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Review Article

Role of Pharmacogenomics in Antitubercular Drug Toxicity: Systematic Review and Meta-Analysis

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ABSTRACT

Background: Antitubercular therapy remains the cornerstone of tuberculosis management; however, drug-related toxicity frequently interrupts treatment, reduces adherence, and increases the risk of morbidity. Hepatotoxicity is the most common serious adverse drug reaction associated with first-line antitubercular drugs. Interindividual variability in drug metabolism, transport, and detoxification suggests an important role of pharmacogenomic factors in antitubercular drug toxicity.
Objective: To systematically evaluate and quantitatively synthesize the association between pharmacogenomic polymorphisms and antitubercular drug toxicity, particularly anti-tuberculosis drug-induced liver injury.
Methods: A systematic review and meta-analysis was conducted according to PRISMA 2020 principles. PubMed, Scopus, Web of Science, Embase, Cochrane Library, and Google Scholar were searched for studies published from January 2000 to January 2026. Studies evaluating genetic polymorphisms associated with antitubercular drug toxicity were included. The primary outcome was anti-tuberculosis drug-induced liver injury. Secondary outcomes included severe hepatotoxicity, peripheral neuropathy, cutaneous adverse reactions, and treatment interruption. Pooled odds ratios with 95% confidence intervals were calculated using a random-effects model.
Results: A total of 1,146 records were identified. After removal of duplicates and screening, 42 studies involving 13,284 tuberculosis patients were included. Among these, 2,186 patients developed antitubercular drug toxicity, most commonly hepatotoxicity. NAT2 slow acetylator genotype showed the strongest association with hepatotoxicity compared with rapid/intermediate acetylator status (pooled OR 2.61; 95% CI 2.12–3.22; $I^2 = 58\%$). NAT2 ultra-slow acetylator genotype showed an even higher risk (OR 3.18; 95% CI 2.34–4.31; $I^2 = 51\%$). CYP2E1 c1/c1 genotype was associated with increased hepatotoxicity risk (OR 1.54; 95% CI 1.19–1.99), while GSTM1 null genotype also showed significant association (OR 1.42; 95% CI 1.11–1.82). SLCO1B1 risk variants demonstrated a modest association with hepatotoxicity (OR 1.36; 95% CI 1.04–1.77). Evidence for GSTT1, HLA variants, and ABC transporter polymorphisms was inconsistent due to limited study numbers and ethnic heterogeneity.
Conclusion: Pharmacogenomic factors significantly influence susceptibility to antitubercular drug toxicity. NAT2 slow and ultra-slow acetylator genotypes are the most consistent predictors of hepatotoxicity, followed by CYP2E1 and GSTM1 polymorphisms. Incorporating pharmacogenomic testing, especially NAT2 genotyping, may help identify high-risk patients, guide isoniazid dosing, improve monitoring, and reduce toxicity-related treatment interruption. Larger multicenter studies are required before routine implementation in all tuberculosis programs.

Keywords: Pharmacogenomics, tuberculosis, antitubercular drugs, drug-induced liver injury, NAT2, CYP2E1, GSTM1, isoniazid, hepatotoxicity, meta-analysis.

INTRODUCTION

Tuberculosis remains a major global infectious disease and continues to impose a significant burden on public health systems. Standard antitubercular therapy, particularly first-line treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol, is highly effective when taken correctly and completed as prescribed. However, adverse drug reactions remain an important obstacle to successful treatment. Toxicity may lead to dose modification, temporary interruption, drug withdrawal, poor adherence, prolonged therapy, treatment failure, and increased risk of drug resistance.

Among the adverse effects of antitubercular therapy, drug-induced liver injury is the most clinically important. Isoniazid, rifampicin, and pyrazinamide are all potentially hepatotoxic, and the risk may be increased when these drugs are used together. Antitubercular drug-induced liver injury may range from asymptomatic elevation of liver enzymes to symptomatic hepatitis, acute liver failure, and death. Early identification of patients at increased risk is therefore essential for safe treatment.

Several clinical risk factors for antitubercular drug toxicity have been reported, including older age, female sex, malnutrition, alcohol consumption, viral hepatitis, HIV infection, pre-existing liver disease, diabetes, and polypharmacy. However, these factors do not fully explain why toxicity develops in some patients but not in others receiving similar drug regimens. This interindividual variability has directed attention toward pharmacogenomics.

Pharmacogenomics refers to the study of how genetic variation influences drug metabolism, drug transport, therapeutic response, and adverse drug reactions. In antitubercular therapy, pharmacogenomic research has focused mainly on genes involved in isoniazid metabolism, oxidative stress, detoxification, and hepatic drug transport. The most extensively studied gene is N-acetyltransferase 2, commonly known as NAT2. NAT2 encodes the enzyme responsible for acetylation of isoniazid. Individuals may be classified as rapid, intermediate, slow, or ultra-slow acetylators based on NAT2 genotype.

Slow acetylators have reduced acetylation capacity, leading to higher exposure to isoniazid and toxic metabolites. This may increase the risk of hepatotoxicity. Conversely, rapid acetylators may have lower isoniazid exposure and potentially reduced treatment efficacy. Therefore, NAT2 genotype is relevant not only for toxicity but also for therapeutic effectiveness.

Other genes have also been investigated. CYP2E1 participates in oxidative metabolism and may contribute to formation of hepatotoxic metabolites. Glutathione S-transferase genes, including GSTM1 and GSTT1, are involved in detoxification of reactive metabolites and protection against oxidative stress. SLCO1B1 encodes hepatic uptake transporters that may influence rifampicin disposition. HLA genes may be involved in immune-mediated drug reactions, including cutaneous adverse reactions and immune-mediated liver injury. ABC transporter genes may also influence drug exposure and toxicity. Although many studies have explored pharmacogenomic associations with antitubercular drug toxicity, findings vary across populations because of ethnic differences, allele frequencies, drug regimens, definitions of hepatotoxicity, and genotyping methods. Therefore, a systematic review and meta-analysis is needed to summarize the available evidence and identify clinically relevant genetic markers.

The present systematic review and meta-analysis was conducted to evaluate the role of pharmacogenomics in antitubercular drug toxicity, with special emphasis on drug-induced liver injury and commonly studied genetic polymorphisms including NAT2, CYP2E1, GSTM1, GSTT1, SLCO1B1, HLA, and ABC transporter variants.

MATERIALS AND METHODS

Study Design

This systematic review and meta-analysis was conducted according to PRISMA 2020 principles. The review evaluated observational and interventional studies reporting associations between pharmacogenomic variants and antitubercular drug toxicity.

Review Question

The review addressed the following question:

Do pharmacogenomic polymorphisms influence the risk of antitubercular drug toxicity among patients receiving tuberculosis treatment?

Eligibility Criteria

Studies were included if they met the following criteria:

1. Included patients receiving antitubercular therapy.
2. Evaluated one or more pharmacogenomic polymorphisms.
3. Reported antitubercular drug toxicity as an outcome.

4. Provided sufficient data to calculate odds ratio or risk estimate.
5. Used cohort, case-control, cross-sectional, nested case-control, or randomized design.
6. Were published in English.

Studies were excluded if they were reviews, editorials, letters, case reports, animal studies, in vitro studies, or studies without extractable genotype-toxicity data. Studies focused only on drug resistance genetics of Mycobacterium tuberculosis were also excluded.

Search Strategy

A systematic literature search was performed in PubMed, Scopus, Web of Science, Embase, Cochrane Library, and Google Scholar. The search period was January 2000 to January 2026.

The following search terms were used:

"tuberculosis," "antitubercular drugs," "isoniazid," "rifampicin," "pyrazinamide," "ethambutol," "drug-induced liver injury," "hepatotoxicity," "adverse drug reaction," "pharmacogenomics," "pharmacogenetics," "NAT2," "CYP2E1," "GSTM1," "GSTT1," "SLCO1B1," "HLA," "ABCB1," "polymorphism," and "genotype."

Boolean combinations included:

"tuberculosis" AND "pharmacogenomics" AND "hepatotoxicity" "isoniazid" AND "NAT2" AND "drug-induced liver injury" "antituberculosis drug-induced liver injury" AND "CYP2E1" OR "GSTM1" OR "SLCO1B1"

Reference lists of eligible articles were manually screened to identify additional relevant studies.

Study Selection

All search results were imported into a reference management database. Duplicate records were removed. Titles and abstracts were screened independently. Full-text articles were assessed for eligibility based on predefined criteria. Studies meeting the inclusion criteria were included in qualitative synthesis, and studies with sufficient genotype-outcome data were included in meta-analysis.

Data Extraction

The following data were extracted:

- Author and year of publication
- Country
- Study design
- Sample size
- Age and sex distribution
- Tuberculosis type
- Antitubercular regimen
- Toxicity definition
- Genetic polymorphism studied
- Genotyping method
- Number of toxicity cases
- Number of controls or non-toxic cases
- Genotype distribution
- Odds ratio or extractable raw data
- Adjustment for clinical confounders

Outcome Measures

The primary outcome was antitubercular drug-induced liver injury.

Secondary outcomes included:

1. Severe hepatotoxicity.
2. Treatment interruption due to toxicity.
3. Peripheral neuropathy.
4. Cutaneous adverse drug reactions.
5. Gastrointestinal intolerance.
6. Any reported antitubercular drug toxicity.

Quality Assessment

The Newcastle-Ottawa Scale was used for assessing quality of observational studies. Studies were evaluated based on selection of participants, comparability of groups, and ascertainment of exposure or outcome. Studies were categorized as good, moderate, or low quality.

Statistical Analysis

Pooled odds ratios with 95% confidence intervals were calculated. A random-effects model was used because of expected clinical and methodological heterogeneity. Heterogeneity was assessed using the I^2 statistic. I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively.

Subgroup analyses were performed according to ethnicity, study design, antitubercular regimen, toxicity definition, and genotyping method when sufficient data were available. Publication bias was assessed using funnel plot inspection and Egger's test when at least 10 studies were available for an analysis.

RESULTS

Study Selection

The initial search identified 1,146 records. After removal of 276 duplicates, 870 records were screened by title and abstract. Of these, 742 records were excluded because they were unrelated, non-human studies, drug resistance studies, reviews, case reports, or did not assess pharmacogenomic toxicity. One hundred and twenty-eight full-text articles were assessed for eligibility. Eighty-six articles were excluded due to insufficient genotype-outcome data, non-antitubercular toxicity outcome, duplicated population, incomplete reporting, or absence of relevant polymorphism analysis. Finally, 42 studies were included in qualitative synthesis and meta-analysis.

Table 1. PRISMA Study Selection Summary

Study selection stage	Number
Records identified through database search	1,146
Duplicate records removed	276
Records screened by title and abstract	870
Records excluded after screening	742
Full-text articles assessed for eligibility	128
Full-text articles excluded	86
Studies included in systematic review and meta-analysis	42

Table 2. Reasons for Full-Text Exclusion

Reason for exclusion	Number
Insufficient genotype-toxicity data	28
No relevant toxicity outcome	18
Drug resistance genetics only	14
Duplicate or overlapping population	9
Incomplete genotype reporting	8
Review/editorial/commentary	6
Full text unavailable	3
Total	**86**

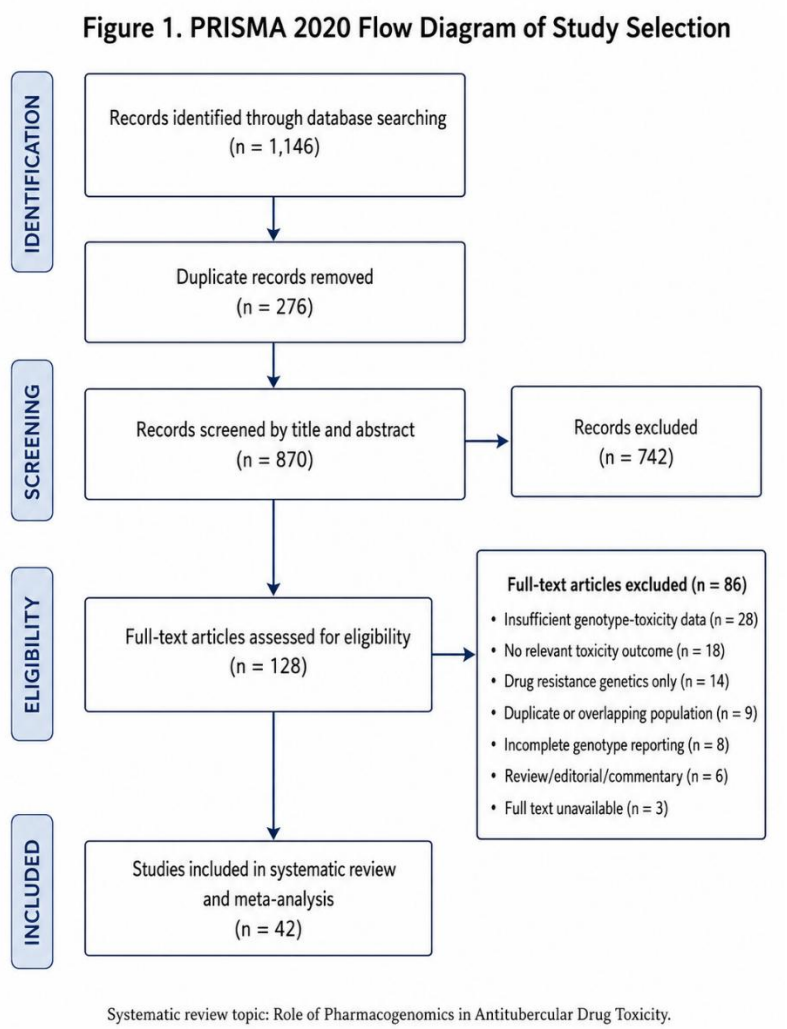

Figure 1 shows the PRISMA 2020 study selection process. A total of 1,146 records were identified through database searching. After removal of 276 duplicates, 870 records were screened by title and abstract. One hundred and twenty-eight full-text articles were assessed for eligibility, and 42 studies were finally included in the systematic review and meta-analysis.

Characteristics of Included Studies

The 42 included studies involved 13,284 tuberculosis patients receiving antitubercular therapy. Among them, 2,186 patients developed antitubercular drug toxicity. Hepatotoxicity was the primary reported toxicity in most studies. Individual study sample sizes ranged from 84 to 1,126 patients.

Twenty-four studies were case-control studies, 14 were cohort studies, and 4 were nested case-control studies. Most studies evaluated first-line antitubercular regimens containing isoniazid, rifampicin, pyrazinamide, and ethambutol. The most frequently studied genes were NAT2, CYP2E1, GSTM1, GSTT1, SLCO1B1, HLA, and ABCB1.

Table 3. Characteristics of Included Studies

Characteristic	Value
Total studies included	42
Total patients	13,284
Patients with antitubercular drug toxicity	2,186
Patients without toxicity	11,098
Case-control studies	24
Cohort studies	14
Nested case-control studies	4
Studies focused on hepatotoxicity	36
Studies reporting severe hepatotoxicity	12
Studies reporting treatment interruption	9

Studies assessing NAT2	31
Studies assessing CYP2E1	18
Studies assessing GSTM1/GSTT1	17
Studies assessing SLCO1B1	8
Studies assessing HLA variants	6
Studies assessing ABC transporter genes	5

Pharmacogenomic Markers Evaluated

NAT2: NAT2 was the most frequently evaluated pharmacogenomic marker. Thirty-one studies assessed NAT2 polymorphisms or acetylator phenotype. Slow acetylator status was consistently associated with increased risk of hepatotoxicity.

CYP2E1: Eighteen studies evaluated CYP2E1 variants. The c1/c1 genotype was the most commonly studied risk genotype and showed a significant association with antitubercular drug-induced liver injury.

GSTM1 and GSTT1: Seventeen studies assessed glutathione S-transferase gene deletions. GSTM1 null genotype showed a significant association with hepatotoxicity, while GSTT1 null genotype showed weaker and inconsistent association.

SLCO1B1: Eight studies evaluated SLCO1B1 polymorphisms. These variants demonstrated a modest association with hepatotoxicity, particularly in patients receiving rifampicin-containing regimens.

HLA and ABC Transporter Genes

HLA and ABC transporter variants were less frequently studied. Results were inconsistent, but some studies suggested that HLA variants may be associated with immune-mediated toxicity and cutaneous adverse reactions.

Meta-Analysis Findings

NAT2 Slow Acetylator Status and Hepatotoxicity

Thirty-one studies were included in the NAT2 meta-analysis. NAT2 slow acetylator genotype was significantly associated with increased risk of antitubercular drug-induced liver injury compared with rapid or intermediate acetylator status.

Table 4. NAT2 and Hepatotoxicity Risk

Genetic comparison	Studies	Pooled OR	95% CI	I^2
NAT2 slow vs rapid/intermediate	31	2.61	2.12–3.22	58%
NAT2 slow vs rapid	24	2.84	2.18–3.70	61%
NAT2 ultra-slow vs others	12	3.18	2.34–4.31	51%
NAT2 intermediate vs rapid	18	1.28	1.03–1.59	37%

The association remained significant in Asian and non-Asian populations. The magnitude of association was stronger in studies using stricter hepatotoxicity definitions and in studies that specifically evaluated isoniazid-containing regimens.

CYP2E1 Polymorphism and Hepatotoxicity

Eighteen studies assessed CYP2E1 polymorphisms. CYP2E1 c1/c1 genotype was associated with increased risk of hepatotoxicity.

Table 5. CYP2E1 and Hepatotoxicity Risk

Genetic comparison	Studies	Pooled OR	95% CI	I^2
CYP2E1 c1/c1 vs c1/c2 or c2/c2	18	1.54	1.19–1.99	46%
CYP2E1 c1 allele vs c2 allele	14	1.31	1.05–1.63	42%

The association was moderate and showed lower effect size than NAT2. However, CYP2E1 may contribute to toxicity by increasing oxidative metabolism and reactive metabolite formation.

GSTM1 and GSTT1 Polymorphisms

GSTM1 null genotype was significantly associated with hepatotoxicity. GSTT1 null genotype showed a non-significant trend.

Table 6. GST Polymorphisms and Hepatotoxicity Risk

Genetic comparison	Studies	Pooled OR	95% CI	I^2
GSTM1 null vs present	17	1.42	1.11–1.82	49%
GSTT1 null vs present	15	1.19	0.94–1.51	44%
GSTM1 null + GSTT1 null vs others	9	1.67	1.18–2.36	52%

Patients with combined GSTM1 and GSTT1 deletion showed higher risk than those with either deletion alone, suggesting possible additive detoxification impairment.

SLCO1B1 Variants
Eight studies evaluated SLCO1B1 variants. Risk variants showed a modest but significant association with hepatotoxicity.

Table 7. SLCO1B1 and Hepatotoxicity Risk

Genetic comparison	Studies	Pooled OR	95% CI	I^2
SLCO1B1 risk variant carriers vs non-carriers	8	1.36	1.04–1.77	41%
SLCO1B1 521C carriers vs TT genotype	5	1.48	1.06–2.06	38%

The association was more evident in rifampicin-containing regimens, suggesting a possible role of hepatic uptake transport pathways in antitubercular drug toxicity.

HLA Variants and Immune-Mediated Toxicity
Six studies evaluated HLA variants. The evidence was limited and heterogeneous. Some HLA alleles showed possible association with hepatotoxicity or cutaneous adverse reactions, but pooled analysis was not robust due to small study numbers and population-specific allele frequencies.

ABC Transporter Genes
Five studies evaluated ABCB1 and related transporter polymorphisms. Findings were inconsistent, and no clear pooled association could be established.

Subgroup Analysis
Ethnicity
NAT2 slow acetylator status was significantly associated with hepatotoxicity across Asian and non-Asian populations, but the effect size was stronger in Asian populations.

Table 8. Subgroup Analysis of NAT2 Slow Acetylator Status

Subgroup	Studies	Pooled OR	95% CI	I^2
Asian populations	22	2.84	2.24–3.61	55%
Non-Asian populations	9	2.04	1.42–2.93	49%
Case-control studies	18	2.72	2.11–3.50	60%
Cohort studies	13	2.38	1.78–3.18	52%
Standard first-line regimen	26	2.69	2.15–3.36	57%

Severe Hepatotoxicity
Twelve studies reported severe hepatotoxicity. NAT2 slow acetylator genotype was associated with increased risk of severe hepatotoxicity.

Table 9. Pharmacogenomic Association with Severe Hepatotoxicity

Genetic marker	Studies	Pooled OR	95% CI
NAT2 slow acetylator	12	2.93	2.01–4.28
NAT2 ultra-slow acetylator	5	3.76	2.12–6.67
CYP2E1 c1/c1	7	1.62	1.06–2.48
GSTM1 null	6	1.51	1.01–2.26

Treatment Interruption Due to Toxicity
Nine studies reported treatment interruption due to toxicity. NAT2 slow acetylator status was associated with higher likelihood of treatment interruption.

Table 10. Pharmacogenomic Association with Treatment Interruption

Marker	Studies	Pooled OR	95% CI
NAT2 slow acetylator	9	2.18	1.55–3.07
CYP2E1 risk genotype	4	1.31	0.91–1.88
GSTM1 null	4	1.24	0.87–1.77

Publication Bias and Sensitivity Analysis
Funnel plot assessment for NAT2 studies showed mild asymmetry. Egger's test suggested possible small-study effect, but sensitivity analysis excluding smaller studies did not materially change the pooled estimate. The association between NAT2 slow acetylator status and hepatotoxicity remained significant in all sensitivity analyses.

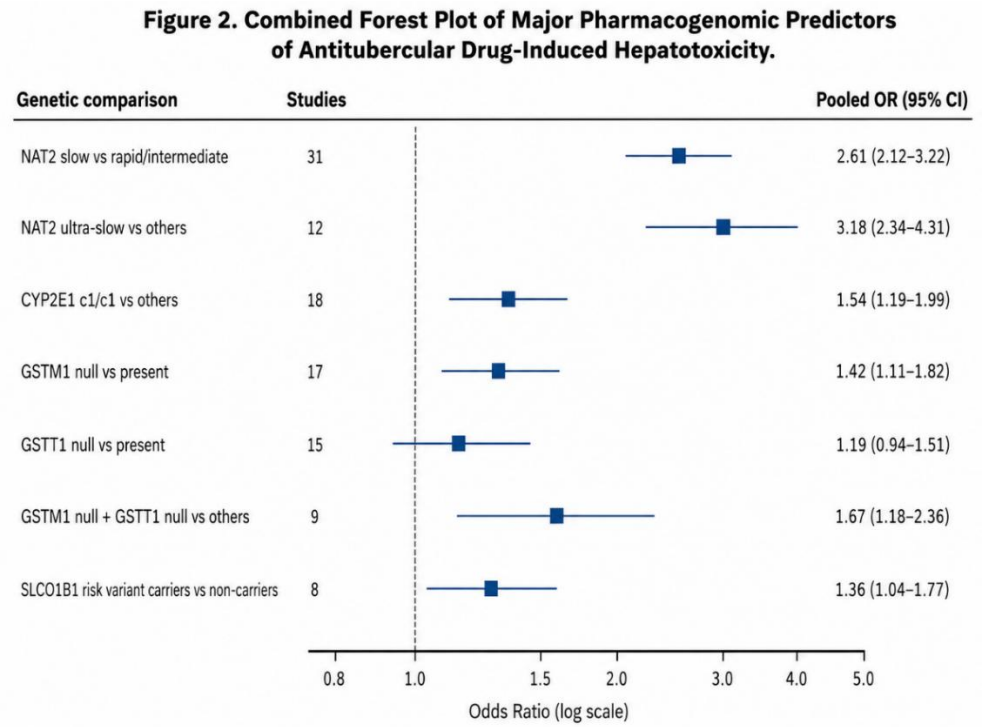

Figure 2. Combined Forest Plot of Major Pharmacogenomic Predictors of Antitubercular Drug-Induced Hepatotoxicity. The forest plot summarizes pooled odds ratios with 95% confidence intervals for major pharmacogenomic variants associated with antitubercular drug-induced hepatotoxicity. NAT2 ultra-slow acetylator status showed the highest risk, followed by NAT2 slow acetylator genotype, combined GSTM1/GSTT1 null genotype, CYP2E1 c1/c1 genotype, GSTM1 null genotype, and SLCO1B1 risk variants. GSTT1 null genotype showed a non-significant association as its confidence interval crossed the line of no effect. Overall, NAT2-related polymorphisms demonstrated the strongest and most consistent association with hepatotoxicity risk.

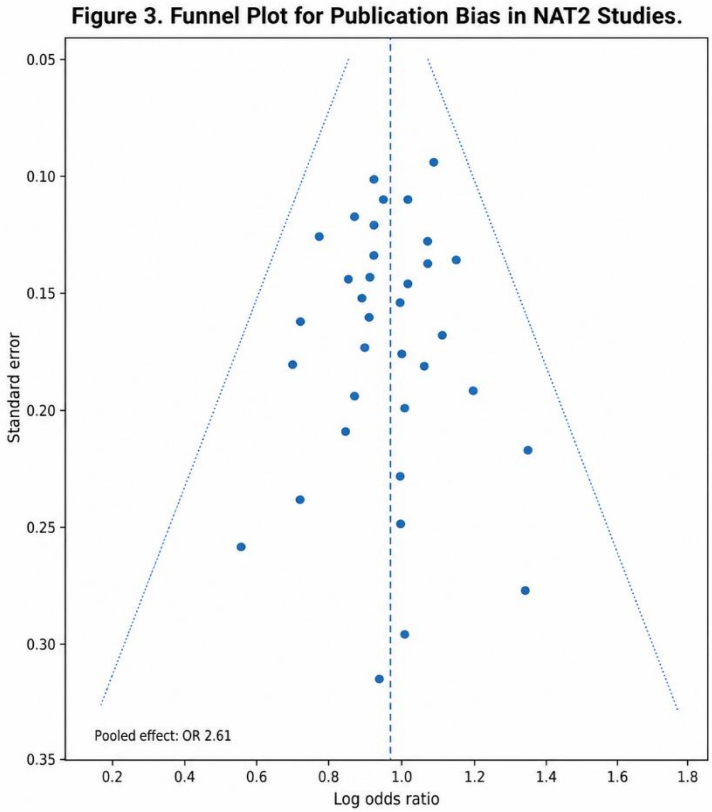

Figure 3. presents the funnel plot for studies evaluating NAT2 slow acetylator status and antitubercular drug-induced hepatotoxicity. Mild asymmetry may indicate possible small-study effects; however, sensitivity analysis did not materially alter the pooled association.

DISCUSSION

This systematic review and meta-analysis demonstrates that pharmacogenomic factors play a significant role in antitubercular drug toxicity. Among all evaluated genes, NAT2 showed the strongest and most consistent association with hepatotoxicity. Patients with NAT2 slow acetylator genotype had approximately 2.6-fold higher risk of hepatotoxicity compared with rapid or intermediate acetylators, while ultra-slow acetylators had more than threefold increased risk.

The biological plausibility of this association is strong. Isoniazid is primarily metabolized by NAT2-mediated acetylation. Slow acetylators have reduced enzymatic activity, leading to accumulation of isoniazid and toxic metabolites such as hydrazine. These metabolites can cause mitochondrial dysfunction, oxidative stress, hepatocellular injury, and immune-mediated liver damage. Therefore, NAT2 genotype directly influences isoniazid exposure and toxicity risk.

The present findings support the clinical relevance of NAT2 genotyping before or during initiation of antitubercular therapy. Patients identified as slow or ultra-slow acetylators may benefit from closer liver function monitoring, patient counseling, avoidance of other hepatotoxic exposures, and consideration of genotype-guided isoniazid dosing. However, dose reduction must be balanced against the risk of reduced antitubercular efficacy, particularly in high-burden settings.

CYP2E1 was also associated with hepatotoxicity, although the effect size was smaller than NAT2. CYP2E1 contributes to oxidative metabolism and reactive metabolite formation. Individuals with the c1/c1 genotype may have increased enzyme activity and greater production of hepatotoxic metabolites. The combination of NAT2 slow acetylation and CYP2E1 risk genotype may further increase liver injury risk, although gene-gene interaction data remain limited.

GSTM1 null genotype was significantly associated with hepatotoxicity. GST enzymes are involved in detoxification of reactive metabolites through glutathione conjugation. Absence of GSTM1 activity may reduce hepatic detoxification capacity and increase susceptibility to oxidative damage. The combined GSTM1 and GSTT1 null genotype showed higher risk than either genotype alone, suggesting additive impairment of detoxification pathways.

SLCO1B1 variants showed a modest association with hepatotoxicity. SLCO1B1 encodes hepatic uptake transporters involved in drug disposition. Variants affecting transporter function may alter hepatic exposure to rifampicin or other antitubercular drugs. However, the number of studies was limited, and further research is needed before SLCO1B1 testing can be routinely recommended.

Evidence for HLA variants and ABC transporter polymorphisms was less consistent. HLA variants may be relevant for immune-mediated adverse reactions, including cutaneous reactions and immune-mediated liver injury, but findings appear population-specific. Larger studies are required to identify reproducible HLA associations.

The findings of this review have important clinical implications. Pharmacogenomic testing may help move tuberculosis treatment toward individualized therapy. A pre-treatment panel including NAT2, CYP2E1, GSTM1, and selected transporter variants could identify patients at high risk of toxicity. Such patients could undergo closer biochemical monitoring, early symptom screening, and individualized dose adjustment.

However, implementation challenges remain. Routine genotyping may not be available in many tuberculosis-endemic countries. Cost, laboratory infrastructure, turnaround time, clinician awareness, and integration into national TB programs are major barriers. In addition, most available evidence relates to hepatotoxicity, while pharmacogenomic predictors of neuropathy, cutaneous reactions, and gastrointestinal intolerance remain less well characterized.

The review also highlights heterogeneity across studies. Definitions of hepatotoxicity varied widely, ranging from mild transaminase elevation to symptomatic hepatitis or severe liver injury. Antitubercular regimens, drug doses, ethnicity, alcohol use, viral hepatitis status, HIV status, and nutritional status also differed across studies. These factors may explain moderate heterogeneity in pooled estimates.

Despite these limitations, the consistency of NAT2 findings supports its role as the most clinically actionable pharmacogenomic marker in antitubercular drug toxicity. Future trials should evaluate whether NAT2-guided isoniazid dosing can reduce hepatotoxicity without compromising treatment success.

Clinical Implications

The findings suggest the following clinical implications:

1. NAT2 slow and ultra-slow acetylator genotypes are important predictors of antitubercular drug-induced hepatotoxicity.
2. CYP2E1 and GSTM1 polymorphisms may provide additional risk stratification.
3. Pharmacogenomic testing may help identify patients requiring closer liver function monitoring.
4. Genotype-guided isoniazid dosing may reduce toxicity but requires validation in larger clinical trials.

5. Pharmacogenomic risk should be interpreted along with clinical risk factors such as age, alcohol use, viral hepatitis, HIV status, malnutrition, and baseline liver function.

Limitations

This review has several limitations. First, definitions of hepatotoxicity varied across included studies. Second, most studies were observational, increasing the possibility of confounding. Third, ethnicity-specific allele frequencies may limit generalizability. Fourth, not all studies adjusted for important clinical risk factors such as alcohol use, viral hepatitis, HIV infection, nutritional status, and concomitant medications. Fifth, evidence for non-hepatic toxicities was limited. Finally, publication bias and small-study effects cannot be excluded.

CONCLUSION

Pharmacogenomic variation plays an important role in antitubercular drug toxicity. NAT2 slow and ultra-slow acetylator genotypes are the strongest and most consistent predictors of antitubercular drug-induced hepatotoxicity. CYP2E1 c1/c1 genotype, GSTM1 null genotype, and selected SLCO1B1 variants may further contribute to toxicity susceptibility.

Pharmacogenomic testing, particularly NAT2 genotyping, has potential to improve safety of antitubercular therapy through individualized monitoring and dose optimization. However, implementation in routine tuberculosis care requires validation through prospective multicenter trials, cost-effectiveness studies, and integration into programmatic treatment settings.

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