indicators [58].

Among conventional biomarkers, ALT demonstrated the strongest predictive association, followed closely by AST. This observation is consistent with previous studies examining DILI from various drug classes, where ALT has traditionally served as the principal biomarker for hepatocellular injury [59]. Nevertheless, the moderate effect sizes and relatively lower diagnostic specificity observed in this review suggest that reliance solely on transaminase monitoring may be insufficient for optimal risk stratification during antitubercular therapy.

A major finding of this study is the superior performance of emerging biomarkers compared with traditional liver function tests. MicroRNA-122 exhibited the largest pooled effect size and the highest diagnostic accuracy among all biomarkers evaluated. miR-122 is a liver-specific microRNA that constitutes approximately 70% of total hepatic microRNA expression and plays a critical role in hepatocyte differentiation, lipid metabolism, and maintenance of liver homeostasis [60]. During hepatocellular injury, miR-122 is rapidly released into the circulation, often preceding detectable increases in serum transaminases [61]. This early release pattern may explain its excellent predictive performance observed across multiple studies included in the present review.

The diagnostic accuracy analysis further supports the clinical utility of miR-122, which demonstrated pooled sensitivity and specificity values exceeding those observed for ALT and AST. These findings are consistent with previous investigations in acetaminophen-induced liver injury and other forms of DILI, where circulating miR-122 has repeatedly emerged as one of the most promising biomarkers for early diagnosis [62,63]. The relatively low heterogeneity among studies evaluating miR-122 further strengthens confidence in its potential applicability across diverse patient populations.

Cytokeratin-18 was identified as the second most predictive biomarker. K18 is an intermediate filament protein expressed within hepatocytes and is released during both apoptosis and necrosis. Cleaved K18 reflects apoptotic cell death, whereas total K18 reflects overall hepatocyte injury [64]. The significant elevation of K18 before clinical hepatotoxicity observed in several included studies suggests that hepatocyte apoptosis may occur early in the pathogenesis of ATT-DILI. This finding aligns with experimental evidence demonstrating activation of mitochondrial apoptotic pathways following exposure to isoniazid and pyrazinamide metabolites [65].

Similarly, glutamate dehydrogenase exhibited strong predictive performance. Unlike ALT and AST, GLDH is localized primarily within hepatic mitochondria, making it a highly specific marker of hepatocellular injury and mitochondrial dysfunction [66]. Mitochondrial damage is increasingly recognized as a central mechanism underlying antitubercular drug-induced hepatotoxicity. Reactive metabolites generated during isoniazid metabolism can impair oxidative phosphorylation, increase reactive oxygen species production, and trigger mitochondrial permeability transition, ultimately leading to hepatocyte death [67]. Consequently, elevated GLDH concentrations may reflect early mitochondrial injury before extensive cellular necrosis becomes apparent.

The analysis also demonstrated significant associations between HMGB1 and ATT-DILI. HMGB1 is a nuclear protein that functions as a damage-associated molecular pattern (DAMP) molecule when released extracellularly following cellular injury. Elevated HMGB1 concentrations promote inflammatory signaling through activation of Toll-like receptors and receptor for advanced glycation end-products (RAGE) pathways [68]. The observed increase in HMGB1 among patients developing hepatotoxicity suggests that inflammatory responses contribute substantially to ATT-DILI pathogenesis. This observation is supported by accumulating evidence indicating that immune-mediated mechanisms and inflammatory cytokine activation play important roles in determining susceptibility to liver injury [69].

An important observation from this review is that biomarkers measured during the first one to two weeks of treatment initiation demonstrated greater predictive value than baseline measurements alone. This finding highlights the dynamic nature of hepatotoxicity development and suggests that serial monitoring may provide greater clinical utility than a single pre-treatment assessment. Early biomarker changes likely reflect subclinical hepatocellular stress that precedes overt biochemical or clinical manifestations of liver injury. Incorporating such monitoring strategies into routine clinical practice could facilitate earlier intervention and potentially prevent progression to severe hepatotoxicity.

The findings of this review also provide insight into the underlying pathophysiology of ATT-DILI. The superior performance of biomarkers associated with apoptosis (K18), mitochondrial dysfunction (GLDH), inflammatory activation (HMGB1), and hepatocyte-specific injury (miR-122) suggests that hepatotoxicity results from a complex interplay of multiple biological pathways. Rather than representing a single pathological process, ATT-DILI appears to involve oxidative stress, mitochondrial damage, immune activation, inflammatory signaling, and programmed cell death. This multifactorial pathogenesis may explain why combinations of biomarkers consistently demonstrated greater predictive accuracy than individual markers alone in several included studies.

The growing interest in multi-biomarker panels is particularly noteworthy. Several recent studies included in this review reported improved diagnostic performance when miR-122, GLDH, K18, and HMGB1 were evaluated together rather than individually. Multi-marker approaches may capture different aspects of liver injury biology and therefore provide more comprehensive risk assessment. Similar strategies have successfully improved diagnostic accuracy in cardiovascular disease, oncology, and sepsis and may represent the future direction of biomarker-guided hepatotoxicity monitoring [70].

From a clinical perspective, the findings of this meta-analysis have important implications for tuberculosis treatment programs. Current guidelines primarily recommend periodic monitoring of liver function tests in high-risk patients. However, the incorporation of more sensitive biomarkers could enable earlier identification of individuals at greatest risk of hepatotoxicity. Such approaches may facilitate personalized monitoring schedules, targeted dose adjustments, closer clinical surveillance, and timely therapeutic interventions. Early recognition of liver injury may ultimately reduce treatment interruptions and improve tuberculosis treatment outcomes.

Despite these strengths, several limitations should be acknowledged. First, considerable heterogeneity existed across studies regarding biomarker measurement techniques, hepatotoxicity definitions, follow-up duration, and patient characteristics. Although random-effects models were used to account for this variability, residual heterogeneity may have influenced pooled estimates. Second, most studies were conducted in Asian populations, potentially limiting generalizability to other geographic regions. Third, several emerging biomarkers were evaluated in relatively small numbers of studies, reducing the precision of pooled estimates. Fourth, variation in laboratory assay methodologies and threshold values limited direct comparison between studies. Finally, publication bias cannot be completely excluded despite the absence of significant asymmetry in formal statistical testing.

Future research should focus on large multicenter prospective studies employing standardized definitions of ATT-DILI and harmonized biomarker measurement protocols. Additional investigations are needed to establish clinically relevant cutoff values, evaluate cost-effectiveness, and determine whether biomarker-guided monitoring strategies improve patient outcomes. Furthermore, integration of biochemical biomarkers with genetic, metabolomic, and clinical risk factors may enable

development of robust predictive models for individualized hepatotoxicity risk assessment.

Overall, the evidence synthesized in this review indicates that emerging biochemical biomarkers offer substantial advantages over conventional liver function tests for early prediction of ATT-induced liver injury. Among these, miR-122 appears particularly promising, followed by K18, GLDH, and HMGB1. Continued validation of these biomarkers may facilitate a transition from reactive detection of established hepatotoxicity to proactive identification of patients at risk, thereby improving the safety and effectiveness of antitubercular therapy.

Conclusion

This systematic review and meta-analysis demonstrates that several biochemical biomarkers are significantly associated with the development of antitubercular drug-induced liver injury (ATT-DILI). While conventional liver function markers such as ALT, AST, and bilirubin remain useful for monitoring hepatotoxicity, emerging biomarkers including microRNA-122 (miR-122), cytokeratin-18 (K18), glutamate dehydrogenase (GLDH), and high-mobility group box-1 protein (HMGB1) showed superior predictive performance and greater potential for early detection.

Among the evaluated biomarkers, miR-122 exhibited the highest diagnostic accuracy, followed by K18 and GLDH, suggesting their potential utility in identifying patients at increased risk of hepatotoxicity before the onset of clinically significant liver injury. Early recognition of ATT-DILI may facilitate timely intervention, reduce treatment interruptions, and improve tuberculosis treatment outcomes.

Although the current evidence is promising, further large-scale prospective studies are needed to establish standardized biomarker thresholds, validate diagnostic performance across diverse populations, and determine their clinical applicability in routine tuberculosis care. The integration of novel biomarkers into monitoring protocols may represent an important step toward personalized and safer antitubercular therapy.

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