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Complete List of Authors:	Yang , Seungwon Hwang, Se Jung Park, Jung Yun Lee , Jangik I. Chung, Eun Kyoung; Kyung Hee University, College of Pharmacy, Department of Pharmacy; Kyung Hee University Hospital at Gangdong, Pharmacy
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Original article

Association of genetic polymorphisms of *CYP2E1, NAT2, GST,* and *SLCO1B1* with the risk of anti-tuberculosis drug-induced liver injury: a systematic review and meta-analysis

Seungwon Yang[1], Se Jung Hwang[2], Jung Yun Park[3], Jangik Ike Lee[3,4*], Eun Kyoung Chung[2*]

[1] Department of Pharmacy and Yonsei Institute of Pharmaceutical Science, College of Pharmacy, Yonsei University, Incheon 21983, Republic of Korea

[2] Department of Pharmacy, College of Pharmacy, Kyung Hee University, Seoul 02447, Republic of Korea

[3] College of Pharmacy, Seoul National University, Seoul 08826, Republic of Korea

[4] College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 08826, Republic of Korea

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[*]Corresponding authors

Prof. Jangik I. Lee, PharmD, Ph.D.

Department of Pharmacy, College of Pharmacy, Seoul National University

103 Daehak-Ro, Jongno-Gu, Seoul 03080

South Korea

Tel: +82-2-3668-7474

Fax: +82-2-3668-7475

E-mail: jangik.lee@snu.ac.kr

Prof., Eun Kyoung Chung, PharmD, Ph.D.

Department of Pharmacy, College of Pharmacy, Kyung Hee University

26 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447

South Korea

Tel: +82-2-962-2122

Fax: +82-2-961-9580

E-mail: cekchung@khu.ac.kr

*Jangik I. Lee and Eun Kyung Chung have equally contributed to this study.

Running head

Genetics of anti-tuberculosis liver injury

ABSTRACT

Objectives The objective of this study is to investigate the association between genetic polymorphisms of *NAT2*, *CYP2E1*, *GST*, and *SLCO1B1* and the risk of anti-tuberculosis drug-induced liver injury (ATDILI).

Design Systematic review and meta-analysis

Methods PubMed, Embase, Web of Science, and Cochrane Reviews databases were systematically searched for case-control or cohort studies evaluating the association between *NAT2, CYP2E1, GST*, or *SLCO1B1* polymorphisms and ATDILI risk. The strength of association was assessed for each gene using the pooled odds ratio (OR) with a 95 % confidence interval (CI) based on the fixed- or random-effects model. Heterogeneity test and subgroup analyses were performed to confirm the reliability and robustness of the results.

Results Fifty-three studies were included in this analysis (n = 26 for *CYP2E1*, n = 34 for *NAT2*, n = 19 for *GST*, n = 4 for *SLCO1B1*). The risk of ATDILI was significantly increased with the following genotypes: *CYP2E1 RsaI/PstI* c1/c1 (OR = 1.39; 95% CI 1.06-1.83), *NAT2* slow acetylator (OR = 3.11, 95% CI 2.53-3.82), and *GSTM1* null (OR = 1.33, 95% CI 1.09-1.62). No significant association with ATDILI was found for the genetic polymorphisms of *CYP2E1 Dra*I, *GSTT1*, *SLCO1B1 338A>C*, and *SLCO1B1 521T>C* (P > 0.05).

Conclusions

ATDILI is more likely to occur in tuberculosis patients with *NAT2* slow acetylator genotype, *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype, and *GSTM1* null genotype. Close monitoring may be warranted for patients with these genotypes.

Strengths and limitations of this study

- This is the first meta-analysis to evaluate the association between the risk of ATDILI and *SLCO1B1* in TB patients.
- We included most updated studies with the large sample sizes to better clarify the association of genetic polymorphisms with the risk of ATDILI.
- The effect of anti-tuberculosis drug dosages on the risk of ATDILI could not be accounted for in our study because this information was not available in the majority of included studies

Introduction

Tuberculosis (TB) is a rampant infectious disease caused by *Mycobacterium tuberculosis.* It poses a major public health threat globally with approximately 1.5 million deaths and 9 million new cases in 2013 [1]. The mainstay of first-line TB treatment is a 4-drug combination regimen of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) during the first 2 months, followed by INH and RIF for additional 4 months [2 3]. The currently recommended therapy for TB is highly effective, resulting in high cure rates if patients are adherent to therapy [4]. However, treatment adherence is often suboptimal in patients receiving the combination anti-TB therapy due to many adverse drug reactions, some of which are considered serious [5]. One of the common adverse drug reactions associated with anti-TB medications is anti-TB drug-induced liver injury (ATDILI) affecting 2-28% of TB patients [6]. ATDILI is primarily mild to moderate in severity; however, it is potentially serious and fatal, resulting in the treatment interruption and ultimately, treatment failure [7 8]. According to previous studies, common risk factors for the development of ATDILI include age, race, nutritional status, alcohol intake, cigarette smoking, and coinfection with HIV or hepatitis B or C virus [7 9].

Recently, increasing evidence suggests an association between the risk of ATDILI and genetic polymorphisms of drug-metabolizing enzymes (DMEs) and drug transporters [10 11]. Reduced enzyme activity due to polymorphic genotypes of various DMEs including cytochrome P450 2E1 (CYP2E1), N-acetyltransferase 2 (NAT2), and glutathione S-transferase (GST) can result in the increased production and accumulation of toxic chemicals in the liver, leading to the development of ATDILI [12]. Previous meta-analyses indicated the association between the risk of ATDILI and the *NAT2* slow acetylator, *CYP2E1*1A*, and *GSTM1 null* genotypes [10 13]. Since their

publication, several case-control pharmacogenetic studies in TB patients were newly published with conflicting results regarding the association between the risk of ATDILI and genetic polymorphisms of various DMEs. Therefore, an updated meta-analysis has been warranted to confirm the association between the ATDILI risk and genetic polymorphisms of DMEs. In addition to DMEs, drug transporters have been emerging as a key determinant of the pharmacokinetics and pharmacodynamics of a drug [14]. Among various drug transporters, organic anion transporting polypeptide 1B1 (OATP1B1), encoded by *SLCO1B1*, is the major influx transporter responsible for hepatic uptake of RIF [15]. Although several studies have previously examined the association between *SLCO1B1* polymorphisms and the risk of ATDILI, conflicting results have been reported regarding the effect of *SLCO1B1* polymorphisms on ATDILI risk.

In our preliminary literature search, several polymorphic genes, including many DMEs, transporters, and other genes such as those involved in the immune system, were identified to have an association with the risk of ATDILI. Among these, sufficient, published information was available to conduct meta-analyses for *CYP2E1*, *NAT2*, *GST*, and *SLCO1B1* genetic polymorphisms.

Objectives

This meta-analysis was to evaluate the association between the risk of ATDILI and genetic polymorphisms of *CYP2E1*, *NAT2*, *GST*, and *SLCO1B1* in TB patients.

Methods

This study was in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for reporting the study design, search strategy, methods,

results, and conclusions. Three authors (SY, JP, and SH) independently conducted a literature search, study selection, quality assessment, and data extraction by reviewing the titles, abstracts, and full texts based on the pre-specified study selection criteria. Any discrepancies were adjudicated by corresponding authors (JIL and EKC).

Search strategy

Electronic databases of PubMed, EMBASE, Web of Science, and Cochrane Reviews were systematically searched from their inception to February 2018 to identify relevant studies evaluating the association of *NAT2*, *CYP2E1*, *GST*, and *SLCO1B1* polymorphisms with ATDILI risk. A comprehensive literature search was conducted using a combination of the following keywords and Medical Subject Heading (MeSH) terms: ("genetic polymorphism" or "*NAT2*" or "*CYP2E1*" or "*GST*" or "*SLCO1B1*" or "drug-metabolizing enzymes" or "drug transporter") AND ("anti-tuberculosis agents drug-induced liver injuries" or "hepatotoxicity"). The reference lists in the selected reviews and meta-analyses were reviewed to ensure the inclusion of all relevant evidence in this analysis.

Study selection

The types of studies included in the analysis were case-control or cohort studies evaluating the association between the risk of ATDILI and genetic polymorphisms of *NAT2*, *CYP2E1*, *GST,* and *SLCO1B1* in TB patients. Excluded studies were as follows: (1) studies available only in the form of abstracts or meeting posters; (2) review or meta-analysis articles; (3) studies providing insufficient data to estimate odds ratios (OR) and their 95% confidence intervals (CI); (4) studies in non-English language; (5) non-human studies including animal and *in vitro* studies; (6) studies with unpublished data; and (7) studies providing insufficient information on genotyping

methods.

Quality assessment and data extraction

The quality of included studies was assessed using the revised Little's recommendation based on the following criteria [16 17]. (1) scientific design; (2) definite inclusion of study population; (3) explicit information on study population; (4) explicit diagnostic criteria of ATDILI; (5) genetic detection method; (6) appropriate statistical analysis; and (7) logical discussion of study bias. Studies with an overall score of ≥ 4 (range 0 to 7) were considered high quality and retained in the analysis. The following data were extracted from each study using a standardized extraction form: (1) name of the first author; (2) year of publication; (3) the polymorphic gene(s) and genotype(s) under investigation; (4) ethnicity; (5) sample size; (6) mean or median age; (7) sex distribution; (8) anti-TB drug regimens; (9) diagnostic criteria of ATDILI; (10) genotyping methods; (11) Hardy-Weinberg equilibrium (HWE) test results; and (12) the number of cases and controls for each polymorphic genotype.

Statistical analysis

The genotypes were analyzed based on the following genetic risk model: (1) *NAT2* (slow acetylator *vs.* intermediate and fast acetylator); (2) *CYP2E1* (c1/c1 *vs.* c1/c2 and c2/c2 for the *RsaI/PstI* polymorphism, D/D *vs.* D/C and C/C for the *Dra*I polymorphism); (3) *GSTM1* (null *vs.* non-null); (4) *GSTT1* (null *vs.* non-null); (5) *GSTM1*/*GSTT1* (dual-null *vs.* one- or non-null); and (6) *SLCO1B1* (AA *vs.* AG and GG for *388A>G* polymorphism, CC *vs.* TC and TT for *521T>C* polymorphism) Fixed- or random-effects models were used depending on the presence of heterogeneity. The random-effects model was used in the presence of significant heterogeneity;

otherwise, the fixed effects model was used. Heterogeneity of study outcomes among included studies was evaluated using Cochran's Q test *(Q)* and quantified using Higgin's I^2 test. Significant heterogeneity was defined as the I^2 score of > 40% accompanied by $P < 0.10$ from the Cochran's Q test [18]. The strength of the association between the genetic polymorphisms and the risk of ATDILI was estimated using pooled ORs with the corresponding 95% CIs. The statistical significance of an OR was defined as $P < 0.05$ from the Z test. Subgroup analyses were performed to identify the source of heterogeneity and to investigate effects of the following covariates on the overall strength of the association between the genetic polymorphisms and the risk of ATDILI: ethnicity, the achievement of HWE, anti-TB drug regimen, the genotyping method used, and diagnostic criteria of ATDILI. In addition, sensitivity analyses were conducted to assess the robustness of the results. Publication bias was evaluated with a symmetrical funnel plot. Statistical analyses were performed using Review Manager Software (Cochrane Collaboration, London, UK).

Patient and public involvement

Patients and public were not involved in the design of this study.

Results

Study selection and characteristics

Overall, 384 articles were identified through electronic database search (n = 381) and through manual search by reviewing the reference lists of retrieved articles (n = 3). After removing 99 duplicates, 285 articles were screened for relevance based on the title and abstract. Among them, 70 relevant articles were assessed for eligibility through full-text evaluations. Finally, a total of

53 articles which met the inclusion criteria were included in our analysis (Figure 1). Among the 53 studies, 26 studies were included for *CYP2E1*, 34 studies for *NAT2*, 19 studies for *GST* (19 for *GSTM1*, 17 for *GSTT1*, and 11 for *GSTM1*/*GSTT1*), and 4 studies for *SLCO1B1*.

Table 1 summarizes the characteristics of the included studies. Across the included studies, large variability in study population was observed in terms of ethnicity (Chinese, Japanese, Korean, Indian, Taiwanese, Brazilian, Caucasian, Iranian, Tunisian, and Turkish), age (mean or median age ranging from 27 to 70 years), and sex (the proportion of males ranging from 13% to 90%). Patients in our included studies received either monotherapy with INH or RIF or a combination therapy including a 4-drug regimen of INH, RIF, PZA, and EMB for the treatment of TB. ATDILI was defined as an elevated serum alanine aminotransferase (ALT) concentration by 1.5- to 5-fold or greater above the upper limit of normal (ULN) depending on the study. The quality score of the included studies was 5 or greater based on the revised Little's recommendation (Table 1) [16 17]. Genotype distribution, the achievement of HWE, and the genotyping method used in the included studies are summarized for each polymorphic gene in S1 to S4 Tables. Funnel plots for *CYP2E1, NAT2, GST*, and *SLCO1B1* are provided in S5 Figure. None of the funnel plots were substantially asymmetrical.

CYP2E1

For the *CYP2E1 Rsa*I/*Pst*I polymorphism, 24 studies with 1293 cases and 5450 controls were included in our primary analysis. Using the random-effects model, the pooled estimates of all included studies (n = 24) showed a significant association between the risk of ATDILI and the *CYP2E1 Rsa*I/*Pst*I polymorphism (OR for the c1/c1 genotype = 1.39; 95% CI 1.06–1.83, P = 0.02; I^2 = 60%, $P_{heterogeneity}$ < 0.0001) (Figure 2A). In the subgroup analysis based on ethnicity,

anti-TB drug regimens, and diagnostic criteria of ATDILI, the risk of ATDILI was significantly increased for the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype in East Asian patients (OR = 1.62, 95% CI 1.26-2.36, P = 0.01; I^2 = 69%, $P_{heterogeneity}$ = 0.0006), in patients receiving a combination of anti-TB medications (OR = 1.35, 95% CI 1.01-1.79, P < 0.00001; I^2 = 61%, $P_{heterogeneity}$ = 0.0002), and in patients with ATDILI defined as a serum ALT concentration elevated by 2-fold or greater above the ULN (OR = 1.54, 95% CI 1.08-2.18, P = 0.02; I^2 = 70%, $P_{heterogeneity}$ < 0.0001) (S6 Table). The association between the risk of ATDILI and the c1/c1 genotype remained significant after excluding the studies where HWE was not achieved (OR = 1.67, 95% CI 1.19-2.34, P = 0.002; I^2 = 58%, $P_{heterogeneity}$ = 0.004) (S6 Table).

In our primary analysis for the *CYP2E1 Dra*I polymorphism with six studies including 233 cases and 1272 controls, no significant association was observed using the fixed-effects model between the risk of ATDILI and the *Dra*I polymorphism (OR for the D/D genotype = 0.93, 95% CI 0.68-1.27, P = 0.64; I^2 = 0%, $P_{heterogeneity}$ = 0.51) (Figure 2B). No subgroup analysis for the *Dra*I polymorphism resulted in a significant association between the ATDILI risk and the *Dra*I polymorphism (S6 Table).

NAT2

Overall, 34 studies with 1270 cases and 7234 controls were included in our primary analysis for the *NAT2* polymorphism. Using the random-effects model, the pooled estimates of all included studies (n = 34) showed a significant association between the risk of ATDILI and the *NAT2* polymorphism (OR for the slow acetylator genotype = 3.11, 95% CI 2.53-3.82, P < 0.00001; I^2 = 47%, $P_{heterogeneity}$ = 0.002) (Figure 3).

In the subgroup analysis based on ethnicity, anti-tuberculosis drug regimens, and

diagnostic criteria of ATDILI, the risk of ATDILI was significantly increased in slow acetylators compared to fast or intermediate acetylators in all subgroups (S7 Table). Additionally, the association between the risk of ATDILI and the *NAT2* slow acetylator genotype remained significant after excluding the studies where HWE was not achieved (S7 Table). Similarly, slow acetylators were at the significantly increased risk of ATDILI regardless of the genotyping method used (e.g., polymerase chain reaction-restriction fragment length polymorphism [PCR-RFLP], sequencing) (S7 Table).

GST

For the *GSTM1* polymorphism, a total of 19 studies with 977 cases and 5119 controls were included in our primary analysis. Using the fixed-effects model, the pooled estimates of all included studies (n = 19) showed a significant association between the risk of ATDILI and the *GSTM1* polymorphism (OR for the *GSTM1* null genotype = 1.30, 95% CI 1.12-1.52, P = 0.0007; I^2 = 33%, $P_{heterogeneity}$ = 0.08) (Figure 4A). In the subgroup analysis based on ethnicity and diagnostic criteria of ATDILI, the risk of ATDILI was significantly increased for the *GSTM1* null genotype in Indians (OR = 1.68, 95% CI 1.30-2.19, P < 0.0001; I^2 = 36%, $P_{heterogeneity}$ = 0.15) and in patients with ATDILI defined as a serum ALT concentration elevated by 2-fold or greater above the ULN (OR = 1.56, 95% CI 1.28-1.91, P < 0.0001; I^2 = 13%, $P_{heterogeneity}$ = 0.32) (S8 Table).

For the *GSTT1* and *GSTM1*/*GSTT1* polymorphisms, 17 studies (768 cases, 4823 controls) and 11 studies (547 cases, 4233 controls) were included in our primary analyses, respectively. The risk of ATDILI was not significantly associated with the *GSTT1* polymorphism (OR for the null genotype = 1.03, 95% CI 0.85-1.25, P = 0.76; I^2 = 16%, $P_{heterogeneity}$ = 0.26) or the

GSTM1/*GSTT1* polymorphism (OR for the dual-null genotype = 1.05, 95% CI 0.67-1.62, P = 0.84; I^2 = 59%, $P_{heterogeneity}$ = 0.006) (Figures 4B and 4C). The associations of the *GSTT1* and the *GSTM1*/*GSTT1* genetic polymorphisms with the risk of ATDILI were not significant in any of the subgroups tested (S8 Table).

SLCO1B1

For the *SLCO1B1 388A>G* polymorphism, four studies with 279 cases and 837 controls were included in our primary analysis. Using the fixed-effects model, no significant association was observed between the risk of ATDILI and the *SLCO1B1 388A>G* polymorphism (OR for the AA genotype = 1.47, 95% CI 0.94-2.29, P = 0.09; I^2 = 0%, $P_{heterogeneity}$ = 0.72) (Figure 5A). For the *SLCO1B1 521T>C* polymorphism, four studies with 310 cases and 901 controls were included in our primary analysis. Using the fixed-effects model, no significant association was found between the ATDILI risk and the *SLCO1B1 521T>C* polymorphism (OR for the CC genotype = 1.21, 95% CI 0.40-3.63, P = 0.74; I^2 = 0%, $P_{heterogeneity}$ = 0.56) (Figure 5B). No significant association was observed between the risk of ATDILI and the *SLCO1B1* polymorphisms (both 388A>G and 521T>C) in any of the tested subgroups based on ethnicity, anti-TB drug regimen, diagnostic criteria of ATDILI, and the genotyping method used (S9 Table).

Discussion

To our knowledge, our current study is a large-scale meta-analysis evaluating the association between the risk of ATDILI and genetic polymorphisms of *SLCO1B1* as well as various DMEs including *CYP2E1*, *NAT2*, and *GST* to provide more updated, comprehensive, and compelling evidence. Compared with previous meta-analyses, our present study included a larger number

of studies and explored various factors which may influence the association between genetic polymorphisms and the risk of ATDILI (S6, S7, S8, S9 Tables). The inclusion of a large number of studies in our current meta-analysis may sufficiently increase the statistical power compared to individual studies; however, a limited number of studies evaluating the association between the risk of ATDILI and the *SLCO1B1* genetic polymorphisms were included (n = 4). Consistent with previous studies, our current study suggested a significantly increased risk of ATDILI in patients with the *NAT2* slow acetylator genotype (OR = 3.11, 95% CI 2.53-3.82), the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype (OR = 1.39, 95% CI 1.06-1.83), and the *GSTM1* null genotype (OR = 1.30, 95% CI 1.12-1.52) [10 13 19]. Among these genotypes, the risk of ATDILI was increased the most in patients with the *NAT2* slow acetylator genotype. In contrast, no significant association was observed between the risk of ATDILI and the genetic polymorphisms of *CYP2E1 Dra*I, *GSTT1*, *GSTM1*/*GSTT1*, *SLCO1B1 388A>G*, and *SLCO1B1 521T>C*. Caution needs to be exercised when interpreting this study finding because the lack of significant association between these polymorphisms and the risk of ATDILI might result from small sample sizes and the low frequency of ATDILI reported in patients with these genetic polymorphisms.

When evaluating the impacts of the *CYP2E1 Rsa*I/*Pst*I and *Dra*I genetic polymorphisms on the risk of ATDILI in our study, patients with the *Rsa*I/*Pst*I c1/c1 genotype were 1.39-times more likely to develop ATDILI. Similarly, in a previous meta-analysis by Deng and colleagues, the risk of ATDILI was 1.4-times higher in patients with the *Rsa*I/*Pst*I c1/c1 genotype compared to other genotypes [20]. In the liver, INH is metabolized by NAT2 to acetylisoniazid which is consequently oxidized by CYP2E1 to reactive intermediates in the formation of hepatotoxins [21 22]. The increased inducibility or greater activity of CYP2E1 in patients with the *CYP2E1*

*Rsa*I/*Pst*I c1/c1 genotype may result in the production of more intermediate hepatotoxins, ultimately leading to the increased risk of ATDILI [21 22]. Our subgroup analysis showed a significantly increased risk of ATDILI in the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype carriers of East Asian and Indian ethnicity (S6 Table), suggesting a potential gene-ethnicity interaction in these ethnic populations due to genetic characteristics of the ethnicity or environmental factors in these populations [23]. In addition to ethnicity, combination anti-TB therapy was shown to significantly increase the risk of ATDILI in patients with the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype (S6 Table). This is consistent with previous study findings because hepatotoxicity commonly occurs with anti-TB drugs and thus, use of more than one hepatotoxic anti-TB medications increases the risk of ATDILI [7]. Moreover, patients with the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype were at a significantly increased risk of ATDILI when ATDILI was defined as serum ALT concentrations elevated > 2 times the ULN and when their genotype was determined by the PCR-RFLP or sequencing method. This may suggest more sensitive diagnostic criteria and genotyping method to identify patients at an increased risk of ATDILI as early in therapy as possible. However, caution needs to be exercised when applying this study finding in practice because of the potentially low specificity associated with the diagnostic criteria of ATDILI and genotyping method. Future studies are warranted to confirm our subgroup analysis results.

Similar to previous studies, our current study suggested a significantly increased risk of ATDILI in patients with the *NAT2* slow acetylator genotype compared to those with intermediate/fast acetylator genotypes [10 19]. The risk of ATDILI in slow acetylators remained significantly increased in all tested subgroups regardless of ethnicity, the anti-TB drug regimen used, the achievement of HWE, diagnostic criteria of ATDILI, and the genotyping method used (S7 Table). Among the subgroups, the ATDILI risk appeared the highest in the West Asian

population (OR = 9.51, 95% CI 4.19-21.61, P < 0.00001). However, caution needs to be exercised when interpreting and applying this finding in practice because it is the result of subgroup analysis. Until more confirmative data are available, clinicians may closely monitor West Asian TB patients with the *NAT2* slow acetylator genotype receiving INH-based treatment.

According to previous studies, GST enzymes, particularly those coded by *GSTM1* and *GSTT1* loci, are associated with the risk of drug-induced hepatotoxicity [10 24]. Consistent with previous studies, our current study demonstrated a significantly increased risk of ATDILI in individuals with the *GSTM1* null genotype compared to those with the non-null genotype; however, the risk of ATDILI was not affected by the *GSTT1* or *GSTM1*/*GSTT1* genetic polymorphisms. GSTs are important enzymes to detoxify various xenobiotics and play an essential role in INH metabolism by eliminating acetyldiazene ketene acetylonium ion (a possibly hepatotoxic free radical metabolite of INH) from the body through *GSTM1*. This may account for the significant association of the ATDILI risk with the *GSTM1* genotype, but not with the *GSTT1* or *GSTM1*/*GSTT1* genotypes [10 24]. Our subgroup analysis showed a significantly increased risk of ATDILI in the *GSTM1* null genotype carriers of Indian ethnicity (S8 Table), suggesting a potential gene-ethnicity interaction due to unknown genetic characteristics or environmental factors such as diet in Indian patients [23]. In addition, the risk of ATDILI was significantly increased in patients with the *GSTM1* null genotype when ATDILI was defined as serum ALT concentrations elevated > 2 times the ULN (S8 Table). Based on this finding, serum ALT concentrations elevated > 2 times the ULN may be suggested as more sensitive diagnostic criteria of ATDILI; however, it may result in the false positive identification of ATDILI patients without clinical significance due to potentially low specificity. Considering this is a subgroup analysis result, caution is warranted in interpreting and applying this finding in practice until

confirmative data are available in the future.

SLCO1B1 encodes organic anion transporting polypeptide 1B1 (OATP1B1) which is a major influx drug transporter responsible for the hepatic uptake of various endogenous and exogenous substances including RIF [25]. Previous studies showed significantly altered systemic exposure of RIF in carriers of the *SLCO1B1* polymorphism [26 27]. To our knowledge, only four studies have been conducted to examine the association between the ATDILI risk and the *SLCO1B1* genetic polymorphisms [11 25 28 29]. Various single nucleotide polymorphisms (SNPs) of *SLCO1B1* were evaluated in these studies; however, *SLCO1B1* 388A>G (rs2306283) and 521T>C (rs4149056) were the only polymorphisms assessed in common [11 25 28 29]. Therefore, to maximize the sample size in our current meta-analysis, we examined the association between the risk of ATDILI and the polymorphic genotypes of *SLCO1B1* 388A>G and 521 T>C. Similar to each of the included studies, we did not find a significantly altered risk of ATDILI in patients with the *SLCO1B1* 388A>G and 521T>C genetic polymorphisms. However, caution should be exercised when interpreting and applying our study findings in practice due to the limited genetic risk model evaluated and a small sample size for the association between the ATDILI risk and the *SLCO1B1* genetic polymorphisms.

In our study, significantly high heterogeneity between studies was observed for *CYP2E1 Rsa*I/*Pst*I (I^2 = 60%, P < 0.0001), *NAT2* (I^2 = 47%, P = 0.002), and *GSTM1*/*GSTT1* (I^2 = 59%, P = 0.006). The high heterogeneity between studies may be due to substantial differences in ethnicity, the achievement of HWE, anti-TB drug regimen, the genotyping method used, and diagnostic criteria of ATDILI among the studies included in our analysis. To address the relatively high heterogeneity, we performed sensitivity analyses using the leave-one-out method by deleting one study after each analysis followed by repeating the meta-analysis. Through the

sensitivity analyses, outlier studies were identified as the major source of heterogeneity. After removing these outlier studies, heterogeneity was remarkably reduced (I^2 = 60% to 34% for *CYP2E1 Rsa*I/*Pst*I, I^2 = 47% to 32% for *NAT2*, I^2 = 33% to 0% for *GSTM1*, I^2 = 59% to 0% for *GSTM1/GSTT1*). The overall results for the association between the risk of ATDILI and genetic polymorphisms of these enzymes after excluding the outlier studies were not changed, indicating the robustness of our analysis result.

There are limitations to this study. First, due to the lack of information regarding other patient characteristics potentially associated with liver injuries, our estimated ORs were not adjusted based on the potential risk factor of drug-induced liver injuries such as age, alcohol consumption, cigarette smoking, and other lifestyle characteristics [7 9]. Second, our literature search limited to the articles published in English may lead to language bias. Third, the effect of anti-tuberculosis drug dosages on the risk of ATDILI could not be accounted for in our study because this information was not available in most of the included studies. In addition, a specific causative agent of ATDILI could not be identified in our analysis because most patients in our included studies received a combination regimen of anti-tuberculosis drugs. Lastly, only the limited number of genotypes were assessed for the association with the risk of ATDILI, particularly for *SLCO1B1* genetic polymorphisms. Future studies are needed to comprehensively and adequately address the relationship between the ATDILI risk and various polymorphisms of the genes for drug-metabolizing enzymes and drug transporters by using different genetic risk models and including more polymorphic genotypes.

In conclusion, the risk of ATDILI during TB therapy was significantly increased in TB patients carrying *NAT2* slow acetylator, *CYP2E1 Rsa*I/*Pst*I c1/c1, or *GSTM1* null genotype. Screening for these genetic polymorphisms, particularly for the *NAT2* slow acetylator genotype,

may be of great clinical benefit to identify patients at high risk for ATDILI and minimize the risk of ATDILI. Future studies are pertinent to develop dose and/or treatment adjustment strategies, to evaluate the feasibility and cost-effectiveness of the genetic screening test, and to assess the effect of more genetic polymorphisms on the risk of ATDILI for appropriate prevention and management of ATDILI.

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Contributors

S.Y. devised and designed the study. S.Y., J.Y.P., and S.J.H. conducted the literature search, performed data extraction and analysis, and. interpreted the data. S.Y., E.K.C., and J.I.L. prepared and reviewed the manuscript. All authors reviewed, amended and approved the submitted manuscript

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Competing interests

None declared

Patient consent

Not required

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Supporting information

Additional supporting information can be found in the online version of this article:

S1 Table. Genotype distribution, the achievement of Hardy-Weinberg equilibrium (HWE), and the genotyping method used for *CYP2E1* in the included studies (n = 26)

S2 Table. Genotype distribution, the achievement of Hardy-Weinberg equilibrium (HWE), and the genotyping method used for *NAT2* in the included studies (n = 34)

S3 Table. Genotype distribution, the achievement of Hardy-Weinberg equilibrium (HWE), and the genotyping method used for *GST* in the included studies (n = 19)

S4 Table. Genotype distribution, the achievement of Hardy-Weinberg equilibrium (HWE), and the genotyping method used for *SLCO1B1* in the included studies (n = 4)

S5 Figure. Funnel plot of the meta-analysis of ATDILI risk and *CYP2E1, NAT2, GST,* and *SLCO* polymorphisms. (A) C*YP2E1 Rsa*I/*Pst*I polymorphism, (B) *CYP2E1 Dra*I polymorphism, (C) *NAT2* polymorphism, (D) *GSTM1* polymorphism, (E) *GSTT1* polymorphism, (F) *GSTT1/M1* polymorphism, and (G) *SLCO1B1 388A>G* and *521T>C* polymorphism.

S6 Table. Subgroup analysis for the association between *CYP2E1* polymorphisms and ATDILI risk

S7 Table. Subgroup analysis for the association between *NAT2* polymorphism and ATDILI risk

S8 Table. Subgroup analysis for the association between *GST* polymorphisms and ATDILI risk

S9 Table. Subgroup analysis for the association between *SLCO1B1* polymorphisms and ATDILI risk

Figure legends

Figure 1. Study selection process flowchart according to the PRISMA guideline.

Figure 2. Risk of anti-tuberculosis drug-induced liver injury in patients with the *CYP2E1* (A) *Rsa*I/*Pst*I c1/c1 genotype compared to c1/c2 + c2/c2 genotypes and (B) *Dra*I D/D genotype compared to D/C + C/C genotypes.

Figure 3. Risk of anti-tuberculosis drug-induced liver injury in patients with the *NAT2* slow acetylator genotype compared to those with the intermediate/fast acetylator genotypes.

Figure 4. Risk of anti-tuberculosis drug-induced liver injury in patients with (A) the *GSTM1* null genotype compared to the non-null genotype, (B) the *GSTT1* null genotype compared to the non-null genotype, and (C) the *GSTM1*/*GSTT1* dual-null genotype compared to the one- and non-null genotypes.

Figure 5. Risk of anti-tuberculosis drug-induced liver injury in patients with the *SLCO1B1* (A) 388 AA genotype compared to the 388 AG + GG genotypes and (B) 521 CC genotype compared to the 521 TC + TT genotypes.

Table 1. Characteristics of the Studies Included in the meta-analysis (n = 53 studies)

First author last name, year	Polymorphic gene	Ethnicity	Sample size (case/control)	Age (years) (case/ control)[a]	Male (%) (case/ control)	Anti-TB drug regimen administered	Diagnostic criteria of ATDILI	Quality score
Ben Mahmoud, 2012 [30]	*NAT2*	Tunisian	14/52	42.4/42.1	42.8/48.1	INH, RIF containing regimen	ALT > 2 × ULN	6
Bozok Cetintas, 2008 [31]	*NAT2*	Turkish	30/70	39.8/37.3	50.0/72.8	INH, RIF, PZA, EMB	ALT > 3 × ULN	5
Higuchi, 2007 [32]	*NAT2*	Japanese	18/82	60.8/64.7	50.0/57.3	INH ,RIF containing regimen	ALT > 2 × ULN	6
Ho, 2013 [33]	*NAT2*	Taiwanese	20/328	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 5 × ULN	5
Huang, 2002[34]	*NAT2*	Taiwanese	33/191	73.3/63.7	87.9/88.5	INH, RIF, PZA, EMB	ALT > 2 × ULN	6
Khalili, 2011 [35]	*NAT2*	Iranian	14/36	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 3 × ULN	6
Leiro-Fernandez, 2011 [36]	*NAT2*	Caucasian	50/67	34.0/30.5[b]	54.0/56.7	INH, RIF, PZA	ALT > 3 × ULN	7
Lv, 2012 [37]	*NAT2*	Chinese	89/356	42.0/42.0[b]	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Ng, 2014 [38]	*NAT2*	Mixed	26/101	48.3/NA	38.5/NA	INH containing regimen	ALT > 5 × ULN	6
Ohno, 2000 [39]	*NAT2*	Japanese	14/63	NA/NA	NA/NA	INH, RIF	ALT > 1.5 × ULN	7
Possuelo, 2008 [40]	*NAT2*	Brazilian	14/240	38.9/36.5	50.0/66.9	INH, RIF, PZA	ALT > 3 × ULN	7
Rana, 2012 [41]	*NAT2*	Indian	50/201	45.3/43.8	76.0/57.2	INH, RIF, PZA, EMB	ALT > 5 × ULN	7
Shimizu, 2006 [42]	*NAT2*	Japanese	10/32	60.5/64.9	70.0/46.9	INH, RIF	ALT > 2 × ULN	5
Yuliwulandari, 2016 [43]	*NAT2*	Indonesian	50/191	NA/NA	NA/NA	NA	ALT > 2 × ULN	6
Feng, 2014 [44]	*CYP2E1*	Chinese	173/173	48.8/48.6	68.0/68.0	INH, RIF, PZA	ALT > 3 × ULN	6

Kim, 2009 [45]	*CYP2E1*	Korean	67/159	42.1/42.8	65.7/65.4	INH, RIF, PZA, EMB	ALT > 2 × ULN	6
Singh, 2014 [46]	*CYP2E1*	Indian	50/135	NA/NA	NA/NA	NA	ALT > 2 × ULN	6
Tang, 2013 [47]	*CYP2E1*	Chinese	89/356	43.7/43.6	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Chatterjee, 2010 [48]	*GSTM1, GSTT1*	Indian	51/100	37.2/33.2	49.0/63.0	INH, RIF, PZA	ALT > 3 × ULN	7
Gupta, 2013 [49]	*GSTM1, GSTT1*	Indian	50/246	37.0/36.5[b]	48.0/56.5	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Huang, 2007 [50]	*GSTM1, GSTT1*	Taiwanese	63/63	62.0/NA	NA/NA	NA	ALT > 5 × ULN	6
Kim, 2010 [51]	*GSTM1, GSTT1*	Korean	57/190	47.3/42.4	59.6/67.9	INH, RIF, PZA, EMB	ALT > 3 × ULN	7
Leiro, 2008 [52]	*GSTM1, GSTT1*	Caucasian	35/60	34.0/31.0 [b]	40.0/41.7	INH, RIF, PZA	ALT > 3 × ULN	7
Liu, 2014 [53]	*GSTM1, GSTT1*	Chinese	20/143	35.9/61.2	60.0/59.4	INH containing regimen	ALT > 2 × ULN	7
Monteiro, 2012 [54]	*GSTM1, GSTT1*	Brazilian	59/118	37.0/38.0 [b]	76.0/61.0	NA	ALT > 2 × ULN	7
Rana, 2013 [55]	*GSTM1, GSTT1*	Indian	30/220	43.6/42.3	60.0/64.5	INH, RIF	ALT > 5 × ULN	6
Roy, 2001 [56]	*GSTM1, GSTT1*	Indian	33/33	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Chen, 2015 [25]	*SLCO1B1*	Chinese	89/356	43.7/43.6	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Kim, 2012 [11]	*SLCO1B1*	Korean	67/159	43.0/42.8	65.7/65.4	INH, RIF, PZA, EMB	ALT > 2 × ULN	6
Li, 2012 [28]	*SLCO1B1*	Chinese	118/155	40.5/39.3	48.3/54.8	RIF	ALT > 3 × ULN	7
An, 2012 [57]	*NAT2, CYP2E1*	Chinese	101/107	36.0/33.4 [b]	55.0/70.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Bose, 2011 [58]	*NAT2, CYP2E1*	Indian	41/177	38.0/36.0	43.9/47.4	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Chamorro, 2013 [59]	*NAT2, CYP2E1*	Mixed (South American)	47/128	29.0/27.0	41.3/64.8	INH, RIF, PZA, EMB	ALT > 3 × ULN	7
Cho, 2007 [60]	*NAT2,*	Korean	18/114	51.2/46.7	66.7/55.3	INH, RIF,	ALT > 2 ×	6

	CYP2E1					PZA, EMB	ULN	
Gupta, 2013 [61]	*NAT2, CYP2E1*	Indian	50/165	37.0/38.0	48.0/60.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Huang, 2003 [62]	*NAT2, CYP2E1*	Taiwanese	49/269	70.0/59.0 [b]	18.4/14.9	INH, RIF, PZA, EMB	ALT > 2 × ULN	6
Lee, 2010 [63]	*NAT2, CYP2E1*	Taiwanese	45/95	58.4/54.9	60.0/66.3	INH, RIF, PZA, EMB	ALT > 2 × ULN	6
Mishra, 2013 [64]	*NAT2, CYP2E1*	Indian	33/173	38.0/NA	52.0/NA	INH, RIF, PZA, EMB	ALT > 3 × ULN	7
Santos, 2013 [65]	*NAT2, CYP2E1*	Brazilian	18/252	47.7/45.6	56.0/49.0	INH, RIF	ALT > 3 × ULN	7
Vuilleumier, 2006 [66]	*NAT2, CYP2E1*	Mixed	8/63	27-35: 2/22[c] >36 : 5/18[c]	38.0/51.0	INH	AST or ALT > 4 × ULN	7
Yamada, 2009 [67]	*NAT2, CYP2E1*	Mixed	23/147	NA/NA	13.0/42.9	INH	ALT > 2 × ULN	7
Zaverucha-do-Valle, 2014 [68]	*NAT2, CYP2E1*	Brazilian	50/79	< 40: 28/43[c] > 40: 20/36[c]	60.4/72.2	INH, RIF, PZA	ALT > 2 × ULN	6
Sharma, 2014 [69]	*CYP2E1, GSTM1*	Indian	105/185	35.2/27.6	55.7/72.1	INH, RIF, PZA, EMB	ALT > 5 × ULN	7
Wang, 2010 [70]	*CYP2E1, GSTM1*	Chinese	104/111	48.6/44.7	67.3/67.6	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Tang, 2012 [71]	*CYP2E1, GSTM1, GSTT1*	Chinese	89/356	43.7/43.6	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Yimer, 2011 [29]	*NAT2, SLCO1B1*	Ethiopian	41/160	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 2 × ULN	6
Brito, 2014 [72]	*NAT2, CYP2E1, GSTM1, GSTT1*	Brazilian	15/230	38.1/36.8	46.7/NA	INH, RIF, PZA	ALT > 3 × ULN	7
Forestiero, 2013 [73]	*NAT2, CYP2E1, GSTM1, GSTT1*	Brazilian	59/40	NA/NA	49.2/60.0	INH, RIF, PZA	ALT > 2.5 × ULN	5
Rana, 2014 [74]	*NAT2, CYP2E1, GSTM1, GSTT1*	Indian	55/245	43.6/42.3	60.0/62.0	INH, RIF, PZA, EMB	ALT > 5 × ULN	6

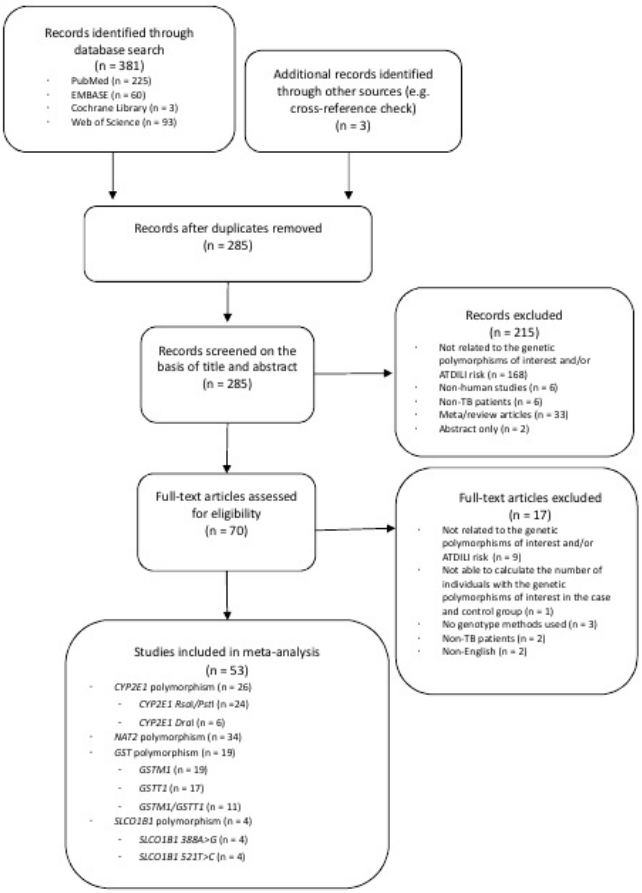
Singla, 2014 [75]	*NAT2, CYP2E1, GSTM1, GSTT1*	Indian	17/391	48.2/32.7	64.7/61.4	INH, RIF, PZA, EMB, STM	ALT > 2 × ULN	7
Sotsuka, 2011 [76]	*NAT2, CYP2E1, GSTM1, GSTT1*	Japanese	20/92	54.9/50.4	90.0/73.9	INH, RIF, PZA, EMB or STM	ALT > 3 × ULN	6
Teixeira, 2011 [77]	*NAT2, CYP2E1, GSTM1, GSTT1*	Brazilian	26/141	47.6/43.0	61.5/52.5	INH containing regimen	ALT > 3 × ULN	7
Xiang, 2014 [78]	*NAT2, CYP2E1, GSTM1, GSTT1*	Chinese	89/2155	37.0/44.5	67.4/55.7	INH, RIF, PZA, EMB	ALT > 2 × ULN	7

Abbreviations: **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **ATDILI**, anti-tuberculosis drug-induced liver injury; **CYP2E1**, cytochrome P450 2E1; **EMB**, ethambutol; **GSTM1**, glutathione S-transferase Mu 1; **GSTT1**, glutathione S-transferase Theta 1; **INH**, isoniazid; **NA**, not available; **NAT2**, N-acetyltransferase 2; **PZA**, pyrazinamide; **RIF**, rifampicin; **SLCO1B1**, solute carrier organic anion transporter family, member 1B1 (encoding organic anion transporting polypeptide 1B1 [OATP1B1]); **STM**, streptomycin; **TB**, tuberculosis; **ULN**, upper limit of normal

[a] Mean unless otherwise stated

[b] Median age

[c] Number of individuals in the age ranges



Study selection process flowchart according to the PRISMA guideline

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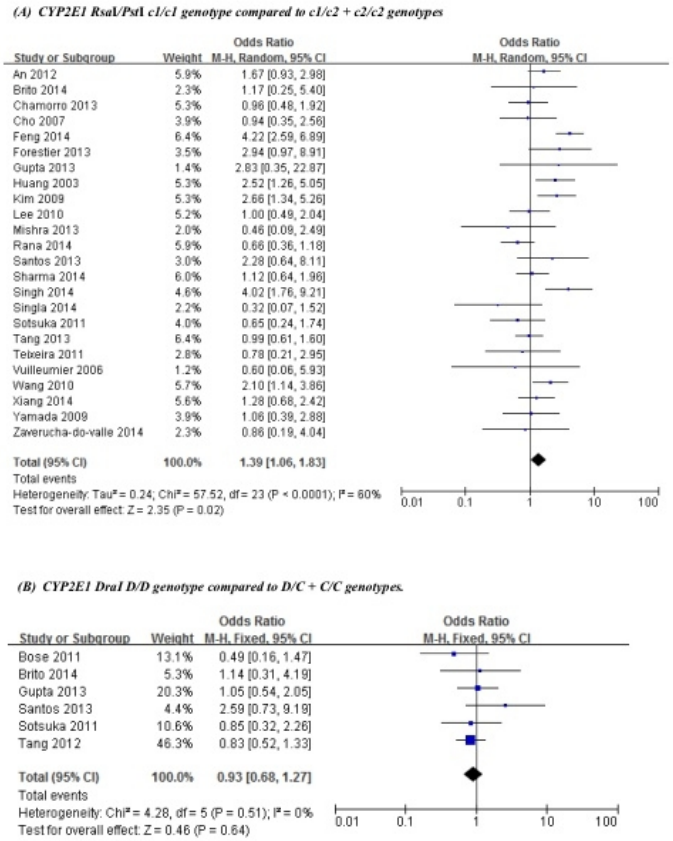

Risk of anti-tuberculosis drug-induced liver injury in patients with the CYP2E1 (A) RsaI/PstI c1/c1 genotype compared to c1/c2 + c2/c2 genotypes and (B) DraI D/D genotype compared to D/C + C/C genotypes

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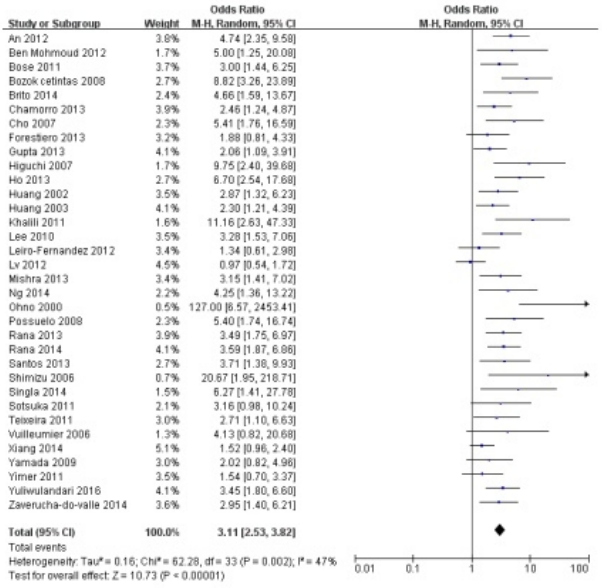

Risk of anti-tuberculosis drug-induced liver injury in patients with the NAT2 slow acetylator genotype compared to those with the intermediate/fast acetylator genotypes

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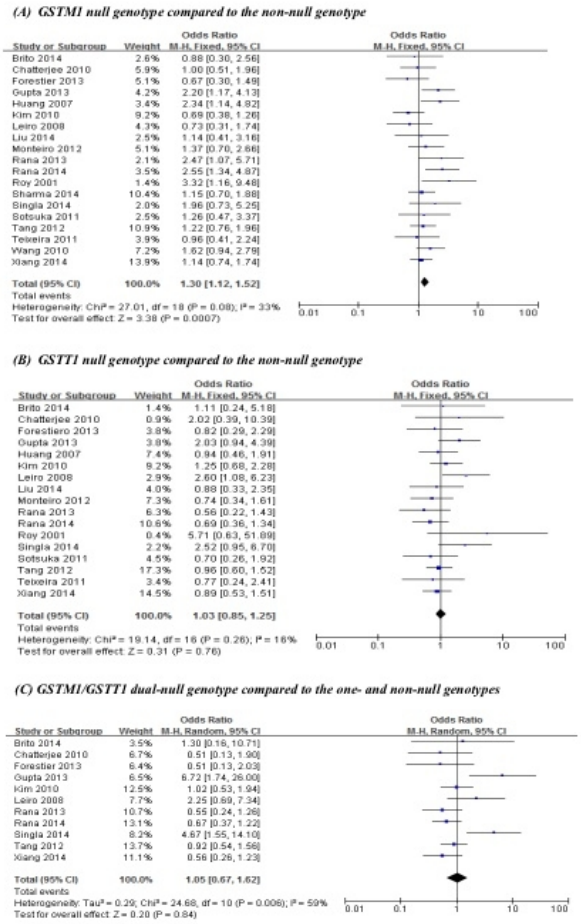
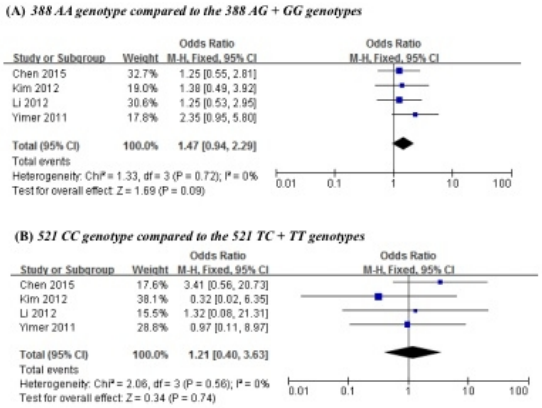


Risk of anti-tuberculosis drug-induced liver injury in patients with (A) the GSTM1 null genotype compared to the non-null genotype, (B) the GSTT1 null genotype compared to the non-null genotype, and (C) the GSTM1/GSTT1 dual-null genotype compared to the one- and non-null genotypes

209x297mm (72 x 72 DPI)



Risk of anti-tuberculosis drug-induced liver injury in patients with the SLCO1B1 (A) 388 AA genotype compared to the 388 AG + GG genotypes and (B) 521 CC genotype compared to the 521 TC + TT genotypes

209x297mm (72 x 72 DPI)

Supplementary data

S1 Table. Genotype distribution, the achievement of Hardy-Weinberg equilibrium (HWE), and the genotyping method used for *CYP2E1* in the included studies (n = 26)

Study	*Rsa*I/*Pst*I genotype (n = 24)				HWE	*Dra*I genotype (n = 6)				HWE	Genotyping method
	Case (number of individuals [%])		Control (number of individuals [%])			Case (number of individuals [%])		Control (number of individuals [%])			
	C1/C1	C1/C2 + C2/C2	C1/C1	C1/C2 + C2/C2		D/D	D/C + C/C	D/D	D/C + C/C		
An[1]	72 (71.3)	29 (28.7)	64 (59.8)	43 (40.2)	Yes	NA	NA	NA	NA	NA	Sequencing
Bose[2]	NA	NA	NA	NA	NA	4 (9.8)	37 (90.2)	32 (18.1)	145 (81.9)	No	PCR-RFLP
Brito[3]	13 (86.7)	2 (13.3)	195 (84.8)	35 (15.2)	No	12 (80.0)	3 (20.0)	179 (76.8)	54 (23.2)	Yes	PCR-RFLP
Chamorro[4]	30 (63.8)	17 (36.2)	83 (64.8)	45 (35.2)	No	NA	NA	NA	NA	NA	PCR-RFLP
Cho[5]	10 (55.6)	8 (44.4)	65 (57.0)	49 (43.0)	No	NA	NA	NA	NA	NA	Sequencing
Feng[6]	142 (82.1)	31 (17.9)	90 (52.0)	83 (48.0)	Yes	NA	NA	NA	NA	NA	Sequencing
Forestiero[7]	53 (89.8)	6 (10.2)	30 (75.0)	10 (25.0)	Yes	NA	NA	NA	NA	NA	PCR-RFLP
Gupta[8]	49 (98.0)	1 (2.0)	156 (94.5)	9 (5.5)	No	33 (66.0)	17 (34.0)	107 (64.9)	58 (35.1)	Yes	PCR-RFLP
Huang[9]	37 (75.5)	12 (24.5)	148 (55.0)	121 (45.0)	Yes	NA	NA	NA	NA	NA	PCR-RFLP

Kim[10]	54 (81.8)	12 (18.2)	97 (63.4)	56 (36.6)	Yes	NA	NA	NA	NA	NA	SNP stream
Lee[11]	26 (57.8)	19 (42.2)	55 (57.9)	40 (42.1)	No	NA	NA	NA	NA	NA	Taqman
Mishra[12]	31 (93.9)	2 (6.1)	168 (97.1)	5 (2.9)	No	NA	NA	NA	NA	NA	PCR-RFLP
Rana[13]	28 (50.9)	27 (49.1)	150 (61.2)	95 (38.8)	No	NA	NA	NA	NA	NA	PCR-RFLP
Santos[14]	15 (83.3)	3 (16.7)	173 (75.6)	56 (24.4)	Yes	15 (83.3)	3 (16.7)	166 (72.8)	62 (27.2)	Yes	Taqman
Sharma[15]	81 (77.1)	24 (22.9)	139 (75.1)	46 (24.9)	Yes	NA	NA	NA	NA	NA	PCR-RFLP
Singh[16]	42 (84.0)	8 (16.0)	77 (56.6)	59 (43.4)	No	NA	NA	NA	NA	NA	PCR-RFLP
Singla[17]	15 (88.0)	2 (12.0)	375 (96.0)	16 (4.0)	No	NA	NA	NA	NA	NA	PCR-RFLP
Sotsuka[18]	11 (55.0)	9 (45.0)	60 (65.2)	32 (34.8)	No	9 (45.0)	11 (55.0)	45 (48.9)	47 (51.1)	Yes	PCR-RFLP
Tang[19]	NA	NA	NA	NA	NA	47 (52.8)	42 (47.2)	204 (57.3)	152 (42.7)	Yes	PCR-RFLP
Tang[20]	56 (62.9)	33 (37.1)	225 (63.2)	131 (36.8)	Yes	NA	NA	NA	NA	NA	Taqman
Teixeira[21]	23 (88.5)	3 (11.5)	128 (90.8)	13 (9.2)	Yes	NA	NA	NA	NA	NA	PCR-RFLP
Vuilleumier[22]	7 (87.5)	1 (12.5)	58 (92.1)	5 (7.9)	Yes	NA	NA	NA	NA	NA	PCR-RFLP

Wang[23]	82 (78.8)	22 (21.2)	71 (64.0)	40 (36.0)	No	NA	NA	NA	NA	NA	PCR-RFLP
Xiang[24]	58 (82.9)	12 (17.1)	1264 (79.0)	336 (21.0)	Yes	NA	NA	NA	NA	NA	PCR/ligase detection reaction assays
Yamada[25]	17 (73.9)	6 (26.1)	107 (72.8)	40 (27.2)	Yes	NA	NA	NA	NA	NA	PCR-RFLP
Zaverucha-do-Valle[26]	48 (94.1)	3 (5.9)	74 (94.9)	4 (5.1)	Yes	NA	NA	NA	NA	NA	PCR-RFLP

Abbreviations: ***HWE***, Hardy-Weinberg equilibrium; ***NA***, not available; ***PCR***, polymerase chain reaction; ***RFLP***, restriction fragment length polymorphism; ***SNP***, single nucleotide polymorphism

S2 Table. Genotype distribution, the achievement of Hardy-Weinberg equilibrium (HWE), and the genotyping method used for *NAT2* in the included studies (n = 34)

Study	Case (number of individuals [%])		Control (number of individuals [%])		HWE	Genotyping method
	Slow acetylator	Intermediate and fast acetylator	Slow acetylator	Intermediate and fast acetylator		
An [1]	40 (39.6)	61 (60.4)	13 (12.1)	94 (87.9)	Yes	Sequencing
Ben Mahmoud [27]	11 (78.5)	3 (21.5)	22 (42.4)	30 (57.6)	Yes	PCR-RFLP
Bose [2]	29 (70.7)	12 (29.3)	79 (44.6)	98 (55.4)	No	PCR-RFLP
Bozok Cetintas [28]	23 (76.7)	7 (23.3)	19 (27.1)	51 (72.9)	No	PCR
Brito [3]	9 (60.0)	6 (40.0)	56 (24.3)	174 (75.7)	No	PCR-RFLP
Chamorro [4]	28 (58.7)	19 (41.3)	48 (37.5)	80 (62.5)	No	PCR-RFLP
Cho [5]	7 (38.9)	11 (61.1)	12 (10.5)	102 (89.5)	No	Sequencing
Forestiero [7]	28 (47.4)	31 (52.6)	13 (32.5)	27 (67.5)	Yes	PCR-RFLP
Gupta [8]	28 (56.0)	22 (44.0)	63 (38.2)	102 (61.8)	Yes	PCR-RFLP
Higuchi [29]	6 (33.3)	12 (66.7)	4 (4.9)	78 (95.1)	Yes	PCR-RFLP
Ho [30]	12 (63.2)	7 (36.8)	67 (20.4)	262 (79.6)	Yes	Sequenom MassARRAY

Huang [31]	14 (42.4)	19 (57.6)	39 (20.4)	152 (79.6)	No	PCR-RFLP
Huang [9]	19 (38.8)	30 (61.2)	58 (21.6)	211 (78.4)	Yes	PCR-RFLP
Khalili, [32]	9 (64.3)	5 (35.7)	5 (13.9)	31 (86.1)	Yes	PCR-RFLP
Lee [11]	21 (46.7)	24 (53.3)	20 (21.1)	75 (78.9)	No	Taqman
Leiro-Fernandez [33]	36 (72.0)	14 (28.0)	44 (65.7)	23 (34.3)	No	PCR-RFLP
Lv [34]	18 (20.2)	71 (79.8)	74 (20.8)	282 (79.2)	Yes	PCR-RFLP
Mishra [12]	23 (70.0)	10 (30.0)	73 (42.0)	100 (58.0)	Yes	PCR-RFLP
Ng [35]	22 (84.6)	4 (15.4)	57 (56.4)	44 (43.6)	Yes	PCR-RFLP
Ohno [36]	7 (50.0)	7 (50.0)	0 (0.0)	63 (100.0)	Yes	PCR-RFLP
Possuelo [37]	9 (64.3)	5 (35.7)	60 (25.0)	180 (75.0)	No	Sequencing
Rana [38]	19 (38.0)	31 (62.0)	30 (14.9)	171 (85.1)	No	PCR-RFLP
Rana [13]	21 (38.2)	34 (61.8)	36 (14.7)	209 (85.3)	Yes	PCR-RFLP
Santos [14]	11 (61.1)	7 (38.9)	75 (29.8)	177 (70.2)	Yes	Sequencing
Shimizu [39]	4 (40.0)	6 (60.0)	1 (3.1)	31 (96.9)	No	PCR-RFLP
Singla [17]	15 (88.2)	2 (11.8)	213 (54.5)	178 (45.5)	No	PCR-RFLP

Sotsuka [18]	8 (15.4)	44 (84.6)	5 (5.4)	87 (94.6)	No	PCR-RFLP
Teixeira [21]	18 (75.0)	6 (25.0)	64 (51.2)	61 (48.8)	Yes	Sequencing
Vuilleumier [22]	3 (37.5)	5 (62.5)	8 (12.7)	55 (87.3)	Yes	PCR- RFLP
Xiang [24]	28 (31.5)	61 (68.5)	501 (23.2)	1654 (76.8)	Yes	PCR/ligase detection reaction assays
Yamada [25]	14 (60.9)	9 (39.1)	64 (43.5)	83 (56.5)	Yes	Sequencing
Yimer [40]	31 (75.6)	10 (24.4)	107 (66.9)	53 (33.1)	Yes	Taqman
Yuliwulandari [41]	32 (64.0)	18 (36.0)	65 (34.0)	126 (66.0)	Yes	Sequencing
Zaverucha-do-Valle [26]	37 (71.2)	15 (28.8)	36 (45.6)	43 (54.4)	Yes	Sequencing

Abbreviations: ***HWE***, Hardy-Weinberg equilibrium; ***NA***, not available; ***PCR***, polymerase chain reaction; ***RFLP***, restriction fragment length polymorphism

S3 Table. Genotype distribution, the achievement of Hardy-Weinberg equilibrium (HWE), and the genotyping method used for *GST* in the included studies (n = 19)

Study	*GSTM1* genotype (n = 19)				*GSTT1* genotype (n = 17)				*GSTM1/GSTT1* genotype (n = 11)				HWE[a]	Genotyping method
	Case (number of individuals [%])		Control (number of individuals [%])		Case (number of individuals [%])		Control (number of individuals [%])		Case (number of individuals [%])		Control (number of individuals [%])			
	Null	Non-null	Null	Non-null	Null	Non-null	Null	Non-null	Dual-null	One-/non-null	Dual-null	One-/non-null		
Brito [3]	6 (40.0)	9 (60.0)	99 (43.0)	131 (57.0)	2 (13.3)	13 (86.7)	28 (12.2)	202 (87.8)	1 (6.7)	14 (93.3)	12 (5.2)	218 (94.8)	No	PCR
Chatterjee [42]	25 (49.0)	26 (51.0)	49 (49.0)	51 (51.0)	3 (5.9)	48 (94.1)	3 (3.0)	97 (97.0)	3 (5.9)	48 (94.1)	11 (11.0)	89 (89.0)	No	Multiplex PCR
Forestiero [7]	25 (42.4)	34 (57.6)	21 (52.5)	19 (47.5)	10 (17.0)	49 (83.0)	8 (20.0)	32 (80.0)	4 (6.8)	55 (93.2)	5 (12.5)	35 (87.5)	Yes	Multiplex PCR
Gupta [43]	21 (42.0)	29 (58.0)	61 (24.8)	185 (75.2)	11 (22.0)	39 (78.0)	30 (12.2)	216 (87.8)	5 (10.0)	45 (90.0)	4 (1.6)	242 (98.4)	No	Multiplex PCR
Huang [44]	42 (66.7)	21 (33.3)	29 (46.0)	34 (54.0)	24 (38.1)	39 (61.9)	25 (39.7)	38 (60.3)	NA	NA	NA	NA	Yes	Multiplex PCR
Kim [45]	26 (45.6)	31 (54.4)	104 (54.7)	86 (45.3)	34 (59.6)	23 (40.4)	103 (54.2)	87 (45.8)	17 (29.8)	40 (70.2)	56 (29.6)	133 (70.4)	No	PCR
Leiro [46]	12 (34.3)	23 (65.7)	25 (41.7)	35 (58.3)	17 (48.6)	18 (51.4)	16 (26.7)	44 (73.3)	7 (20.0)	28 (80.0)	6 (10.0)	54 (90.0)	No	PCR
Liu [47]	14 (70.0)	6 (30.0)	96 (67.1)	47 (32.9)	13 (65.0)	7 (35.0)	97 (67.8)	46 (32.2)	NA	NA	NA	NA	No	Multiplex PCR

Monteiro [48]	21 (35.6)	38 (64.4)	34 (28.8)	84 (71.2)	11 (18.7)	48 (81.3)	28 (23.8)	90 (76.2)	NA	NA	NA	NA	No	PCR
Rana [49]	10 (41.6)	20 (58.4)	37 (18.5)	183 (81.5)	6 (25.0)	24 (75.0)	68 (33.8)	152 (66.2)	9 (37.5)	21 (62.5)	96 (47.7)	124 (52.3)	No	PCR
Rana [13]	19 (34.5)	36 (65.5)	42 (17.1)	203 (82.9)	14 (25.5)	41 (74.5)	81 (33.1)	164 (66.9)	22 (40.0)	33 (60.0)	122 (49.8)	123 (50.2)	Yes	PCR
Roy [50]	17 (52.0)	15 (48.0)	8 (24.0)	25 (76.0)	5 (15.0)	28 (85.0)	1 (3.0)	32 (97.0)	NA	NA	NA	NA	No	PCR
Sharma [15]	42 (40.0)	63 (60.0)	68 (36.7)	117 (63.3)	NA	NA	NA	NA	NA	NA	NA	NA	No	PCR
Singla [17]	10 (59.0)	7 (41.0)	165 (42.0)	226 (58.0)	8 (47.0)	9 (53.0)	102 (26.0)	289 (74.0)	5 (29.0)	12 (71.0)	32 (8.0)	359 (92.0)	No	Multiplex PCR
Sotsuka [18]	12 (60.0)	8 (40.0)	50 (54.3)	42 (45.7)	7 (35.0)	13 (65.0)	40 (43.5)	52 (56.5)	NA	NA	NA	NA	No	PCR
Tang [19]	55 (61.8)	34 (38.2)	203 (57.0)	153 (43.0)	40 (44.9)	49 (55.1)	164 (46.1)	192 (53.9)	22 (24.7)	67 (75.3)	94 (26.4)	262 (73.6)	Yes	Multiplex PCR
Teixeira [21]	11 (42.3)	15 (41.7)	61 (43.3)	80 (56.7)	4 (15.4)	22 (84.6)	27 (19.2)	114 (80.8)	NA	NA	NA	NA	Yes	Multiplex PCR
Wang [23]	63 (60.6)	41 (39.4)	54 (48.6)	57 (51.4)	NA	NA	NA	NA	NA	NA	NA	NA	No	PCR
Xiang [24]	41 (46.1)	48 (53.9)	925 (42.9)	1230 (57.1)	18 (20.2)	71 (79.8)	477 (22.1)	1678 (77.9)	7 (9.3)	68 (90.7)	283 (16.5)	1427 (83.5)	Yes	PCR

Abbreviations: ***HWE***, Hardy-Weinberg equilibrium; ***NA***, not available; ***PCR***, polymerase chain reaction

[a] HWE tested for *GSTM1*, *GSTT1*, and *GSTM1*/*GSTT1* genotypes simultaneously

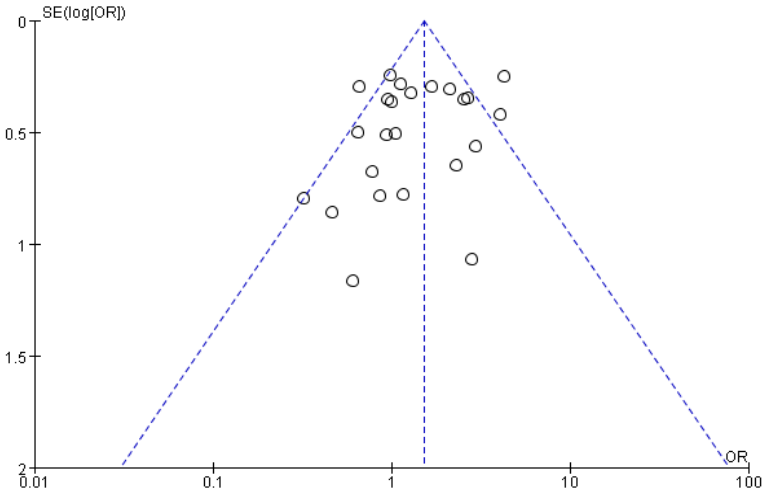
S4 Table. Genotype distribution, the achievement of Hardy-Weinberg equilibrium (HWE), and the genotyping method used for *SLCO1B1* in the included studies (n = 4)

Study	*SLCO1B1* 388A>G (rs2306283)				*SLCO1B1* 521T>C (rs4149056)				HWE[a]	Genotyping method
	Case (number of individuals [%])		Control (number of individuals [%])		Case (number of individuals [%])		Control (number of individuals [%])			
	AA	AG + GG	AA	AG + GG	CC	TC + TT	CC	TC + TT		
Chen [51]	8 (9.0)	81 (91.0)	33 (55.4)	409 (44.6)	2 (2.2)	87 (97.8)	3 (0.7)	438 (99.3)	Yes	Taqman
Kim [52]	6 (9.2)	59 (90.8)	11 (54.5)	145 (45.5)	0 (0.0)	66 (100.0)	3 (1.9)	153 (98.1)	Yes	SNPstream
Li [53]	11 (9.3)	107 (90.7)	12 (61.3)	143 (38.7)	1 (0.8)	117 (99.2)	1 (0.6)	154 (99.4)	Yes	PCR direct sequencing
Yimer [40]	9 (22.0)	32 (78.0)	20 (33.1)	140 (66.9)	1 (2.4)	40 (97.6)	4 (2.5)	156 (97.5)	Yes	Taqman

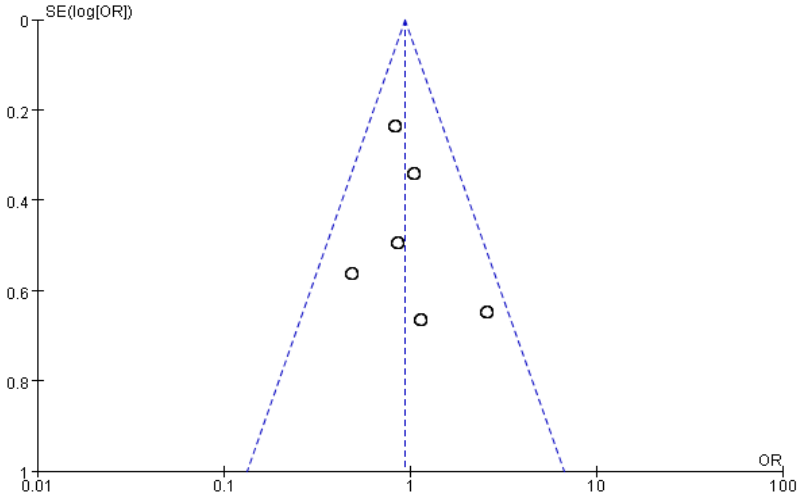
Abbreviations: ***HWE***, Hardy-Weinberg equilibrium; ***PCR***, polymerase chain reaction; ***SNP***, single nucleotide polymorphism

[a] HWE tested for *SLCO1B1* 388A>G and *SLCO1B1* 521T>C genotypes simultaneously

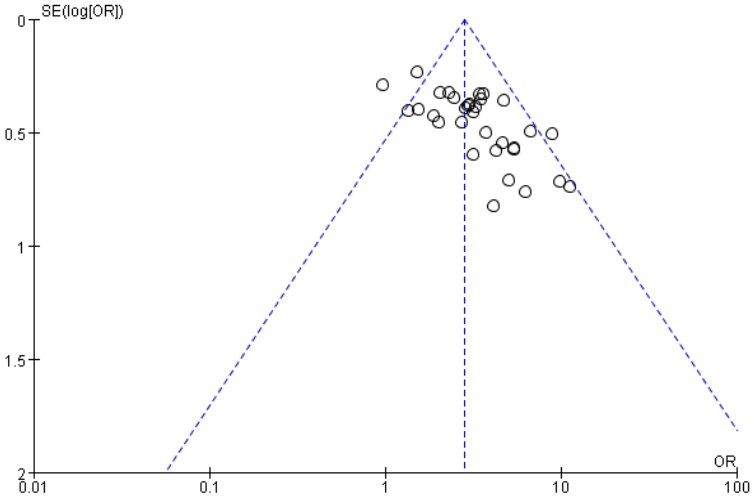
(A) *CYP2E1 RsaI/PstI* polymorphism



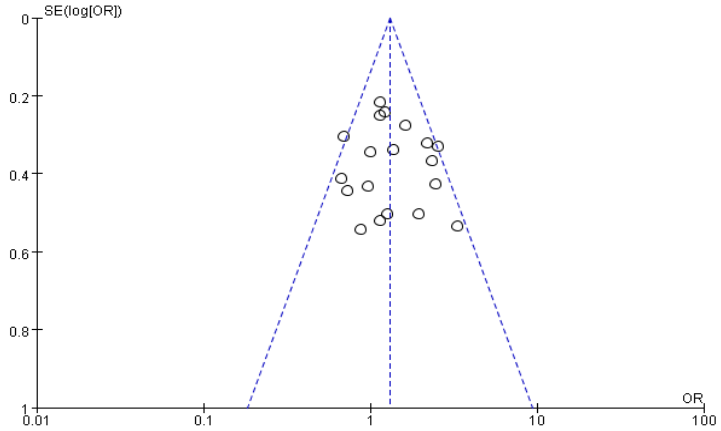
(B) *CYP2E1 DraI* polymorphism



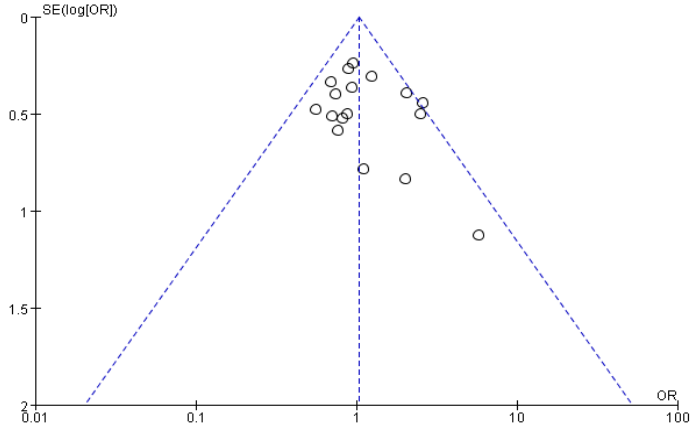
(C) *NAT2* polymorphism



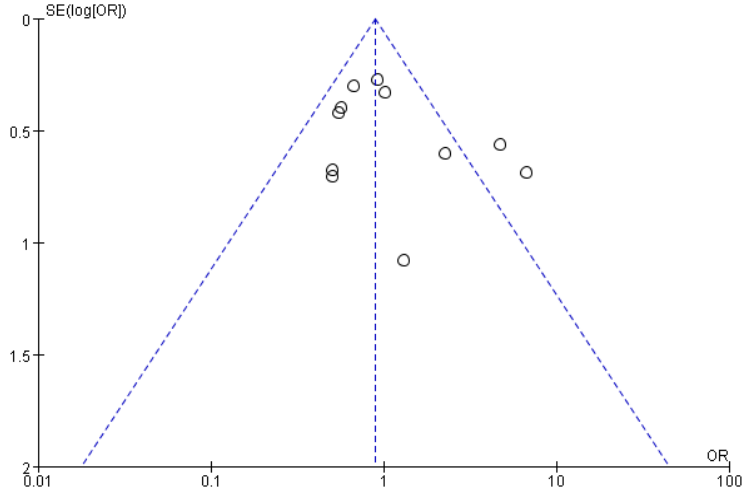
(D) *GSTM1* polymorphism



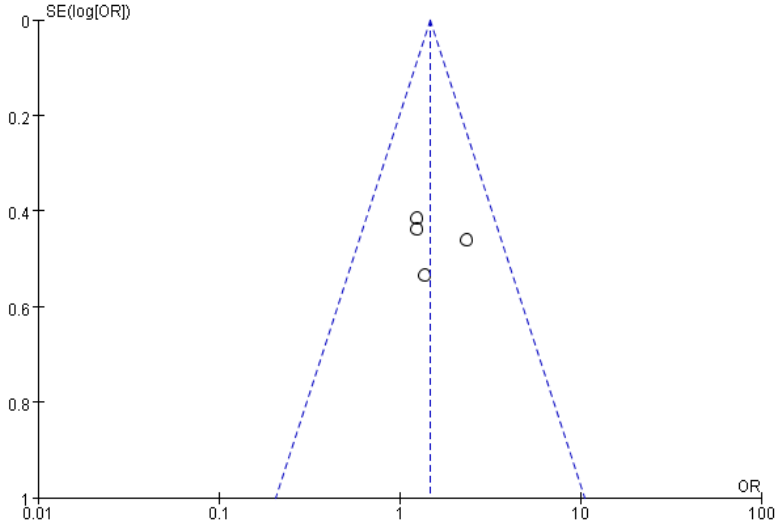
(E) *GSTT1* polymorphism



(F) *GSTT1/M1* polymorphism



(G) *SLCO1B1 388A>G* and *521T>C* polymorphism



S5 Figure. Funnel plots to evaluate publication bias for the *CYP2E1, NAT2, GST,* and *SLCO1B1* polymorphisms associated with the ATDILI risk. (A) C*YP2E1 Rsa*I/*Pst*I polymorphism, (B) *CYP2E1 Dra*I polymorphism, (C) *NAT2* polymorphism, (D) *GSTM1* polymorphism, (E) *GSTT1* polymorphism, (F) *GSTT1/M1* polymorphism, and (G) *SLCO1B1 388A>G* and *521T>C* polymorphism.

S6 Table. Subgroup analysis for the association between *CYP2E1* polymorphisms and ATDILI risk

Polymorphic gene	Subgroup		Number of studies	Case/ control (n)	Test of association		Model of meta-analysis	Test of heterogeneity	
					OR [95% CI]	P value[a]		I^2 ,%	P value[b]
*CYP2E1 Rsa*I/*Pst*I (c1/c1 vs. c1/c2 + c2/c2)	Total		24	1293/5450	1.39 [1.06, 1.83]	0.02	Random	60	<0.0001
	Ethnicity	East Asian	10	736/3076	1.62 [1.12, 2.36]	0.01	Random	69	0.0006
		Indian	6	310/1295	1.08 [0.52, 2.25]	0.85	Random	70	0.005
		South American	6	216/869	1.30 [0.83, 2.03]	0.25	Fixed	0	0.49
		Others	2	31/210	0.98 [0.39, 2.45]	0.96	Fixed	0	0.66
	Anti-TB drug regimen	INH alone	2	31/210	0.98 [0.39, 2.45]	0.96	Fixed	0	0.66
		Combination	21	1212/5104	1.35 [1.01, 1.79]	<0.00001	Random	61	0.0002
	HWE test	HWE achieved	13	839/3570	1.67 [1.19, 2.34]	0.002	Random	58	0.004
	Diagnostic criteria of ATDILI	ALT > 2 × ULN	15	981/4701	1.54 [1.08, 2.18]	0.02	Random	70	<0.0001
		ALT > 3-5 × ULN	9	331/1034	1.11 [0.80, 1.54]	0.52	Fixed	0	0.52
	Genotyping method	PCR-RELP	17	782/4194	1.24 [0.91, 1.70]	0.18	Random	46	0.02
		Sequencing	3	292/394	2.03 [0.87, 4.71]	0.10	Random	80	0.007
		Taqman	3	152/703	1.09 [0.74, 1.58]	0.67	Fixed	0	0.47
*CYP2E1 Dra*I[c] (D/D vs. D/C + C/C)	Total		6	233/1272	0.93 [0.68, 1.27]	0.64	Fixed	0	0.51
	Ethnicity	East Asian	2	109/448	0.84 [0.55, 1.28]	0.41	Fixed	0	0.96
		Indian	2	91/342	0.83 [0.48, 1.45]	0.51	Fixed	27	0.24
		South American	2	33/482	1.80 [0.73, 4.45]	0.20	Fixed	0	0.37

HWE test	HWE achieved	5	116/701	1.00 [0.72, 1.38]	0.98	Fixed	0	0.57
Diagnostic criteria of ATDILI	ALT > 2 × ULN	3	108/698	0.83 [0.58, 1.19]	0.32	Fixed	0	0.51
	ALT > 3-5 × ULN	3	53/574	1.31 [0.69, 2.48]	0.41	Fixed	0	0.39
Genotyping method	PCR-RELP	5	215/1020	0.85 [0.62, 1.18]	0.33	Fixed	0	0.82
	Taqman	1	18/252	2.59 [0.73, 9.19]	0.14	NA	NA	NA

Abbreviations: ***ALT***, alanine aminotransferase; ***ATDILI***, anti-tuberculosis drug-induced liver injury; ***CI***, confidence interval; ***CYP2E1***, cytochrome P450 2E1; ***HWE***, Hardy-Weinberg equilibrium; ***INH***, isoniazid; ***NA***, not applicable; ***OR***, odds ratio; ***PCR-RFLP***, polymerase chain reaction-restriction fragment length polymorphism; ***TB***, tuberculosis; ***ULN***, upper limit of normal

[a] P value from Z test

[b] P value from Cochran's Q test based on chi-square statistic

[c] Subgroup analysis based on anti-TB drug regimen could not be performed due to insufficient information provided.

S7 Table. Subgroup analysis for the association between *NAT2* polymorphism and ATDILI risk

Abbreviations: ***ALT***, alanine aminotransferase; ***ATDILI***, anti-tuberculosis drug-induced liver injury; ***CI***, confidence interval; ***HWE***, Hardy-Weinberg equilibrium; ***INH***, isoniazid; ***NAT2***, N-acetyltransferase 2; ***OR***, odds ratio; ***PCR-RFLP***, polymerase chain reaction-restriction fragment length polymorphism; ***TB***, tuberculosis; ***ULN***, upper limit of normal

Polymorphic gene	Subgroup		Number of studies	Case/ control (n)	Test of association		Model of meta-analysis	Test of heterogeneity	
					OR [95% CI]	P value[a]		I^2,%	P value[b]
NAT2 (Slow acetylator vs. fast and intermediate acetylator)	Total		34	1270/7234	3.11 [2.53, 3.82]	<0.00001	Random	47	0.002
	Ethnicity	East Asian	12	537/3885	3.48 [2.16, 5.60]	<0.00001	Random	71	<0.0001
		Indian	6	246/1352	3.07 [2.26, 4.16]	<0.00001	Fixed	0	0.74
		West Asian	2	44/106	9.51 [4.19, 21.61]	<0.00001	Fixed	0	0.79
		South American	7	231/1110	2.94 [2.11, 4.08]	<0.00001	Fixed	0	0.75
		African	2	55/212	2.08 [1.06, 4.10]	0.03	Fixed	52	0.15
		Others	5	157/569	2.56 [1.72, 3.79]	<0.00001	Fixed	15	0.32
	Anti-TB drug regimen	INH alone	2	31/210	2.32 [1.05, 5.13]	0.04	Fixed	0	0.45
		Combination	31	591/1894	3.16 [2.52, 3.95]	<0.00001	Random	51	0.0007
	HWE test	HWE achieved	21	848/5206	2.92 [2.21, 3.85]	<0.00001	Random	55	0.001
	Diagnostic criteria of ATDILI	ALT > 2 × ULN	20	859/5272	2.90 [2.21, 3.81]	<0.00001	Random	55	0.002
		ALT > 3-5 × ULN	14	411/1692	3.30 [2.56, 4.27]	<0.00001	Fixed	26	0.18
	Genotyping method	PCR-RELP	23	792/3476	3.23 [2.44, 4.26]	<0.00001	Random	50	0.003
		Sequencing	7	284/1019	3.45 [2.52, 4.71]	<0.00001	Fixed	0	0.70
		Others	4	194/2739	2.47 [1.31, 4.67]	0.005	Random	68	0.02

[a] P value from Z test

[b] P value from Cochran's Q test based on chi-square statistic

S8 Table. Subgroup analysis for the association between *GST* polymorphisms and ATDILI risk

Polymorphic gene	Subgroup		Number of studies	Case/ control (n)	Test of association		Model of meta-analysis	Test of heterogeneity	
					OR [95% CI]	P value[a]		I^2,%	P value[b]
GSTM1[c] (null vs. non-null)	Total		19	977/5119	1.30 [1.12, 1.52]	0.0007	Fixed	33	0.08
	Ethnicity	East Asian	7	442/3110	1.23 [0.99, 1.54]	0.06	Fixed	23	0.25
		Indian	7	341/1420	1.68 [1.30, 2.19]	<0.0001	Fixed	36	0.15
		Brazilian	4	159/529	0.98 [0.66, 1.47]	0.94	Fixed	0	0.60
	HWE test	HWE achieved	6	381/3000	1.34 [0.93, 1.93]	0.12	Random	52	0.07
	Diagnostic criteria of ATDILI	ALT > 2 × ULN	10	546/4018	1.56 [1.28, 1.91]	<0.0001	Fixed	13	0.32
		ALT > 3-5 × ULN	9	431/1101	1.01 [0.80, 1.29]	0.91	Fixed	10	0.35
GSTT1[c] (null vs. non-null)	Total		17	768/4823	1.03 [0.85, 1.25]	0.76	Fixed	16	0.26
	Ethnicity	East Asian	6	338/2999	0.96 [0.74, 1.24]	0.75	Fixed	0	0.94
		Indian	6	236/1235	1.37 [0.72, 2.59]	0.33	Random	57	0.04
		Brazilian	4	159/529	0.80 [0.47, 1.33]	0.39	Fixed	0	0.97
	HWE test	HWE achieved	6	381/3000	0.87 [0.66, 1.13]	0.29	Fixed	0	0.98
	Diagnostic criteria of ATDILI	ALT > 2 × ULN	9	442/3907	0.97 [0.77, 1.24]	0.83	Fixed	37	0.13
		ALT > 3-5 × ULN	8	101/250	1.14 [0.83, 1.57]	0.42	Fixed	0	0.54
GSTM1/GSTT1[c] (dual-null vs. one-/non-null)	Total		11	547/4233	1.05 [0.67, 1.62]	0.84	Random	59	0.006
	Ethnicity	East Asian	3	235/2701	0.83 [0.58, 1.20]	0.33	Fixed	0	0.49
		Indian	5	203/1202	1.33 [0.50, 3.53]	0.56	Random	80	0.0005
		Brazilian	2	74/270	0.67 [0.20, 2.18]	0.50	Fixed	0	0.47
	HWE test	HWE achieved	4	55/504	0.72 [0.51, 1.01]	0.06	Fixed	0	0.70
	Diagnostic criteria of	ALT > 2 × ULN	6	330/3613	1.16 [0.60, 2.24]	0.67	Random	76	0.0009

	ATDILI	ALT > 3-5 × ULN	5	217/620	0.97 [0.61, 1.55]	0.90	Fixed	0	0.43

Abbreviations: ***ALT***, alanine aminotransferase; ***ATDILI***, anti-tuberculosis drug-induced liver injury; ***CI***, confidence interval; ***GSTM1***, glutathione S-transferase Mu 1; ***GSTT1***, glutathione S-transferase Theta 1; ***HWE***, Hardy-Weinberg equilibrium; ***OR***, odds ratio; ***PCR-RFLP***, polymerase chain reaction-restriction fragment length polymorphism; ***ULN***, upper limit of normal

[a] P value from Z test

[b] P value from Cochran's Q test based on chi-square statistic

[c] Subgroup analyses based on anti-tuberculosis drug regimen and genotyping method could not be performed due to insufficient information available

S9 Table. Subgroup analysis for the association between *SLCO1B1* polymorphisms and ATDILI risk

Polymorphic gene	Subgroup		Number of studies	Case/ Control (n)	Test of association		Model of meta-analysis	Test of heterogeneity	
					OR [95% CI]	P value[a]		I^2,%	P value[b]
SLCO1B1 388A>G[c] *(rs2306283)* (AA vs. AG + GG)	Total		4	279/837	1.47 [0.94, 2.29]	0.09	Fixed	0	0.72
	Ethnicity	East Asian	3	274/670	1.28 [0.77, 2.14]	0.35	Fixed	0	0.99
	Anti-TB drug regimen	Combination	3	195/758	1.57 [0.93, 2.63]	0.09	Fixed	0	0.57
	Diagnostic criteria of ATDILI	ALT > 2 × ULN	3	195/758	1.57 [0.93, 2.63]	0.09	Fixed	0	0.57
	Genotyping method	Taqman	2	130/602	1.64 [0.90, 2.97]	0.11	Fixed	4	0.31
		Others	2	183/311	1.30 [0.67, 2.53]	0.44	Fixed	0	0.89
SLCO1B1 521T>C[c] *(rs4149056)* (CC vs. TC + TT)	Total		4	310/901	1.21 [0.40, 3.63]	0.74	Fixed	0	0.56
	Ethnicity	East Asian	3	273/752	1.30 [0.36, 4.66]	0.68	Fixed	0	0.38
	Anti-TB drug regimen	Combination	3	196/757	1.19 [0.36, 3.95]	0.78	Fixed	4	0.35
	Diagnostic criteria of ATDILI	ALT > 2 × ULN	3	196/757	1.19 [0.36, 3.95]	0.78	Fixed	4	0.35
	Genotyping method	Taqman	2	130/601	1.90 [0.49, 7.40]	0.36	Fixed	0	0.39
		Others	2	184/311	0.61 [0.09, 4.11]	0.61	Fixed	0	0.49

Abbreviations: ***ALT***, alanine aminotransferase; ***ATDILI***, anti-tuberculosis drug-induced liver injury; ***CI***, confidence interval; ***OR***, odds ratio; ***SLCO1B1***, solute carrier organic anion transporter family, member 1B1 (encoding organic anion transporting polypeptide 1B1 [OATP1B1]); ***TB***, tuberculosis; ***ULN***, upper limit of normal

[a] P value from Z test

[b] P value from Cochran's Q test based on chi-square statistic

[c] Subgroup analysis based on the achievement of Hardy-Weinberg equilibrium could not be performed due to insufficient information provided

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 8-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 8-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary Figure S5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Supplementary Table S6-S9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 13-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 19

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Association of genetic polymorphisms of CYP2E1, NAT2, GST, and SLCO1B1 with the risk of anti-tuberculosis drug-induced liver injury: a systematic review and meta-analysis

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Original article

Association of genetic polymorphisms of *CYP2E1, NAT2, GST,* and *SLCO1B1* with the risk of anti-tuberculosis drug-induced liver injury: a systematic review and meta-analysis

Seungwon Yang[1], Se Jung Hwang[2], Jung Yun Park[3], Eun Kyoung Chung[2,4*], Jangik Ike Lee[3,,5*]

[1] Department of Pharmacy and Yonsei Institute of Pharmaceutical Science, College of Pharmacy, Yonsei University, Incheon 21983, Republic of Korea

[2] Department of Pharmacy, College of Pharmacy, Kyung Hee University, Seoul 02447, Republic of Korea

[3] College of Pharmacy, Seoul National University, Seoul 08826, Republic of Korea

[4] Department of Pharmacy, Kyung Hee University Hospital at Gangdong, Seoul, 05278, Republic of Korea

[5] College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 08826, Republic of Korea

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*Corresponding authors

Prof., Eun Kyoung Chung, PharmD, Ph.D.

Department of Pharmacy, College of Pharmacy, Kyung Hee University

26 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447

South Korea

Tel: +82-2-962-2122

Fax: +82-2-961-9580

E-mail: cekchung@khu.ac.kr

Prof. Jangik I. Lee, PharmD, Ph.D.

Department of Pharmacy, College of Pharmacy, Seoul National University

103 Daehak-Ro, Jongno-Gu, Seoul 03080

South Korea

Tel: +82-2-3668-7474

Fax: +82-2-3668-7475

E-mail: jangik.lee@snu.ac.kr

*Jangik I. Lee and Eun Kyung Chung have equally contributed to this study.

Running head

Genetics of anti-tuberculosis liver injury

ABSTRACT

Objectives The objective of this study was to investigate the association between genetic polymorphisms of *NAT2*, *CYP2E1*, *GST*, and *SLCO1B1* and the risk of anti-tuberculosis drug-induced liver injury (ATDILI).

Design Systematic review and meta-analysis

Data Sources PubMed, EMBASE, Web of Science, and Cochrane Reviews databases were searched through February 2018.

Eligibility Criteria We included case-control or cohort studies investigating an association between *NAT2, CYP2E1, GST*, or *SLCO1B1* polymorphisms and the ATDILI risk in tuberculosis patients.

Data extraction and synthesis Three authors screened articles, extracted data, and assessed study quality. The strength of association was evaluated for each gene using the pooled odds ratio (OR) with a 95% confidence interval (CI) based on the fixed- or random-effects model. Sensitivity analysis was performed to confirm the reliability and robustness of the results.

Results Fifty-four studies were included in this analysis (n = 26 for *CYP2E1*, n = 35 for *NAT2*, n = 19 for *GST*, n = 4 for *SLCO1B1*). The risk of ATDILI was significantly increased with the following genotypes: *CYP2E1 Rsa*I/*Pst*I c1/c1 (OR = 1.39; 95% CI 1.06–1.83), *NAT2* slow acetylator (OR = 3.30, 95% CI 2.65–4.11), and *GSTM1* null (OR = 1.30, 95% CI 1.12–1.52). No significant association with ATDILI was found for the genetic polymorphisms of *CYP2E1 Dra*I, *GSTT1*, *GSTM1/GSTT1*, *SLCO1B1* 388A>G, and *SLCO1B1* 521T>C (P > 0.05).

Conclusions

ATDILI is more likely to occur in tuberculosis patients with *NAT2* slow acetylator genotype,

*CYP2E1 Rsa*I/*Pst*I c1/c1 genotype, and *GSTM1* null genotype. Close monitoring may be warranted for patients with these genotypes.

Strengths and limitations of this study

- This is the first meta-analysis to evaluate the association between the risk of ATDILI and *SLCO1B1* in TB patients.
- We included most updated studies with the large sample sizes to better clarify the association of genetic polymorphisms with the risk of ATDILI.
- The effect of anti-tuberculosis drug dosages on the risk of ATDILI could not be accounted for in this study due to the lack of drug dosing information in the majority of the included studies.

Introduction

Tuberculosis (TB) is a rampant infectious disease caused by *Mycobacterium tuberculosis.* It poses a major public health threat globally with approximately 1.3 million deaths and 10 million new cases in 2017 [1]. The mainstay of first-line TB treatment is a 4-drug combination regimen of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) during the first 2 months, followed by INH and RIF for additional 4 months [2 3]. The currently recommended therapy for TB is highly effective, resulting in high cure rates if patients are adherent to therapy [4]. However, treatment adherence is often suboptimal in patients receiving the combination anti-TB therapy due to many adverse drug reactions, some of which are considered detrimental [5]. One of the common adverse drug reactions associated with anti-TB medications is anti-TB drug-induced liver injury (ATDILI) affecting 2–28% of tuberculosis patients[6]. ATDILI could be potentially serious and fatal, resulting in the treatment interruption and ultimately, treatment failure [7 8].

Recently, increasing evidence suggests an association between the risk of ATDILI and genetic polymorphisms of drug-metabolizing enzymes (DMEs) and drug transporters [9 10]. Altered enzyme activity due to polymorphic genotypes of various DMEs including cytochrome P450 2E1 (CYP2E1), N-acetyltransferase 2 (NAT2), and glutathione S-transferase (GST) can result in the accumulation of toxic substances in the liver, leading to the development of ATDILI [11]. However, conflicting results have been reported regarding the association between the risk of ATDILI and genetic polymorphisms of various DMEs in tuberculosis patients [9 12 13]. In addition to DMEs, drug transporters have been emerging as a key determinant of the pharmacokinetics and pharmacodynamics of a drug [14]. Among various drug transporters, organic anion

transporting polypeptide 1B1 (OATP1B1), encoded by *SLCO1B1*, is the major influx transporter responsible for hepatic uptake of RIF [15]. Although several studies have previously examined the association between *SLCO1B1* polymorphisms and the risk of ATDILI, conflicting results have been reported regarding the effect of *SLCO1B1* polymorphisms on ATDILI risk. Therefore, an updated meta-analysis has been warranted to confirm the association between the ATDILI risk and genetic polymorphisms of DMEs. In our preliminary literature search, several polymorphic genes, including many DMEs, transporters, and other genes such as those involved in the immune system, were identified to have an association with the risk of ATDILI. Among these, sufficient, published information was available to confirm the effect of *CYP2E1*, *NAT2*, *GST*, and *SLCO1B1* genetic polymorphisms on the ATDILI risk through meta-analysis.

Objectives

The objective of this meta-analysis was to evaluate the association between the risk of ATDILI and genetic polymorphisms of *CYP2E1*, *NAT2*, *GST*, and *SLCO1B1* in tuberculosis patients.

Methods

This study was in compliance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist for reporting the study design, search strategy, methods, results, and conclusions (S1 Table). Three authors (SY, JP, and SH) independently conducted a literature search, study selection, quality assessment, and data extraction. Any discrepancies were adjudicated by corresponding authors (JIL and EKC).

Search strategy

Electronic databases of PubMed, EMBASE, Web of Science, and Cochrane Reviews were systematically searched from their inception to February 2018 to identify relevant studies evaluating the association of *NAT2*, *CYP2E1*, *GST*, and *SLCO1B1* polymorphisms with ATDILI risk. A comprehensive literature search was conducted using a combination of the following keywords and Medical Subject Heading (MeSH) terms: ("genetic polymorphism" or "*NAT2*" or "*CYP2E1*" or "*GST*" or "*SLCO1B1*" or "drug-metabolizing enzymes" or "drug transporter") AND ("anti-tuberculosis agents drug-induced liver injuries" or "hepatotoxicity"). The detailed search strategies for each electronic database used in this analysis are presented in S2 Table. The reference lists in the selected reviews and meta-analyses were reviewed to ensure the inclusion of all relevant evidence in this analysis.

Study selection

Studies were considered eligible if they met all of the following inclusion criteria: (1) studies with TB patients receiving anti-TB drug regimen; (2) studies with the control group of TB patients tolerant of anti-TB medications; (3) studies evaluating the association between the occurrence of ATDILI and genetic polymorphisms of *CYP2E1*, *NAT2*, *GST,* and *SLCO1B1* 388A>G and 521T>C; and (4) case-control or cohort observational studies.Excluded studies were as follows: (1) studies available only in the form of abstracts or meeting posters; (2) review or meta-analysis articles; (3) studies providing insufficient data necessary for the statistical data analysis; (4) studies in non-English language; (5) non-human studies including animal and *in vitro* studies; (6) studies with unpublished data; (7) studies providing insufficient information on genotyping methods; and (8) healthy controls.

Quality assessment and data extraction

The quality of included studies was assessed using the revised Little's recommendation based on the following criteria [16 17]: (1) scientific design; (2) definite inclusion of study population; (3) explicit information on study population; (4) explicit diagnostic criteria of ATDILI; (5) genetic detection method; (6) appropriate statistical analysis; and (7) logical discussion of study bias. Studies with an overall score of ≥ 4 (range 0 to 7) were considered high quality and retained in the analysis.

The following data were extracted from each study using a standardized extraction form: (1) name of the first author; (2) year of publication; (3) the polymorphic gene(s) and genotype(s) under investigation; (4) ethnicity; (5) sample size; (6) mean or median age; (7) sex distribution; (8) anti-TB drug regimens; (9) diagnostic criteria of ATDILI; (10) genotyping methods; and (11) the number of cases and controls for each polymorphic genotype.

Statistical analysis

The genotypes were analyzed based on the following proposed genetic risk model: (1) *NAT2* (slow acetylator *vs.* intermediate and fast acetylator); (2) *CYP2E1* (c1/c1 *vs.* c1/c2 and c2/c2 for the *Rsa*I/*Pst*I polymorphism, D/D *vs.* D/C and C/C for the *Dra*I polymorphism); (3) *GSTM1* (null *vs.* non-null); (4) *GSTT1* (null *vs.* non-null); (5) *GSTM1*/*GSTT1* (dual-null *vs.* one- or non-null); and (6) *SLCO1B1* 388A>G and 521T>C polymorphisms. The genetic risk models for *NAT2*, *CYP2E1*, *GSTM1*, *GSTT1*, and *GSTM1/GSTT1* have been studied in previous studies[9 18 19]. Based on these previous studies, the most clinically significant and plausible model for each polymorphic gene was selected. Due to the relative paucity of data suggesting the most clinically relevant genetic model for *SLCO1B1* 388A>G and 521T>C polymorphisms, all three genomic

models including dominant, recessive, and additive models were evaluated. The Mantel-Haenszel or DerSimonian-Laird method based on fixed- or random-effects models, respectively, were used depending on the presence of heterogeneity [20 21]. The random-effects model was used in the presence of significant heterogeneity; otherwise, the fixed-effects model was used to estimate the total effect of a polymorphic gene genotype on the risk of ATDILI. Heterogeneity of study outcomes among included studies was evaluated using Cochran's Q test *(Q)* and quantified using Higgin's I^2 test. Significant heterogeneity was defined as the I^2 score of > 40% accompanied by $P < 0.10$ from the Cochran's Q test [22]. The strength of the association between the genetic polymorphisms and the risk of ATDILI was estimated using pooled odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). The statistical significance of an OR was defined as $P < 0.05$ from the Z test.

Subgroup analysis was performed based on ethnicity, anti-TB drug regimen used, and the type of study design. Sensitivity analysis was conducted to assess the robustness of the results and to identify the source of heterogeneity using the leave-one-out method. In each analysis, one study was deleted, and with the one study left out, the meta-analysis was performed; this process was repeated until every study had been deleted from our included study pool for each tested polymorphic gene. Publication bias was evaluated with a symmetrical funnel plot. Statistical analyses were performed using Review Manager Software version 5.3 (Cochrane Collaboration, London, UK).

Patient and public involvement

Patients and public were not involved in the design of this study.

Results

Study selection and characteristics

Overall, 388 articles were identified through electronic database search and 3 articles through manual search by reviewing the reference lists of retrieved articles. After removing 99 duplicates, 289 articles were screened for relevance based on the title and abstract. Among them, 72 relevant articles were assessed for eligibility through full-text evaluations. Finally, a total of 54 articles which met the inclusion criteria were included in our analysis (Figure 1). Among the 54 studies, 26 studies were included for *CYP2E1*, 35 studies for *NAT2*, 19 studies for *GST* (19 for *GSTM1*, 17 for *GSTT1*, and 11 for *GSTM1*/*GSTT1*), and 4 studies for *SLCO1B1* 388A>G and 521T>C.

Table 1 summarizes the characteristics of the included studies. Across the included studies, large variability in study population was observed in terms of ethnicity (Chinese, Japanese, Korean, Indian, Taiwanese, Brazilian, Caucasian, Iranian, Tunisian, and Turkish), age (mean or median age ranging from 27 to 70 years), and sex (the proportion of males ranging from 13% to 90%). Patients in our included studies received either monotherapy with INH or RIF or a combination therapy including a 4-drug regimen of INH, RIF, PZA, and EMB for the treatment of TB. ATDILI was defined as an elevated serum alanine aminotransferase (ALT) concentration by 1.5- to 5-fold or greater above the upper limit of normal (ULN) depending on the study. The quality score of the included studies was 6 or greater based on the revised Little's recommendation (Table 1, S3 Table)[16 17]. Genotype distribution and genotyping method used in the included studies are summarized for each polymorphic gene in S4 to S7 Tables. Funnel plots

for *CYP2E1, NAT2, GST*, and *SLCO1B1* are provided in S8 Figure. None of the funnel plots showed an asymmetric inverted funnel shape, indicating the absence of potential publication bias.

CYP2E1

For the *CYP2E1 Rsa*I/*Pst*I polymorphism, 24 studies with 1293 cases and 5450 controls were included in our primary analysis. Using the random-effects model, the pooled estimates of all included studies (n = 24) showed a significant association between the risk of ATDILI and the *CYP2E1 Rsa*I/*Pst*I polymorphism (OR for the c1/c1 genotype = 1.39, 95% CI 1.06–1.83, P = 0.02; I^2 = 60%, $P_{heterogeneity}$ < 0.0001) (Figure 2A). In the subgroup analysis based on ethnicity, and anti-TB drug regimens, the risk of ATDILI was significantly increased for the *CYP2E1 Rsa*I/*Pst*I *c1/c1* genotype in East Asian patients (OR = 1.62, 95% CI 1.26–2.36, P = 0.01; I^2 = 69%, $P_{heterogeneity}$ = 0.0006) and in patients receiving a combination of anti-TB medications (OR = 1.35, 95% CI 1.01–1.79, P < 0.00001; I^2 = 61%, $P_{heterogeneity}$ = 0.0002) (S9 Table). No significant association was observed between the risk of ATDILI and the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype when evaluating studies with the same study design only (i.e., either case-control studies or cohort studies) (S9 Table).

In our primary analysis for the *CYP2E1 Dra*I polymorphism with six studies including 233 cases and 1272 controls, no significant association was observed using the fixed-effects model between the risk of ATDILI and the *Dra*I polymorphism (OR for the D/D genotype = 0.93, 95% CI 0.68–1.27, P = 0.64; I^2 = 0%, $P_{heterogeneity}$ = 0.51) (Figure 2B).

NAT2

Overall, 35 studies with 1323 cases and 7319 controls were included in our primary analysis for

the *NAT2* polymorphism. Using the random-effects model, the pooled estimates of all included studies (n = 35) showed a significant association between the risk of ATDILI and the *NAT2* polymorphism (OR for the slow acetylator genotype = 3.30, 95% CI 2.65–4.11, P < 0.00001; I^2 = 54%, $P_{heterogeneity}$ < 0.0001) (Figure 3). In the subgroup analysis based on ethnicity, anti-TB drug regimens used, and study design, the risk of ATDILI was significantly increased in slow acetylators compared to fast or intermediate acetylators in all subgroups (S10 Table).

GST

For the *GSTM1* polymorphism, a total of 19 studies with 977 cases and 5119 controls were included in our primary analysis. Using the fixed-effects model, the pooled estimates of all included studies (n = 19) showed a significant association between the risk of ATDILI and the *GSTM1* polymorphism (OR for the *GSTM1* null genotype = 1.30, 95% CI 1.12–1.52, P = 0.0007; I^2 = 33%, $P_{heterogeneity}$ = 0.08) (Figure 4A). When studies were stratified for ethnicity, the risk of ATDILI was significantly increased for the *GSTM1* null genotype in Indians (OR = 1.68, 95% CI 1.30–2.19, P < 0.0001; I^2 = 36%, $P_{heterogeneity}$ = 0.15) (S11 Table). In the subgroup analyses by study design, the estimated OR (95% CI, P-value; I^2, $P_{heterogeneity}$) for the *GSTM1* null genotype relative to the non-null genotype was 1.41 (1.04-1.93, P = 0.03; I^2 = 44%, $P_{heterogeneity}$ = 0.08) in cohort studies and 1.25 (1.01-1.55, P = 0.20; I^2 = 29%, $P_{heterogeneity}$ = 0.17) in case-control studies, respectively (S11 Table).

For the *GSTT1* and *GSTM1*/*GSTT1* polymorphisms, 17 studies (768 cases, 4823 controls) and 11 studies (547 cases, 4233 controls) were included in our primary analyses, respectively. The risk of ATDILI was not significantly associated with the *GSTT1* polymorphism (OR for the null genotype = 1.03, 95% CI 0.85–1.25, P = 0.76; I^2 = 16%, $P_{heterogeneity}$ = 0.26) or the

GSTM1/*GSTT1* polymorphism (OR for the dual-null genotype = 1.05, 95% CI 0.67–1.62, P = 0.84; I^2 = 59%, $P_{heterogeneity}$ = 0.006) (Figures 4B and 4C). When studies were stratified for ethnicity, anti-TB drug regimens used, and study design, no subgroups showed significant association between the risk of ATDILI and the *GSTT1* and the *GSTM1/GSTT1* polymorphisms (S11 Table).

SLCO1B1

For the *SLCO1B1* 388A>G polymorphism, four studies with 302 cases and 913 controls were included in our primary analysis. Using the dominant, recessive, or additive genomic model, no significant association was observed between the risk of ATDILI and the *SLCO1B1* 388A>*G* polymorphism (Table 2). For the *SLCO1B1* 521T>*C* polymorphism, four studies with 314 cases and 912 controls were included in our primary analysis. No significant association was found between the ATDILI risk and the *SLCO1B1 521T>C* polymorphism under the dominant, recessive, or additive genetic model (Table 2). Due to the lack of significant association between the risk of ATDILI and the tested *SLCO1B1* genetic polymorphisms in our primary meta-analysis, subgroup analyses were not performed for these genetic polymorphisms.

Sensitivity analysis

Our primary analysis results showed significantly high heterogeneity between studies for *CYP2E1 Rsa*I/*Pst*I (I^2 = 60%, P < 0.0001), *NAT2* (I^2 = 54%, P < 0.0001), *GSTM1*/*GSTT1* (I^2 = 59%, P = 0.006), and *SLCO1B1* 521T>C (dominant genetic model: I^2 = 66%, P = 0.03) polymorphisms. This high heterogeneity between studies may be due to substantial differences in ethnicity, anti-TB drug regimen, the genotyping method used, study design, and diagnostic criteria of ATDILI among the included studies (Table 1). Through the sensitivity analyses,

outlier studies were identified as the major source of heterogeneity. After removing these outlier studies, heterogeneity was substantially reduced (I^2 = 60% to 42% for *CYP2E1 Rsa*I/*Pst*I [23], I^2 = 54% to 34% for *NAT2* [24 25], I^2 = 59% to 0% for *GSTM1/GSTT1* [26 27], and I^2 = 66 % to 0% for *SLCO1B1* 521T>C dominant genetic model [28]). The overall results for the association between the risk of ATDILI and these genetic polymorphisms after excluding the outlier studies stayed the same as those from our primary analysis results.

Discussion

In this study, we conducted a large-scale meta-analysis evaluating the association between the risk of ATDILI and genetic polymorphisms of *SLCO1B1* as well as various DMEs including *CYP2E1*, *NAT2*, and *GST* to provide more updated, comprehensive, and compelling evidence. Compared with previous meta-analyses, our present study included a larger number of studies, whichc may sufficiently increase the statistical power compared to individual studies. However, a limited number of studies for the *SLCO1B1* genetic polymorphisms were included (n = 4). Consistently with previous studies, our current study suggested a significantly increased risk of ATDILI in patients with the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype (OR = 1.39, 95% CI 1.06–1.83), the *NAT2* slow acetylator genotype (OR = 3.30, 95% CI 2.65–4.11), and the *GSTM1* null genotype (OR = 1.30, 95% CI 1.12–1.52) [9 12 29]. Among these genotypes, the largest increase in the risk of ATDILI was shown in patients with the *NAT2* slow acetylator genotype. In contrast, no significant association was observed between the risk of ATDILI and the genetic polymorphisms of *CYP2E1 Dra*I, *GSTT1*, *GSTM1*/*GSTT1*, *SLCO1B1 388A>G*, and *SLCO1B1 521T>C*. Caution needs to be exercised when interpreting this study finding because the lack of

significant association between these polymorphisms and the risk of ATDILI might be due to small sample sizes and the low frequency of ATDILI reported in patients with these genetic polymorphisms.

When evaluating the impact of the *CYP2E1 Rsa*I/*Pst*I and *Dra*I genetic polymorphisms on the risk of ATDILI in our study, patients with the *Rsa*I/*Pst*I c1/c1 genotype were 1.39-times more likely to develop ATDILI. Similarly, in a previous meta-analysis by Deng and colleagues, the risk of ATDILI was 1.4-times higher in patients with the *Rsa*I/*Pst*I c1/c1 genotype compared to other genotypes [30]. In the liver, INH is metabolized by NAT2 to acetylisoniazid which is consequently oxidized by CYP2E1 to reactive hepatotoxic intermediates [31 32]. The increased inducibility or greater activity of CYP2E1 in patients with the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype may result in the production of more intermediate hepatotoxins, ultimately leading to the increased risk of ATDILI [31 32]. Our subgroup analysis showed a significantly increased risk of ATDILI in the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype carriers of East Asian ethnicity (S9 Table), suggesting a potential gene-ethnicity interaction [33]. A previous study identified age, female sex, white race, non-Hispanic ethnicity, lower body mass index, elevated plasma aspartate transaminase concentrations at baseline, and nine months of daily INH use as risk factors for ATDILI [34]. Considering their race, ethnicity, and relatively lower body mass index compared to other ethnicities, East Asians may be at an increased risk of ATDILI. As the *CYP2E1 Rsa*I/*Pst*I c1 allele frequency is relatively low in this population (79.8% *vs.* 88.5% to 99.8% in other ethnicities), the ethnicity itself might play an important role in developing hepatotoxicity through gene-ethnicity interaction[35]. Furthermore, the relatively high frequency of c2 allele in this population might serve as a good control to estimate the effect of c1 allele on the risk of ATDILI; the rarity of this minor allele in other ethnicities could make it difficult to evaluate the

association between the ATDILI risk and this genetic polymorphism[35]. In addition to ethnicity, combination anti-TB therapy was shown to significantly increase the risk of ATDILI in patients with the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype (S9 Table). This is consistent with previous study findings because hepatotoxicity commonly occurs with anti-TB drugs such as INH and RIF and thus, use of more than one hepatotoxic anti-TB medication increases the risk of ATDILI [7].

Similar to previous studies, our current study suggested a significantly increased risk of ATDILI in patients with the *NAT2* slow acetylator genotype compared to those with intermediate/fast acetylator genotypes [9 29]. The risk of ATDILI in slow acetylators remained significantly increased in all tested subgroups regardless of ethnicity and the anti-TB drug regimen used (S10 Table). The frequencies of *NAT2* slow acetylator alleles are highly variable between ethnic groups, ranging from 32% in Koreans to 76% in Caucasians [36]. Despite this large inter-ethnic variability in the *NAT2* polymorphic allele frequency, the *NAT2* slow acetylator genotype consistently and significantly increased the risk of ATDILI across all ethnicities, suggesting the critical role of *NAT2* polymorphism in the development of ATDILI. In addition, the increased risk of ATDILI in slow acetylators receiving INH monotherapy or combination therapy further highlights the importance of the *NAT2* polymorphism in the development of INH-induced hepatotoxicity. The clearance of INH is slower in slow acetylators compared to rapid or intermediate acetylators, resulting in the accumulation of INH in these patients [37 38]. This high level of INH may increase the risk of ATDILI in tuberculosis patients with the *NAT2* slow acetylator genotype due to immune-mediated liver injury through the binding of INH to liver proteins [39]. Therefore, clinicians should closely monitor tuberculosis patients with the *NAT2* slow acetylator genotype for hepatotoxicity when INH-based treatment is administered to these patients.

According to previous studies, GST enzymes, particularly those coded by *GSTM1* and *GSTT1* loci, are associated with the risk of drug-induced hepatotoxicity [9 40]. Similar to previous studies, our current study demonstrated a significantly increased risk of ATDILI in individuals with the *GSTM1* null genotype compared to those with the non-null genotype; however, the risk of ATDILI was not affected by the *GSTT1* or *GSTM1*/*GSTT1* genetic polymorphisms. GSTs are important enzymes to detoxify various xenobiotics and play an essential role in INH metabolism by eliminating acetyldiazene ketene acetylonium ion, which is a possibly hepatotoxic free radical metabolite of INH, from the body through *GSTM1*. This may account for the significant association of the ATDILI risk with the *GSTM1* genotype, but not with the *GSTT1* or *GSTM1*/*GSTT1* genotypes [9 40]. Our subgroup analysis showed a significantly increased risk of ATDILI in the *GSTM1* null genotype carriers of Indian ethnicity; although not statistically significant, the risk of ATDILI was relatively high in the East Asian population with the *GSTM1* null genotype (S11 Table). Considering the substantial difference in the GSTM1 null allele frequency between Indians (29.6%) and East Asians (52.1%), a potential gene-ethnicity interaction may exist based on their race, ethnicity, and body size as aforementioned [34 41]. Other characteristics than the *GSTM1* polymorphism in these ethnicities may play a more important role in the development of ATDILI. In addition, when studies were stratified by study design, the risk of ATDILI was significantly increased in patients with the *GSTM1* null genotype for cohort studies only, but not for case-control studies, probably due to a relatively larger sample size with cohort studies compared to case-control studies.

SLCO1B1 encodes organic anion transporting polypeptide 1B1 (OATP1B1) which is a major influx drug transporter responsible for the hepatic uptake of various endogenous and exogenous substances including RIF [42]. Previous studies showed significantly altered systemic

exposure of RIF in carriers of the *SLCO1B1* polymorphism [43 44]. To our knowledge, only four studies have been conducted to examine the association between the ATDILI risk and the *SLCO1B1* genetic polymorphisms [10 28 42 45]. Various single nucleotide polymorphisms (SNPs) of *SLCO1B1* were evaluated in these studies; however, *SLCO1B1* 388A>G (rs2306283) and 521T>C (rs4149056) were the only polymorphisms assessed in common [10 28 42 45]. Therefore, to maximize the sample size in our current meta-analysis, we examined the association between the risk of ATDILI and the polymorphic genotypes of *SLCO1B1* 388A>G and 521T>C. Similar to each of the included studies, we did not find significant difference in the risk of ATDILI among patients with different *SLCO1B1* 388A>G and 521T>C genotypes.

There are limitations to this study. First, due to the lack of information regarding other patient characteristics potentially associated with ATDILI, our estimated ORs were not adjusted based on the potential risk factors such as age, anti-TB drug dosages, alcohol consumption, cigarette smoking, and other lifestyle characteristics [7 46]. Second, our literature search limited to the articles published in English may lead to language bias. Third, a specific causative agent of ATDILI could not be identified in our analysis because most patients in our included studies received a combination regimen of anti-TB drugs. Fourth, only the limited number of polymorphic genotypes were assessed for the association with the risk of ATDILI, particularly for *SLCO1B1*. In addition, only one genetic model was used for *CYP2E1*, *NAT2*, and *GST* when evaluating the association between genetic polymorphisms of these genes and the risk of ATDILI. Although we acknowledge dominant, recessive, and additive genomic models can be used for two alleles, it could not be applied to our meta-analysis because we compared patients with different genotype-based phenotype, i.e., slow acetylator *vs.* fast/intermediate acetylator and null vs. non-null *GST*s. Multiple allelic variants or allele subgroups may represent the same

phenotype (e.g., *NAT2**5B, *6A, and *7B all represent slow acetylator genotypes), and the genetic model selection can be varied depending on the specific allelic variant[47] . Therefore, the genetic models used in previous original and meta-analysis studies were adopted for these polymorphic genes in our current study [9 18 19]. Future studies are needed to comprehensively and adequately address the relationship between the ATDILI risk and various genetic polymorphisms by using different genetic risk models and including more polymorphic genotypes.

In conclusion, the risk of ATDILI during TB therapy was significantly increased in tuberculosis patients carrying *NAT2* slow acetylator, *CYP2E1 Rsa*I/*Pst*I c1/c1, or *GSTM1* null genotypes. Screening for these genetic polymorphisms, particularly for the *NAT2* slow acetylator genotype, may be of great clinical benefit to identify patients at high risk for ATDILI and minimize the risk of ATDILI. Future studies are pertinent to develop dose and/or treatment adjustment strategies, to evaluate the feasibility and cost-effectiveness of the genetic screening test, and to assess the effect of more genetic polymorphisms on the risk of ATDILI for optimal prevention and management of ATDILI.

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Contributors

S.Y. devised and designed the study. S.Y., J.Y.P., and S.J.H. conducted the literature search,

performed data extraction and analysis, and. interpreted the data. S.Y., E.K.C., and J.I.L. prepared and reviewed the manuscript. All authors reviewed, amended and approved the submitted manuscript

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Supporting information

Additional supporting information can be found in the online version of this article:

S1 Table. Completed MOOSE (Meta-analysis Of Observational Studies in Epidemiology) checklist

S2 Table. Search strategies

S3 Table. Study quality assessment

S4 Table. Genotype distribution and the genotyping method used for the *CYP2E1* genetic polymorphisms in the included studies (n = 26)

S5 Table. Genotype distribution and the genotyping method used for the *NAT2* genetic polymorphism in the included studies (n = 35)

S6 Table. Genotype distribution and the genotyping method used for the *GST* genetic polymorphisms in the included studies (n = 19)

S7 Table. Genotype distribution and the genotyping method used for the *SLCO1B1* genetic polymorphisms in the included studies (n = 4)

S8 Figure. Funnel plots to evaluate publication bias for the *CYP2E1, NAT2, GST,* and *SLCO1B1* polymorphisms associated with the risk of anti-tuberculosis drug-induced liver injury. (A) C*YP2E1 Rsa*I/*Pst*I polymorphism, (B) *CYP2E1 Dra*I polymorphism, (C) *NAT2* polymorphism, (D) *GSTM1* polymorphism, (E) *GSTT1* polymorphism, (F) *GSTT1/M1* polymorphism, and (G) *SLCO1B1* 388A>G and 521T>C polymorphism.

S9 Table. Subgroup analysis for the association between *CYP2E1* polymorphisms and the risk of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug regimen, and study design

S10 Table. Subgroup analysis for the association between *NAT2* polymorphism and the risk of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug regimen, and study design

S11 Table. Subgroup analysis for the association between *GST* polymorphisms and the risk of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug regimen, and study design

Figure legends

Figure 1. Study selection process flowchart.

Figure 2. Risk of anti-tuberculosis drug-induced liver injury in patients with the *CYP2E1* (A) *Rsa*I/*Pst*I c1/c1 genotype compared to c1/c2 + c2/c2 genotypes and (B) *Dra*I D/D genotype compared to D/C + C/C genotypes.

Figure 3. Risk of anti-tuberculosis drug-induced liver injury in patients with the *NAT2* slow acetylator genotype compared to those with the intermediate/fast acetylator genotypes.

Figure 4. Risk of anti-tuberculosis drug-induced liver injury in patients with (A) the *GSTM1* null genotype compared to the non-null genotype, (B) the *GSTT1* null genotype compared to the non-null genotype, and (C) the *GSTM1*/*GSTT1* dual-null genotype compared to the one- and non-null genotypes.

Table 1. Characteristics of the studies included in the meta-analysis (n = 54 studies)

Last name of the first author, year	Polymorphic gene	Study design	Ethnicity	Sample size (case/control)	Age (years) (case/ control)[a]	Male (%) (case/ control)	Anti-TB drug regimen administered	Diagnostic criteria of ATDILI	Quality score[d]
Feng, 2014 [23]	*CYP2E1*	Case-control	Chinese	173/173	48.8/48.6	68.0/68.0	INH, RIF, PZA	ALT > 3 × ULN	6
Kim, 2009 [48]	*CYP2E1*	Case-control	Korean	67/159	42.1/42.8	65.7/65.4	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Singh, 2014 [49]	*CYP2E1*	Cohort	Indian	50/135	NA/NA	NA/NA	NA	ALT > 2 × ULN	7
Tang, 2013 [50]	*CYP2E1*	Case-control	Chinese	89/356	43.7/43.6	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Ben Mahmoud, 2012 [51]	*NAT2*	Cohort	Tunisian	14/52	42.4/42.1	42.8/48.1	INH, RIF containing regimen	ALT > 2 × ULN	7
Bozok Cetintas, 2008 [52]	*NAT2*	Case-control	Turkish	30/70	39.8/37.3	50.0/72.8	INH, RIF, PZA, EMB	ALT > 3 × ULN	6
Higuchi, 2007 [53]	*NAT2*	Cohort	Japanese	18/82	60.8/64.7	50.0/57.3	INH ,RIF containing regimen	ALT > 2 × ULN	7
Ho, 2013 [54]	*NAT2*	Cohort	Taiwanese	20/328	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 5 × ULN	6
Huang, 2002[55]	*NAT2*	Cohort	Taiwanese	33/191	73.3/63.7	87.9/88.5	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Khalili, 2011 [56]	*NAT2*	Case-control	Iranian	14/36	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 3 × ULN	6
Leiro-Fernandez, 2011 [57]	*NAT2*	Case-control	Caucasian	50/67	34.0/30.5[b]	54.0/56.7	INH, RIF, PZA	ALT > 3 × ULN	7
Lv, 2012 [24]	*NAT2*	Case-	Chinese	89/356	42.0/42.0[b]	73.0/73.0	INH, RIF, PZA,	ALT > 2 × ULN	7

		control					EMB		
Ng, 2014 [58]	*NAT2*	Case-control	Mixed	26/101	48.3/NA	38.5/NA	INH containing regimen	ALT > 5 × ULN	7
Ohno, 2000 [59]	*NAT2*	Cohort	Japanese	14/63	NA/NA	NA/NA	INH, RIF	ALT > 1.5 × ULN	7
Possuelo, 2008 [60]	*NAT2*	Cohort	Brazilian	14/240	38.9/36.5	50.0/66.9	INH, RIF, PZA	ALT > 3 × ULN	7
Rana, 2012 [61]	*NAT2*	Cohort	Indian	50/201	45.3/43.8	76.0/57.2	INH, RIF, PZA, EMB	ALT > 5 × ULN	7
Shimizu, 2006 [62]	*NAT2*	Case-control	Japanese	10/32	60.5/64.9	70.0/46.9	INH, RIF	ALT > 2 × ULN	6
Yuliwulandari, 2016 [63]	*NAT2*	Case-control	Indonesian	50/191	NA/NA	NA/NA	NA	ALT > 2 × ULN	7
Wattanapokayakit, 2016 [25]	*NAT2*	Case-control	Thai	53/85	51.4/50.2	58.5/60.0	INH containing regimen	ALT > 2 × ULN	7
Chatterjee, 2010 [64]	*GSTM1, GSTT1*	Case-control	Indian	51/100	37.2/33.2	49.0/63.0	INH, RIF, PZA	ALT > 3 × ULN	7
Gupta, 2013 [65]	*GSTM1, GSTT1*	Cohort	Indian	50/246	37.0/36.5[b]	48.0/56.5	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Huang, 2007 [66]	*GSTM1, GSTT1*	Case-control	Taiwanese	63/63	62.0/NA	NA/NA	NA	ALT > 5 × ULN	6
Kim, 2010 [67]	*GSTM1, GSTT1*	Case-control	Korean	57/190	47.3/42.4	59.6/67.9	INH, RIF, PZA, EMB	ALT > 3 × ULN	7
Leiro, 2008 [68]	*GSTM1, GSTT1*	Case-control	Caucasian	35/60	34.0/31.0[b]	40.0/41.7	INH, RIF, PZA	ALT > 3 × ULN	7
Liu, 2014 [69]	*GSTM1, GSTT1*	Case-control	Chinese	20/143	35.9/61.2	60.0/59.4	INH containing regimen	ALT > 2 × ULN	7
Monteiro, 2012 [70]	*GSTM1, GSTT1*	Cohort	Brazilian	59/118	37.0/38.0[b]	76.0/61.0	NA	ALT > 2 × ULN	7

Rana, 2013 [71]	*GSTM1, GSTT1*	Cohort	Indian	30/220	43.6/42.3	60.0/64.5	INH, RIF	ALT > 5 × ULN	6
Roy, 2001 [72]	*GSTM1, GSTT1*	Case-control	Indian	33/33	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Chen, 2015 [42]	*SLCO1B1*	Case-control	Chinese	89/356	43.7/43.6	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Kim, 2012 [10]	*SLCO1B1*	Case-control	Korean	67/159	43.0/42.8	65.7/65.4	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Li, 2012 [28]	*SLCO1B1*	Case-control	Chinese	118/155	40.5/39.3	48.3/54.8	RIF	ALT > 3 × ULN	7
An, 2012 [73]	*NAT2, CYP2E1*	Case-control	Chinese	101/107	36.0/33.4[b]	55.0/70.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Bose, 2011 [74]	*NAT2, CYP2E1*	Cohort	Indian	41/177	38.0/36.0	43.9/47.4	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Chamorro, 2013 [75]	*NAT2, CYP2E1*	Cohort	Mixed (South American)	47/128	29.0/27.0	41.3/64.8	INH, RIF, PZA, EMB	ALT > 3 × ULN	7
Cho, 2007 [76]	*NAT2, CYP2E1*	Cohort	Korean	18/114	51.2/46.7	66.7/55.3	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Gupta, 2013 [27]	*NAT2, CYP2E1*	Case-control	Indian	50/165	37.0/38.0	48.0/60.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Huang, 2003 [77]	*NAT2, CYP2E1*	Cohort	Taiwanese	49/269	70.0/59.0[b]	18.4/14.9	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Lee, 2010 [78]	*NAT2, CYP2E1*	Cohort	Taiwanese	45/95	58.4/54.9	60.0/66.3	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Mishra, 2013 [79]	*NAT2, CYP2E1*	Case-control	Indian	33/173	38.0/NA	52.0/NA	INH, RIF, PZA, EMB	ALT > 3 × ULN	7
Santos, 2013 [80]	*NAT2,*	Case-	Brazilian	18/252	47.7/45.6	56.0/49.0	INH, RIF	ALT > 3 × ULN	7

	CYP2E1	control							
Vuilleumier, 2006 [81]	*NAT2, CYP2E1*	Case-control	Mixed	8/63	27-35: 2/22[c] >36 : 5/18[c]	38.0/51.0	INH	AST or ALT > 4 × ULN	7
Yamada, 2009 [82]	*NAT2, CYP2E1*	Case-control	Mixed	23/147	NA/NA	13.0/42.9	INH	ALT > 2 × ULN	7
Zaverucha-do-Valle, 2014 [83]	*NAT2, CYP2E1*	Cohort	Brazilian	50/79	< 40: 28/43[c] > 40: 20/36[c]	60.4/72.2	INH, RIF, PZA	ALT > 2 × ULN	6
Sharma, 2014 [84]	*CYP2E1, GSTM1*	Cohort	Indian	105/185	35.2/27.6	55.7/72.1	INH, RIF, PZA, EMB	ALT > 5 × ULN	7
Wang, 2010 [85]	*CYP2E1, GSTM1*	Case-control	Chinese	104/111	48.6/44.7	67.3/67.6	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Tang, 2012 [86]	*CYP2E1, GSTM1, GSTT1*	Case-control	Chinese	89/356	43.7/43.6	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Yimer, 2011 [45]	*NAT2, SLCO1B1*	Cohort	Ethiopian	41/160	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 2 × ULN	6
Brito, 2014 [87]	*NAT2, CYP2E1, GSTM1, GSTT1*	Cohort	Brazilian	15/230	38.1/36.8	46.7/NA	INH, RIF, PZA	ALT > 3 × ULN	7
Forestiero, 2013 [88]	*NAT2, CYP2E1, GSTM1, GSTT1*	Cohort	Brazilian	59/40	NA/NA	49.2/60.0	INH, RIF, PZA	ALT > 2.5 × ULN	6
Rana, 2014 [89]	*NAT2, CYP2E1, GSTM1, GSTT1*	Cohort	Indian	55/245	43.6/42.3	60.0/62.0	INH, RIF, PZA, EMB	ALT > 5 × ULN	6
Singla, 2014 [26]	*NAT2, CYP2E1, GSTM1,*	Case-control	Indian	17/391	48.2/32.7	64.7/61.4	INH, RIF, PZA, EMB, STM	ALT > 2 × ULN	7

	GSTT1								
Sotsuka, 2011 [90]	*NAT2, CYP2E1, GSTM1, GSTT1*	Case-control	Japanese	20/92	54.9/50.4	90.0/73.9	INH, RIF, PZA, EMB or STM	ALT > 3 × ULN	7
Teixeira, 2011 [91]	*NAT2, CYP2E1, GSTM1, GSTT1*	Case-control	Brazilian	26/141	47.6/43.0	61.5/52.5	INH containing regimen	ALT > 3 × ULN	7
Xiang, 2014 [92]	*NAT2, CYP2E1, GSTM1, GSTT1*	Cohort	Chinese	89/2155	37.0/44.5	67.4/55.7	INH, RIF, PZA, EMB	ALT > 2 × ULN	7

Abbreviations: **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **ATDILI**, anti-tuberculosis drug-induced liver injury; **CYP2E1**, cytochrome P450 2E1; **EMB**, ethambutol; **GSTM1**, glutathione S-transferase Mu 1; **GSTT1**, glutathione S-transferase Theta 1; **INH**, isoniazid; **NA**, not available; **NAT2**, N-acetyltransferase 2; **PZA**, pyrazinamide; **RIF**, rifampicin; **SLCO1B1**, solute carrier organic anion transporter family, member 1B1 (encoding organic anion transporting polypeptide 1B1 [OATP1B1]); **STM**, streptomycin; **TB**, tuberculosis; **ULN**, upper limit of normal

[a] Mean unless otherwise stated

[b] Median age

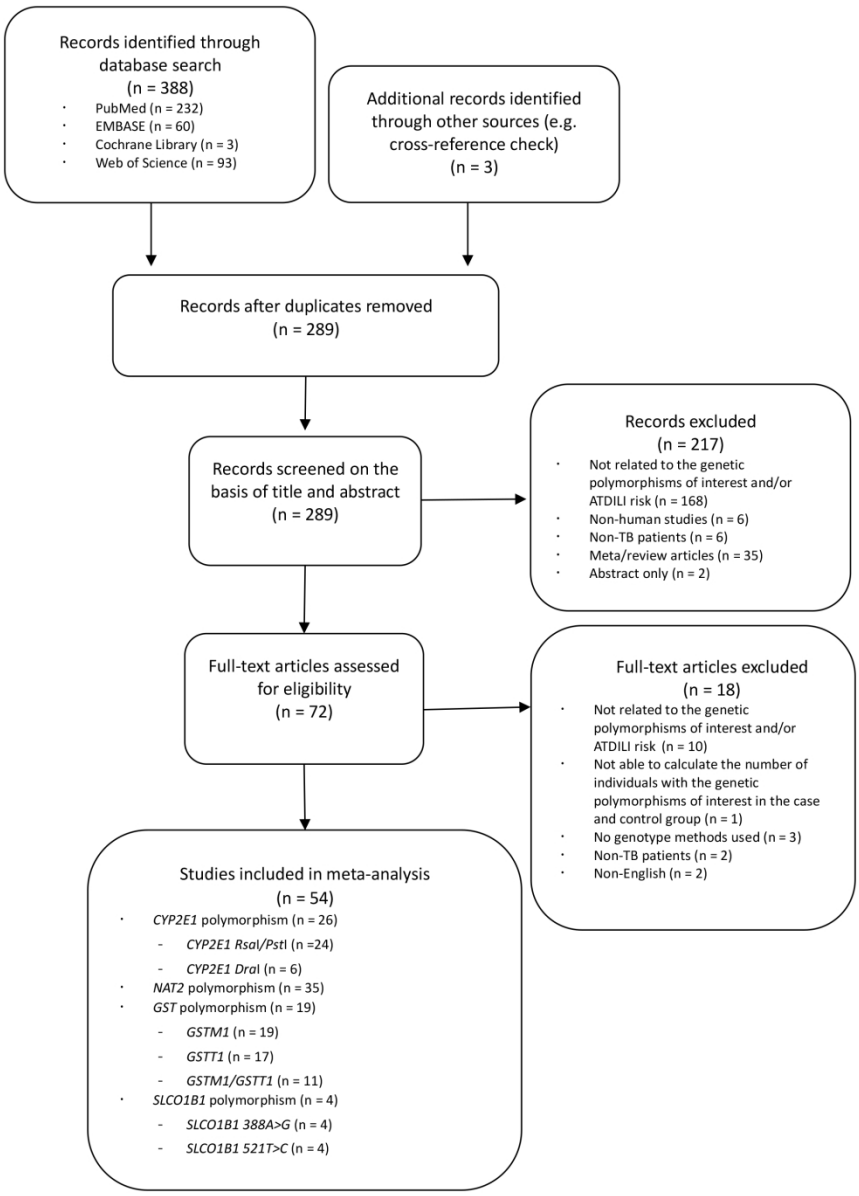
[c] Number of individuals in the age ranges

[d] Detailed scoring for each quality assessment criterion based on the revised Little's recommendation in supplementary data S2 Table.

Table 2. Association between the *SLCO1B1* polymorphisms and the risk of anti-tuberculosis drug-induced liver injury

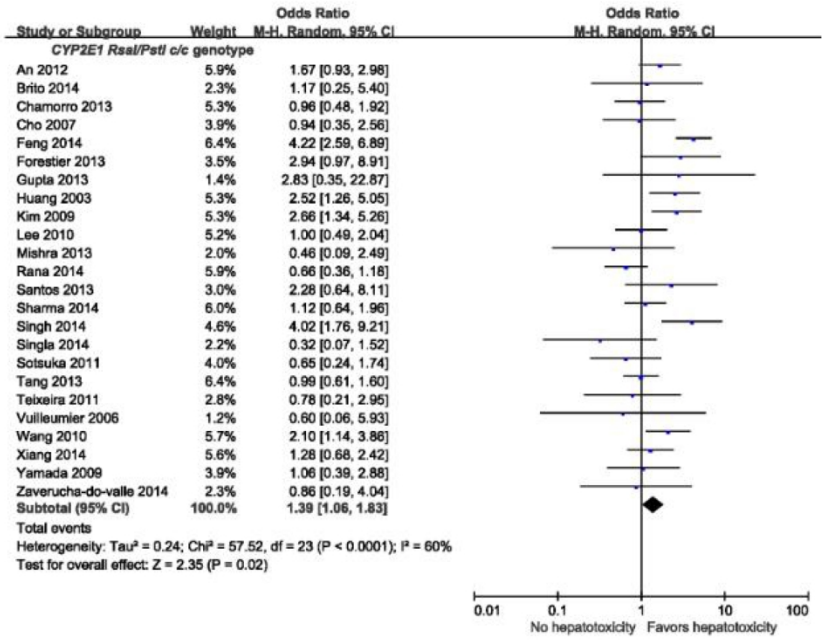
Polymorphism	Genetic model		Number of studies	OR (95% CI)	P value	I^2, %	$P_{heterogeneity}$	Model of meta-analysis
SLCO1B1 388A>G (rs2306283)	dominant model	AA + AG vs.GG	4	1.00 [0.76, 1.31]	1.00	0	0.73	Fixed
	recessive model	AA vs. AG + GG	4	1.45 [0.93, 2.25]	0.10	0	0.84	Fixed
	additive model	AA vs. GG	4	1.36 [0.85, 2.15]	0.20	0	0.98	Fixed
SLCO1B1 521T>C[c] (rs4149056)	dominant model	CC + TC vs. TT	4	0.74 [0.43, 1.28]	0.28	66	0.03	Random
	recessive model	CC vs. TC + TT	4	1.21 [0.40, 3.64]	0.73	0	0.57	Fixed
	additive model	CC vs. TT	4	1.27 [0.42, 3.84]	0.67	0	0.61	Fixed

Abbreviations: ***OR*, odds ratio*; CI***, confidence interval

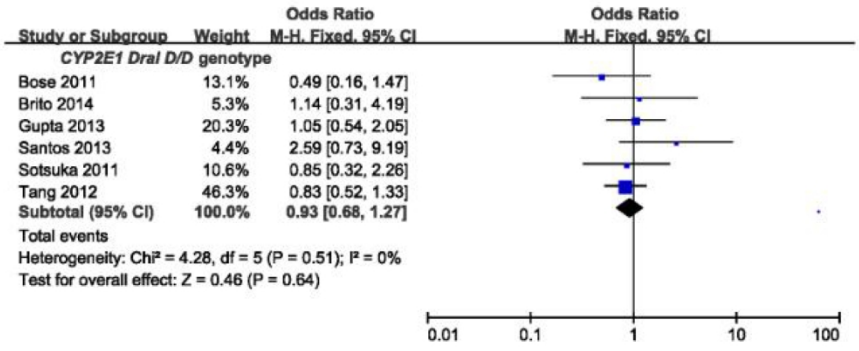


Study selection process flowchart.

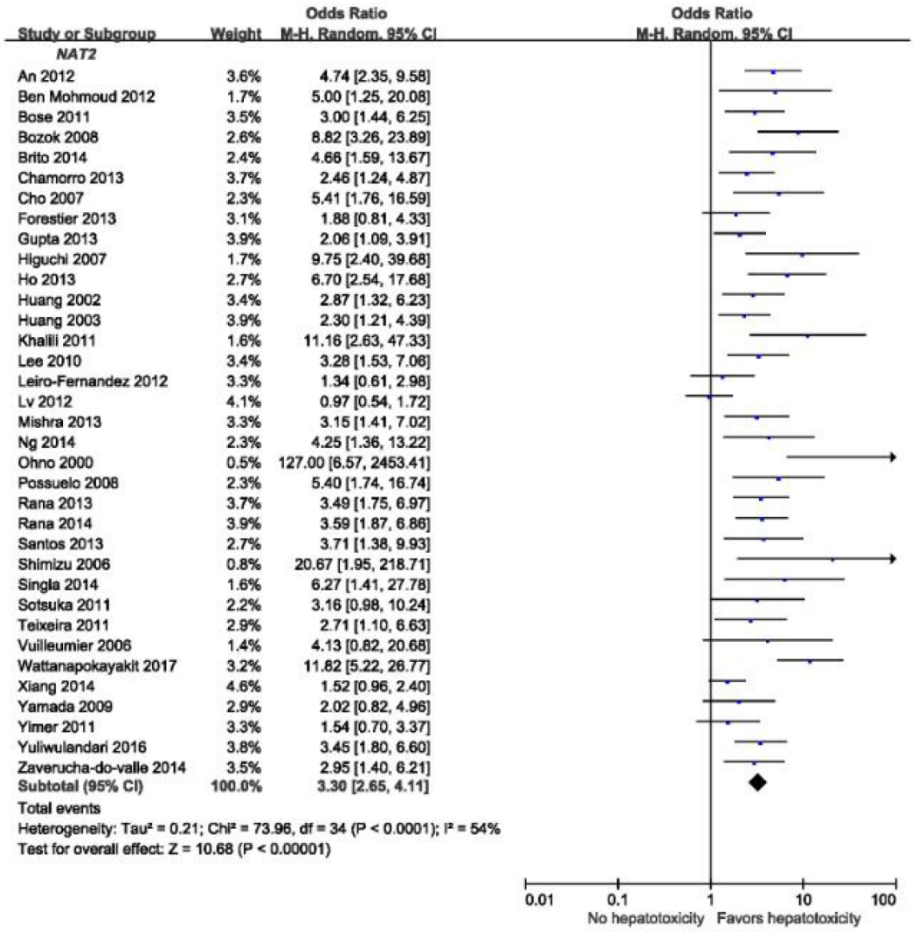
(A) CYP2E1 RsaI/PstI c1/c1 genotype compared to c1/c2 + c2/c2 genotypes



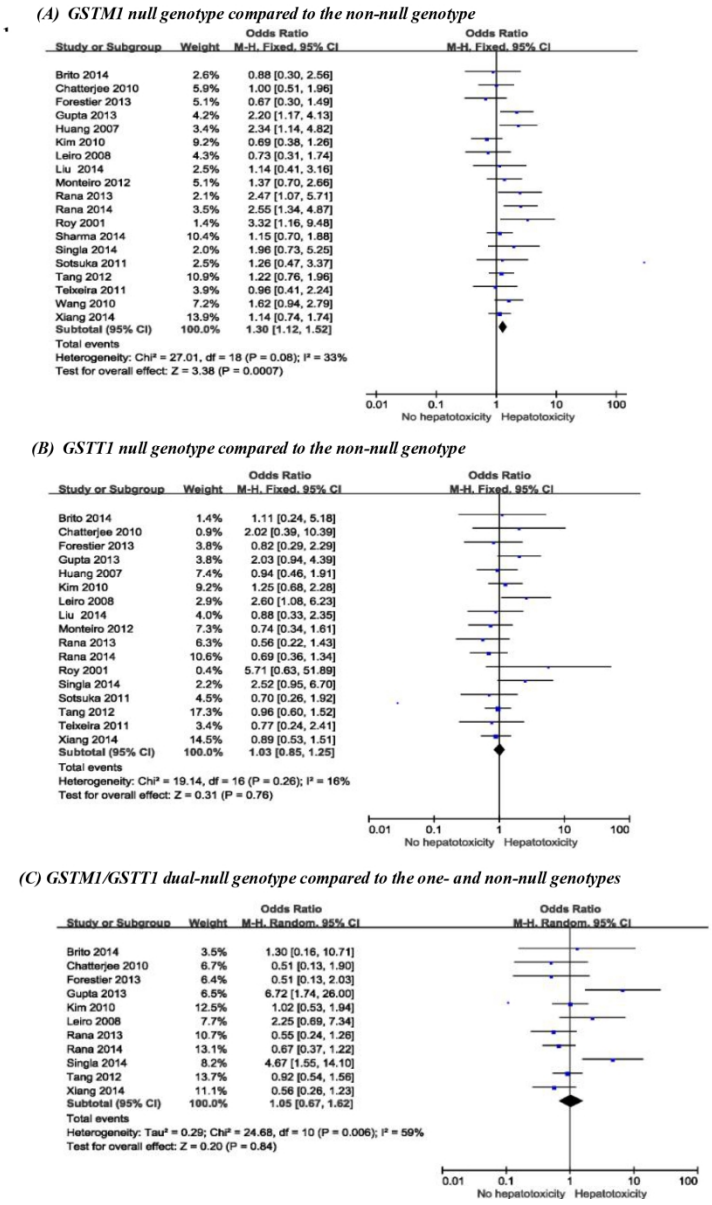
(B) CYP2E1 DraI D/D genotype compared to D/C + C/C genotypes.



Risk of anti-tuberculosis drug-induced liver injury in patients with the CYP2E1 (A) RsaI/PstI c1/c1 genotype compared to c1/c2 + c2/c2 genotypes and (B) DraI D/D genotype compared to D/C + C/C genotypes.



Risk of anti-tuberculosis drug-induced liver injury in patients with the NAT2 slow acetylator genotype compared to those with the intermediate/fast acetylator genotypes.



Risk of anti-tuberculosis drug-induced liver injury in patients with (A) the GSTM1 null genotype compared to the non-null genotype, (B) the GSTT1 null genotype compared to the non-null genotype, and (C) the GSTM1/GSTT1 dual-null genotype compared to the one- and non-null genotypes.

Supplementary data

S1 Table. Completed MOOSE (Meta-analysis Of Observational Studies in Epidemiology) checklist

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	7
2	Hypothesis statement (Objectives)	7
3	Description of study outcome(s)	7
4	Type of exposure or intervention used	NA
5	Type of study designs used	7
6	Study population	8-9
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	NA
8	Search strategy, including time period included in the synthesis and key words	8 S2 Table
9	Effort to include all available studies, including contact with authors	8
10	Databases and registries searched	8
11	Search software used, name and version, including special features used (eg, explosion)	8
12	Use of hand searching (eg, reference lists of obtained articles)	8
13	List of citations located and those excluded, including justification	Fig 1
14	Method of addressing articles published in languages other than English	9
15	Method of handling abstracts and unpublished studies	9, Fig 1
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	NA
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	12
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	12
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	NA
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Table 1, S3 Table
22	Assessment of heterogeneity	16
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	10-11
24	Provision of appropriate tables and graphics	Table 1-2, Fig 1-4

Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Fig 2-4
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	16, S9-11 Table
28	Indication of statistical uncertainty of findings	-

S2 Table. Search strategies

Electronic database	Search strategies
PubMed	((((((((((("glutathione S transferase") OR GST)) OR ("glutathione S-transferase T1" [Supplementary Concept] OR "glutathione S-transferase M1" [Supplementary Concept])) AND Humans[Mesh] AND English[lang])) OR ((("SLCO1B1 protein, human" [Supplementary Concept]) OR "solute carrier organic anion transporter") AND Humans[Mesh] AND English[lang])) OR ("isoniazid acetyltransferase" [Supplementary Concept]OR "ArylamineN-Acetyltransferase"[Mesh] OR "NAT2 protein, human" [Supplementary Concept])) OR "Cytochrome P-450 CYP2E1"[Mesh]) OR #51) OR "Genetic Predisposition to Disease"[Mesh]) AND (("Drug-Induced Liver Injury"[Mesh] OR "Drug-Induced Liver Injury, Chronic"[Mesh]))) AND ((("AntitubercularAgents"[Mesh]) OR tuberculosis OR antituberculo*)) Filters: Humans; English
EMBASE	'solute carrier organic anion transporter 1b1'/expOR 'solute carrier organic anion transporter 1b1' OR 'multidrug resistance protein 1'/expOR 'multidrug resistance protein 1' OR 'organic anion transporter'/expOR 'organic anion transporter' AND [humans]/limAND [english]/limOR slco1b1 OR 'drug transporter gene*' OR abcb1 AND ('hepatitis'/expOR hepatitis OR 'liver toxicity'/expOR ('drug induced' AND ('liver'/expOR liver) AND ('toxicity'/expOR toxicity)) OR 'toxic hepatitis'/expOR 'hepatotoxicity'/expOR hepatotoxicity) AND ('tuberculostaticagent'/expOR 'tuberculostaticagent' OR antituberculosisOR 'isoni*' OR 'rifampi*') AND [humans]/limAND [english]/lim
Web of Science	(((((("Glutathione S transferase") OR GST) OR GSTT1) OR GSTM1) OR (((NAT2) OR "arylaminN acetyltransferase") OR N acetyltransferase*) OR ((drug metaboli?er*) OR (drug metabli?ingenzyme*)) OR (("Cytochrome 2E1") OR "CYP 2E1") OR (("The solute carrier organic anion transporter family member 1B1") OR SLCO1B1) OR (genotyp* OR acetylator*) OR (gene* susceptibilit*) OR (*polymorphism*)) AND ((drug NEAR/3 liver) OR (hepatotoxi*) OR (drug induced liver injury) OR (hepatitis)) AND ((rifampi*) OR (isoni*) OR (antituberculosis) OR ("antitubercul* agent* "))
Cochrane Reviews	[AntitubercularAgents] explode all trees AND [Drug-Induced Liver Injury] explode all trees AND ([Cytochrome P-450 CYP2E1] explode all trees OR nat2 OR "N acetyltrasferase" " glutathione S transferase" OR GST OR GSTM1 OR GSTT1 "Solute carrier organic anion transporter" OR SLCO1B1)(Limitation : Trials)

S3 Table. Study quality assessment

Studies	Scientific design	Definite inclusion of study population[a]	Explicit information on study population[a]	Explicit diagnostic criteria on ATDILI[a]	Genetic detection method[a]	Correct statistical analysis[a]	Logical discussion of study bias[a]
Feng, 2014 [1]	1	1	1	1	1	1	0
Kim, 2009 [2]	1	1	1	1	1	1	1
Singh, 2014 [3]	1	1	1	1	1	1	1
Tang, 2013 [4]	1	1	1	1	1	1	1
Ben Mahmoud, 2012 [5]	1	1	1	1	1	1	1
Bozok Cetintas, 2008 [6]	1	1	1	1	1	0	1
Higuchi, 2007 [7]	1	1	1	1	1	1	1
Ho, 2013 [8]	1	1	1	1	1	1	0
Huang, 2002[9]	1	1	1	1	1	1	1
Khalili, 2011 [10]	1	1	1	1	1	1	0
Leiro-Fernandez, 2011 [11]	1	1	1	1	1	1	1
Lv, 2012 [12]	1	1	1	1	1	1	1
Ng, 2014 [13]	1	1	1	1	1	1	1
Ohno, 2000 [14]	1	1	1	1	1	1	1
Possuelo, 2008 [15]	1	1	1	1	1	1	1
Rana, 2012 [16]	1	1	1	1	1	1	1
Shimizu, 2006 [17]	1	1	1	1	1	1	0
Yuliwulandari, 2016 [18]	1	1	1	1	1	1	1
Wattanapokayakit, 2016 [19]	1	1	1	1	1	1	1
Chatterjee, 2010 [20]	1	1	1	1	1	1	1
Gupta, 2013 [21]	1	1	1	1	1	1	1
Huang, 2007 [22]	1	1	1	1	1	1	0
Kim, 2010 [23]	1	1	1	1	1	1	1
Leiro, 2008 [24]	1	1	1	1	1	1	1
Liu, 2014 [25]	1	1	1	1	1	1	1
Monteiro, 2012 [26]	1	1	1	1	1	1	1
Rana, 2013 [27]	1	1	1	1	1	1	0
Roy, 2001 [28]	1	1	1	1	1	1	1
Chen, 2015 [29]	1	1	1	1	1	1	1
Kim, 2012 [30]	1	1	1	1	1	1	1
Li, 2012 [31]	1	1	1	1	1	1	1
An, 2012 [32]	1	1	1	1	1	1	1
Bose, 2011 [33]	1	1	1	1	1	1	1

Chamorro, 2013 [34]	1	1	1	1	1	1	1
Cho, 2007 [35]	1	1	1	1	1	1	1
Gupta, 2013 [36]	1	1	1	1	1	1	1
Huang, 2003 [37]	1	1	1	1	1	1	1
Lee, 2010 [38]	1	1	1	1	1	1	1
Mishra, 2013 [39]	1	1	1	1	1	1	1
Santos, 2013 [40]	1	1	1	1	1	1	1
Vuilleumier, 2006 [41]	1	1	1	1	1	1	1
Yamada, 2009 [42]	1	1	1	1	1	1	1
Zaverucha-do-Valle, 2014 [43]	1	1	1	1	1	1	0
Sharma, 2014 [44]	1	1	1	1	1	1	1
Wang, 2010 [45]	1	1	1	1	1	1	1
Tang, 2012 [46]	1	1	1	1	1	1	1
Yimer, 2011 [47]	1	1	1	1	1	1	0
Brito, 2014 [48]	1	1	1	1	1	1	1
Forestiero, 2013 [49]	1	1	1	1	1	1	0
Rana, 2014 [50]	1	1	1	1	1	1	0
Singla, 2014 [51]	1	1	1	1	1	1	1
Sotsuka, 2011 [52]	1	1	1	1	1	1	1
Teixeira, 2011 [53]	1	1	1	1	1	1	1
Xiang, 2014 [54]	1	1	1	1	1	1	1

Abbreviation: ATDILI, anti-tuberculosis drug-induced liver injury

[a] 0 indicates 'not mentioned' in the study; 1 indicates 'sufficient information provided' in the study

S4 Table. Genotype distribution and the genotyping method used for the *CYP2E1* genetic polymorphisms in the included studies (n = 26)

Study	*Rsa*I/*Pst*I genotype (n = 24)				*Dra*I genotype (n = 6)				Genotyping method
	Case (number of individuals [%])		Control (number of individuals [%])		Case (number of individuals [%])		Control (number of individuals [%])		
	C1/C1	C1/C2 + C2/C2	C1/C1	C1/C2 + C2/C2	D/D	D/C + C/C	D/D	D/C + C/C	
An[32]	72 (71.3)	29 (28.7)	64 (59.8)	43 (40.2)	NA	NA	NA	NA	Sequencing
Bose[33]	NA	NA	NA	NA	4 (9.8)	37 (90.2)	32 (18.1)	145 (81.9)	PCR-RFLP
Brito[48]	13 (86.7)	2 (13.3)	195 (84.8)	35 (15.2)	12 (80.0)	3 (20.0)	179 (76.8)	54 (23.2)	PCR-RFLP
Chamorro[34]	30 (63.8)	17 (36.2)	83 (64.8)	45 (35.2)	NA	NA	NA	NA	PCR-RFLP
Cho[35]	10 (55.6)	8 (44.4)	65 (57.0)	49 (43.0)	NA	NA	NA	NA	Sequencing
Feng[1]	142 (82.1)	31 (17.9)	90 (52.0)	83 (48.0)	NA	NA	NA	NA	Sequencing
Forestiero[49]	53 (89.8)	6 (10.2)	30 (75.0)	10 (25.0)	NA	NA	NA	NA	PCR-RFLP
Gupta[36]	49 (98.0)	1 (2.0)	156 (94.5)	9 (5.5)	33 (66.0)	17 (34.0)	107 (64.9)	58 (35.1)	PCR-RFLP
Huang[37]	37 (75.5)	12 (24.5)	148 (55.0)	121 (45.0)	NA	NA	NA	NA	PCR-RFLP

Kim[2]	54 (81.8)	12 (18.2)	97 (63.4)	56 (36.6)	NA	NA	NA	NA	SNP stream
Lee[55]	26 (57.8)	19 (42.2)	55 (57.9)	40 (42.1)	NA	NA	NA	NA	Taqman
Mishra[39]	31 (93.9)	2 (6.1)	168 (97.1)	5 (2.9)	NA	NA	NA	NA	PCR-RFLP
Rana[56]	28 (50.9)	27 (49.1)	150 (61.2)	95 (38.8)	NA	NA	NA	NA	PCR-RFLP
Santos[57]	15 (83.3)	3 (16.7)	173 (75.6)	56 (24.4)	15 (83.3)	3 (16.7)	166 (72.8)	62 (27.2)	Taqman
Sharma[44]	81 (77.1)	24 (22.9)	139 (75.1)	46 (24.9)	NA	NA	NA	NA	PCR-RFLP
Singh[3]	42 (84.0)	8 (16.0)	77 (56.6)	59 (43.4)	NA	NA	NA	NA	PCR-RFLP
Singla[51]	15 (88.0)	2 (12.0)	375 (96.0)	16 (4.0)	NA	NA	NA	NA	PCR-RFLP
Sotsuka[52]	11 (55.0)	9 (45.0)	60 (65.2)	32 (34.8)	9 (45.0)	11 (55.0)	45 (48.9)	47 (51.1)	PCR-RFLP
Tang[46]	NA	NA	NA	NA	47 (52.8)	42 (47.2)	204 (57.3)	152 (42.7)	PCR-RFLP
Tang[4]	56 (62.9)	33 (37.1)	225 (63.2)	131 (36.8)	NA	NA	NA	NA	Taqman
Teixeira[53]	23 (88.5)	3 (11.5)	128 (90.8)	13 (9.2)	NA	NA	NA	NA	PCR-RFLP
Vuilleumier[41]	7 (87.5)	1 (12.5)	58 (92.1)	5 (7.9)	NA	NA	NA	NA	PCR-RFLP

Wang[45]	82 (78.8)	22 (21.2)	71 (64.0)	40 (36.0)	NA	NA	NA	NA	PCR-RFLP
Xiang[54]	58 (82.9)	12 (17.1)	1264 (79.0)	336 (21.0)	NA	NA	NA	NA	PCR/ligase detection reaction assays
Yamada[42]	17 (73.9)	6 (26.1)	107 (72.8)	40 (27.2)	NA	NA	NA	NA	PCR-RFLP
Zaverucha-do-Valle[43]	48 (94.1)	3 (5.9)	74 (94.9)	4 (5.1)	NA	NA	NA	NA	PCR-RFLP

Abbreviations: ***NA***, not available; ***PCR***, polymerase chain reaction; ***RFLP***, restriction fragment length polymorphism; ***SNP***, single nucleotide polymorphism

S5 Table. Genotype distribution and the genotyping method used for the *NAT2* genetic polymorphism in the included studies (n = 35)

Study	Case (number of individuals [%])		Control (number of individuals [%])		Genotyping method
	Slow acetylator	Intermediate and fast acetylator	Slow acetylator	Intermediate and fast acetylator	
An [32]	40 (39.6)	61 (60.4)	13 (12.1)	94 (87.9)	Sequencing
Ben Mahmoud [5]	11 (78.5)	3 (21.5)	22 (42.4)	30 (57.6)	PCR-RFLP
Bose [33]	29 (70.7)	12 (29.3)	79 (44.6)	98 (55.4)	PCR-RFLP
Bozok Cetintas [6]	23 (76.7)	7 (23.3)	19 (27.1)	51 (72.9)	PCR
Brito [48]	9 (60.0)	6 (40.0)	56 (24.3)	174 (75.7)	PCR-RFLP
Chamorro [34]	28 (58.7)	19 (41.3)	48 (37.5)	80 (62.5)	PCR-RFLP
Cho [35]	7 (38.9)	11 (61.1)	12 (10.5)	102 (89.5)	Sequencing
Forestiero [49]	28 (47.4)	31 (52.6)	13 (32.5)	27 (67.5)	PCR-RFLP
Gupta [36]	28 (56.0)	22 (44.0)	63 (38.2)	102 (61.8)	PCR-RFLP
Higuchi [7]	6 (33.3)	12 (66.7)	4 (4.9)	78 (95.1)	PCR-RFLP
Ho[8]	12 (63.2)	7 (36.8)	67 (20.4)	262 (79.6)	Sequenom MassARRAY

Huang [9]	14 (42.4)	19 (57.6)	39 (20.4)	152 (79.6)	PCR-RFLP
Huang [37]	19 (38.8)	30 (61.2)	58 (21.6)	211 (78.4)	PCR-RFLP
Khalili [10]	9 (64.3)	5 (35.7)	5 (13.9)	31 (86.1)	PCR-RFLP
Lee [38]	21 (46.7)	24 (53.3)	20 (21.1)	75 (78.9)	Taqman
Leiro-Fernandez [11]	36 (72.0)	14 (28.0)	44 (65.7)	23 (34.3)	PCR-RFLP
Lv [58]	18 (20.2)	71 (79.8)	74 (20.8)	282 (79.2)	PCR-RFLP
Mishra [39]	23 (70.0)	10 (30.0)	73 (42.0)	100 (58.0)	PCR-RFLP
Ng [13]	22 (84.6)	4 (15.4)	57 (56.4)	44 (43.6)	PCR-RFLP
Ohno [14]	7 (50.0)	7 (50.0)	0 (0.0)	63 (100.0)	PCR-RFLP
Possuelo[15]	9 (64.3)	5 (35.7)	60 (25.0)	180 (75.0)	Sequencing
Rana [16]	19 (38.0)	31 (62.0)	30 (14.9)	171 (85.1)	PCR-RFLP
Rana [50]	21 (38.2)	34 (61.8)	36 (14.7)	209 (85.3)	PCR-RFLP
Santos [40]	11 (61.1)	7 (38.9)	75 (29.8)	177 (70.2)	Sequencing
Shimizu [17]	4 (40.0)	6 (60.0)	1 (3.1)	31 (96.9)	PCR-RFLP
Singla [51]	15 (88.2)	2 (11.8)	213 (54.5)	178 (45.5)	PCR-RFLP

Sotsuka [52]	8 (15.4)	44 (84.6)	5 (5.4)	87 (94.6)	PCR-RFLP
Teixeira [53]	18 (75.0)	6 (25.0)	64 (51.2)	61 (48.8)	Sequencing
Vuilleumier [41]	3 (37.5)	5 (62.5)	8 (12.7)	55 (87.3)	PCR- RFLP
Wattanapokayakit [19]	38 (71.7)	15 (28.3)	15 (17.7)	70 (82.3)	Sequencing
Xiang [54]	28 (31.5)	61 (68.5)	501 (23.2)	1654 (76.8)	PCR/ligase detection reaction assays
Yamada [42]	14 (60.9)	9 (39.1)	64 (43.5)	83 (56.5)	Sequencing
Yimer [47]	31 (75.6)	10 (24.4)	107 (66.9)	53 (33.1)	Taqman
Yuliwulandari [18]	32 (64.0)	18 (36.0)	65 (34.0)	126 (66.0)	Sequencing
Zaverucha-do-Valle [43]	37 (71.2)	15 (28.8)	36 (45.6)	43 (54.4)	Sequencing

Abbreviations: ***NA***, not available; ***PCR***, polymerase chain reaction; ***RFLP***, restriction fragment length polymorphism

S6 Table. Genotype distribution and the genotyping method used for the *GST* genetic polymorphisms in the included studies (n = 19)

Study	*GSTM1* genotype (n = 19)				*GSTT1* genotype (n = 17)				*GSTM1/GSTT1* genotype (n = 11)				Genotyping method
	Case (number of individuals [%])		Control (number of individuals [%])		Case (number of individuals [%])		Control (number of individuals [%])		Case (number of individuals [%])		Control (number of individuals [%])		
	Null	Non-null	Null	Non-null	Null	Non-null	Null	Non-null	Dual-null	One-/non-null	Dual-null	One-/non-null	
Brito [48]	6 (40.0)	9 (60.0)	99 (43.0)	131 (57.0)	2 (13.3)	13 (86.7)	28 (12.2)	202 (87.8)	1 (6.7)	14 (93.3)	12 (5.2)	218 (94.8)	PCR
Chatterjee [20]	25 (49.0)	26 (51.0)	49 (49.0)	51 (51.0)	3 (5.9)	48 (94.1)	3 (3.0)	97 (97.0)	3 (5.9)	48 (94.1)	11 (11.0)	89 (89.0)	Multiplex PCR
Forestiero [49]	25 (42.4)	34 (57.6)	21 (52.5)	19 (47.5)	10 (17.0)	49 (83.0)	8 (20.0)	32 (80.0)	4 (6.8)	55 (93.2)	5 (12.5)	35 (87.5)	Multiplex PCR
Gupta [21]	21 (42.0)	29 (58.0)	61 (24.8)	185 (75.2)	11 (22.0)	39 (78.0)	30 (12.2)	216 (87.8)	5 (10.0)	45 (90.0)	4 (1.6)	242 (98.4)	Multiplex PCR
Huang [22]	42 (66.7)	21 (33.3)	29 (46.0)	34 (54.0)	24 (38.1)	39 (61.9)	25 (39.7)	38 (60.3)	NA	NA	NA	NA	Multiplex PCR
Kim [23]	26 (45.6)	31 (54.4)	104 (54.7)	86 (45.3)	34 (59.6)	23 (40.4)	103 (54.2)	87 (45.8)	17 (29.8)	40 (70.2)	56 (29.6)	133 (70.4)	PCR
Leiro [24]	12 (34.3)	23 (65.7)	25 (41.7)	35 (58.3)	17 (48.6)	18 (51.4)	16 (26.7)	44 (73.3)	7 (20.0)	28 (80.0)	6 (10.0)	54 (90.0)	PCR
Liu [25]	14 (70.0)	6 (30.0)	96 (67.1)	47 (32.9)	13 (65.0)	7 (35.0)	97 (67.8)	46 (32.2)	NA	NA	NA	NA	Multiplex PCR

Monteiro [26]	21 (35.6)	38 (64.4)	34 (28.8)	84 (71.2)	11 (18.7)	48 (81.3)	28 (23.8)	90 (76.2)	NA	NA	NA	NA	PCR
Rana [27]	10 (41.6)	20 (58.4)	37 (18.5)	183 (81.5)	6 (25.0)	24 (75.0)	68 (33.8)	152 (66.2)	9 (37.5)	21 (62.5)	96 (47.7)	124 (52.3)	PCR
Rana [16]	19 (34.5)	36 (65.5)	42 (17.1)	203 (82.9)	14 (25.5)	41 (74.5)	81 (33.1)	164 (66.9)	22 (40.0)	33 (60.0)	122 (49.8)	123 (50.2)	PCR
Roy [28]	17 (52.0)	15 (48.0)	8 (24.0)	25 (76.0)	5 (15.0)	28 (85.0)	1 (3.0)	32 (97.0)	NA	NA	NA	NA	PCR
Sharma [44]	42 (40.0)	63 (60.0)	68 (36.7)	117 (63.3)	NA	NA	NA	NA	NA	NA	NA	NA	PCR
Singla [51]	10 (59.0)	7 (41.0)	165 (42.0)	226 (58.0)	8 (47.0)	9 (53.0)	102 (26.0)	289 (74.0)	5 (29.0)	12 (71.0)	32 (8.0)	359 (92.0)	Multiplex PCR
Sotsuka [52]	12 (60.0)	8 (40.0)	50 (54.3)	42 (45.7)	7 (35.0)	13 (65.0)	40 (43.5)	52 (56.5)	NA	NA	NA	NA	PCR
Tang [46]	55 (61.8)	34 (38.2)	203 (57.0)	153 (43.0)	40 (44.9)	49 (55.1)	164 (46.1)	192 (53.9)	22 (24.7)	67 (75.3)	94 (26.4)	262 (73.6)	Multiplex PCR
Teixeira [53]	11 (42.3)	15 (57.7)	61 (43.3)	80 (56.7)	4 (15.4)	22 (84.6)	27 (19.2)	114 (80.8)	NA	NA	NA	NA	Multiplex PCR
Wang [45]	63 (60.6)	41 (39.4)	54 (48.6)	57 (51.4)	NA	NA	NA	NA	NA	NA	NA	NA	PCR
Xiang [54]	41 (46.1)	48 (53.9)	925 (42.9)	1230 (57.1)	18 (20.2)	71 (79.8)	477 (22.1)	1678 (77.9)	7 (9.3)	68 (90.7)	283 (16.5)	1427 (83.5)	PCR

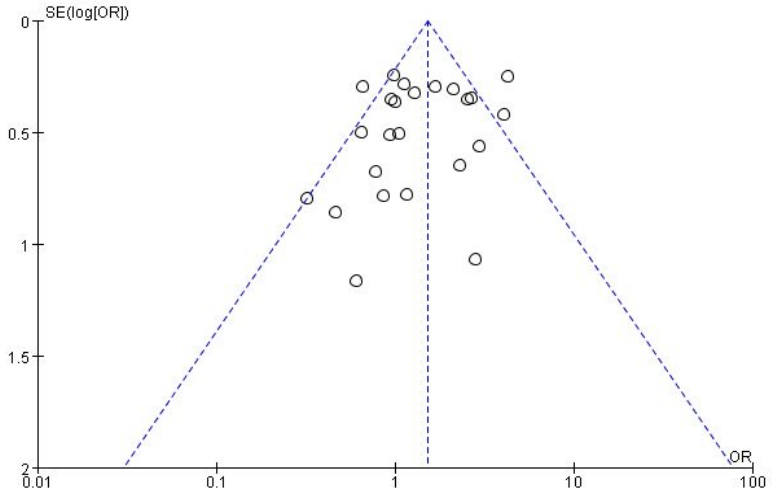
Abbreviations: ***NA***, not available; ***PCR***, polymerase chain reaction

S7 Table. Genotype distribution and the genotyping method used for the *SLCO1B1* genetic polymorphisms in the included studies (n = 4)

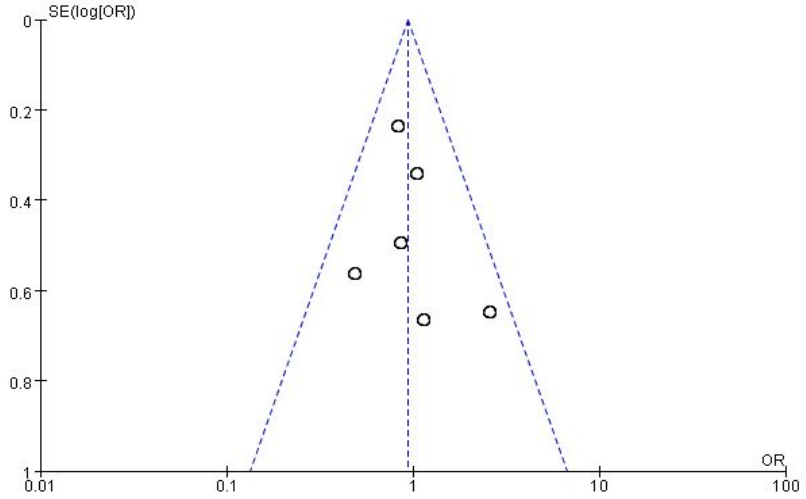
Abbreviations: ***PCR***, polymerase chain reaction; ***SNP***, single nucleotide polymorphism

Study	*SLCO1B1* 388A>G (rs2306283)						*SLCO1B1* 521T>C (rs4149056)						Genotyping method
	Case (number of individuals [%])			Control (number of individuals [%])			Case (number of individuals [%])			Control (number of individuals [%])			
	AA	**AG**	**GG**	**AA**	**AG**	**GG**	**TT**	**CT**	**CC**	**TT**	**CT**	**CC**	
Chen [29]	8 (9.0)	34 (38.2)	47 (52.8)	33 (7.5)	164 (37.1)	245 (55.4)	72 (80.9)	15 (16.9)	2 (2.2)	351 (79.6)	87 (19.7)	3 (0.7)	Taqman
Kim [30]	6 (9.2)	26 (40.0)	33 (50.8)	11 (7.1)	60 (38.5)	85 (54.5)	46 (69.7)	20 (30.3)	0 (0.0)	113 (72.4)	40 (25.6)	3 (1.9)	SNPstream
Li [31]	11 (9.3)	38 (32.2)	69 (58.5)	12 (7.7)	48 (31.0)	95 (61.3)	83 (70.3)	34 (28.8)	1 (0.8)	136 (87.7)	18 (11.6)	1 (0.7)	PCR direct sequencing
Yimer [47]	9 (22.0)	17 (41.5)	15 (36.6)	20 (12.5)	87 (54.4)	53 (33.1)	27 (65.9)	13 (31.7)	1 (2.4)	107 (66.9)	49 (30.6)	4 (2.5)	Taqman

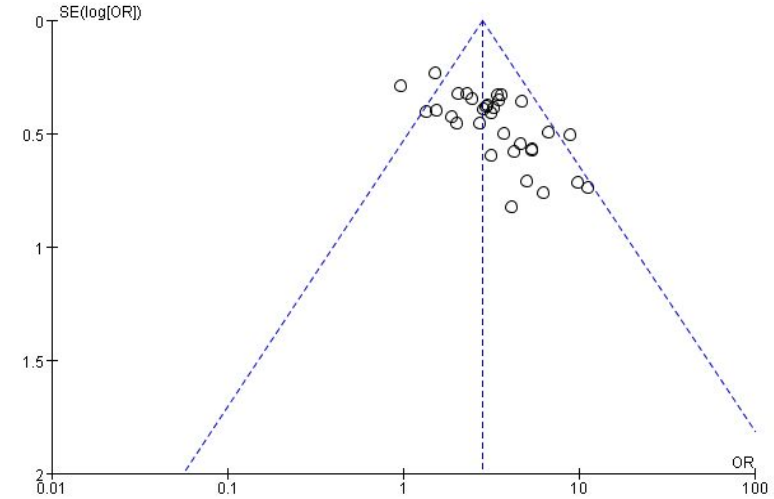
(A) *CYP2E1 Rsa*I/*Pst*I polymorphism



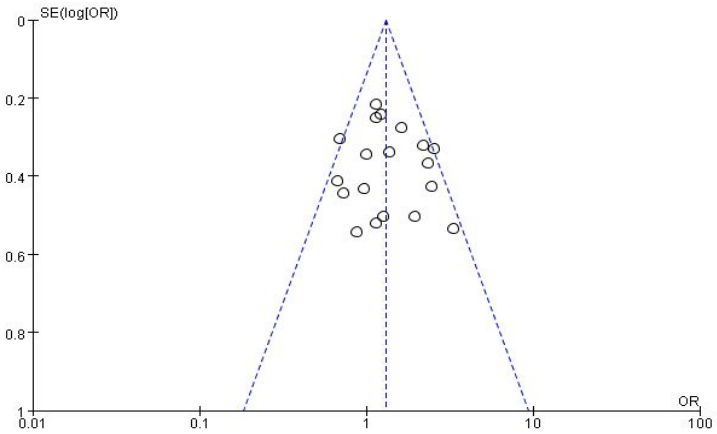
(B) *CYP2E1 Dra*I polymorphism



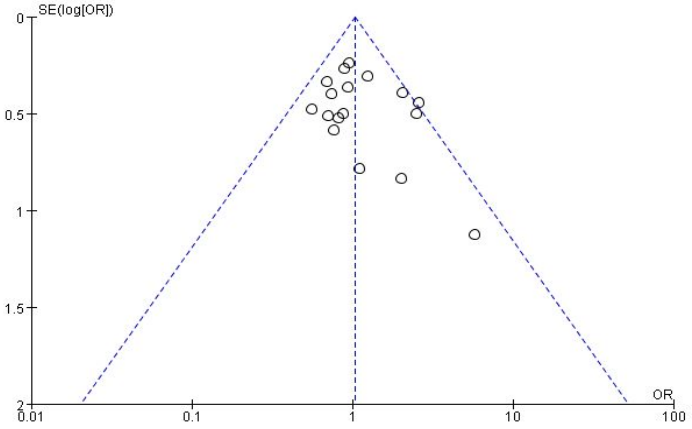
(C) *NAT2* polymorphism



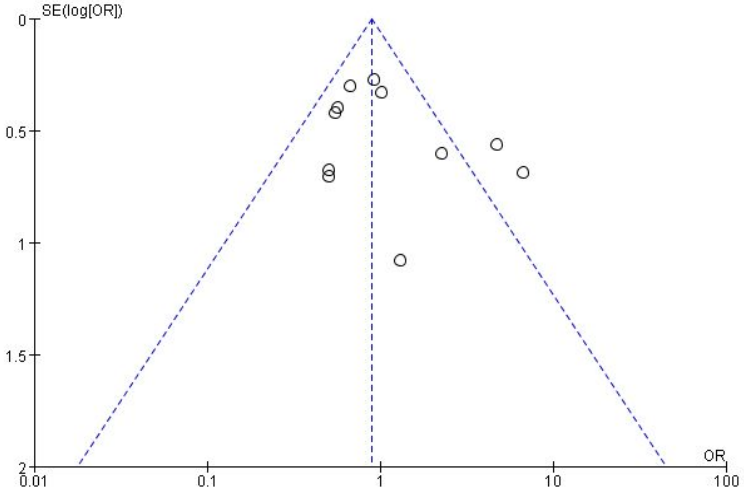
(D) *GSTM1* polymorphism



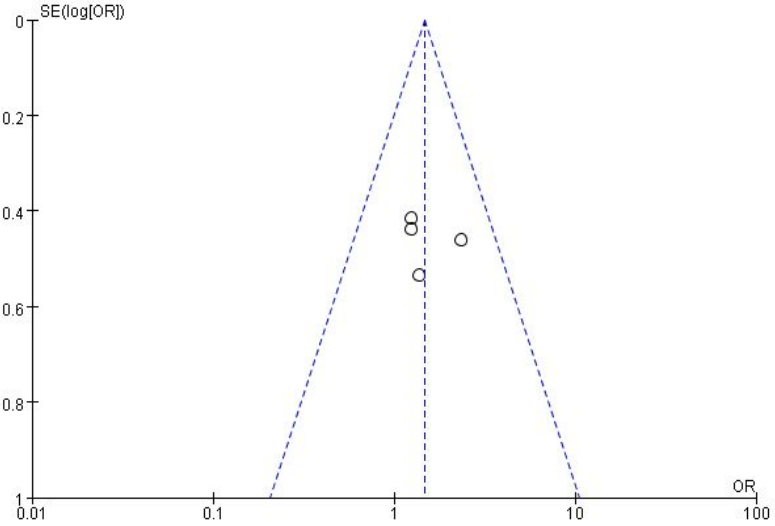
(E) *GSTT1* polymorphism



(F) *GSTT1/M1* polymorphism



(G) *SLCO1B1 388A>G* and *521T>C* polymorphism



S8 Figure. Funnel plots to evaluate publication bias for the *CYP2E1, NAT2, GST,* and *SLCO1B1* polymorphisms associated with the risk of anti-tuberculosis drug-induced liver injury. (A) C*YP2E1 Rsa*I*/Pst*I polymorphism, (B) *CYP2E1 Dra*I polymorphism, (C) *NAT2* polymorphism, (D) *GSTM1* polymorphism, (E) *GSTT1* polymorphism, (F) *GSTT1/M1* polymorphism, and (G) *SLCO1B1 388A>G* and *521T>C* polymorphism.

S9 Table. Subgroup analysis for the association between *CYP2E1* polymorphisms and the risk of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug regimen, and study design

Polymorphic gene	Subgroup		Number of studies	Case/ control (n)	Test of association		Model of meta-analysis	Test of heterogeneity	
					OR [95% CI]	P value[a]		I^2,%	P value[b]
*CYP2E1 Rsa*I/*Pst*I (c1/c1 vs. c1/c2 + c2/c2)	Total		24	1293/5450	1.39 [1.06, 1.83]	0.02	Random	60	<0.0001
	Ethnicity	East Asian	10	736/3076	1.62 [1.12, 2.36]	0.01	Random	69	0.0006
		Indian	6	310/1295	1.08 [0.52, 2.25]	0.85	Random	70	0.005
		South American	6	216/869	1.30 [0.83, 2.03]	0.25	Fixed	0	0.49
		Others	2	31/210	0.98 [0.39, 2.45]	0.96	Fixed	0	0.66
	Anti-TB drug regimen	INH alone	2	31/210	0.98 [0.39, 2.45]	0.96	Fixed	0	0.66
		Combination	21	1212/5104	1.35 [1.01, 1.79]	<0.00001	Random	61	0.0002
	Study design	Cohort	11	564/3120	1.32 [0.94, 1.87]	0.11	Random	50	0.03
		Case-control	12	729/2330	1.42 [0.93, 2.16]	0.10	Random	65	0.0006
*CYP2E1 Dra*I[c] (D/D vs. D/C + C/C)	Total		6	233/1272	0.93 [0.68, 1.27]	0.64	Fixed	0	0.51
	Ethnicity	East Asian	2	109/448	0.84 [0.55, 1.28]	0.41	Fixed	0	0.96
		Indian	2	91/342	0.83 [0.48, 1.45]	0.51	Fixed	27	0.24
		South American	2	33/482	1.80 [0.73, 4.45]	0.20	Fixed	0	0.37
	Study design	Cohort	2	56/407	0.68 [0.31,1.50]	0.33	Fixed	0	0.33
		Case-control	4	177/865	0.99 [0.70, 1.38]	0.94	Fixed	0	0.42

Abbreviations: ***CI***, confidence interval; ***CYP2E1***, cytochrome P450 2E1; ***INH***, isoniazid; ***OR***, odds ratio; ***TB***, tuberculosis

[a] P value from Z test

[b] P value from Cochran's Q test based on chi-square statistic

[c] Subgroup analysis based on anti-TB drug regimen could not be performed due to insufficient information provided.

S10 Table. Subgroup analysis for the association between *NAT2* polymorphism and the risk of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug regimen, and study design

Polymorphic gene	Subgroup		Number of studies	Case/ control (n)	Test of association		Model of meta-analysis	Test of heterogeneity	
					OR [95% CI]	P value[a]		I^2,%	P value[b]
NAT2 (Slow acetylator vs. fast and intermediate acetylator)	Total		35	1323/7319	3.30 [2.65, 4.11]	<0.00001	Random	47	0.002
	Ethnicity	East Asian	13	590/3970	4.00 [2.42,6.60]	<0.00001	Random	77	<0.00001
		Indian	6	246/1352	3.07 [2.26, 4.16]	<0.00001	Fixed	0	0.74
		West Asian	2	44/106	9.51 [4.19, 21.61]	<0.00001	Fixed	0	0.79
		South American	7	231/1110	2.94 [2.11, 4.08]	<0.00001	Fixed	0	0.75
		African	2	55/212	2.08 [1.06, 4.10]	0.03	Fixed	52	0.15
		Others	5	157/569	2.56 [1.72, 3.79]	<0.00001	Fixed	15	0.32
	Anti-TB drug regimen	INH alone	2	31/210	2.32 [1.05, 5.13]	0.04	Fixed	0	0.45
		Combination	32	1256/6954	3.37 [2.67, 4.25]	<0.00001	Random	56	<0.0001
	Study design	Cohort	18	673/4850	2.82 [2.35, 3.40]	<0.00001	Fixed	40	0.04
		Case-control	17	650/2469	3.53 [2.42, 5.16]	<0.00001	Random	65	0.0001

Abbreviations: ***CI***, confidence interval; ***INH***, isoniazid; ***NAT2***, N-acetyltransferase 2; ***OR***, odds ratio; ***TB***, tuberculosis

[a] P value from Z test

[b] P value from Cochran's Q test based on chi-square statistic

S11 Table. Subgroup analysis for the association between *GST* polymorphisms and the risk of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug regimen, and study design

Polymorphic gene	Subgroup		Number of studies	Case/ control (n)	Test of association		Model of meta-analysis	Test of heterogeneity	
					OR [95% CI]	P value[a]		I^2,%	P value[b]
GSTM1[c] (null vs. non-null)	Total		19	977/5119	1.30 [1.12, 1.52]	0.0007	Fixed	33	0.08
	Ethnicity	East Asian	7	442/3110	1.23 [0.99, 1.54]	0.06	Fixed	23	0.25
		Indian	7	341/1420	1.68 [1.30, 2.19]	<0.0001	Fixed	36	0.15
		Brazilian	4	159/529	0.98 [0.66, 1.47]	0.94	Fixed	0	0.60
	Study design	Cohort	8	462/3439	1.41 [1.04, 1.93]	0.03	Random	44	0.08
		Case-control	11	515/1680	1.25 [1.01, 1.55]	0.20	Fixed	29	0.17
GSTT1[c] (null vs. non-null)	Total		17	768/4823	1.03 [0.85, 1.25]	0.76	Fixed	16	0.26
	Ethnicity	East Asian	6	338/2999	0.96 [0.74, 1.24]	0.75	Fixed	0	0.94
		Indian	6	236/1235	1.37 [0.72, 2.59]	0.33	Random	57	0.04
		Brazilian	4	159/529	0.80 [0.47, 1.33]	0.39	Fixed	0	0.97
	Study design	Cohort	8	408/3354	0.89 [0.67, 1.19]	0.44	Fixed	3	0.41
		Case-control	9	360/1469	1.16 [0.90, 1.50]	0.26	Fixed	24	0.23
GSTM1/GSTT1[c] (dual-null vs. one-/non-null)	Total		11	547/4233	1.05 [0.67, 1.62]	0.84	Random	59	0.006
	Ethnicity	East Asian	3	235/2701	0.83 [0.58, 1.20]	0.33	Fixed	0	0.49
		Indian	5	203/1202	1.33 [0.50, 3.53]	0.56	Random	80	0.0005
		Brazilian	2	74/270	0.67 [0.20, 2.18]	0.50	Fixed	0	0.47
	Study design	Cohort	6	298/3136	0.85 [0.45, 1.61]	0.62	Random	58	0.04
		Case-control	5	249/1097	1.31 [0.71, 2.43]	0.39	Random	59	0.04

Abbreviations: ***CI***, confidence interval; ***GSTM1***, glutathione S-transferase Mu 1; ***GSTT1***, glutathione S-transferase Theta 1; ***OR***, odds ratio

[a] P value from Z test

[b] P value from Cochran's Q test based on chi-square statistic

[c] Subgroup analysis based on anti-tuberculosis drug regimen could not be performed due to insufficient information provided

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Original article

Association of genetic polymorphisms of *CYP2E1, NAT2, GST,* and *SLCO1B1* with the risk of anti-tuberculosis drug-induced liver injury: a systematic review and meta-analysis

Seungwon Yang[1], Se Jung Hwang[2], Jung Yun Park[3], Eun Kyoung Chung[2,4*], Jangik Ike Lee[3,5*]

[1] Department of Pharmacy and Yonsei Institute of Pharmaceutical Science, College of Pharmacy, Yonsei University, Incheon 21983, Republic of Korea

[2] Department of Pharmacy, College of Pharmacy, Kyung Hee University, Seoul 02447, Republic of Korea

[3] College of Pharmacy, Seoul National University, Seoul 08826, Republic of Korea

[4] Department of Pharmacy, Kyung Hee University Hospital at Gangdong, Seoul, 05278, Republic of Korea

[5] College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 08826, Republic of Korea

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[*]**Corresponding authors**

Prof., Eun Kyoung Chung, Pharm.D., Ph.D.

Department of Pharmacy, College of Pharmacy, Kyung Hee University

26 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447

South Korea

Tel: +82-2-962-2122

Fax: +82-2-961-9580

E-mail: cekchung@khu.ac.kr

Prof. Jangik I. Lee, Pharm.D., Ph.D.

Department of Pharmacy, College of Pharmacy, Seoul National University

103 Daehak-Ro, Jongno-Gu, Seoul 03080

South Korea

Tel: +82-2-3668-7474

Fax: +82-2-3668-7475

E-mail: jangik.lee@snu.ac.kr

*Jangik I. Lee and Eun Kyoung Chung have equally contributed to this study.

Running head

Genetics of anti-tuberculosis liver injury

ABSTRACT

Objectives The objective of this study was to investigate the association between genetic polymorphisms of *NAT2*, *CYP2E1*, *GST*, and *SLCO1B1* and the risk of anti-tuberculosis drug-induced liver injury (ATDILI).

Design Systematic review and meta-analysis

Data Sources PubMed, EMBASE, Web of Science, and Cochrane Reviews databases were searched through April 2019.

Eligibility Criteria We included case-control or cohort studies investigating an association between *NAT2, CYP2E1, GST*, or *SLCO1B1* polymorphisms and the ATDILI risk in patients with tuberculosis.

Data extraction and synthesis Three authors screened articles, extracted data, and assessed study quality. The strength of association was evaluated for each gene using the pooled odds ratio (OR) with a 95% confidence interval (CI) based on the fixed- or random-effects model. Sensitivity analysis was performed to confirm the reliability and robustness of the results.

Results Fifty-four studies were included in this analysis (n = 26 for *CYP2E1*, n = 35 for *NAT2*, n = 19 for *GST*, n = 4 for *SLCO1B1*). The risk of ATDILI was significantly increased with the following genotypes: *CYP2E1 Rsa*I/*Pst*I c1/c1 (OR = 1.39; 95% CI 1.06–1.83), *NAT2* slow acetylator (OR = 3.30, 95% CI 2.65–4.11), and *GSTM1* null (OR = 1.30, 95% CI 1.12–1.52). No significant association with ATDILI was found for the genetic polymorphisms of *CYP2E1 Dra*I, *GSTT1*, *GSTM1/GSTT1*, *SLCO1B1* 388A>G, and *SLCO1B1* 521T>C (P > 0.05).

Conclusions

ATDILI is more likely to occur in patients with *NAT2* slow acetylator genotype, *CYP2E1*

*Rsa*I/*Pst*I c1/c1 genotype, and *GSTM1* null genotype. Close monitoring may be warranted for patients with these genotypes.

Strengths and limitations of this study

- This is the first meta-analysis to evaluate the association between the risk of ATDILI and *SLCO1B1* in patients with tuberculosis.
- We included most updated studies with the large sample sizes to better clarify the association of genetic polymorphisms with the risk of ATDILI.
- The effect of anti-tuberculosis drug dosages on the risk of ATDILI could not be accounted for in this study due to the lack of drug dosing information in the majority of the included studies.

Introduction

Tuberculosis is a rampant infectious disease caused by *Mycobacterium tuberculosis.* It poses a major public health threat globally with approximately 1.3 million deaths and 10 million new cases in 2017 [1]. The mainstay of first-line tuberculosis treatment is a 4-drug combination regimen of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) during the first 2 months, followed by INH and RIF for additional 4 months [2 3]. The currently recommended therapy for tuberculosis is highly effective, resulting in high cure rates if patients are adherent to therapy [4]. However, treatment adherence is often suboptimal in patients receiving the combination anti-tuberculosis therapy due to many adverse drug reactions, some of which are considered detrimental [5]. One of the common adverse drug reactions associated with anti-tuberculosis medications is anti-tuberculosis drug-induced liver injury (ATDILI) affecting 2−28% of patients with tuberculosis [6]. ATDILI could be potentially serious and fatal, resulting in the treatment interruption and ultimately, treatment failure [7 8].

Recently, increasing evidence suggests an association between the risk of ATDILI and genetic polymorphisms of drug-metabolizing enzymes (DMEs) and drug transporters [9 10]. Altered enzyme activity due to polymorphic genotypes of various DMEs including cytochrome P450 2E1 (CYP2E1), N-acetyltransferase 2 (NAT2), and glutathione S-transferase (GST) can result in the accumulation of toxic substances in the liver, leading to the development of ATDILI [11]. However, conflicting results have been reported regarding the association between the risk of ATDILI and genetic polymorphisms of various DMEs in patients with tuberculosis [9 12 13]. In addition to DMEs, drug transporters have been emerging as a key determinant of the pharmacokinetics and pharmacodynamics of a drug [14]. Among various drug transporters, organic

anion transporting polypeptide 1B1 (OATP1B1), encoded by *SLCO1B1*, is the major influx transporter responsible for hepatic uptake of RIF [15]. Although several studies have previously examined the association between *SLCO1B1* polymorphisms and the risk of ATDILI, conflicting results have been reported regarding the effect of *SLCO1B1* polymorphisms on ATDILI risk. Therefore, an updated meta-analysis has been warranted to confirm the association between the ATDILI risk and genetic polymorphisms of DMEs. In our preliminary literature search, several polymorphic genes, including many DMEs, transporters, and other genes such as those involved in the immune system, were identified to have an association with the risk of ATDILI. Among these, sufficient, published information was available to confirm the effect of *CYP2E1*, *NAT2*, *GST*, and *SLCO1B1* genetic polymorphisms on the ATDILI risk through meta-analysis.

Objectives

The objective of this meta-analysis was to evaluate the association between the risk of ATDILI and genetic polymorphisms of *CYP2E1*, *NAT2*, *GST*, and *SLCO1B1* in patients with tuberculosis.

Methods

This study was in compliance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist for reporting the study design, search strategy, methods, results, and conclusions (S1 Table). Three authors (SY, JP, and SH) independently conducted a literature search, study selection, quality assessment, and data extraction. Any discrepancies were adjudicated by corresponding authors (JIL and EKC).

Search strategy

Electronic databases of PubMed, EMBASE, Web of Science, and Cochrane Reviews were systematically searched from their inception to April 2019 to identify relevant studies evaluating the association of *NAT2*, *CYP2E1*, *GST*, and *SLCO1B1* polymorphisms with ATDILI risk. A comprehensive literature search was conducted using a combination of the following keywords and Medical Subject Heading (MeSH) terms: ("genetic polymorphism" or "*NAT2*" or "*CYP2E1*" or "*GST*" or "*SLCO1B1*" or "drug-metabolizing enzymes" or "drug transporter") AND ("anti-tuberculosis agents drug-induced liver injuries" or "hepatotoxicity"). The detailed search strategies for each electronic database used in this analysis are presented in S2 Table. The reference lists in the selected reviews and meta-analyses were reviewed to ensure the inclusion of all relevant evidence in this analysis.

Study selection

Studies were considered eligible if they met all of the following inclusion criteria: (1) studies in patients with tuberculosis receiving anti-tuberculosis drug regimen; (2) studies with the control group of patients with tuberculosis, tolerant of anti-tuberculosis medications; (3) studies evaluating the association between the occurrence of ATDILI and genetic polymorphisms of *CYP2E1*, *NAT2*, *GST,* and *SLCO1B1* 388A>G and 521T>C; and (4) case-control or cohort observational studies. Excluded studies were as follows: (1) studies available only in the form of abstracts or meeting posters; (2) review or meta-analysis articles; (3) studies providing insufficient data necessary for the statistical data analysis; (4) studies in non-English language; (5) non-human studies including animal and *in vitro* studies; (6) studies with unpublished data; (7) studies providing insufficient information on genotyping methods; and (8) healthy controls.

Quality assessment and data extraction

The quality of included studies was assessed using the revised Little's recommendation based on the following criteria [16 17]: (1) scientific design; (2) definite inclusion of study population; (3) explicit information on study population; (4) explicit diagnostic criteria of ATDILI; (5) genetic detection method; (6) appropriate statistical analysis; and (7) logical discussion of study bias. Studies with an overall score of ≥ 4 (range 0 to 7) were considered high quality and retained in the analysis.

The following data were extracted from each study using a standardized extraction form: (1) name of the first author; (2) year of publication; (3) the polymorphic gene(s) and genotype(s) under investigation; (4) ethnicity; (5) sample size; (6) mean or median age; (7) sex distribution; (8) anti-tuberculosis drug regimens; (9) diagnostic criteria of ATDILI; (10) genotyping methods; and (11) the number of cases and controls for each polymorphic genotype.

Statistical analysis

The genotypes were analyzed based on the following proposed genetic risk model: (1) *NAT2* (slow acetylator *vs.* intermediate and fast acetylator); (2) *CYP2E1* (c1/c1 *vs.* c1/c2 and c2/c2 for the *Rsa*I/*Pst*I polymorphism, D/D *vs.* D/C and C/C for the *Dra*I polymorphism); (3) *GSTM1* (null *vs.* non-null); (4) *GSTT1* (null *vs.* non-null); (5) *GSTM1*/*GSTT1* (dual-null *vs.* one- or non-null); and (6) *SLCO1B1* 388A>G and 521T>C polymorphisms. The genetic risk models for *NAT2*, *CYP2E1*, *GSTM1*, *GSTT1*, and *GSTM1/GSTT1* have been studied in previous studies[9 18 19]. Based on these previous studies, the most clinically significant and plausible model for each polymorphic gene was selected. Due to the relative paucity of data suggesting the most clinically

relevant genetic model for *SLCO1B1* 388A>G and 521T>C polymorphisms, all three genomic models including dominant, recessive, and additive models were evaluated. The Mantel-Haenszel or DerSimonian-Laird method based on fixed- or random-effects models, respectively, were used depending on the presence of heterogeneity [20 21]. The random-effects model was used in the presence of significant heterogeneity; otherwise, the fixed-effects model was used to estimate the total effect of a polymorphic gene genotype on the risk of ATDILI. Heterogeneity of study outcomes among included studies was evaluated using Cochran's Q test *(Q)* and quantified using Higgin's I^2 test. Significant heterogeneity was defined as the I^2 score of > 40% accompanied by $P < 0.10$ from the Cochran's Q test [22]. The strength of the association between the genetic polymorphisms and the risk of ATDILI was estimated using pooled odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). The statistical significance of an OR was defined as $P < 0.05$ from the Z test.

Subgroup analysis was performed based on ethnicity, anti-tuberculosis drug regimen used, and the type of study design. Sensitivity analysis was conducted to assess the robustness of the results and to identify the source of heterogeneity using the leave-one-out method. In each analysis, one study was deleted, and with the one study left out, the meta-analysis was performed; this process was repeated until every study had been deleted from our included study pool for each tested polymorphic gene. Publication bias was evaluated with a symmetrical funnel plot. Statistical analyses were performed using Review Manager Software version 5.3 (Cochrane Collaboration, London, UK).

Patient and public involvement

Patients and public were not involved in the design of this study.

Results

Study selection and characteristics

Overall, 388 articles were identified through electronic database search and 3 articles through manual search by reviewing the reference lists of retrieved articles. After removing 99 duplicates, 289 articles were screened for relevance based on the title and abstract. Among them, 72 relevant articles were assessed for eligibility through full-text evaluations. Finally, a total of 54 articles which met the inclusion criteria were included in our analysis (Figure 1). Among the 54 studies, 26 studies were included for *CYP2E1*, 35 studies for *NAT2*, 19 studies for *GST* (19 for *GSTM1*, 17 for *GSTT1*, and 11 for *GSTM1*/*GSTT1*), and 4 studies for *SLCO1B1* 388A>G and 521T>C.

Table 1 summarizes the characteristics of the included studies. Across the included studies, large variability in study population was observed in terms of ethnicity (Chinese, Japanese, Korean, Indian, Taiwanese, Brazilian, Caucasian, Iranian, Tunisian, and Turkish), age (mean or median age ranging from 27 to 70 years), and sex (the proportion of males ranging from 13% to 90%). Patients in our included studies received either monotherapy with INH or RIF or a combination therapy including a 4-drug regimen of INH, RIF, PZA, and EMB for the treatment of tuberculosis. ATDILI was defined as an elevated serum alanine aminotransferase (ALT) concentration by 1.5- to 5-fold or greater above the upper limit of normal (ULN) depending on the study. The quality score of the included studies was 6 or greater based on the revised Little's recommendation (Table 1, S3 Table) [16 17]. Genotype distribution and genotyping

method used in the included studies are summarized for each polymorphic gene in S4 to S7 Tables. Funnel plots for *CYP2E1, NAT2, GST*, and *SLCO1B1* are provided in S8 Figure. None of the funnel plots showed an asymmetric inverted funnel shape, indicating the absence of potential publication bias.

CYP2E1

For the *CYP2E1 Rsa*I/*Pst*I polymorphism, 24 studies with 1293 cases and 5450 controls were included in our primary analysis. Using the random-effects model, the pooled estimates of all included studies (n = 24) showed a significant association between the risk of ATDILI and the *CYP2E1 Rsa*I/*Pst*I polymorphism (OR for the c1/c1 genotype = 1.39, 95% CI 1.06–1.83, P = 0.02; I^2 = 60%, $P_{heterogeneity}$ < 0.0001) (Figure 2A). In the subgroup analysis based on ethnicity, and anti-tuberculosis drug regimens, the risk of ATDILI was significantly increased for the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype in East Asian patients (OR = 1.62, 95% CI 1.26–2.36, P = 0.01; I^2 = 69%, $P_{heterogeneity}$ = 0.0006) and in patients receiving a combination of anti-tuberculosis medications (OR = 1.35, 95% CI 1.01–1.79, P < 0.00001; I^2 = 61%, $P_{heterogeneity}$ = 0.0002) (S9 Table). No significant association was observed between the risk of ATDILI and the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype when evaluating studies with the same study design only (i.e., either case-control studies or cohort studies) (S9 Table).

In our primary analysis for the *CYP2E1 Dra*I polymorphism with six studies including 233 cases and 1272 controls, no significant association was observed using the fixed-effects model between the risk of ATDILI and the *Dra*I polymorphism (OR for the D/D genotype = 0.93, 95% CI 0.68–1.27, P = 0.64; I^2 = 0%, $P_{heterogeneity}$ = 0.51) (Figure 2B).

NAT2

Overall, 35 studies with 1323 cases and 7319 controls were included in our primary analysis for the *NAT2* polymorphism. Using the random-effects model, the pooled estimates of all included studies (n = 35) showed a significant association between the risk of ATDILI and the *NAT2* polymorphism (OR for the slow acetylator genotype = 3.30, 95% CI 2.65–4.11, P < 0.00001; I^2 = 54%, $P_{heterogeneity}$ < 0.0001) (Figure 3). In the subgroup analysis based on ethnicity, anti-tuberculosis drug regimens used, and study design, the risk of ATDILI was significantly increased in slow acetylators compared to fast or intermediate acetylators in all subgroups (S10 Table).

GST

For the *GSTM1* polymorphism, a total of 19 studies with 977 cases and 5119 controls were included in our primary analysis. Using the fixed-effects model, the pooled estimates of all included studies (n = 19) showed a significant association between the risk of ATDILI and the *GSTM1* polymorphism (OR for the *GSTM1* null genotype = 1.30, 95% CI 1.12–1.52, P = 0.0007; I^2 = 33%, $P_{heterogeneity}$ = 0.08) (Figure 4A). When studies were stratified for ethnicity, the risk of ATDILI was significantly increased for the *GSTM1* null genotype in Indians (OR = 1.68, 95% CI 1.30–2.19, P < 0.0001; I^2 = 36%, $P_{heterogeneity}$ = 0.15) (S11 Table). In the subgroup analyses by study design, the estimated OR (95% CI, P-value; I^2, $P_{heterogeneity}$) for the *GSTM1* null genotype relative to the non-null genotype was 1.41 (1.04-1.93, P = 0.03; I^2 = 44%, $P_{heterogeneity}$ = 0.08) in cohort studies and 1.25 (1.01-1.55, P = 0.20; I^2 = 29%, $P_{heterogeneity}$ = 0.17) in case-control studies, respectively (S11 Table).

For the *GSTT1* and *GSTM1*/*GSTT1* polymorphisms, 17 studies (768 cases, 4823 controls) and 11 studies (547 cases, 4233 controls) were included in our primary analyses, respectively.

The risk of ATDILI was not significantly associated with the *GSTT1* polymorphism (OR for the null genotype = 1.03, 95% CI 0.85–1.25, P = 0.76; I^2 = 16%, $P_{heterogeneity}$ = 0.26) or the *GSTM1*/*GSTT1* polymorphism (OR for the dual-null genotype = 1.05, 95% CI 0.67–1.62, P = 0.84; I^2 = 59%, $P_{heterogeneity}$ = 0.006) (Figures 4B and 4C). When studies were stratified for ethnicity, anti-tuberculosis drug regimens used, and study design, no subgroups showed significant association between the risk of ATDILI and the *GSTT1* and the *GSTM1/GSTT1* polymorphisms (S11 Table).

SLCO1B1

For the *SLCO1B1* 388A>G polymorphism, four studies with 302 cases and 913 controls were included in our primary analysis. Using the dominant, recessive, or additive genomic model, no significant association was observed between the risk of ATDILI and the *SLCO1B1* 388A>G polymorphism (Table 2). For the *SLCO1B1* 521T>C polymorphism, four studies with 314 cases and 912 controls were included in our primary analysis. No significant association was found between the ATDILI risk and the *SLCO1B1* 521T>C polymorphism under the dominant, recessive, or additive genetic model (Table 2). Due to the lack of significant association between the risk of ATDILI and the tested *SLCO1B1* genetic polymorphisms in our primary meta-analysis, subgroup analyses were not performed for these genetic polymorphisms.

Sensitivity analysis

Our primary analysis results showed significantly high heterogeneity between studies for *CYP2E1 Rsa*I/*Pst*I (I^2 = 60%, P < 0.0001), *NAT2* (I^2 = 54%, P < 0.0001), *GSTM1*/*GSTT1* (I^2 = 59%, P = 0.006), and *SLCO1B1* 521T>C (dominant genetic model: I^2 = 66%, P = 0.03) polymorphisms. This high heterogeneity between studies may be due to substantial differences in

ethnicity, anti-tuberculosis drug regimen, the genotyping method used, study design, and diagnostic criteria of ATDILI among the included studies (Table 1). Through the sensitivity analyses, outlier studies were identified as the major source of heterogeneity. After removing these outlier studies, heterogeneity was substantially reduced (I^2 = 60% to 42% for *CYP2E1 Rsa*I/*Pst*I [23], I^2 = 54% to 34% for *NAT2* [24 25], I^2 = 59% to 0% for *GSTM1/GSTT1* [26 27], and I^2 = 66 % to 0% for *SLCO1B1* 521T>C dominant genetic model [28]). The overall results for the association between the risk of ATDILI and these genetic polymorphisms after excluding the outlier studies stayed the same as those from our primary analysis results.

Discussion

In this study, we conducted a large-scale meta-analysis evaluating the association between the risk of ATDILI and genetic polymorphisms of *SLCO1B1* as well as various DMEs including *CYP2E1*, *NAT2*, and *GST* to provide more updated, comprehensive, and compelling evidence. Compared with previous meta-analyses, our present study included a larger number of studies, which may sufficiently increase the statistical power compared to individual studies. However, a limited number of studies for the *SLCO1B1* genetic polymorphisms were included (n = 4). Consistently with previous studies, our current study suggested a significantly increased risk of ATDILI in patients with the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype (OR = 1.39, 95% CI 1.06–1.83), the *NAT2* slow acetylator genotype (OR = 3.30, 95% CI 2.65–4.11), and the *GSTM1* null genotype (OR = 1.30, 95% CI 1.12–1.52) [9 12 29]. Among these genotypes, the largest increase in the risk of ATDILI was shown in patients with the *NAT2* slow acetylator genotype. In contrast, no significant association was observed between the risk of ATDILI and the genetic

polymorphisms of *CYP2E1 Dra*I, *GSTT1*, *GSTM1*/*GSTT1*, *SLCO1B1 388A>G*, and *SLCO1B1 521T>C*. Caution needs to be exercised when interpreting this study finding because the lack of significant association between these polymorphisms and the risk of ATDILI might be due to small sample sizes and the low frequency of ATDILI reported in patients with these genetic polymorphisms.

When evaluating the impact of the *CYP2E1 Rsa*I/*Pst*I and *Dra*I genetic polymorphisms on the risk of ATDILI in our study, patients with the *Rsa*I/*Pst*I c1/c1 genotype were 1.39-times more likely to develop ATDILI. Similarly, in a previous meta-analysis by Deng and colleagues, the risk of ATDILI was 1.4-times higher in patients with the *Rsa*I/*Pst*I c1/c1 genotype compared to other genotypes [30]. In the liver, INH is metabolized by NAT2 to acetylisoniazid which is consequently oxidized by CYP2E1 to reactive hepatotoxic intermediates [31 32]. The increased inducibility or greater activity of CYP2E1 in patients with the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype may result in the production of more intermediate hepatotoxins, ultimately leading to the increased risk of ATDILI [31 32]. Our subgroup analysis showed a significantly increased risk of ATDILI in the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype carriers of East Asian ethnicity (S9 Table), suggesting a potential gene-ethnicity interaction [33]. A previous study identified age, female sex, white race, non-Hispanic ethnicity, lower body mass index, elevated plasma aspartate transaminase concentrations at baseline, and nine months of daily INH use as risk factors for ATDILI [34]. Considering their race, ethnicity, and relatively lower body mass index compared to other ethnicities, East Asians may be at an increased risk of ATDILI. As the *CYP2E1 Rsa*I/*Pst*I c1 allele frequency is relatively low in this population (79.8% *vs.* 88.5% to 99.8% in other ethnicities), the ethnicity itself might play an important role in developing hepatotoxicity through gene-ethnicity interaction [35]. Furthermore, the relatively high frequency of c2 allele in this

population might serve as a good control to estimate the effect of c1 allele on the risk of ATDILI; the rarity of this minor allele in other ethnicities could make it difficult to evaluate the association between the ATDILI risk and this genetic polymorphism [35]. In addition to ethnicity, combination anti-tuberculosis therapy was shown to significantly increase the risk of ATDILI in patients with the *CYP2E1 Rsa*I/*Pst*I c1/c1 genotype (S9 Table). This is consistent with previous study findings because hepatotoxicity commonly occurs with anti-tuberculosis drugs such as INH and RIF and thus, use of more than one hepatotoxic anti-tuberculosis medication increases the risk of ATDILI [7].

Similar to previous studies, our current study suggested a significantly increased risk of ATDILI in patients with the *NAT2* slow acetylator genotype compared to those with intermediate/fast acetylator genotypes [9 29]. The risk of ATDILI in slow acetylators remained significantly increased in all tested subgroups regardless of ethnicity and the anti-tuberculosis drug regimen used (S10 Table). The frequencies of *NAT2* slow acetylator alleles are highly variable between ethnic groups, ranging from 32% in Koreans to 76% in Caucasians [36]. Despite this large inter-ethnic variability in the *NAT2* polymorphic allele frequency, the *NAT2* slow acetylator genotype consistently and significantly increased the risk of ATDILI across all ethnicities, suggesting the critical role of *NAT2* polymorphism in the development of ATDILI. In addition, the increased risk of ATDILI in slow acetylators receiving INH monotherapy or combination therapy further highlights the importance of the *NAT2* polymorphism in the development of INH-induced hepatotoxicity. The clearance of INH is slower in slow acetylators compared to rapid or intermediate acetylators, resulting in the accumulation of INH in these patients [37 38]. This high level of INH may increase the risk of ATDILI in patients with tuberculosis carrying *NAT2* slow acetylator genotype due to immune-mediated liver injury

through the binding of INH to liver proteins [39]. Therefore, clinicians should closely monitor patients with tuberculosis carrying the *NAT2* slow acetylator genotype for hepatotoxicity when INH-based treatment is administered to these patients.

According to previous studies, GST enzymes, particularly those coded by *GSTM1* and *GSTT1* loci, are associated with the risk of drug-induced hepatotoxicity [9 40]. Similar to previous studies, our current study demonstrated a significantly increased risk of ATDILI in individuals with the *GSTM1* null genotype compared to those with the non-null genotype; however, the risk of ATDILI was not affected by the *GSTT1* or *GSTM1*/*GSTT1* genetic polymorphisms. GSTs are important enzymes to detoxify various xenobiotics and play an essential role in INH metabolism by eliminating acetyldiazene ketene acetylonium ion, which is a possibly hepatotoxic free radical metabolite of INH, from the body through *GSTM1*. This may account for the significant association of the ATDILI risk with the *GSTM1* genotype, but not with the *GSTT1* or *GSTM1*/*GSTT1* genotypes [9 40]. Our subgroup analysis showed a significantly increased risk of ATDILI in the *GSTM1* null genotype carriers of Indian ethnicity; although not statistically significant, the risk of ATDILI was relatively high in the East Asian population with the *GSTM1* null genotype (S11 Table). Considering the substantial difference in the GSTM1 null allele frequency between Indians (29.6%) and East Asians (52.1%), a potential gene-ethnicity interaction may exist based on their race, ethnicity, and body size as aforementioned [34 41]. Other characteristics than the *GSTM1* polymorphism in these ethnicities may play a more important role in the development of ATDILI. In addition, when studies were stratified by study design, the risk of ATDILI was significantly increased in patients with the *GSTM1* null genotype for cohort studies only, but not for case-control studies, probably due to a relatively larger sample size with cohort studies compared to case-control studies.

SLCO1B1 encodes organic anion transporting polypeptide 1B1 (OATP1B1) which is a major influx drug transporter responsible for the hepatic uptake of various endogenous and exogenous substances including RIF [42]. Previous studies showed significantly altered systemic exposure of RIF in carriers of the *SLCO1B1* polymorphism [43 44]. To our knowledge, only four studies have been conducted to examine the association between the ATDILI risk and the *SLCO1B1* genetic polymorphisms [10 28 42 45]. Various single nucleotide polymorphisms (SNPs) of *SLCO1B1* were evaluated in these studies; however, *SLCO1B1* 388A>G (rs2306283) and 521T>C (rs4149056) were the only polymorphisms assessed in common [10 28 42 45]. Therefore, to maximize the sample size in our current meta-analysis, we examined the association between the risk of ATDILI and the polymorphic genotypes of *SLCO1B1* 388A>G and 521T>C. Similar to each of the included studies, we did not find significant difference in the risk of ATDILI among patients with different *SLCO1B1* 388A>G and 521T>C genotypes.

There are limitations to this study. First, due to the lack of information regarding other patient characteristics potentially associated with ATDILI, our estimated ORs were not adjusted based on the potential risk factors such as age, anti-tuberculosis drug dosages, alcohol consumption, cigarette smoking, and other lifestyle characteristics [7 46]. Second, our literature search limited to the articles published in English may lead to language bias. Third, a specific causative agent of ATDILI could not be identified in our analysis because most patients in our included studies received a combination regimen of anti-tuberculosis drugs. Fourth, only the limited number of polymorphic genotypes were assessed for the association with the risk of ATDILI, particularly for *SLCO1B1*. In addition, only one genetic model was used for *CYP2E1*, *NAT2*, and *GST* when evaluating the association between genetic polymorphisms of these genes and the risk of ATDILI. Although we acknowledge dominant, recessive, and additive genomic

models can be used for two alleles, it could not be applied to our meta-analysis because we compared patients with different genotype-based phenotype, i.e., slow acetylator *vs.* fast/intermediate acetylator and null vs. non-null *GST*s. Multiple allelic variants or allele subgroups may represent the same phenotype (e.g., *NAT2**5B, *6A, and *7B all represent slow acetylator genotypes), and the genetic model selection can be varied depending on the specific allelic variant [47] . Therefore, the genetic models used in previous original and meta-analysis studies were adopted for these polymorphic genes in our current study [9 18 19]. Future studies are needed to comprehensively and adequately address the relationship between the ATDILI risk and various genetic polymorphisms by using different genetic risk models and including more polymorphic genotypes.

In conclusion, the risk of ATDILI during tuberculosis therapy was significantly increased in patients with tuberculosis carrying *NAT2* slow acetylator, *CYP2E1 Rsa*I/*Pst*I c1/c1, or *GSTM1* null genotypes. Screening for these genetic polymorphisms, particularly for the *NAT2* slow acetylator genotype, may be of great clinical benefit to identify patients at high risk for ATDILI and minimize the risk of ATDILI. Future studies are pertinent to develop dose and/or treatment adjustment strategies, to evaluate the feasibility and cost-effectiveness of the genetic screening test, and to assess the effect of more genetic polymorphisms on the risk of ATDILI for optimal prevention and management of ATDILI.

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Contributors

S.Y. devised and designed the study. S.Y., J.Y.P., and S.J.H. conducted the literature search, performed data extraction and analysis, and. interpreted the data. S.Y., E.K.C., and J.I.L. prepared and reviewed the manuscript. All authors reviewed, amended and approved the submitted manuscript

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Supporting information

Additional supporting information can be found in the online version of this article:

S1 Table. Completed MOOSE (Meta-analysis Of Observational Studies in Epidemiology) checklist

S2 Table. Search strategies

S3 Table. Study quality assessment

S4 Table. Genotype distribution and the genotyping method used for the *CYP2E1* genetic polymorphisms in the included studies (n = 26)

S5 Table. Genotype distribution and the genotyping method used for the *NAT2* genetic polymorphism in the included studies (n = 35)

S6 Table. Genotype distribution and the genotyping method used for the *GST* genetic polymorphisms in the included studies (n = 19)

S7 Table. Genotype distribution and the genotyping method used for the *SLCO1B1* genetic polymorphisms in the included studies (n = 4)

S8 Figure. Funnel plots to evaluate publication bias for the *CYP2E1, NAT2, GST,* and *SLCO1B1* polymorphisms associated with the risk of anti-tuberculosis drug-induced liver injury. (A) C*YP2E1 Rsa*I/*Pst*I polymorphism, (B) *CYP2E1 Dra*I polymorphism, (C) *NAT2* polymorphism, (D) *GSTM1* polymorphism, (E) *GSTT1* polymorphism, (F) *GSTT1/M1* polymorphism, and (G) *SLCO1B1* 388A>G and 521T>C polymorphism.

S9 Table. Subgroup analysis for the association between *CYP2E1* polymorphisms and the risk of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug regimen, and study design

S10 Table. Subgroup analysis for the association between *NAT2* polymorphism and the risk of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug regimen, and study design

S11 Table. Subgroup analysis for the association between *GST* polymorphisms and the risk of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug regimen, and study design

Figure legends

Figure 1. Study selection process flowchart.

Figure 2. Risk of anti-tuberculosis drug-induced liver injury in patients with the *CYP2E1* (A) *Rsa*I/*Pst*I c1/c1 genotype compared to c1/c2 + c2/c2 genotypes and (B) *Dra*I D/D genotype compared to D/C + C/C genotypes.

Figure 3. Risk of anti-tuberculosis drug-induced liver injury in patients with the *NAT2* slow acetylator genotype compared to those with the intermediate/fast acetylator genotypes.

Figure 4. Risk of anti-tuberculosis drug-induced liver injury in patients with (A) the *GSTM1* null genotype compared to the non-null genotype, (B) the *GSTT1* null genotype compared to the non-null genotype, and (C) the *GSTM1*/*GSTT1* dual-null genotype compared to the one- and non-null genotypes.

Table 1. Characteristics of the studies included in the meta-analysis (n = 54 studies)

Last name of the first author, year	Polymorphic gene	Study design	Ethnicity	Sample size (case/control)	Age (years) (case/ control)[a]	Male (%) (case/ control)	Anti-TB drug regimen administered	Diagnostic criteria of ATDILI	Quality score[d]
Feng, 2014 [23]	*CYP2E1*	Case-control	Chinese	173/173	48.8/48.6	68.0/68.0	INH, RIF, PZA	ALT > 3 × ULN	6
Kim, 2009 [48]	*CYP2E1*	Case-control	Korean	67/159	42.1/42.8	65.7/65.4	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Singh, 2014 [49]	*CYP2E1*	Cohort	Indian	50/135	NA/NA	NA/NA	NA	ALT > 2 × ULN	7
Tang, 2013 [50]	*CYP2E1*	Case-control	Chinese	89/356	43.7/43.6	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Ben Mahmoud, 2012 [51]	*NAT2*	Cohort	Tunisian	14/52	42.4/42.1	42.8/48.1	INH, RIF containing regimen	ALT > 2 × ULN	7
Bozok Cetintas, 2008 [52]	*NAT2*	Case-control	Turkish	30/70	39.8/37.3	50.0/72.8	INH, RIF, PZA, EMB	ALT > 3 × ULN	6
Higuchi, 2007 [53]	*NAT2*	Cohort	Japanese	18/82	60.8/64.7	50.0/57.3	INH ,RIF containing regimen	ALT > 2 × ULN	7
Ho, 2013 [54]	*NAT2*	Cohort	Taiwanese	20/328	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 5 × ULN	6
Huang, 2002 [55]	*NAT2*	Cohort	Taiwanese	33/191	73.3/63.7	87.9/88.5	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Khalili, 2011 [56]	*NAT2*	Case-control	Iranian	14/36	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 3 × ULN	6
Leiro-Fernandez, 2011 [57]	*NAT2*	Case-control	Caucasian	50/67	34.0/30.5[b]	54.0/56.7	INH, RIF, PZA	ALT > 3 × ULN	7
Lv, 2012 [24]	*NAT2*	Case-	Chinese	89/356	42.0/42.0[b]	73.0/73.0	INH, RIF, PZA,	ALT > 2 × ULN	7

		control					EMB		
Ng, 2014 [58]	*NAT2*	Case-control	Mixed	26/101	48.3/NA	38.5/NA	INH containing regimen	ALT > 5 × ULN	7
Ohno, 2000 [59]	*NAT2*	Cohort	Japanese	14/63	NA/NA	NA/NA	INH, RIF	ALT > 1.5 × ULN	7
Possuelo, 2008 [60]	*NAT2*	Cohort	Brazilian	14/240	38.9/36.5	50.0/66.9	INH, RIF, PZA	ALT > 3 × ULN	7
Rana, 2012 [61]	*NAT2*	Cohort	Indian	50/201	45.3/43.8	76.0/57.2	INH, RIF, PZA, EMB	ALT > 5 × ULN	7
Shimizu, 2006 [62]	*NAT2*	Case-control	Japanese	10/32	60.5/64.9	70.0/46.9	INH, RIF	ALT > 2 × ULN	6
Yuliwulandari, 2016 [63]	*NAT2*	Case-control	Indonesian	50/191	NA/NA	NA/NA	NA	ALT > 2 × ULN	7
Wattanapokayakit, 2016 [25]	*NAT2*	Case-control	Thai	53/85	51.4/50.2	58.5/60.0	INH containing regimen	ALT > 2 × ULN	7
Chatterjee, 2010 [64]	*GSTM1, GSTT1*	Case-control	Indian	51/100	37.2/33.2	49.0/63.0	INH, RIF, PZA	ALT > 3 × ULN	7
Gupta, 2013 [65]	*GSTM1, GSTT1*	Cohort	Indian	50/246	37.0/36.5[b]	48.0/56.5	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Huang, 2007 [66]	*GSTM1, GSTT1*	Case-control	Taiwanese	63/63	62.0/NA	NA/NA	NA	ALT > 5 × ULN	6
Kim, 2010 [67]	*GSTM1, GSTT1*	Case-control	Korean	57/190	47.3/42.4	59.6/67.9	INH, RIF, PZA, EMB	ALT > 3 × ULN	7
Leiro, 2008 [68]	*GSTM1, GSTT1*	Case-control	Caucasian	35/60	34.0/31.0[b]	40.0/41.7	INH, RIF, PZA	ALT > 3 × ULN	7
Liu, 2014 [69]	*GSTM1, GSTT1*	Case-control	Chinese	20/143	35.9/61.2	60.0/59.4	INH containing regimen	ALT > 2 × ULN	7
Monteiro, 2012 [70]	*GSTM1, GSTT1*	Cohort	Brazilian	59/118	37.0/38.0[b]	76.0/61.0	NA	ALT > 2 × ULN	7

Rana, 2013 [71]	*GSTM1, GSTT1*	Cohort	Indian	30/220	43.6/42.3	60.0/64.5	INH, RIF	ALT > 5 × ULN	6
Roy, 2001 [72]	*GSTM1, GSTT1*	Case-control	Indian	33/33	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Chen, 2015 [42]	*SLCO1B1*	Case-control	Chinese	89/356	43.7/43.6	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Kim, 2012 [10]	*SLCO1B1*	Case-control	Korean	67/159	43.0/42.8	65.7/65.4	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Li, 2012 [28]	*SLCO1B1*	Case-control	Chinese	118/155	40.5/39.3	48.3/54.8	RIF	ALT > 3 × ULN	7
An, 2012 [73]	*NAT2, CYP2E1*	Case-control	Chinese	101/107	36.0/33.4[b]	55.0/70.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Bose, 2011 [74]	*NAT2, CYP2E1*	Cohort	Indian	41/177	38.0/36.0	43.9/47.4	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Chamorro, 2013 [75]	*NAT2, CYP2E1*	Cohort	Mixed (South American)	47/128	29.0/27.0	41.3/64.8	INH, RIF, PZA, EMB	ALT > 3 × ULN	7
Cho, 2007 [76]	*NAT2, CYP2E1*	Cohort	Korean	18/114	51.2/46.7	66.7/55.3	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Gupta, 2013 [27]	*NAT2, CYP2E1*	Case-control	Indian	50/165	37.0/38.0	48.0/60.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Huang, 2003 [77]	*NAT2, CYP2E1*	Cohort	Taiwanese	49/269	70.0/59.0[b]	18.4/14.9	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Lee, 2010 [78]	*NAT2, CYP2E1*	Cohort	Taiwanese	45/95	58.4/54.9	60.0/66.3	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Mishra, 2013 [79]	*NAT2, CYP2E1*	Case-control	Indian	33/173	38.0/NA	52.0/NA	INH, RIF, PZA, EMB	ALT > 3 × ULN	7
Santos, 2013 [80]	*NAT2,*	Case-	Brazilian	18/252	47.7/45.6	56.0/49.0	INH, RIF	ALT > 3 × ULN	7

	CYP2E1	control							
Vuilleumier, 2006 [81]	*NAT2, CYP2E1*	Case-control	Mixed	8/63	27-35: 2/22[c] >36 : 5/18[c]	38.0/51.0	INH	AST or ALT > 4 × ULN	7
Yamada, 2009 [82]	*NAT2, CYP2E1*	Case-control	Mixed	23/147	NA/NA	13.0/42.9	INH	ALT > 2 × ULN	7
Zaverucha-do-Valle, 2014 [83]	*NAT2, CYP2E1*	Cohort	Brazilian	50/79	< 40: 28/43[c] > 40: 20/36[c]	60.4/72.2	INH, RIF, PZA	ALT > 2 × ULN	6
Sharma, 2014 [84]	*CYP2E1, GSTM1*	Cohort	Indian	105/185	35.2/27.6	55.7/72.1	INH, RIF, PZA, EMB	ALT > 5 × ULN	7
Wang, 2010 [85]	*CYP2E1, GSTM1*	Case-control	Chinese	104/111	48.6/44.7	67.3/67.6	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Tang, 2012 [86]	*CYP2E1, GSTM1, GSTT1*	Case-control	Chinese	89/356	43.7/43.6	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Yimer, 2011 [45]	*NAT2, SLCO1B1*	Cohort	Ethiopian	41/160	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 2 × ULN	6
Brito, 2014 [87]	*NAT2, CYP2E1, GSTM1, GSTT1*	Cohort	Brazilian	15/230	38.1/36.8	46.7/NA	INH, RIF, PZA	ALT > 3 × ULN	7
Forestiero, 2013 [88]	*NAT2, CYP2E1, GSTM1, GSTT1*	Cohort	Brazilian	59/40	NA/NA	49.2/60.0	INH, RIF, PZA	ALT > 2.5 × ULN	6
Rana, 2014 [89]	*NAT2, CYP2E1, GSTM1, GSTT1*	Cohort	Indian	55/245	43.6/42.3	60.0/62.0	INH, RIF, PZA, EMB	ALT > 5 × ULN	6
Singla, 2014 [26]	*NAT2, CYP2E1, GSTM1,*	Case-control	Indian	17/391	48.2/32.7	64.7/61.4	INH, RIF, PZA, EMB, STM	ALT > 2 × ULN	7

	GSTT1								
Sotsuka, 2011 [90]	*NAT2, CYP2E1, GSTM1, GSTT1*	Case-control	Japanese	20/92	54.9/50.4	90.0/73.9	INH, RIF, PZA, EMB or STM	ALT > 3 × ULN	7
Teixeira, 2011 [91]	*NAT2, CYP2E1, GSTM1, GSTT1*	Case-control	Brazilian	26/141	47.6/43.0	61.5/52.5	INH containing regimen	ALT > 3 × ULN	7
Xiang, 2014 [92]	*NAT2, CYP2E1, GSTM1, GSTT1*	Cohort	Chinese	89/2155	37.0/44.5	67.4/55.7	INH, RIF, PZA, EMB	ALT > 2 × ULN	7

Abbreviations: **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **ATDILI**, anti-tuberculosis drug-induced liver injury; **CYP2E1**, cytochrome P450 2E1; **EMB**, ethambutol; **GSTM1**, glutathione S-transferase Mu 1; **GSTT1**, glutathione S-transferase Theta 1; **INH**, isoniazid; **NA**, not available; **NAT2**, N-acetyltransferase 2; **PZA**, pyrazinamide; **RIF**, rifampicin; **SLCO1B1**, solute carrier organic anion transporter family, member 1B1 (encoding organic anion transporting polypeptide 1B1 [OATP1B1]); **STM**, streptomycin; **TB**, tuberculosis; **ULN**, upper limit of normal

[a] Mean unless otherwise stated

[b] Median age

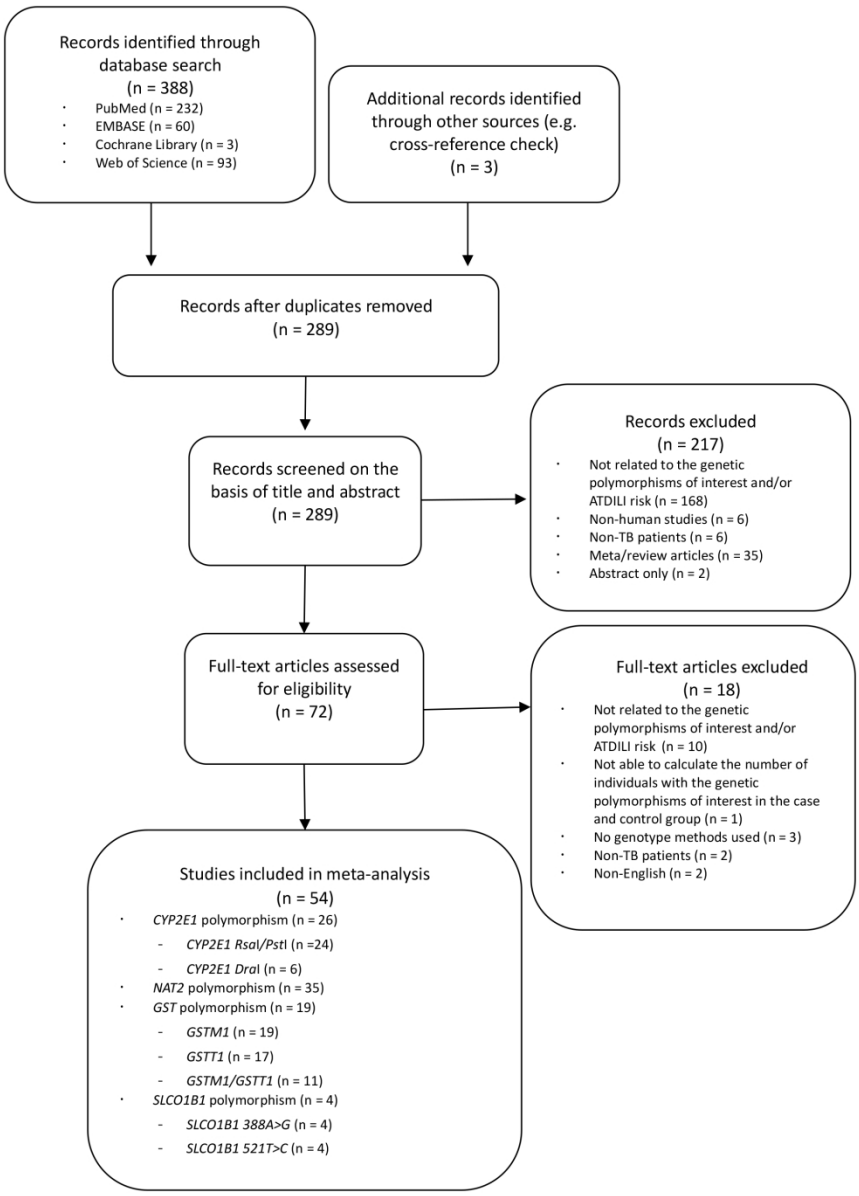
[c] Number of individuals in the age ranges

[d] Detailed scoring for each quality assessment criterion based on the revised Little's recommendation in supplementary data S2 Table.

Table 2. Association between the *SLCO1B1* polymorphisms and the risk of anti-tuberculosis drug-induced liver injury

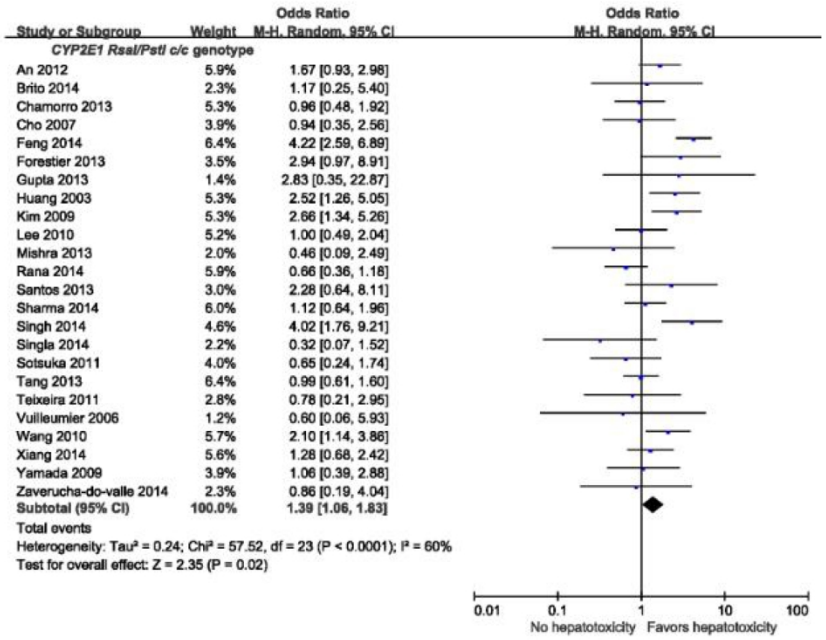
Polymorphism	Genetic model		Number of studies	OR (95% CI)	P value	I^2, %	$P_{heterogeneity}$	Model of meta-analysis
SLCO1B1 388A>G (rs2306283)	dominant model	AA + AG vs.GG	4	1.00 [0.76, 1.31]	1.00	0	0.73	Fixed
	recessive model	AA vs. AG + GG	4	1.45 [0.93, 2.25]	0.10	0	0.84	Fixed
	additive model	AA vs. GG	4	1.36 [0.85, 2.15]	0.20	0	0.98	Fixed
SLCO1B1 521T>C (rs4149056)	dominant model	CC + TC vs. TT	4	0.74 [0.43, 1.28]	0.28	66	0.03	Random
	recessive model	CC vs. TC + TT	4	1.21 [0.40, 3.64]	0.73	0	0.57	Fixed
	additive model	CC vs. TT	4	1.27 [0.42, 3.84]	0.67	0	0.61	Fixed

Abbreviations: ***OR***, odds ratio*;* ***CI***, confidence interval

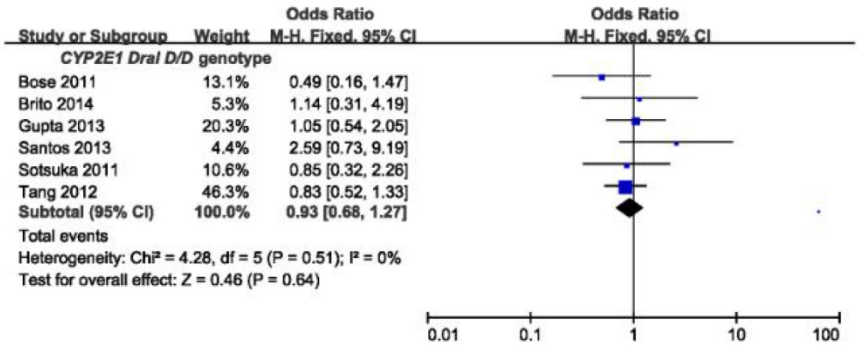


Study selection process flowchart.

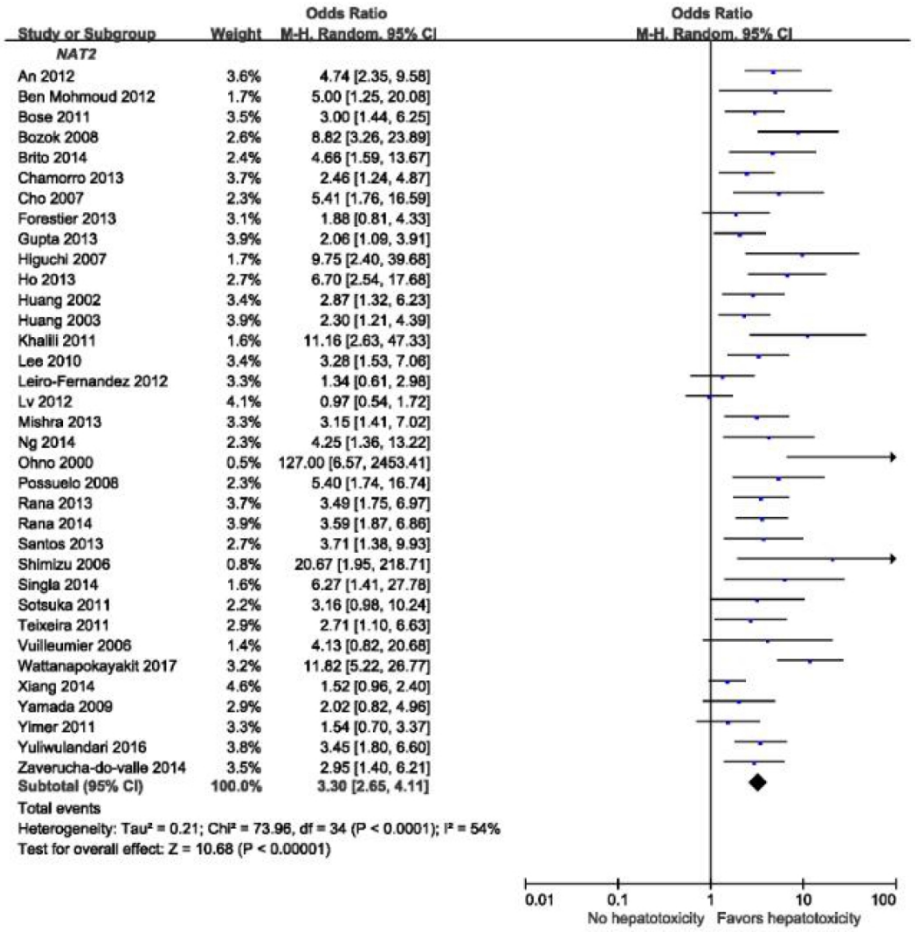
(A) CYP2E1 RsaI/PstI c1/c1 genotype compared to c1/c2 + c2/c2 genotypes



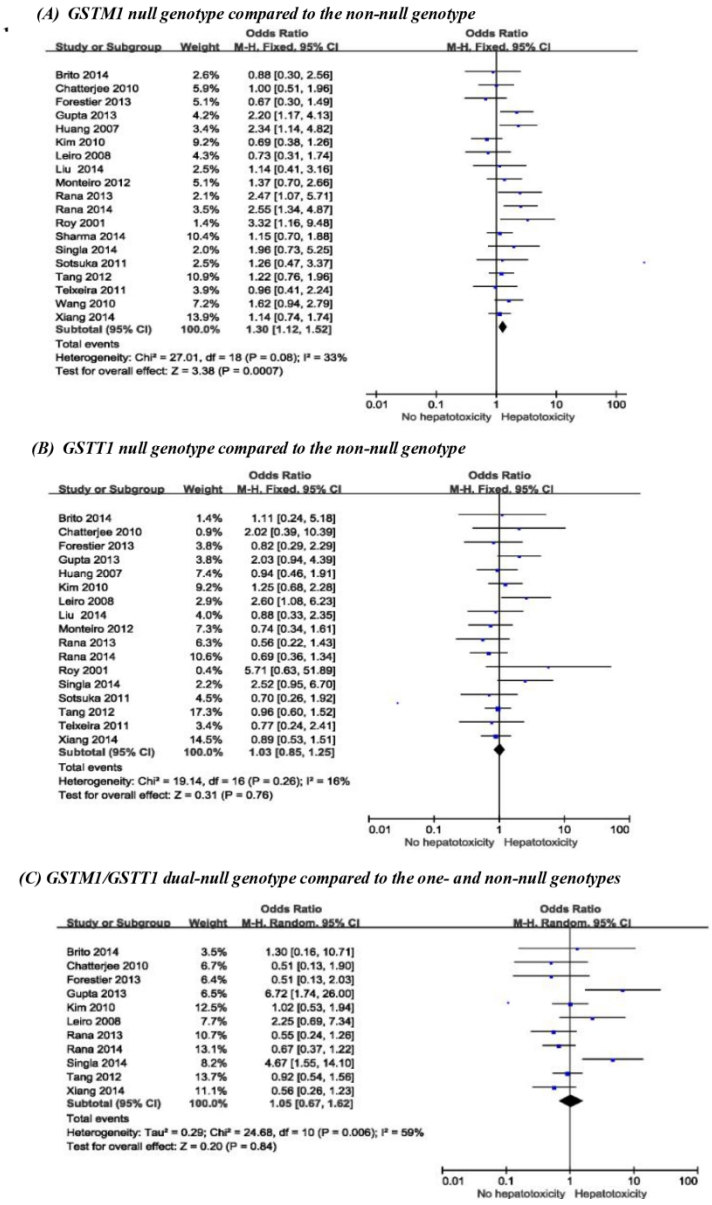
(B) CYP2E1 DraI D/D genotype compared to D/C + C/C genotypes.



Risk of anti-tuberculosis drug-induced liver injury in patients with the CYP2E1 (A) RsaI/PstI c1/c1 genotype compared to c1/c2 + c2/c2 genotypes and (B) DraI D/D genotype compared to D/C + C/C genotypes.



Risk of anti-tuberculosis drug-induced liver injury in patients with the NAT2 slow acetylator genotype compared to those with the intermediate/fast acetylator genotypes.



Risk of anti-tuberculosis drug-induced liver injury in patients with (A) the GSTM1 null genotype compared to the non-null genotype, (B) the GSTT1 null genotype compared to the non-null genotype, and (C) the GSTM1/GSTT1 dual-null genotype compared to the one- and non-null genotypes.

Supplementary data

S1 Table. Completed MOOSE (Meta-analysis Of Observational Studies in Epidemiology) checklist

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	5-6
2	Hypothesis statement (Objectives)	6
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	NA
5	Type of study designs used	7
6	Study population	7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	NA
8	Search strategy, including time period included in the synthesis and key words	7 S2 Table
9	Effort to include all available studies, including contact with authors	7
10	Databases and registries searched	7
11	Search software used, name and version, including special features used (eg, explosion)	7
12	Use of hand searching (eg, reference lists of obtained articles)	7
13	List of citations located and those excluded, including justification	Fig 1
14	Method of addressing articles published in languages other than English	7
15	Method of handling abstracts and unpublished studies	7, Fig 1
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	NA
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	NA
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Table 1, S3 Table
22	Assessment of heterogeneity	9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8-9
24	Provision of appropriate tables and graphics	Table 1-2, Fig 1-4

Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Fig 2-4
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	13-14, S9-11 Table
28	Indication of statistical uncertainty of findings	-

S2 Table. Search strategies

Electronic database	Search strategies
PubMed	((((((((((("glutathione S transferase") OR GST)) OR ("glutathione S-transferase T1" [Supplementary Concept] OR "glutathione S-transferase M1" [Supplementary Concept])) AND Humans[Mesh] AND English[lang])) OR ((("SLCO1B1 protein, human" [Supplementary Concept]) OR "solute carrier organic anion transporter") AND Humans[Mesh] AND English[lang])) OR ("isoniazid acetyltransferase" [Supplementary Concept]OR "ArylamineN-Acetyltransferase"[Mesh] OR "NAT2 protein, human" [Supplementary Concept])) OR "Cytochrome P-450 CYP2E1"[Mesh]) OR drug metaboli#er*) OR "Genetic Predisposition to Disease"[Mesh]) AND (("Drug-Induced Liver Injury"[Mesh] OR "Drug-Induced Liver Injury, Chronic"[Mesh]))) AND ((("AntitubercularAgents"[Mesh]) OR tuberculosis OR antituberculo*)) Filters: Humans; English
EMBASE	'solute carrier organic anion transporter 1b1'/expOR 'solute carrier organic anion transporter 1b1' OR 'multidrug resistance protein 1'/expOR 'multidrug resistance protein 1' OR 'organic anion transporter'/expOR 'organic anion transporter' AND [humans]/limAND [english]/limOR slco1b1 OR 'drug transporter gene*' OR abcb1 AND ('hepatitis'/expOR hepatitis OR 'liver toxicity'/expOR ('drug induced' AND ('liver'/expOR liver) AND ('toxicity'/expOR toxicity)) OR 'toxic hepatitis'/expOR 'hepatotoxicity'/expOR hepatotoxicity) AND ('tuberculostaticagent'/expOR 'tuberculostaticagent' OR antituberculosisOR 'isoni*' OR 'rifampi*') AND [humans]/limAND [english]/lim
Web of Science	(((((("Glutathione S transferase") OR GST) OR GSTT1) OR GSTM1) OR (((NAT2) OR "arylaminN acetyltransferase") OR N acetyltransferase*) OR ((drug metaboli?er*) OR (drug metabli?ingenzyme*)) OR (("Cytochrome 2E1") OR "CYP 2E1") OR (("The solute carrier organic anion transporter family member 1B1") OR SLCO1B1) OR (genotyp* OR acetylator*) OR (gene* susceptibilit*) OR (*polymorphism*)) AND ((drug NEAR/3 liver) OR (hepatotoxi*) OR (drug induced liver injury) OR (hepatitis)) AND ((rifampi*) OR (isoni*) OR (antituberculosis) OR ("antitubercul* agent* "))
Cochrane Reviews	[AntitubercularAgents] explode all trees AND [Drug-Induced Liver Injury] explode all trees AND ([Cytochrome P-450 CYP2E1] explode all trees OR nat2 OR "N acetyltrasferase" "glutathione S transferase" OR GST OR GSTM1 OR GSTT1 "Solute carrier organic anion transporter" OR SLCO1B1)(Limitation : Trials)

S3 Table. Study quality assessment

Studies	Scientific design	Definite inclusion of study population[a]	Explicit information on study population[a]	Explicit diagnostic criteria on ATDILI[a]	Genetic detection method[a]	Correct statistical analysis[a]	Logical discussion of study bias[a]
Feng, 2014 [1]	1	1	1	1	1	1	0
Kim, 2009 [2]	1	1	1	1	1	1	1
Singh, 2014 [3]	1	1	1	1	1	1	1
Tang, 2013 [4]	1	1	1	1	1	1	1
Ben Mahmoud, 2012 [5]	1	1	1	1	1	1	1
Bozok Cetintas, 2008 [6]	1	1	1	1	1	0	1
Higuchi, 2007 [7]	1	1	1	1	1	1	1
Ho, 2013 [8]	1	1	1	1	1	1	0
Huang, 2002 [9]	1	1	1	1	1	1	1
Khalili, 2011 [10]	1	1	1	1	1	1	0
Leiro-Fernandez, 2011 [11]	1	1	1	1	1	1	1
Lv, 2012 [12]	1	1	1	1	1	1	1
Ng, 2014 [13]	1	1	1	1	1	1	1
Ohno, 2000 [14]	1	1	1	1	1	1	1
Possuelo, 2008 [15]	1	1	1	1	1	1	1
Rana, 2012 [16]	1	1	1	1	1	1	1
Shimizu, 2006 [17]	1	1	1	1	1	1	0
Yuliwulandari, 2016 [18]	1	1	1	1	1	1	1
Wattanapokayakit, 2016 [19]	1	1	1	1	1	1	1
Chatterjee, 2010 [20]	1	1	1	1	1	1	1
Gupta, 2013 [21]	1	1	1	1	1	1	1
Huang, 2007 [22]	1	1	1	1	1	1	0
Kim, 2010 [23]	1	1	1	1	1	1	1
Leiro, 2008 [24]	1	1	1	1	1	1	1
Liu, 2014 [25]	1	1	1	1	1	1	1
Monteiro, 2012 [26]	1	1	1	1	1	1	1
Rana, 2013 [27]	1	1	1	1	1	1	0
Roy, 2001 [28]	1	1	1	1	1	1	1
Chen, 2015 [29]	1	1	1	1	1	1	1
Kim, 2012 [30]	1	1	1	1	1	1	1
Li, 2012 [31]	1	1	1	1	1	1	1
An, 2012 [32]	1	1	1	1	1	1	1
Bose, 2011 [33]	1	1	1	1	1	1	1

Chamorro, 2013 [34]	1	1	1	1	1	1	1
Cho, 2007 [35]	1	1	1	1	1	1	1
Gupta, 2013 [36]	1	1	1	1	1	1	1
Huang, 2003 [37]	1	1	1	1	1	1	1
Lee, 2010 [38]	1	1	1	1	1	1	1
Mishra, 2013 [39]	1	1	1	1	1	1	1
Santos, 2013 [40]	1	1	1	1	1	1	1
Vuilleumier, 2006 [41]	1	1	1	1	1	1	1
Yamada, 2009 [42]	1	1	1	1	1	1	1
Zaverucha-do-Valle, 2014 [43]	1	1	1	1	1	1	0
Sharma, 2014 [44]	1	1	1	1	1	1	1
Wang, 2010 [45]	1	1	1	1	1	1	1
Tang, 2012 [46]	1	1	1	1	1	1	1
Yimer, 2011 [47]	1	1	1	1	1	1	0
Brito, 2014 [48]	1	1	1	1	1	1	1
Forestiero, 2013 [49]	1	1	1	1	1	1	0
Rana, 2014 [50]	1	1	1	1	1	1	0
Singla, 2014 [51]	1	1	1	1	1	1	1
Sotsuka, 2011 [52]	1	1	1	1	1	1	1
Teixeira, 2011 [53]	1	1	1	1	1	1	1
Xiang, 2014 [54]	1	1	1	1	1	1	1

Abbreviation: ATDILI, anti-tuberculosis drug-induced liver injury

[a] 0 indicates 'not mentioned' in the study; 1 indicates 'sufficient information provided' in the study

S4 Table. Genotype distribution and the genotyping method used for the *CYP2E1* genetic polymorphisms in the included studies (n = 26)

Study	*Rsa*I/*Pst*I genotype (n = 24)				*Dra*I genotype (n = 6)				Genotyping method
	Case (number of individuals [%])		Control (number of individuals [%])		Case (number of individuals [%])		Control (number of individuals [%])		
	C1/C1	C1/C2 + C2/C2	C1/C1	C1/C2 + C2/C2	D/D	D/C + C/C	D/D	D/C + C/C	
An [32]	72 (71.3)	29 (28.7)	64 (59.8)	43 (40.2)	NA	NA	NA	NA	Sequencing
Bose [33]	NA	NA	NA	NA	4 (9.8)	37 (90.2)	32 (18.1)	145 (81.9)	PCR-RFLP
Brito [48]	13 (86.7)	2 (13.3)	195 (84.8)	35 (15.2)	12 (80.0)	3 (20.0)	179 (76.8)	54 (23.2)	PCR-RFLP
Chamorro [34]	30 (63.8)	17 (36.2)	83 (64.8)	45 (35.2)	NA	NA	NA	NA	PCR-RFLP
Cho [35]	10 (55.6)	8 (44.4)	65 (57.0)	49 (43.0)	NA	NA	NA	NA	Sequencing
Feng [1]	142 (82.1)	31 (17.9)	90 (52.0)	83 (48.0)	NA	NA	NA	NA	Sequencing
Forestiero [49]	53 (89.8)	6 (10.2)	30 (75.0)	10 (25.0)	NA	NA	NA	NA	PCR-RFLP
Gupta [36]	49 (98.0)	1 (2.0)	156 (94.5)	9 (5.5)	33 (66.0)	17 (34.0)	107 (64.9)	58 (35.1)	PCR-RFLP
Huang [37]	37 (75.5)	12 (24.5)	148 (55.0)	121 (45.0)	NA	NA	NA	NA	PCR-RFLP

Kim [2]	54 (81.8)	12 (18.2)	97 (63.4)	56 (36.6)	NA	NA	NA	NA	SNP stream
Lee [55]	26 (57.8)	19 (42.2)	55 (57.9)	40 (42.1)	NA	NA	NA	NA	Taqman
Mishra [39]	31 (93.9)	2 (6.1)	168 (97.1)	5 (2.9)	NA	NA	NA	NA	PCR-RFLP
Rana [56]	28 (50.9)	27 (49.1)	150 (61.2)	95 (38.8)	NA	NA	NA	NA	PCR-RFLP
Santos [57]	15 (83.3)	3 (16.7)	173 (75.6)	56 (24.4)	15 (83.3)	3 (16.7)	166 (72.8)	62 (27.2)	Taqman
Sharma [44]	81 (77.1)	24 (22.9)	139 (75.1)	46 (24.9)	NA	NA	NA	NA	PCR-RFLP
Singh [3]	42 (84.0)	8 (16.0)	77 (56.6)	59 (43.4)	NA	NA	NA	NA	PCR-RFLP
Singla [51]	15 (88.0)	2 (12.0)	375 (96.0)	16 (4.0)	NA	NA	NA	NA	PCR-RFLP
Sotsuka [52]	11 (55.0)	9 (45.0)	60 (65.2)	32 (34.8)	9 (45.0)	11 (55.0)	45 (48.9)	47 (51.1)	PCR-RFLP
Tang [46]	NA	NA	NA	NA	47 (52.8)	42 (47.2)	204 (57.3)	152 (42.7)	PCR-RFLP
Tang [4]	56 (62.9)	33 (37.1)	225 (63.2)	131 (36.8)	NA	NA	NA	NA	Taqman
Teixeira [53]	23 (88.5)	3 (11.5)	128 (90.8)	13 (9.2)	NA	NA	NA	NA	PCR-RFLP
Vuilleumier [41]	7 (87.5)	1 (12.5)	58 (92.1)	5 (7.9)	NA	NA	NA	NA	PCR-RFLP

Wang [45]	82 (78.8)	22 (21.2)	71 (64.0)	40 (36.0)	NA	NA	NA	NA	PCR-RFLP
Xiang [54]	58 (82.9)	12 (17.1)	1264 (79.0)	336 (21.0)	NA	NA	NA	NA	PCR/ligase detection reaction assays
Yamada [42]	17 (73.9)	6 (26.1)	107 (72.8)	40 (27.2)	NA	NA	NA	NA	PCR-RFLP
Zaverucha-do-Valle [43]	48 (94.1)	3 (5.9)	74 (94.9)	4 (5.1)	NA	NA	NA	NA	PCR-RFLP

Abbreviations: ***NA***, not available; ***PCR***, polymerase chain reaction; ***RFLP***, restriction fragment length polymorphism; ***SNP***, single nucleotide polymorphism

S5 Table. Genotype distribution and the genotyping method used for the *NAT2* genetic polymorphism in the included studies (n = 35)

Study	Case (number of individuals [%])		Control (number of individuals [%])		Genotyping method
	Slow acetylator	Intermediate and fast acetylator	Slow acetylator	Intermediate and fast acetylator	
An [32]	40 (39.6)	61 (60.4)	13 (12.1)	94 (87.9)	Sequencing
Ben Mahmoud [5]	11 (78.5)	3 (21.5)	22 (42.4)	30 (57.6)	PCR-RFLP
Bose [33]	29 (70.7)	12 (29.3)	79 (44.6)	98 (55.4)	PCR-RFLP
Bozok Cetintas [6]	23 (76.7)	7 (23.3)	19 (27.1)	51 (72.9)	PCR
Brito [48]	9 (60.0)	6 (40.0)	56 (24.3)	174 (75.7)	PCR-RFLP
Chamorro [34]	28 (58.7)	19 (41.3)	48 (37.5)	80 (62.5)	PCR-RFLP
Cho [35]	7 (38.9)	11 (61.1)	12 (10.5)	102 (89.5)	Sequencing
Forestiero [49]	28 (47.4)	31 (52.6)	13 (32.5)	27 (67.5)	PCR-RFLP
Gupta [36]	28 (56.0)	22 (44.0)	63 (38.2)	102 (61.8)	PCR-RFLP
Higuchi [7]	6 (33.3)	12 (66.7)	4 (4.9)	78 (95.1)	PCR-RFLP
Ho [8]	12 (63.2)	7 (36.8)	67 (20.4)	262 (79.6)	Sequenom MassARRAY

Huang [9]	14 (42.4)	19 (57.6)	39 (20.4)	152 (79.6)	PCR-RFLP
Huang [37]	19 (38.8)	30 (61.2)	58 (21.6)	211 (78.4)	PCR-RFLP
Khalili [10]	9 (64.3)	5 (35.7)	5 (13.9)	31 (86.1)	PCR-RFLP
Lee [38]	21 (46.7)	24 (53.3)	20 (21.1)	75 (78.9)	Taqman
Leiro-Fernandez [11]	36 (72.0)	14 (28.0)	44 (65.7)	23 (34.3)	PCR-RFLP
Lv [58]	18 (20.2)	71 (79.8)	74 (20.8)	282 (79.2)	PCR-RFLP
Mishra [39]	23 (70.0)	10 (30.0)	73 (42.0)	100 (58.0)	PCR-RFLP
Ng [13]	22 (84.6)	4 (15.4)	57 (56.4)	44 (43.6)	PCR-RFLP
Ohno [14]	7 (50.0)	7 (50.0)	0 (0.0)	63 (100.0)	PCR-RFLP
Possuelo [15]	9 (64.3)	5 (35.7)	60 (25.0)	180 (75.0)	Sequencing
Rana [16]	19 (38.0)	31 (62.0)	30 (14.9)	171 (85.1)	PCR-RFLP
Rana [50]	21 (38.2)	34 (61.8)	36 (14.7)	209 (85.3)	PCR-RFLP
Santos [40]	11 (61.1)	7 (38.9)	75 (29.8)	177 (70.2)	Sequencing
Shimizu [17]	4 (40.0)	6 (60.0)	1 (3.1)	31 (96.9)	PCR-RFLP
Singla [51]	15 (88.2)	2 (11.8)	213 (54.5)	178 (45.5)	PCR-RFLP

Sotsuka [52]	8 (15.4)	44 (84.6)	5 (5.4)	87 (94.6)	PCR-RFLP
Teixeira [53]	18 (75.0)	6 (25.0)	64 (51.2)	61 (48.8)	Sequencing
Vuilleumier [41]	3 (37.5)	5 (62.5)	8 (12.7)	55 (87.3)	PCR-RFLP
Wattanapokayakit [19]	38 (71.7)	15 (28.3)	15 (17.7)	70 (82.3)	Sequencing
Xiang [54]	28 (31.5)	61 (68.5)	501 (23.2)	1654 (76.8)	PCR/ligase detection reaction assays
Yamada [42]	14 (60.9)	9 (39.1)	64 (43.5)	83 (56.5)	Sequencing
Yimer [47]	31 (75.6)	10 (24.4)	107 (66.9)	53 (33.1)	Taqman
Yuliwulandari [18]	32 (64.0)	18 (36.0)	65 (34.0)	126 (66.0)	Sequencing
Zaverucha-do-Valle [43]	37 (71.2)	15 (28.8)	36 (45.6)	43 (54.4)	Sequencing

Abbreviations: ***NA***, not available; ***PCR***, polymerase chain reaction; ***RFLP***, restriction fragment length polymorphism

S6 Table. Genotype distribution and the genotyping method used for the *GST* genetic polymorphisms in the included studies (n = 19)

Study	*GSTM1* genotype (n = 19)				*GSTT1* genotype (n = 17)				*GSTM1/GSTT1* genotype (n = 11)				Genotyping method
	Case (number of individuals [%])		Control (number of individuals [%])		Case (number of individuals [%])		Control (number of individuals [%])		Case (number of individuals [%])		Control (number of individuals [%])		
	Null	Non-null	Null	Non-null	Null	Non-null	Null	Non-null	Dual-null	One-/non-null	Dual-null	One-/non-null	
Brito [48]	6 (40.0)	9 (60.0)	99 (43.0)	131 (57.0)	2 (13.3)	13 (86.7)	28 (12.2)	202 (87.8)	1 (6.7)	14 (93.3)	12 (5.2)	218 (94.8)	PCR
Chatterjee [20]	25 (49.0)	26 (51.0)	49 (49.0)	51 (51.0)	3 (5.9)	48 (94.1)	3 (3.0)	97 (97.0)	3 (5.9)	48 (94.1)	11 (11.0)	89 (89.0)	Multiplex PCR
Forestiero [49]	25 (42.4)	34 (57.6)	21 (52.5)	19 (47.5)	10 (17.0)	49 (83.0)	8 (20.0)	32 (80.0)	4 (6.8)	55 (93.2)	5 (12.5)	35 (87.5)	Multiplex PCR
Gupta [21]	21 (42.0)	29 (58.0)	61 (24.8)	185 (75.2)	11 (22.0)	39 (78.0)	30 (12.2)	216 (87.8)	5 (10.0)	45 (90.0)	4 (1.6)	242 (98.4)	Multiplex PCR
Huang [22]	42 (66.7)	21 (33.3)	29 (46.0)	34 (54.0)	24 (38.1)	39 (61.9)	25 (39.7)	38 (60.3)	NA	NA	NA	NA	Multiplex PCR
Kim [23]	26 (45.6)	31 (54.4)	104 (54.7)	86 (45.3)	34 (59.6)	23 (40.4)	103 (54.2)	87 (45.8)	17 (29.8)	40 (70.2)	56 (29.6)	133 (70.4)	PCR
Leiro [24]	12 (34.3)	23 (65.7)	25 (41.7)	35 (58.3)	17 (48.6)	18 (51.4)	16 (26.7)	44 (73.3)	7 (20.0)	28 (80.0)	6 (10.0)	54 (90.0)	PCR
Liu [25]	14 (70.0)	6 (30.0)	96 (67.1)	47 (32.9)	13 (65.0)	7 (35.0)	97 (67.8)	46 (32.2)	NA	NA	NA	NA	Multiplex PCR

Monteiro [26]	21 (35.6)	38 (64.4)	34 (28.8)	84 (71.2)	11 (18.7)	48 (81.3)	28 (23.8)	90 (76.2)	NA	NA	NA	NA	PCR
Rana [27]	10 (41.6)	20 (58.4)	37 (18.5)	183 (81.5)	6 (25.0)	24 (75.0)	68 (33.8)	152 (66.2)	9 (37.5)	21 (62.5)	96 (47.7)	124 (52.3)	PCR
Rana [16]	19 (34.5)	36 (65.5)	42 (17.1)	203 (82.9)	14 (25.5)	41 (74.5)	81 (33.1)	164 (66.9)	22 (40.0)	33 (60.0)	122 (49.8)	123 (50.2)	PCR
Roy [28]	17 (52.0)	15 (48.0)	8 (24.0)	25 (76.0)	5 (15.0)	28 (85.0)	1 (3.0)	32 (97.0)	NA	NA	NA	NA	PCR
Sharma [44]	42 (40.0)	63 (60.0)	68 (36.7)	117 (63.3)	NA	NA	NA	NA	NA	NA	NA	NA	PCR
Singla [51]	10 (59.0)	7 (41.0)	165 (42.0)	226 (58.0)	8 (47.0)	9 (53.0)	102 (26.0)	289 (74.0)	5 (29.0)	12 (71.0)	32 (8.0)	359 (92.0)	Multiplex PCR
Sotsuka [52]	12 (60.0)	8 (40.0)	50 (54.3)	42 (45.7)	7 (35.0)	13 (65.0)	40 (43.5)	52 (56.5)	NA	NA	NA	NA	PCR
Tang [46]	55 (61.8)	34 (38.2)	203 (57.0)	153 (43.0)	40 (44.9)	49 (55.1)	164 (46.1)	192 (53.9)	22 (24.7)	67 (75.3)	94 (26.4)	262 (73.6)	Multiplex PCR
Teixeira [53]	11 (42.3)	15 (57.7)	61 (43.3)	80 (56.7)	4 (15.4)	22 (84.6)	27 (19.2)	114 (80.8)	NA	NA	NA	NA	Multiplex PCR
Wang [45]	63 (60.6)	41 (39.4)	54 (48.6)	57 (51.4)	NA	NA	NA	NA	NA	NA	NA	NA	PCR
Xiang [54]	41 (46.1)	48 (53.9)	925 (42.9)	1230 (57.1)	18 (20.2)	71 (79.8)	477 (22.1)	1678 (77.9)	7 (9.3)	68 (90.7)	283 (16.5)	1427 (83.5)	PCR

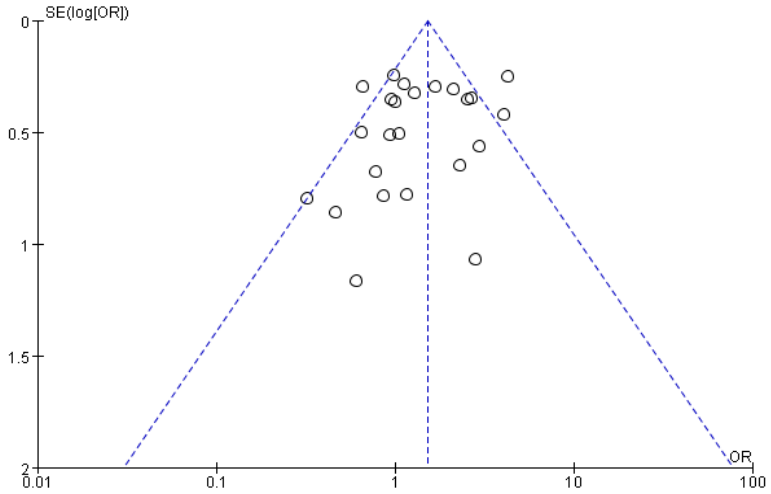
Abbreviations: ***NA***, not available; ***PCR***, polymerase chain reaction

S7 Table. Genotype distribution and the genotyping method used for the *SLCO1B1* genetic polymorphisms in the included studies (n = 4)

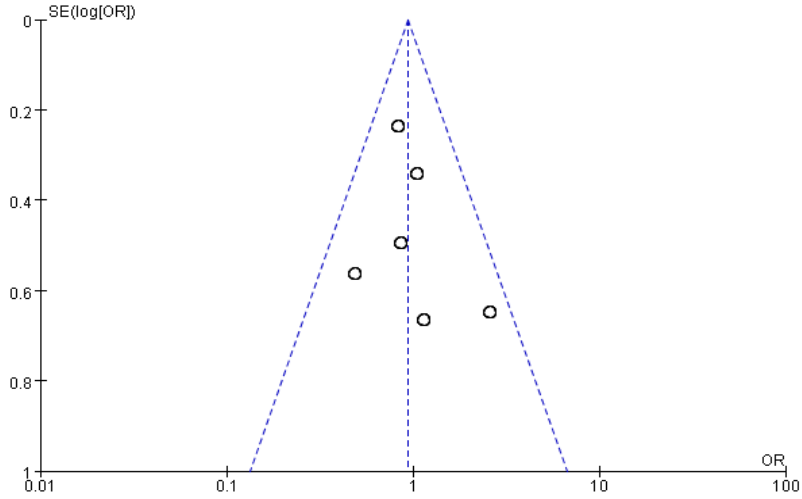
Study	*SLCO1B1* 388A>G (rs2306283)						*SLCO1B1* 521T>C (rs4149056)						Genotyping method
	Case (number of individuals [%])			Control (number of individuals [%])			Case (number of individuals [%])			Control (number of individuals [%])			
	AA	**AG**	**GG**	**AA**	**AG**	**GG**	**TT**	**CT**	**CC**	**TT**	**CT**	**CC**	
Chen [29]	8 (9.0)	34 (38.2)	47 (52.8)	33 (7.5)	164 (37.1)	245 (55.4)	72 (80.9)	15 (16.9)	2 (2.2)	351 (79.6)	87 (19.7)	3 (0.7)	Taqman
Kim [30]	6 (9.2)	26 (40.0)	33 (50.8)	11 (7.1)	60 (38.5)	85 (54.5)	46 (69.7)	20 (30.3)	0 (0.0)	113 (72.4)	40 (25.6)	3 (1.9)	SNPstream
Li [31]	11 (9.3)	38 (32.2)	69 (58.5)	12 (7.7)	48 (31.0)	95 (61.3)	83 (70.3)	34 (28.8)	1 (0.8)	136 (87.7)	18 (11.6)	1 (0.7)	PCR direct sequencing
Yimer [47]	9 (22.0)	17 (41.5)	15 (36.6)	20 (12.5)	87 (54.4)	53 (33.1)	27 (65.9)	13 (31.7)	1 (2.4)	107 (66.9)	49 (30.6)	4 (2.5)	Taqman

Abbreviations: ***PCR***, polymerase chain reaction; ***SNP***, single nucleotide polymorphism

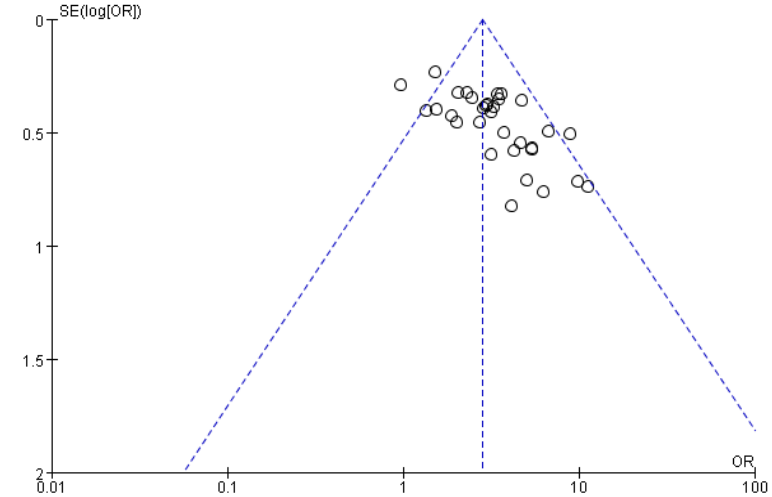
(A) *CYP2E1 Rsa*I/*Pst*I polymorphism



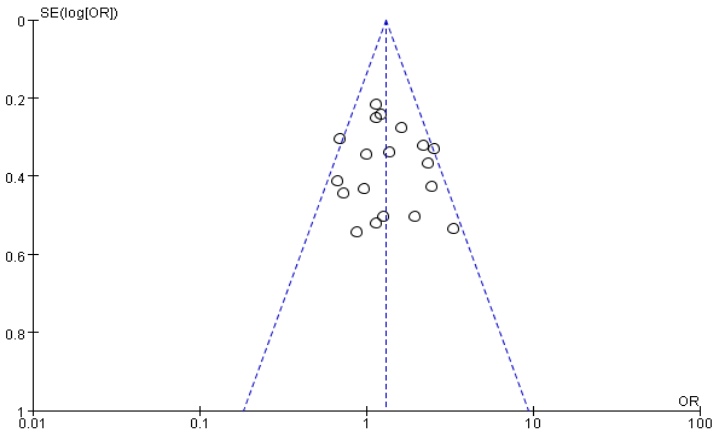
(B) *CYP2E1 Dra*I polymorphism



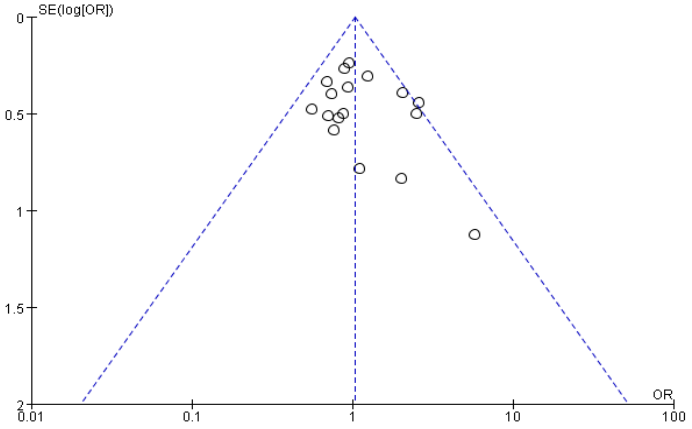
(C) *NAT2* polymorphism



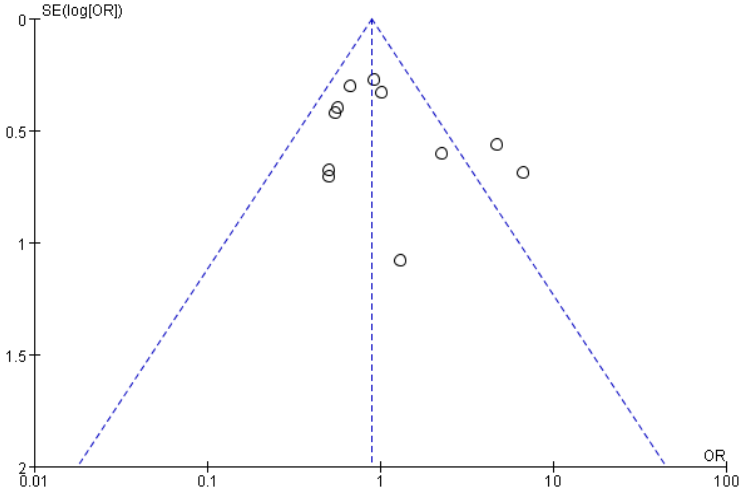
(D) *GSTM1* polymorphism



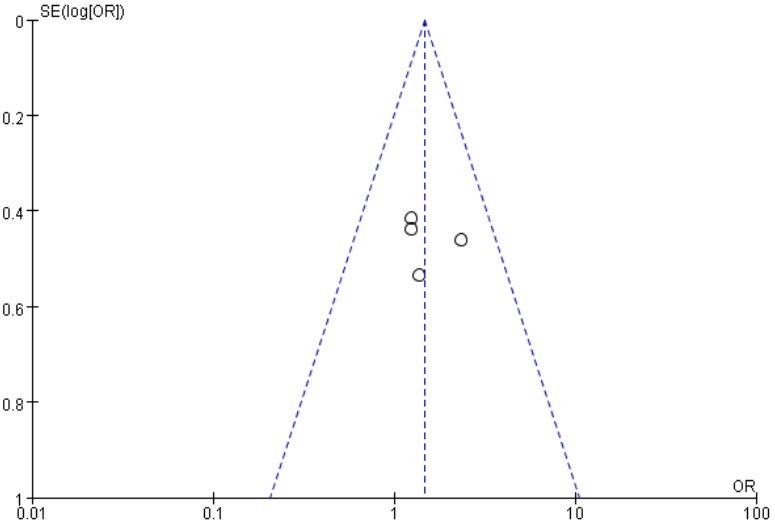
(E) *GSTT1* polymorphism



(F) *GSTT1/M1* polymorphism



(G) *SLCO1B1 388A>G* and *521T>C* polymorphism



S8 Figure. Funnel plots to evaluate publication bias for the *CYP2E1, NAT2, GST,* and *SLCO1B1* polymorphisms associated with the risk of anti-tuberculosis drug-induced liver injury. (A) C*YP2E1 Rsa*I/*Pst*I polymorphism, (B) *CYP2E1 Dra*I polymorphism, (C) *NAT2* polymorphism, (D) *GSTM1* polymorphism, (E) *GSTT1* polymorphism, (F) *GSTT1/M1* polymorphism, and (G) *SLCO1B1* 388A>G and 521T>C polymorphism.

S9 Table. Subgroup analysis for the association between *CYP2E1* polymorphisms and the risk of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug regimen, and study design

Polymorphic gene	Subgroup		Number of studies	Case/ control (n)	Test of association		Model of meta-analysis	Test of heterogeneity	
					OR [95% CI]	P value[a]		I^2,%	P value[b]
*CYP2E1 Rsa*I/*Pst*I (c1/c1 vs. c1/c2 + c2/c2)	Total		24	1293/5450	1.39 [1.06, 1.83]	0.02	Random	60	<0.0001
	Ethnicity	East Asian	10	736/3076	1.62 [1.12, 2.36]	0.01	Random	69	0.0006
		Indian	6	310/1295	1.08 [0.52, 2.25]	0.85	Random	70	0.005
		South American	6	216/869	1.30 [0.83, 2.03]	0.25	Fixed	0	0.49
		Others	2	31/210	0.98 [0.39, 2.45]	0.96	Fixed	0	0.66
	Anti-TB drug regimen	INH alone	2	31/210	0.98 [0.39, 2.45]	0.96	Fixed	0	0.66
		Combination	21	1212/5104	1.35 [1.01, 1.79]	<0.00001	Random	61	0.0002
	Study design	Cohort	11	564/3120	1.32 [0.94, 1.87]	0.11	Random	50	0.03
		Case-control	12	729/2330	1.42 [0.93, 2.16]	0.10	Random	65	0.0006
*CYP2E1 Dra*I[c] (D/D vs. D/C + C/C)	Total		6	233/1272	0.93 [0.68, 1.27]	0.64	Fixed	0	0.51
	Ethnicity	East Asian	2	109/448	0.84 [0.55, 1.28]	0.41	Fixed	0	0.96
		Indian	2	91/342	0.83 [0.48, 1.45]	0.51	Fixed	27	0.24
		South American	2	33/482	1.80 [0.73, 4.45]	0.20	Fixed	0	0.37
	Study design	Cohort	2	56/407	0.68 [0.31, 1.50]	0.33	Fixed	0	0.33
		Case-control	4	177/865	0.99 [0.70, 1.38]	0.94	Fixed	0	0.42

Abbreviations: ***CI***, confidence interval; ***CYP2E1***, cytochrome P450 2E1; ***INH***, isoniazid; ***OR***, odds ratio; ***TB***, tuberculosis

[a] P value from Z test

[b] P value from Cochran's Q test based on chi-square statistic

[c] Subgroup analysis based on anti-TB drug regimen could not be performed due to insufficient information provided.

S10 Table. Subgroup analysis for the association between *NAT2* polymorphism and the risk of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug regimen, and study design

Polymorphic gene	Subgroup		Number of studies	Case/ control (n)	Test of association		Model of meta-analysis	Test of heterogeneity	
					OR [95% CI]	P value[a]		I^2,%	P value[b]
NAT2 (Slow acetylator vs. fast and intermediate acetylator)	Total		35	1323/7319	3.30 [2.65, 4.11]	<0.00001	Random	47	0.002
	Ethnicity	East Asian	13	590/3970	4.00 [2.42, 6.60]	<0.00001	Random	77	<0.00001
		Indian	6	246/1352	3.07 [2.26, 4.16]	<0.00001	Fixed	0	0.74
		West Asian	2	44/106	9.51 [4.19, 21.61]	<0.00001	Fixed	0	0.79
		South American	7	231/1110	2.94 [2.11, 4.08]	<0.00001	Fixed	0	0.75
		African	2	55/212	2.08 [1.06, 4.10]	0.03	Fixed	52	0.15
		Others	5	157/569	2.56 [1.72, 3.79]	<0.00001	Fixed	15	0.32
	Anti-TB drug regimen	INH alone	2	31/210	2.32 [1.05, 5.13]	0.04	Fixed	0	0.45
		Combination	32	1256/6954	3.37 [2.67, 4.25]	<0.00001	Random	56	<0.0001
		Cohort	18	673/4850	2.82 [2.35, 3.40]	<0.00001	Fixed	40	0.04
	Study design	Case-control	17	650/2469	3.53 [2.42, 5.16]	<0.00001	Random	65	0.0001

Abbreviations: ***CI***, confidence interval; ***INH***, isoniazid; ***NAT2***, N-acetyltransferase 2; ***OR***, odds ratio; ***TB***, tuberculosis

[a] P value from Z test

[b] P value from Cochran's Q test based on chi-square statistic

S11 Table. Subgroup analysis for the association between *GST* polymorphisms and the risk of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug regimen, and study design

Polymorphic gene	Subgroup		Number of studies	Case/ control (n)	Test of association		Model of meta-analysis	Test of heterogeneity	
					OR [95% CI]	P value[a]		I^2 ,%	P value[b]
GSTM1[c] (null vs. non-null)	Total		19	977/5119	1.30 [1.12, 1.52]	0.0007	Fixed	33	0.08
	Ethnicity	East Asian	7	442/3110	1.23 [0.99, 1.54]	0.06	Fixed	23	0.25
		Indian	7	341/1420	1.68 [1.30, 2.19]	<0.0001	Fixed	36	0.15
		Brazilian	4	159/529	0.98 [0.66, 1.47]	0.94	Fixed	0	0.60
	Study design	Cohort	8	462/3439	1.41 [1.04, 1.93]	0.03	Random	44	0.08
		Case-control	11	515/1680	1.25 [1.01, 1.55]	0.20	Fixed	29	0.17
GSTT1[c] (null vs. non-null)	Total		17	768/4823	1.03 [0.85, 1.25]	0.76	Fixed	16	0.26
	Ethnicity	East Asian	6	338/2999	0.96 [0.74, 1.24]	0.75	Fixed	0	0.94
		Indian	6	236/1235	1.37 [0.72, 2.59]	0.33	Random	57	0.04
		Brazilian	4	159/529	0.80 [0.47, 1.33]	0.39	Fixed	0	0.97
	Study design	Cohort	8	408/3354	0.89 [0.67, 1.19]	0.44	Fixed	3	0.41
		Case-control	9	360/1469	1.16 [0.90, 1.50]	0.26	Fixed	24	0.23
GSTM1/GSTT1[c] (dual-null vs. one-/non-null)	Total		11	547/4233	1.05 [0.67, 1.62]	0.84	Random	59	0.006
	Ethnicity	East Asian	3	235/2701	0.83 [0.58, 1.20]	0.33	Fixed	0	0.49
		Indian	5	203/1202	1.33 [0.50, 3.53]	0.56	Random	80	0.0005
		Brazilian	2	74/270	0.67 [0.20, 2.18]	0.50	Fixed	0	0.47
	Study design	Cohort	6	298/3136	0.85 [0.45, 1.61]	0.62	Random	58	0.04
		Case-control	5	249/1097	1.31 [0.71, 2.43]	0.39	Random	59	0.04

Abbreviations: ***CI***, confidence interval; ***GSTM1***, glutathione S-transferase Mu 1; ***GSTT1***, glutathione S-transferase Theta 1; ***OR***, odds ratio

[a] P value from Z test

[b] P value from Cochran's Q test based on chi-square statistic

[c] Subgroup analysis based on anti-tuberculosis drug regimen could not be performed due to insufficient information provided

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