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

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39 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 DraI*, *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 RsaI/PstI* 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 2013¹. 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 therapy⁴. 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 serious⁵. 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 patients⁶. 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 ATDILI¹². 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

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4 publication, several case-control pharmacogenetic studies in TB patients were newly published
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6 with conflicting results regarding the association between the risk of ATDILI and genetic
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8 polymorphisms of various DMEs. Therefore, an updated meta-analysis has been warranted to
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10 confirm the association between the ATDILI risk and genetic polymorphisms of DMEs. In
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12 addition to DMEs, drug transporters have been emerging as a key determinant of the
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14 pharmacokinetics and pharmacodynamics of a drug¹⁴. Among various drug transporters, organic
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16 anion transporting polypeptide 1B1 (OATP1B1), encoded by *SLCO1B1*, is the major influx
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18 transporter responsible for hepatic uptake of RIF¹⁵. Although several studies have previously
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20 examined the association between *SLCO1B1* polymorphisms and the risk of ATDILI, conflicting
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22 results have been reported regarding the effect of *SLCO1B1* polymorphisms on ATDILI risk.
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27 In our preliminary literature search, several polymorphic genes, including many DMEs,
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29 transporters, and other genes such as those involved in the immune system, were identified to
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31 have an association with the risk of ATDILI. Among these, sufficient, published information was
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33 available to conduct meta-analyses for *CYP2E1*, *NAT2*, *GST*, and *SLCO1B1* genetic
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35 polymorphisms.
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40 Objectives

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

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52 This study was in compliance with the Preferred Reporting Items for Systematic Reviews and
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54 Meta-Analyses (PRISMA) checklist for reporting the study design, search strategy, methods,
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4 results, and conclusions. Three authors (SY, JP, and SH) independently conducted a literature
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6 search, study selection, quality assessment, and data extraction by reviewing the titles, abstracts,
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8 and full texts based on the pre-specified study selection criteria. Any discrepancies were
9
10 adjudicated by corresponding authors (JIL and EKC).
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13 **Search strategy**

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16 Electronic databases of PubMed, EMBASE, Web of Science, and Cochrane Reviews were
17
18 systematically searched from their inception to February 2018 to identify relevant studies
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20 evaluating the association of *NAT2*, *CYP2E1*, *GST*, and *SLCO1B1* polymorphisms with ATDILI
21
22 risk. A comprehensive literature search was conducted using a combination of the following
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24 keywords and Medical Subject Heading (MeSH) terms: (“genetic polymorphism” or “*NAT2*” or
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26 “*CYP2E1*” or “*GST*” or “*SLCO1B1*” or “drug-metabolizing enzymes” or “drug transporter”)
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28 AND (“anti-tuberculosis agents drug-induced liver injuries” or “hepatotoxicity”). The reference
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30 lists in the selected reviews and meta-analyses were reviewed to ensure the inclusion of all
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32 relevant evidence in this analysis.
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38 **Study selection**

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

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

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38 The genotypes were analyzed based on the following genetic risk model: (1) *NAT2* (slow
39 acetylator vs. intermediate and fast acetylator); (2) *CYP2E1* (c1/c1 vs. c1/c2 and c2/c2 for the
40 *RsaI/PstI* polymorphism, D/D vs. D/C and C/C for the *DraI* polymorphism); (3) *GSTMI* (null vs.
41 non-null); (4) *GSTTI* (null vs. non-null); (5) *GSTMI/GSTTI* (dual-null vs. one- or non-null); and
42 (6) *SLCO1B1* (AA vs. AG and GG for 388A>G polymorphism, CC vs. TC and TT for 521T>C
43 polymorphism) Fixed- or random-effects models were used depending on the presence of
44 heterogeneity. The random-effects model was used in the presence of significant heterogeneity;
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4 otherwise, the fixed effects model was used. Heterogeneity of study outcomes among included
5 studies was evaluated using Cochran's Q test (Q) and quantified using Higgin's I^2 test.
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7 Significant heterogeneity was defined as the I^2 score of $> 40\%$ accompanied by $P < 0.10$ from
8 the Cochran's Q test ¹⁸. The strength of the association between the genetic polymorphisms and
9 the risk of ATDILI was estimated using pooled ORs with the corresponding 95% CIs. The
10 statistical significance of an OR was defined as $P < 0.05$ from the Z test. Subgroup analyses were
11 performed to identify the source of heterogeneity and to investigate effects of the following
12 covariates on the overall strength of the association between the genetic polymorphisms and the
13 risk of ATDILI: ethnicity, the achievement of HWE, anti-TB drug regimen, the genotyping
14 method used, and diagnostic criteria of ATDILI. In addition, sensitivity analyses were conducted
15 to assess the robustness of the results. Publication bias was evaluated with a symmetrical funnel
16 plot. Statistical analyses were performed using Review Manager Software (Cochrane
17 Collaboration, London, UK).

34 Patient and public involvement

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

43 Study selection and characteristics

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45 Overall, 384 articles were identified through electronic database search ($n = 381$) and through
46 manual search by reviewing the reference lists of retrieved articles ($n = 3$). After removing 99
47 duplicates, 285 articles were screened for relevance based on the title and abstract. Among them,
48 70 relevant articles were assessed for eligibility through full-text evaluations. Finally, a total of
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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 *GSTMI*, 17 for *GSTT1*, and 11 for *GSTMI/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 RsaI/PstI* 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 RsaI/PstI* polymorphism (OR for the c1/c1 genotype = 1.39; 95% CI 1.06–1.83, P = 0.02; I² = 60%, P_{heterogeneity} < 0.0001) (Figure 2A). In the subgroup analysis based on ethnicity,

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4 anti-TB drug regimens, and diagnostic criteria of ATDILI, the risk of ATDILI was significantly
5 increased for the *CYP2E1 RsaI/PstI* c1/c1 genotype in East Asian patients (OR = 1.62, 95% CI
6 1.26-2.36, P = 0.01; I² = 69%, P_{heterogeneity} = 0.0006), in patients receiving a combination of anti-
7 TB medications (OR = 1.35, 95% CI 1.01-1.79, P < 0.00001; I² = 61%, P_{heterogeneity} = 0.0002), and
8 in patients with ATDILI defined as a serum ALT concentration elevated by 2-fold or greater
9 above the ULN (OR = 1.54, 95% CI 1.08-2.18, P = 0.02; I² = 70%, P_{heterogeneity} < 0.0001) (S6
10 Table). The association between the risk of ATDILI and the c1/c1 genotype remained significant
11 after excluding the studies where HWE was not achieved (OR = 1.67, 95% CI 1.19-2.34, P =
12 0.002; I² = 58%, P_{heterogeneity} = 0.004) (S6 Table).

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14 In our primary analysis for the *CYP2E1 DraI* polymorphism with six studies including
15 233 cases and 1272 controls, no significant association was observed using the fixed-effects
16 model between the risk of ATDILI and the *DraI* polymorphism (OR for the D/D genotype =
17 0.93, 95% CI 0.68-1.27, P = 0.64; I² = 0%, P_{heterogeneity} = 0.51) (Figure 2B). No subgroup analysis
18 for the *DraI* polymorphism resulted in a significant association between the ATDILI risk and the
19 *DraI* polymorphism (S6 Table).

20 ***NAT2***

21 Overall, 34 studies with 1270 cases and 7234 controls were included in our primary analysis for
22 the *NAT2* polymorphism. Using the random-effects model, the pooled estimates of all included
23 studies (n = 34) showed a significant association between the risk of ATDILI and the *NAT2*
24 polymorphism (OR for the slow acetylator genotype = 3.11, 95% CI 2.53-3.82, P < 0.00001; I² =
25 47%, P_{heterogeneity} = 0.002) (Figure 3).

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

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

21 ***GST***

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24 For the *GSTM1* polymorphism, a total of 19 studies with 977 cases and 5119 controls were
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26 included in our primary analysis. Using the fixed-effects model, the pooled estimates of all
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28 included studies (n = 19) showed a significant association between the risk of ATDILI and the
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30 *GSTM1* polymorphism (OR for the *GSTM1* null genotype = 1.30, 95% CI 1.12-1.52, P = 0.0007;
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32 $I^2 = 33\%$, $P_{heterogeneity} = 0.08$) (Figure 4A). In the subgroup analysis based on ethnicity and
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34 diagnostic criteria of ATDILI, the risk of ATDILI was significantly increased for the *GSTM1*
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36 null genotype in Indians (OR = 1.68, 95% CI 1.30-2.19, P < 0.0001; $I^2 = 36\%$, $P_{heterogeneity} = 0.15$)
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38 and in patients with ATDILI defined as a serum ALT concentration elevated by 2-fold or greater
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40 above the ULN (OR = 1.56, 95% CI 1.28-1.91, P < 0.0001; $I^2 = 13\%$, $P_{heterogeneity} = 0.32$) (S8
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42 Table).

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45 For the *GSTT1* and *GSTM1/GSTT1* polymorphisms, 17 studies (768 cases, 4823 controls)
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47 and 11 studies (547 cases, 4233 controls) were included in our primary analyses, respectively.
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49 The risk of ATDILI was not significantly associated with the *GSTT1* polymorphism (OR for the
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51 null genotype = 1.03, 95% CI 0.85-1.25, P = 0.76; $I^2 = 16\%$, $P_{heterogeneity} = 0.26$) or the
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4 *GSTM1/GSTT1* polymorphism (OR for the dual-null genotype = 1.05, 95% CI 0.67-1.62, P =
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6 0.84; $I^2 = 59\%$, $P_{heterogeneity} = 0.006$) (Figures 4B and 4C). The associations of the *GSTT1* and the
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8 *GSTM1/GSTT1* genetic polymorphisms with the risk of ATDILI were not significant in any of
9
10 the subgroups tested (S8 Table).

11 ***SLCO1B1***

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14 For the *SLCO1B1 388A>G* polymorphism, four studies with 279 cases and 837 controls were
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16 included in our primary analysis. Using the fixed-effects model, no significant association was
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18 observed between the risk of ATDILI and the *SLCO1B1 388A>G* polymorphism (OR for the AA
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20 genotype = 1.47, 95% CI 0.94-2.29, P = 0.09; $I^2 = 0\%$, $P_{heterogeneity} = 0.72$) (Figure 5A). For the
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22 *SLCO1B1 521T>C* polymorphism, four studies with 310 cases and 901 controls were included in
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24 our primary analysis. Using the fixed-effects model, no significant association was found
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26 between the ATDILI risk and the *SLCO1B1 521T>C* polymorphism (OR for the CC genotype =
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28 1.21, 95% CI 0.40-3.63, P = 0.74; $I^2 = 0\%$, $P_{heterogeneity} = 0.56$) (Figure 5B). No significant
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30 association was observed between the risk of ATDILI and the *SLCO1B1* polymorphisms (both
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32 388A>G and 521T>C) in any of the tested subgroups based on ethnicity, anti-TB drug regimen,
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34 diagnostic criteria of ATDILI, and the genotyping method used (S9 Table).
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44 **Discussion**

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47 To our knowledge, our current study is a large-scale meta-analysis evaluating the association
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49 between the risk of ATDILI and genetic polymorphisms of *SLCO1B1* as well as various DMEs
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51 including *CYP2E1*, *NAT2*, and *GST* to provide more updated, comprehensive, and compelling
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53 evidence. Compared with previous meta-analyses, our present study included a larger number
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4 of studies and explored various factors which may influence the association between genetic
5 polymorphisms and the risk of ATDILI (S6, S7, S8, S9 Tables). The inclusion of a large
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7 number of studies in our current meta-analysis may sufficiently increase the statistical power
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9 compared to individual studies; however, a limited number of studies evaluating the association
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11 between the risk of ATDILI and the *SLCO1B1* genetic polymorphisms were included (n = 4).
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13 Consistent with previous studies, our current study suggested a significantly increased risk of
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15 ATDILI in patients with the *NAT2* slow acetylator genotype (OR = 3.11, 95% CI 2.53-3.82), the
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17 *CYP2E1 RsaI/PstI* c1/c1 genotype (OR = 1.39, 95% CI 1.06-1.83), and the *GSTM1* null
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19 genotype (OR = 1.30, 95% CI 1.12-1.52)^{10 13 19}. Among these genotypes, the risk of ATDILI
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21 was increased the most in patients with the *NAT2* slow acetylator genotype. In contrast, no
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23 significant association was observed between the risk of ATDILI and the genetic
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25 polymorphisms of *CYP2E1 DraI*, *GSTT1*, *GSTM1/GSTT1*, *SLCO1B1 388A>G*, and *SLCO1B1*
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27 *521T>C*. Caution needs to be exercised when interpreting this study finding because the lack of
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29 significant association between these polymorphisms and the risk of ATDILI might result from
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31 small sample sizes and the low frequency of ATDILI reported in patients with these genetic
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33 polymorphisms.
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41 When evaluating the impacts of the *CYP2E1 RsaI/PstI* and *DraI* genetic polymorphisms
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43 on the risk of ATDILI in our study, patients with the *RsaI/PstI* c1/c1 genotype were 1.39-times
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45 more likely to develop ATDILI. Similarly, in a previous meta-analysis by Deng and colleagues,
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47 the risk of ATDILI was 1.4-times higher in patients with the *RsaI/PstI* c1/c1 genotype compared
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49 to other genotypes²⁰. In the liver, INH is metabolized by NAT2 to acetylisoniazid which is
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51 consequently oxidized by CYP2E1 to reactive intermediates in the formation of hepatotoxins²¹
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55²². The increased inducibility or greater activity of CYP2E1 in patients with the *CYP2E1*
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4 *RsaI/PstI* c1/c1 genotype may result in the production of more intermediate hepatotoxins,
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6 ultimately leading to the increased risk of ATDILI ^{21 22}. Our subgroup analysis showed a
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8 significantly increased risk of ATDILI in the *CYP2E1 RsaI/PstI* c1/c1 genotype carriers of East
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10 Asian and Indian ethnicity (S6 Table), suggesting a potential gene-ethnicity interaction in these
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12 ethnic populations due to genetic characteristics of the ethnicity or environmental factors in these
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14 populations ²³. In addition to ethnicity, combination anti-TB therapy was shown to significantly
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16 increase the risk of ATDILI in patients with the *CYP2E1 RsaI/PstI* c1/c1 genotype (S6 Table).
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18 This is consistent with previous study findings because hepatotoxicity commonly occurs with
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20 anti-TB drugs and thus, use of more than one hepatotoxic anti-TB medications increases the risk
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22 of ATDILI ⁷. Moreover, patients with the *CYP2E1 RsaI/PstI* c1/c1 genotype were at a
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24 significantly increased risk of ATDILI when ATDILI was defined as serum ALT concentrations
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26 elevated > 2 times the ULN and when their genotype was determined by the PCR-RFLP or
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28 sequencing method. This may suggest more sensitive diagnostic criteria and genotyping method
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30 to identify patients at an increased risk of ATDILI as early in therapy as possible. However,
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32 caution needs to be exercised when applying this study finding in practice because of the
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34 potentially low specificity associated with the diagnostic criteria of ATDILI and genotyping
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36 method. Future studies are warranted to confirm our subgroup analysis results.
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44 Similar to previous studies, our current study suggested a significantly increased risk of
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46 ATDILI in patients with the *NAT2* slow acetylator genotype compared to those with
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48 intermediate/fast acetylator genotypes ^{10 19}. The risk of ATDILI in slow acetylators remained
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50 significantly increased in all tested subgroups regardless of ethnicity, the anti-TB drug regimen
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52 used, the achievement of HWE, diagnostic criteria of ATDILI, and the genotyping method used
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54 (S7 Table). Among the subgroups, the ATDILI risk appeared the highest in the West Asian
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4 population (OR = 9.51, 95% CI 4.19-21.61, P < 0.00001). However, caution needs to be
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6 exercised when interpreting and applying this finding in practice because it is the result of
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8 subgroup analysis. Until more confirmative data are available, clinicians may closely monitor
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10 West Asian TB patients with the *NAT2* slow acetylator genotype receiving INH-based treatment.
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13 According to previous studies, GST enzymes, particularly those coded by *GSTM1* and
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15 *GSTT1* loci, are associated with the risk of drug-induced hepatotoxicity^{10 24}. Consistent with
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17 previous studies, our current study demonstrated a significantly increased risk of ATDILI in
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19 individuals with the *GSTM1* null genotype compared to those with the non-null genotype;
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21 however, the risk of ATDILI was not affected by the *GSTT1* or *GSTM1/GSTT1* genetic
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23 polymorphisms. GSTs are important enzymes to detoxify various xenobiotics and play an
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25 essential role in INH metabolism by eliminating acetyldiazene ketene acetylonium ion (a
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27 possibly hepatotoxic free radical metabolite of INH) from the body through *GSTM1*. This may
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29 account for the significant association of the ATDILI risk with the *GSTM1* genotype, but not
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31 with the *GSTT1* or *GSTM1/GSTT1* genotypes^{10 24}. Our subgroup analysis showed a significantly
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33 increased risk of ATDILI in the *GSTM1* null genotype carriers of Indian ethnicity (S8 Table),
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35 suggesting a potential gene-ethnicity interaction due to unknown genetic characteristics or
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37 environmental factors such as diet in Indian patients²³. In addition, the risk of ATDILI was
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39 significantly increased in patients with the *GSTM1* null genotype when ATDILI was defined as
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41 serum ALT concentrations elevated > 2 times the ULN (S8 Table). Based on this finding, serum
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43 ALT concentrations elevated > 2 times the ULN may be suggested as more sensitive diagnostic
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45 criteria of ATDILI; however, it may result in the false positive identification of ATDILI patients
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47 without clinical significance due to potentially low specificity. Considering this is a subgroup
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49 analysis result, caution is warranted in interpreting and applying this finding in practice until
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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 RIF²⁵. 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* *RsaI/PstI* ($I^2 = 60\%$, $P < 0.0001$), *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

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4 sensitivity analyses, outlier studies were identified as the major source of heterogeneity. After
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6 removing these outlier studies, heterogeneity was remarkably reduced ($I^2 = 60\%$ to 34% for
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8 *CYP2E1 RsaI/PstI*, $I^2 = 47\%$ to 32% for *NAT2*, $I^2 = 33\%$ to 0% for *GSTMI*, $I^2 = 59\%$ to 0% for
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10 *GSTMI/GSTT1*). The overall results for the association between the risk of ATDILI and genetic
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12 polymorphisms of these enzymes after excluding the outlier studies were not changed, indicating
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14 the robustness of our analysis result.
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18 There are limitations to this study. First, due to the lack of information regarding other
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20 patient characteristics potentially associated with liver injuries, our estimated ORs were not
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22 adjusted based on the potential risk factor of drug-induced liver injuries such as age, alcohol
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24 consumption, cigarette smoking, and other lifestyle characteristics⁷⁹. Second, our literature
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26 search limited to the articles published in English may lead to language bias. Third, the effect of
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28 anti-tuberculosis drug dosages on the risk of ATDILI could not be accounted for in our study
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30 because this information was not available in most of the included studies. In addition, a specific
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32 causative agent of ATDILI could not be identified in our analysis because most patients in our
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34 included studies received a combination regimen of anti-tuberculosis drugs. Lastly, only the
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36 limited number of genotypes were assessed for the association with the risk of ATDILI,
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38 particularly for *SLCO1B1* genetic polymorphisms. Future studies are needed to comprehensively
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40 and adequately address the relationship between the ATDILI risk and various polymorphisms of
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42 the genes for drug-metabolizing enzymes and drug transporters by using different genetic risk
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44 models and including more polymorphic genotypes.
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51 In conclusion, the risk of ATDILI during TB therapy was significantly increased in TB
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53 patients carrying *NAT2* slow acetylator, *CYP2E1 RsaI/PstI* c1/c1, or *GSTMI* null genotype.
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55 Screening for these genetic polymorphisms, particularly for the *NAT2* slow acetylator genotype,
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4 may be of great clinical benefit to identify patients at high risk for ATDILI and minimize the risk
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6 of ATDILI. Future studies are pertinent to develop dose and/or treatment adjustment strategies,
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8 to evaluate the feasibility and cost-effectiveness of the genetic screening test, and to assess the
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10 effect of more genetic polymorphisms on the risk of ATDILI for appropriate prevention and
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12 management of ATDILI.
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38 prepared and reviewed the manuscript. All authors reviewed, amended and approved the
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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) *CYP2E1* *RsaI/PstI* polymorphism, (B) *CYP2E1* *DraI* polymorphism, (C) *NAT2* polymorphism, (D) *GSTM1* polymorphism, (E) *GSTT1* polymorphism, (F) *GSTT1/MI* 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

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

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

12 13 14 15 16 **Figure legends**

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

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21 **Figure 2.** Risk of anti-tuberculosis drug-induced liver injury in patients with the *CYP2E1* (A)
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23 *RsaI/PstI* c1/c1 genotype compared to c1/c2 + c2/c2 genotypes and (B) *DraI* D/D genotype
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25 compared to D/C + C/C genotypes.

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30 acetylator genotype compared to those with the intermediate/fast acetylator genotypes.

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42 **Figure 5.** Risk of anti-tuberculosis drug-induced liver injury in patients with the *SLCO1B1* (A)
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44 388 AA genotype compared to the 388 AG + GG genotypes and (B) 521 CC genotype compared
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46 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	<i>NAT2</i>	Tunisian	14/52	42.4/42.1	42.8/48.1	INH, RIF containing regimen	ALT > 2 × ULN	6
Bozok Cetintas, 2008 ³¹	<i>NAT2</i>	Turkish	30/70	39.8/37.3	50.0/72.8	INH, RIF, PZA, EMB	ALT > 3 × ULN	5
Higuchi, 2007 ³²	<i>NAT2</i>	Japanese	18/82	60.8/64.7	50.0/57.3	INH, RIF containing regimen	ALT > 2 × ULN	6
Ho, 2013 ³³	<i>NAT2</i>	Taiwanese	20/328	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 5 × ULN	5
Huang, 2002 ³⁴	<i>NAT2</i>	Taiwanese	33/191	73.3/63.7	87.9/88.5	INH, RIF, PZA, EMB	ALT > 2 × ULN	6
Khalili, 2011 ³⁵	<i>NAT2</i>	Iranian	14/36	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 3 × ULN	6
Leiro-Fernandez, 2011 ³⁶	<i>NAT2</i>	Caucasian	50/67	34.0/30.5 ^b	54.0/56.7	INH, RIF, PZA	ALT > 3 × ULN	7
Lv, 2012 ³⁷	<i>NAT2</i>	Chinese	89/356	42.0/42.0 ^b	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Ng, 2014 ³⁸	<i>NAT2</i>	Mixed	26/101	48.3/NA	38.5/NA	INH containing regimen	ALT > 5 × ULN	6
Ohno, 2000 ³⁹	<i>NAT2</i>	Japanese	14/63	NA/NA	NA/NA	INH, RIF	ALT > 1.5 × ULN	7
Possuelo, 2008 ⁴⁰	<i>NAT2</i>	Brazilian	14/240	38.9/36.5	50.0/66.9	INH, RIF, PZA	ALT > 3 × ULN	7
Rana, 2012 ⁴¹	<i>NAT2</i>	Indian	50/201	45.3/43.8	76.0/57.2	INH, RIF, PZA, EMB	ALT > 5 × ULN	7
Shimizu, 2006 ⁴²	<i>NAT2</i>	Japanese	10/32	60.5/64.9	70.0/46.9	INH, RIF	ALT > 2 × ULN	5
Yuliwulandari, 2016 ⁴³	<i>NAT2</i>	Indonesian	50/191	NA/NA	NA/NA	NA	ALT > 2 × ULN	6
Feng, 2014 ⁴⁴	<i>CYP2E1</i>	Chinese	173/173	48.8/48.6	68.0/68.0	INH, RIF, PZA	ALT > 3 × ULN	6

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

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

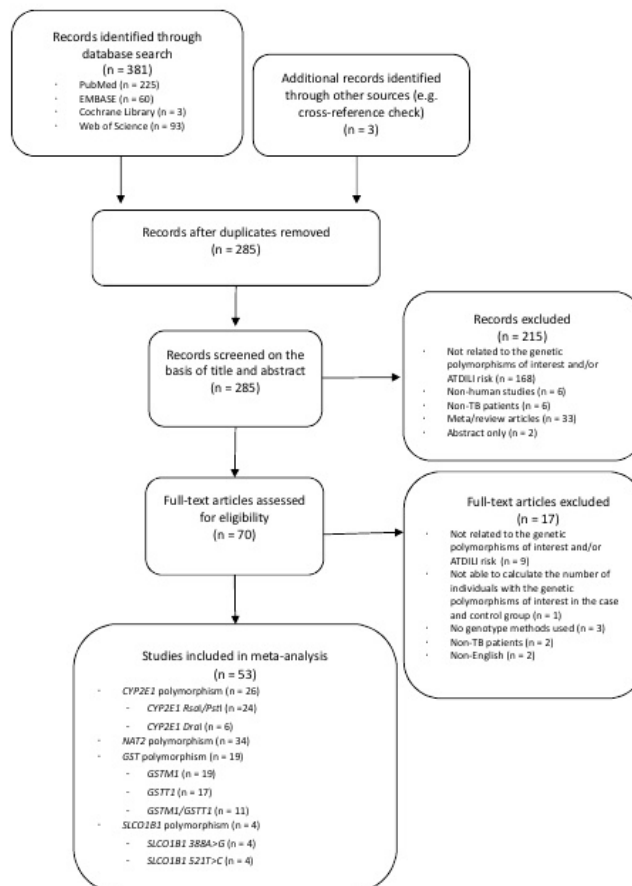
Singla, 2014 ⁷⁵	<i>NAT2</i> , <i>CYP2E1</i> , <i>GSTM1</i> , <i>GSTT1</i>	Indian	17/391	48.2/32.7	64.7/61.4	INH, RIF, PZA, EMB, STM	ALT > 2 × ULN	7
Sotsuka, 2011 ⁷⁶	<i>NAT2</i> , <i>CYP2E1</i> , <i>GSTM1</i> , <i>GSTT1</i>	Japanese	20/92	54.9/50.4	90.0/73.9	INH, RIF, PZA, EMB or STM	ALT > 3 × ULN	6
Teixeira,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

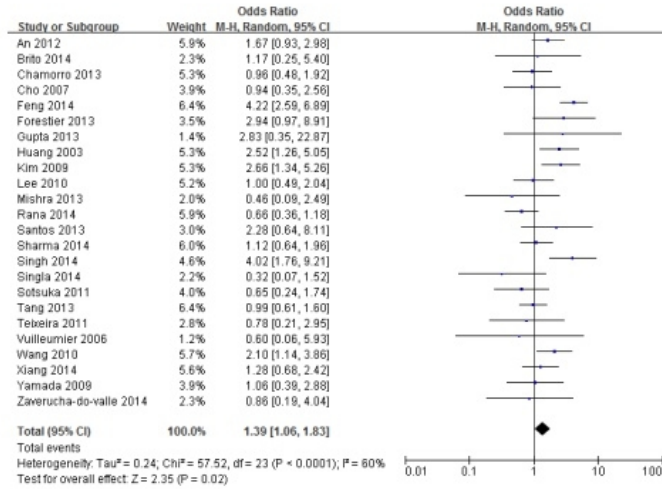
^c Number of individuals in the age ranges



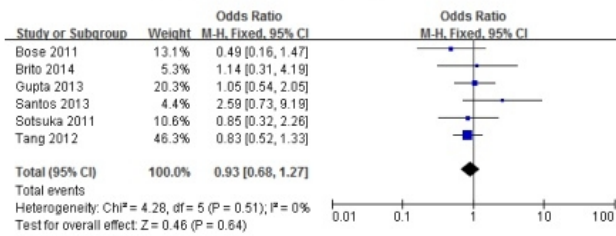
Study selection process flowchart according to the PRISMA guideline

209x297mm (72 x 72 DPI)

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

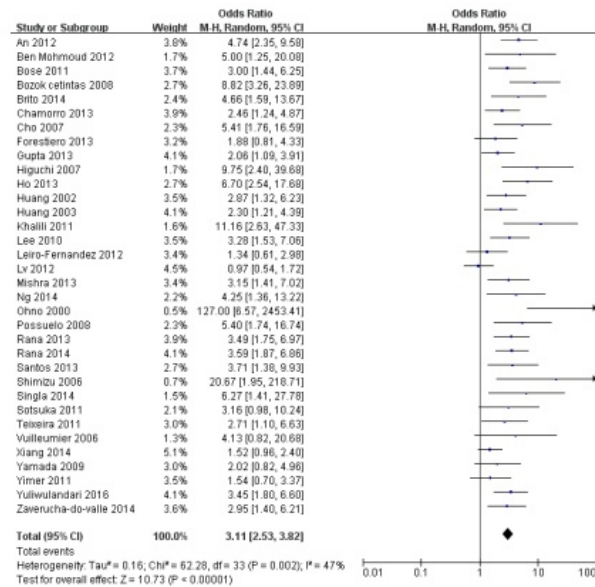


(B) CYP2E1 DraI D/D genotype compared to D/C + C/C genotypes.



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

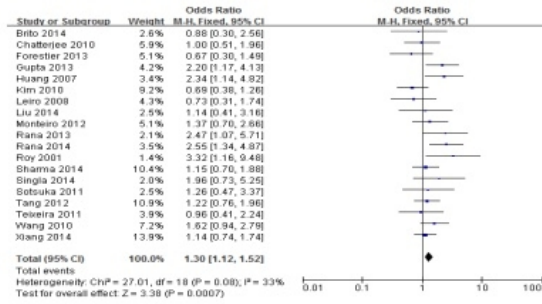
209x297mm (72 x 72 DPI)



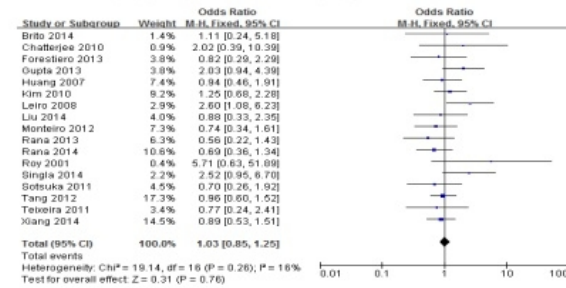
Risk of anti-tuberculosis drug-induced liver injury in patients with the NAT2 slow acetylator genotype compared to those with the intermediate/fast acetylator genotypes

209x297mm (72 x 72 DPI)

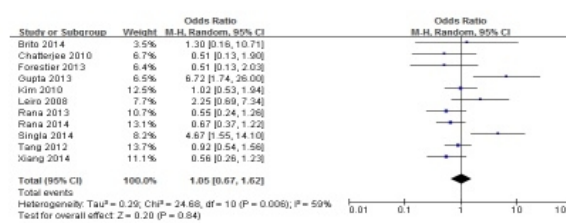
(A) *GSTM1* null genotype compared to the non-null genotype



(B) *GSTT1* null genotype compared to the non-null genotype

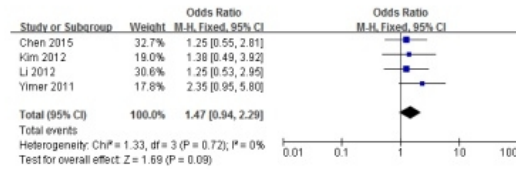
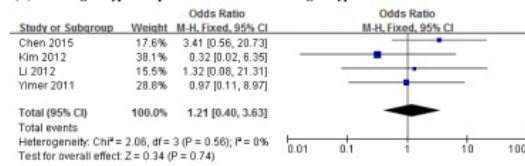


(C) *GSTM1/GSTT1* dual-null genotype compared to the one- and non-null genotypes



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

209x297mm (72 x 72 DPI)

(A) 388 AA genotype compared to the 388 AG + GG genotypes**(B) 521 CC genotype compared to the 521 TC + TT genotypes**

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	<i>RsaI/PstI</i> genotype (n = 24)				HWE	<i>DraI</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

1												
2												
3	Kim ¹⁰	54 (81.8)	12 (18.2)	97 (63.4)	56 (36.6)	Yes	NA	NA	NA	NA	NA	SNP stream
4												
5												
6	Lee ¹¹	26 (57.8)	19 (42.2)	55 (57.9)	40 (42.1)	No	NA	NA	NA	NA	NA	Taqman
7												
8	Mishra ¹²	31 (93.9)	2 (6.1)	168 (97.1)	5 (2.9)	No	NA	NA	NA	NA	NA	PCR-RFLP
9												
10												
11	Rana ¹³	28 (50.9)	27 (49.1)	150 (61.2)	95 (38.8)	No	NA	NA	NA	NA	NA	PCR-RFLP
12												
13												
14	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
15												
16	Sharma ¹⁵	81 (77.1)	24 (22.9)	139 (75.1)	46 (24.9)	Yes	NA	NA	NA	NA	NA	PCR-RFLP
17												
18												
19	Singh ¹⁶	42 (84.0)	8 (16.0)	77 (56.6)	59 (43.4)	No	NA	NA	NA	NA	NA	PCR-RFLP
20												
21												
22	Singla ¹⁷	15 (88.0)	2 (12.0)	375 (96.0)	16 (4.0)	No	NA	NA	NA	NA	NA	PCR-RFLP
23												
24												
25	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
26												
27												
28	Tang ¹⁹	NA	NA	NA	NA	NA	47 (52.8)	42 (47.2)	204 (57.3)	152 (42.7)	Yes	PCR-RFLP
29												
30	Tang ²⁰	56 (62.9)	33 (37.1)	225 (63.2)	131 (36.8)	Yes	NA	NA	NA	NA	NA	Taqman
31												
32												
33	Teixeira ²¹	23 (88.5)	3 (11.5)	128 (90.8)	13 (9.2)	Yes	NA	NA	NA	NA	NA	PCR-RFLP
34												
35												
36	Vuilleumier ²²	7 (87.5)	1 (12.5)	58 (92.1)	5 (7.9)	Yes	NA	NA	NA	NA	NA	PCR-RFLP
37												
38												
39												
40												
41												
42												
43												
44												
45												
46												

1												
2												
3	Wang ²³	82 (78.8)	22 (21.2)	71 (64.0)	40 (36.0)	No	NA	NA	NA	NA	NA	PCR-RFLP
4												
5												
6	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
7												
8												
9	Yamada ²⁵	17 (73.9)	6 (26.1)	107 (72.8)	40 (27.2)	Yes	NA	NA	NA	NA	NA	PCR-RFLP
10												
11												
12	Zaverucha-do-Valle ²⁶	48 (94.1)	3 (5.9)	74 (94.9)	4 (5.1)	Yes	NA	NA	NA	NA	NA	PCR-RFLP
13												
14												

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

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3	Huang ³¹	14 (42.4)	19 (57.6)	39 (20.4)	152 (79.6)	No	PCR-RFLP
4							
5	Huang ⁹	19 (38.8)	30 (61.2)	58 (21.6)	211 (78.4)	Yes	PCR-RFLP
6							
7	Khalili, ³²	9 (64.3)	5 (35.7)	5 (13.9)	31 (86.1)	Yes	PCR-RFLP
8							
9							
10	Lee ¹¹	21 (46.7)	24 (53.3)	20 (21.1)	75 (78.9)	No	Taqman
11							
12	Leiro-Fernandez ³³	36 (72.0)	14 (28.0)	44 (65.7)	23 (34.3)	No	PCR-RFLP
13							
14							
15	Lv ³⁴	18 (20.2)	71 (79.8)	74 (20.8)	282 (79.2)	Yes	PCR-RFLP
16							
17	Mishra ¹²	23 (70.0)	10 (30.0)	73 (42.0)	100 (58.0)	Yes	PCR-RFLP
18							
19	Ng ³⁵	22 (84.6)	4 (15.4)	57 (56.4)	44 (43.6)	Yes	PCR-RFLP
20							
21							
22	Ohno ³⁶	7 (50.0)	7 (50.0)	0 (0.0)	63 (100.0)	Yes	PCR-RFLP
23							
24	Possuelo ³⁷	9 (64.3)	5 (35.7)	60 (25.0)	180 (75.0)	No	Sequencing
25							
26							
27	Rana ³⁸	19 (38.0)	31 (62.0)	30 (14.9)	171 (85.1)	No	PCR-RFLP
28							
29	Rana ¹³	21 (38.2)	34 (61.8)	36 (14.7)	209 (85.3)	Yes	PCR-RFLP
30							
31	Santos ¹⁴	11 (61.1)	7 (38.9)	75 (29.8)	177 (70.2)	Yes	Sequencing
32							
33							
34	Shimizu ³⁹	4 (40.0)	6 (60.0)	1 (3.1)	31 (96.9)	No	PCR-RFLP
35							
36	Singla ¹⁷	15 (88.2)	2 (11.8)	213 (54.5)	178 (45.5)	No	PCR-RFLP
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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	<i>GSTMI</i> genotype (n = 19)				<i>GSTT1</i> genotype (n = 17)				<i>GSTMI/GSTT1</i> 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 ^{e 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
Forestier ^{o 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

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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

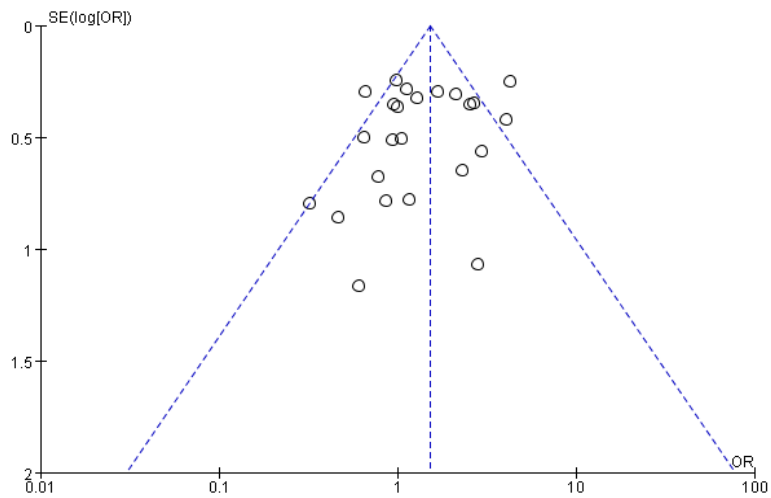
S4 Table. Genotype distribution, the achievement of Hardy-Weinberg equilibrium (HWE), and the genotyping method used for *SLCO1B1* in the included studies (n = 4)

Study	<i>SLCO1B1</i> 388A>G (rs2306283)				<i>SLCO1B1</i> 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

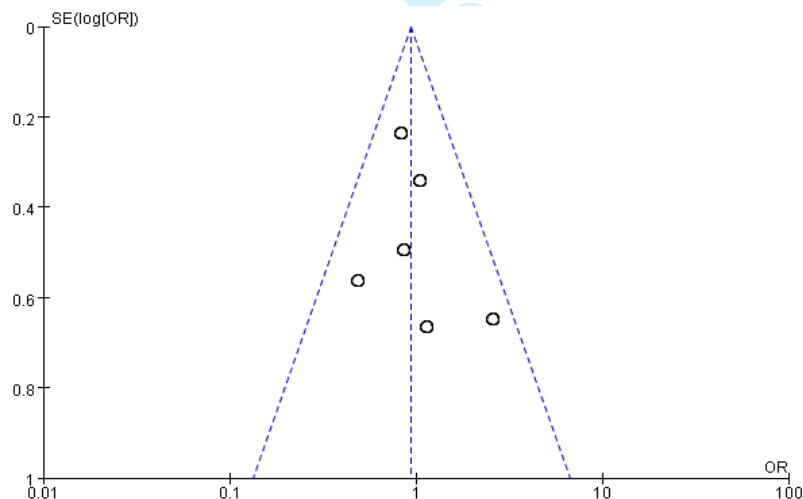
Abbreviations: **HWE**, Hardy-Weinberg equilibrium; **PCR**, polymerase chain reaction; **SNP**, single nucleotide polymorphism

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

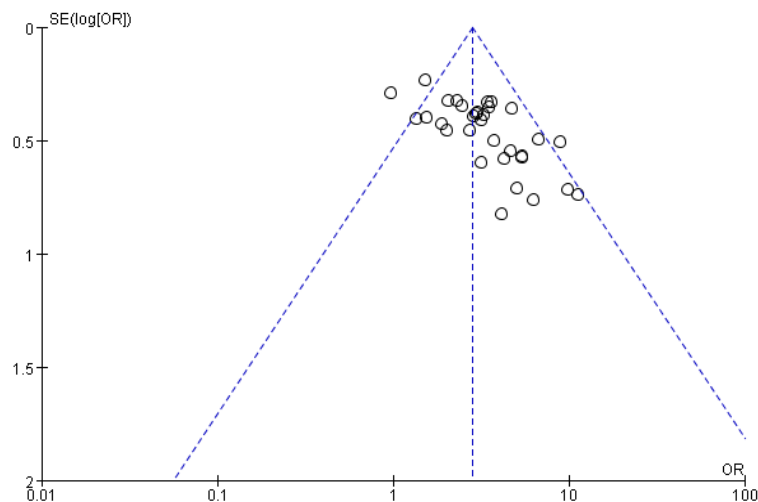
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3 **(A) CYP2E1 RsaI/PstI polymorphism**
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22 **(B) CYP2E1 DraI polymorphism**
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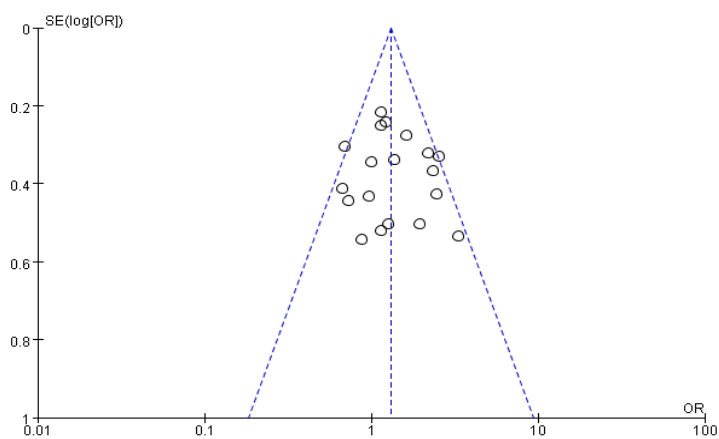


42 **(C) NAT2 polymorphism**
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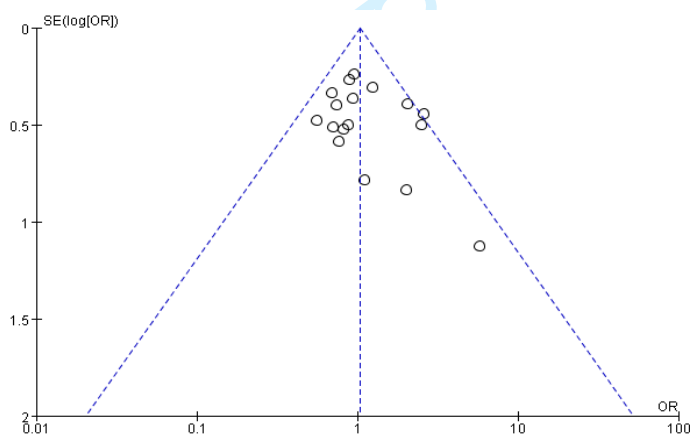


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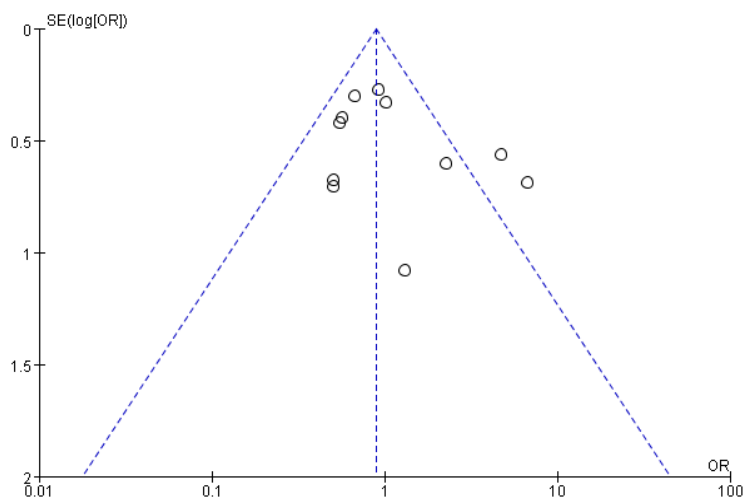
(D) *GSTM1* polymorphism



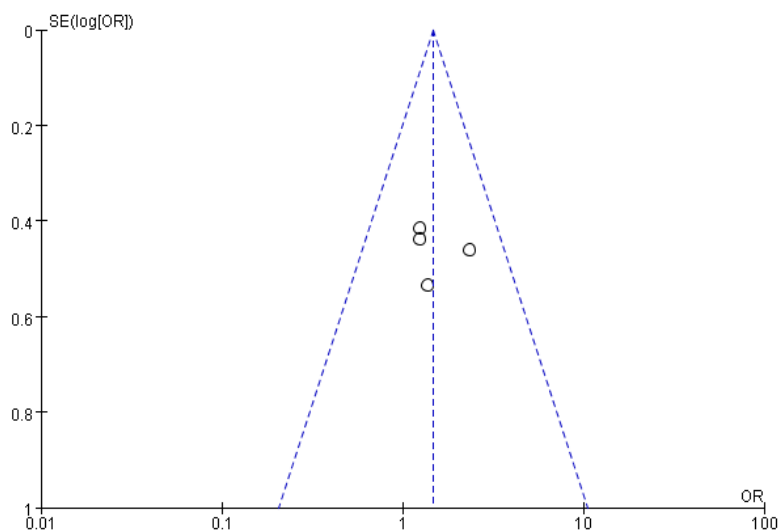
(E) *GSTT1* polymorphism



(F) *GSTT1/M1* polymorphism



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3 **(G) *SLCO1B1* 388A>G and 521T>C polymorphism**
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S5 Figure. Funnel plots to evaluate publication bias for the *CYP2E1*, *NAT2*, *GST*, and *SLCO1B1* polymorphisms associated with the ATDILI risk. (A) *CYP2E1* *RsaI/PstI* polymorphism, (B) *CYP2E1* *DraI* polymorphism, (C) *NAT2* polymorphism, (D) *GSTM1* polymorphism, (E) *GSTT1* polymorphism, (F) *GSTT1/MI* 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	
<i>CYP2E1</i> <i>RsaI/PstI</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
<i>CYP2E1</i> <i>DraI</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

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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 riskAbbreviations: *ALT*, alanine aminotransferase; *ATDILI*, anti-tuberculosis drug-induced liver injury; *CI*, confidence interval; *HWE*, Hardy-Weinberg equilibrium; *INH*,

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	
<i>NAT2</i> (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
		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	

isoniazid; *NAT2*, N-acetyltransferase 2; *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

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	
<i>GSTM1</i> ^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	
<i>GSTT1</i> ^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	
<i>GSTM1/GSTT1</i> ^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 ATDILI	ALT > 2 × ULN	6	330/3613	1.16 [0.60, 2.24]	0.67	Random	76	0.0009

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

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

8 ^a P value from Z test

9 ^b P value from Cochran's Q test based on chi-square statistic

10 ^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
<i>SLCO1B1</i> 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
<i>SLCO1B1</i> 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

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3 ^a P value from Z test

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5 ^b P value from Cochran's Q test based on chi-square statistic

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7 ^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

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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

Page 1 of 2

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

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

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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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Genetics and genomics, Infectious diseases, Evidence based practice
Keywords:	Anti-tuberculosis drug-induced liver injury, genetic polymorphisms, meta-analysis, drug-metabolizing enzyme, drug transporter, Tuberculosis < INFECTIOUS DISEASES

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8 2 **Association of genetic polymorphisms of *CYP2E1*, *NAT2*, *GST*, and**
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14 4 **injury: a systematic review and meta-analysis**
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35 34 *Jangik I. Lee and Eun Kyung Chung have equally contributed to this study.

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41 36 **Running head**

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44 37 Genetics of anti-tuberculosis liver injury

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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* *RsaI/PstI* 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* *DraI*, *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,

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4 61 *CYP2E1* *RsaI/PstI* c1/c1 genotype, and *GSTM1* null genotype. Close monitoring may be
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7 62 warranted for patients with these genotypes.
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11 64 **Strengths and limitations of this study**

- 14 65 ● This is the first meta-analysis to evaluate the association between the risk of ATDILI
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16 and *SLCO1B1* in TB patients.
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19 67 ● We included most updated studies with the large sample sizes to better clarify the
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21 association of genetic polymorphisms with the risk of ATDILI.
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- 23
24 69 ● The effect of anti-tuberculosis drug dosages on the risk of ATDILI could not be
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26 accounted for in this study due to the lack of drug dosing information in the majority of
27 70
28 the included studies.
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74 Introduction

75 Tuberculosis (TB) is a rampant infectious disease caused by *Mycobacterium tuberculosis*. It
76 poses a major public health threat globally with approximately 1.3 million deaths and 10 million
77 new cases in 2017 ¹. The mainstay of first-line TB treatment is a 4-drug combination regimen of
78 isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) during the first 2
79 months, followed by INH and RIF for additional 4 months ^{2,3}. The currently recommended
80 therapy for TB is highly effective, resulting in high cure rates if patients are adherent to therapy
81 ⁴. However, treatment adherence is often suboptimal in patients receiving the combination anti-
82 TB therapy due to many adverse drug reactions, some of which are considered detrimental ⁵. One
83 of the common adverse drug reactions associated with anti-TB medications is anti-TB drug-
84 induced liver injury (ATDILI) affecting 2–28% of tuberculosis patients⁶. ATDILI could be
85 potentially serious and fatal, resulting in the treatment interruption and ultimately, treatment
86 failure ^{7,8}.

87 Recently, increasing evidence suggests an association between the risk of ATDILI and genetic
88 polymorphisms of drug-metabolizing enzymes (DMEs) and drug transporters ^{9,10}. Altered
89 enzyme activity due to polymorphic genotypes of various DMEs including cytochrome P450
90 2E1 (CYP2E1), N-acetyltransferase 2 (NAT2), and glutathione S-transferase (GST) can result in
91 the accumulation of toxic substances in the liver, leading to the development of ATDILI ¹¹.
92 However, conflicting results have been reported regarding the association between the risk of
93 ATDILI and genetic polymorphisms of various DMEs in tuberculosis patients ^{9,12,13}. In addition
94 to DMEs, drug transporters have been emerging as a key determinant of the pharmacokinetics
95 and pharmacodynamics of a drug ¹⁴. Among various drug transporters, organic anion

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4 96 transporting polypeptide 1B1 (OATP1B1), encoded by *SLCO1B1*, is the major influx transporter
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6 97 responsible for hepatic uptake of RIF¹⁵. Although several studies have previously examined the
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8 98 association between *SLCO1B1* polymorphisms and the risk of ATDILI, conflicting results have
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10 99 been reported regarding the effect of *SLCO1B1* polymorphisms on ATDILI risk. Therefore, an
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12 100 updated meta-analysis has been warranted to confirm the association between the ATDILI risk
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14 101 and genetic polymorphisms of DMEs. In our preliminary literature search, several polymorphic
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16 102 genes, including many DMEs, transporters, and other genes such as those involved in the
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18 103 immune system, were identified to have an association with the risk of ATDILI. Among these,
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20 104 sufficient, published information was available to confirm the effect of *CYP2E1*, *NAT2*, *GST*,
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22 105 and *SLCO1B1* genetic polymorphisms on the ATDILI risk through meta-analysis.
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106 **Objectives**

31 107 The objective of this meta-analysis was to evaluate the association between the risk of ATDILI
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33 108 and genetic polymorphisms of *CYP2E1*, *NAT2*, *GST*, and *SLCO1B1* in tuberculosis patients.
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110 **Methods**

41 111 This study was in compliance with the Meta-analysis Of Observational Studies in Epidemiology
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43 112 (MOOSE) checklist for reporting the study design, search strategy, methods, results, and
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45 113 conclusions (S1 Table). Three authors (SY, JP, and SH) independently conducted a literature
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47 114 search, study selection, quality assessment, and data extraction. Any discrepancies were
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49 115 adjudicated by corresponding authors (JIL and EKC).
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116 **Search strategy**

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4 117 Electronic databases of PubMed, EMBASE, Web of Science, and Cochrane Reviews were
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6 118 systematically searched from their inception to February 2018 to identify relevant studies
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8 119 evaluating the association of *NAT2*, *CYP2E1*, *GST*, and *SLCO1B1* polymorphisms with ATDILI
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11 120 risk. A comprehensive literature search was conducted using a combination of the following
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13 121 keywords and Medical Subject Heading (MeSH) terms: (“genetic polymorphism” or “*NAT2*” or
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15 122 “*CYP2E1*” or “*GST*” or “*SLCO1B1*” or “drug-metabolizing enzymes” or “drug transporter”)
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18 123 AND (“anti-tuberculosis agents drug-induced liver injuries” or “hepatotoxicity”). The detailed
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20 124 search strategies for each electronic database used in this analysis are presented in S2 Table. The
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22 125 reference lists in the selected reviews and meta-analyses were reviewed to ensure the inclusion of
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24
25 126 all relevant evidence in this analysis.

127 **Study selection**

31 128 Studies were considered eligible if they met all of the following inclusion criteria: (1) studies
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33 129 with TB patients receiving anti-TB drug regimen; (2) studies with the control group of TB
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35 130 patients tolerant of anti-TB medications; (3) studies evaluating the association between the
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37 131 occurrence of ATDILI and genetic polymorphisms of *CYP2E1*, *NAT2*, *GST*, and *SLCO1B1*
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39 132 388A>G and 521T>C; and (4) case-control or cohort observational studies. Excluded studies
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41 133 were as follows: (1) studies available only in the form of abstracts or meeting posters; (2) review
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43 134 or meta-analysis articles; (3) studies providing insufficient data necessary for the statistical data
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45 135 analysis; (4) studies in non-English language; (5) non-human studies including animal and *in*
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47 136 *vitro* studies; (6) studies with unpublished data; (7) studies providing insufficient information on
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50 137 genotyping methods; and (8) healthy controls.

138 **Quality assessment and data extraction**

139 The quality of included studies was assessed using the revised Little's recommendation based on
140 the following criteria^{16 17}: (1) scientific design; (2) definite inclusion of study population; (3)
141 explicit information on study population; (4) explicit diagnostic criteria of ATDILI; (5) genetic
142 detection method; (6) appropriate statistical analysis; and (7) logical discussion of study bias.

143 Studies with an overall score of ≥ 4 (range 0 to 7) were considered high quality and retained in
144 the analysis.

145 The following data were extracted from each study using a standardized extraction form:

146 (1) name of the first author; (2) year of publication; (3) the polymorphic gene(s) and genotype(s)
147 under investigation; (4) ethnicity; (5) sample size; (6) mean or median age; (7) sex distribution;
148 (8) anti-TB drug regimens; (9) diagnostic criteria of ATDILI; (10) genotyping methods; and (11)
149 the number of cases and controls for each polymorphic genotype.

150 **Statistical analysis**

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

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4 160 models including dominant, recessive, and additive models were evaluated. The Mantel-
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6 161 Haenszel or DerSimonian-Laird method based on fixed- or random-effects models, respectively,
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8 162 were used depending on the presence of heterogeneity^{20 21}. The random-effects model was used
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11 163 in the presence of significant heterogeneity; otherwise, the fixed-effects model was used to
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13 164 estimate the total effect of a polymorphic gene genotype on the risk of ATDILI. Heterogeneity of
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15 165 study outcomes among included studies was evaluated using Cochran's Q test (*Q*) and quantified
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17 166 using Higgin's *I*² test. Significant heterogeneity was defined as the *I*² score of > 40%
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20 167 accompanied by $P < 0.10$ from the Cochran's Q test²². The strength of the association between
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22 168 the genetic polymorphisms and the risk of ATDILI was estimated using pooled odds ratios (ORs)
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24 169 with the corresponding 95% confidence intervals (CIs). The statistical significance of an OR was
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26 170 defined as $P < 0.05$ from the Z test.

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29 171 Subgroup analysis was performed based on ethnicity, anti-TB drug regimen used, and the type of
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31 172 study design. Sensitivity analysis was conducted to assess the robustness of the results and to
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33 173 identify the source of heterogeneity using the leave-one-out method. In each analysis, one study
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35 174 was deleted, and with the one study left out, the meta-analysis was performed; this process was
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37 175 repeated until every study had been deleted from our included study pool for each tested
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39 176 polymorphic gene. Publication bias was evaluated with a symmetrical funnel plot. Statistical
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41 177 analyses were performed using Review Manager Software version 5.3 (Cochrane Collaboration,
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43 178 London, UK).

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51 180 **Patient and public involvement**

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54 181 Patients and public were not involved in the design of this study.
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183 Results

184 Study selection and characteristics

185 Overall, 388 articles were identified through electronic database search and 3 articles through
186 manual search by reviewing the reference lists of retrieved articles. After removing 99
187 duplicates, 289 articles were screened for relevance based on the title and abstract. Among them,
188 72 relevant articles were assessed for eligibility through full-text evaluations. Finally, a total of
189 54 articles which met the inclusion criteria were included in our analysis (Figure 1). Among the
190 54 studies, 26 studies were included for *CYP2E1*, 35 studies for *NAT2*, 19 studies for *GST* (19
191 for *GSTMI*, 17 for *GSTTI*, and 11 for *GSTMI/GSTTI*), and 4 studies for *SLCO1B1* 388A>G and
192 521T>C.

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

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4 226 the *NAT2* polymorphism. Using the random-effects model, the pooled estimates of all included
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6 227 studies (n = 35) showed a significant association between the risk of ATDILI and the *NAT2*
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8 228 polymorphism (OR for the slow acetylator genotype = 3.30, 95% CI 2.65–4.11, P < 0.00001; $I^2 =$
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10 229 54%, $P_{heterogeneity} < 0.0001$) (Figure 3). In the subgroup analysis based on ethnicity, anti-TB drug
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12 230 regimens used, and study design, the risk of ATDILI was significantly increased in slow
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14 231 acetylators compared to fast or intermediate acetylators in all subgroups (S10 Table).

18 232 ***GST***

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21 233 For the *GSTM1* polymorphism, a total of 19 studies with 977 cases and 5119 controls were
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23 234 included in our primary analysis. Using the fixed-effects model, the pooled estimates of all
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25 235 included studies (n = 19) showed a significant association between the risk of ATDILI and the
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27 236 *GSTM1* polymorphism (OR for the *GSTM1* null genotype = 1.30, 95% CI 1.12–1.52, P = 0.0007;
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29 237 $I^2 = 33%$, $P_{heterogeneity} = 0.08$) (Figure 4A). When studies were stratified for ethnicity, the risk of
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31 238 ATDILI was significantly increased for the *GSTM1* null genotype in Indians (OR = 1.68, 95% CI
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33 239 1.30–2.19, P < 0.0001; $I^2 = 36%$, $P_{heterogeneity} = 0.15$) (S11 Table). In the subgroup analyses by
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35 240 study design, the estimated OR (95% CI, P-value; I^2 , $P_{heterogeneity}$) for the *GSTM1* null genotype
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37 241 relative to the non-null genotype was 1.41 (1.04-1.93, P = 0.03; $I^2 = 44%$, $P_{heterogeneity} = 0.08$) in
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39 242 cohort studies and 1.25 (1.01-1.55, P = 0.20; $I^2 = 29%$, $P_{heterogeneity} = 0.17$) in case-control studies,
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41 243 respectively (S11 Table).

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44 244 For the *GSTT1* and *GSTM1/GSTT1* polymorphisms, 17 studies (768 cases, 4823 controls)
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46 245 and 11 studies (547 cases, 4233 controls) were included in our primary analyses, respectively.
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48 246 The risk of ATDILI was not significantly associated with the *GSTT1* polymorphism (OR for the
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50 247 null genotype = 1.03, 95% CI 0.85–1.25, P = 0.76; $I^2 = 16%$, $P_{heterogeneity} = 0.26$) or the

248 *GSTM1/GSTT1* polymorphism (OR for the dual-null genotype = 1.05, 95% CI 0.67–1.62, $P =$
249 0.84; $I^2 = 59%$, $P_{heterogeneity} = 0.006$) (Figures 4B and 4C). When studies were stratified for
250 ethnicity, anti-TB drug regimens used, and study design, no subgroups showed significant
251 association between the risk of ATDILI and the *GSTT1* and the *GSTM1/GSTT1* polymorphisms
252 (S11 Table).

253 ***SLCO1B1***

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

263 **Sensitivity analysis**

264 Our primary analysis results showed significantly high heterogeneity between studies for
265 *CYP2E1* *RsaI/PstI* ($I^2 = 60%$, $P < 0.0001$), *NAT2* ($I^2 = 54%$, $P < 0.0001$), *GSTM1/GSTT1* ($I^2 =$
266 59%, $P = 0.006$), and *SLCO1B1* 521T>C (dominant genetic model: $I^2 = 66%$, $P = 0.03$)
267 polymorphisms. This high heterogeneity between studies may be due to substantial differences in
268 ethnicity, anti-TB drug regimen, the genotyping method used, study design, and diagnostic
269 criteria of ATDILI among the included studies (Table 1). Through the sensitivity analyses,

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4 270 outlier studies were identified as the major source of heterogeneity. After removing these outlier
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6 271 studies, heterogeneity was substantially reduced ($I^2 = 60\%$ to 42% for *CYP2E1* *RsaI/PstI* ²³, $I^2 =$
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8 272 54% to 34% for *NAT2* ^{24 25}, $I^2 = 59\%$ to 0% for *GSTM1/GSTT1* ^{26 27}, and $I^2 = 66\%$ to 0% for
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10 273 *SLCO1B1* 521T>C dominant genetic model ²⁸). The overall results for the association between
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12 274 the risk of ATDILI and these genetic polymorphisms after excluding the outlier studies stayed
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14 275 the same as those from our primary analysis results.
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21 277 Discussion

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24 278 In this study, we conducted a large-scale meta-analysis evaluating the association between the
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26 279 risk of ATDILI and genetic polymorphisms of *SLCO1B1* as well as various DMEs including
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28 280 *CYP2E1*, *NAT2*, and *GST* to provide more updated, comprehensive, and compelling evidence.
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30 281 Compared with previous meta-analyses, our present study included a larger number of studies,
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32 282 which may sufficiently increase the statistical power compared to individual studies. However,
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34 283 a limited number of studies for the *SLCO1B1* genetic polymorphisms were included ($n = 4$).
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36 284 Consistently with previous studies, our current study suggested a significantly increased risk of
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38 285 ATDILI in patients with the *CYP2E1* *RsaI/PstI* c1/c1 genotype (OR = 1.39, 95% CI 1.06–1.83),
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40 286 the *NAT2* slow acetylator genotype (OR = 3.30, 95% CI 2.65–4.11), and the *GSTM1* null
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42 287 genotype (OR = 1.30, 95% CI 1.12–1.52) ^{9 12 29}. Among these genotypes, the largest increase in
43
44 288 the risk of ATDILI was shown in patients with the *NAT2* slow acetylator genotype. In contrast,
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46 289 no significant association was observed between the risk of ATDILI and the genetic
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48 290 polymorphisms of *CYP2E1* *DraI*, *GSTT1*, *GSTM1/GSTT1*, *SLCO1B1* 388A>G, and *SLCO1B1*
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50 291 521T>C. Caution needs to be exercised when interpreting this study finding because the lack of
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4 292 significant association between these polymorphisms and the risk of ATDILI might be due to
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6 293 small sample sizes and the low frequency of ATDILI reported in patients with these genetic
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9 294 polymorphisms.

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11 295 When evaluating the impact of the *CYP2E1 RsaI/PstI* and *DraI* genetic polymorphisms
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13 296 on the risk of ATDILI in our study, patients with the *RsaI/PstI* c1/c1 genotype were 1.39-times
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15 297 more likely to develop ATDILI. Similarly, in a previous meta-analysis by Deng and colleagues,
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17 298 the risk of ATDILI was 1.4-times higher in patients with the *RsaI/PstI* c1/c1 genotype compared
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19 299 to other genotypes³⁰. In the liver, INH is metabolized by NAT2 to acetylisoniazid which is
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21 300 consequently oxidized by CYP2E1 to reactive hepatotoxic intermediates^{31 32}. The increased
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23 301 inducibility or greater activity of CYP2E1 in patients with the *CYP2E1 RsaI/PstI* c1/c1 genotype
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25 302 may result in the production of more intermediate hepatotoxins, ultimately leading to the
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27 303 increased risk of ATDILI^{31 32}. Our subgroup analysis showed a significantly increased risk of
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29 304 ATDILI in the *CYP2E1 RsaI/PstI* c1/c1 genotype carriers of East Asian ethnicity (S9 Table),
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31 305 suggesting a potential gene-ethnicity interaction³³. A previous study identified age, female sex,
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33 306 white race, non-Hispanic ethnicity, lower body mass index, elevated plasma aspartate
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35 307 transaminase concentrations at baseline, and nine months of daily INH use as risk factors for
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37 308 ATDILI³⁴. Considering their race, ethnicity, and relatively lower body mass index compared to
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39 309 other ethnicities, East Asians may be at an increased risk of ATDILI. As the *CYP2E1 RsaI/PstI*
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41 310 c1 allele frequency is relatively low in this population (79.8% vs. 88.5% to 99.8% in other
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43 311 ethnicities), the ethnicity itself might play an important role in developing hepatotoxicity through
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45 312 gene-ethnicity interaction³⁵. Furthermore, the relatively high frequency of c2 allele in this
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47 313 population might serve as a good control to estimate the effect of c1 allele on the risk of
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49 314 ATDILI; the rarity of this minor allele in other ethnicities could make it difficult to evaluate the

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4 315 association between the ATDILI risk and this genetic polymorphism³⁵. In addition to ethnicity,
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6 316 combination anti-TB therapy was shown to significantly increase the risk of ATDILI in patients
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9 317 with the *CYP2E1 RsaI/PstI* c1/c1 genotype (S9 Table). This is consistent with previous study
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11 318 findings because hepatotoxicity commonly occurs with anti-TB drugs such as INH and RIF and
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13 319 thus, use of more than one hepatotoxic anti-TB medication increases the risk of ATDILI⁷.

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16 320 Similar to previous studies, our current study suggested a significantly increased risk of
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18 321 ATDILI in patients with the *NAT2* slow acetylator genotype compared to those with
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20 322 intermediate/fast acetylator genotypes^{9 29}. The risk of ATDILI in slow acetylators remained
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22 323 significantly increased in all tested subgroups regardless of ethnicity and the anti-TB drug
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24 324 regimen used (S10 Table). The frequencies of *NAT2* slow acetylator alleles are highly variable
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27 325 between ethnic groups, ranging from 32% in Koreans to 76% in Caucasians³⁶. Despite this large
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29 326 inter-ethnic variability in the *NAT2* polymorphic allele frequency, the *NAT2* slow acetylator
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31 327 genotype consistently and significantly increased the risk of ATDILI across all ethnicities,
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33 328 suggesting the critical role of *NAT2* polymorphism in the development of ATDILI. In addition,
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36 329 the increased risk of ATDILI in slow acetylators receiving INH monotherapy or combination
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38 330 therapy further highlights the importance of the *NAT2* polymorphism in the development of
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40 331 INH-induced hepatotoxicity. The clearance of INH is slower in slow acetylators compared to
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42 332 rapid or intermediate acetylators, resulting in the accumulation of INH in these patients^{37 38}. This
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44 333 high level of INH may increase the risk of ATDILI in tuberculosis patients with the *NAT2* slow
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46 334 acetylator genotype due to immune-mediated liver injury through the binding of INH to liver
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48 335 proteins³⁹. Therefore, clinicians should closely monitor tuberculosis patients with the *NAT2* slow
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50 336 acetylator genotype for hepatotoxicity when INH-based treatment is administered to these
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52 337 patients.
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4 338 According to previous studies, GST enzymes, particularly those coded by *GSTM1* and
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6 339 *GSTT1* loci, are associated with the risk of drug-induced hepatotoxicity^{9 40}. Similar to previous
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9 340 studies, our current study demonstrated a significantly increased risk of ATDILI in individuals
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11 341 with the *GSTM1* null genotype compared to those with the non-null genotype; however, the risk
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13 342 of ATDILI was not affected by the *GSTT1* or *GSTM1/GSTT1* genetic polymorphisms. GSTs are
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15 343 important enzymes to detoxify various xenobiotics and play an essential role in INH metabolism
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17 344 by eliminating acetyldiazene ketene acetylonium ion, which is a possibly hepatotoxic free radical
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19 345 metabolite of INH, from the body through *GSTM1*. This may account for the significant
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21 346 association of the ATDILI risk with the *GSTM1* genotype, but not with the *GSTT1* or
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23 347 *GSTM1/GSTT1* genotypes^{9 40}. Our subgroup analysis showed a significantly increased risk of
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25 348 ATDILI in the *GSTM1* null genotype carriers of Indian ethnicity; although not statistically
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27 349 significant, the risk of ATDILI was relatively high in the East Asian population with the *GSTM1*
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29 350 null genotype (S11 Table). Considering the substantial difference in the *GSTM1* null allele
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31 351 frequency between Indians (29.6%) and East Asians (52.1%), a potential gene-ethnicity
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33 352 interaction may exist based on their race, ethnicity, and body size as aforementioned^{34 41}. Other
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35 353 characteristics than the *GSTM1* polymorphism in these ethnicities may play a more important
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37 354 role in the development of ATDILI. In addition, when studies were stratified by study design, the
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39 355 risk of ATDILI was significantly increased in patients with the *GSTM1* null genotype for cohort
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41 356 studies only, but not for case-control studies, probably due to a relatively larger sample size with
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43 357 cohort studies compared to case-control studies.

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45 358 *SLCO1B1* encodes organic anion transporting polypeptide 1B1 (OATP1B1) which is a
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47 359 major influx drug transporter responsible for the hepatic uptake of various endogenous and
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49 360 exogenous substances including RIF⁴². Previous studies showed significantly altered systemic

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4 361 exposure of RIF in carriers of the *SLCO1B1* polymorphism^{43 44}. To our knowledge, only four
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6 362 studies have been conducted to examine the association between the ATDILI risk and the
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8 363 *SLCO1B1* genetic polymorphisms^{10 28 42 45}. Various single nucleotide polymorphisms (SNPs) of
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10 364 *SLCO1B1* were evaluated in these studies; however, *SLCO1B1* 388A>G (rs2306283) and
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12 365 521T>C (rs4149056) were the only polymorphisms assessed in common^{10 28 42 45}. Therefore, to
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14 366 maximize the sample size in our current meta-analysis, we examined the association between the
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16 367 risk of ATDILI and the polymorphic genotypes of *SLCO1B1* 388A>G and 521T>C. Similar to
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18 368 each of the included studies, we did not find significant difference in the risk of ATDILI among
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20 369 patients with different *SLCO1B1* 388A>G and 521T>C genotypes.
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25 370 There are limitations to this study. First, due to the lack of information regarding other
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27 371 patient characteristics potentially associated with ATDILI, our estimated ORs were not adjusted
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29 372 based on the potential risk factors such as age, anti-TB drug dosages, alcohol consumption,
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31 373 cigarette smoking, and other lifestyle characteristics^{7 46}. Second, our literature search limited to
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33 374 the articles published in English may lead to language bias. Third, a specific causative agent of
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35 375 ATDILI could not be identified in our analysis because most patients in our included studies
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37 376 received a combination regimen of anti-TB drugs. Fourth, only the limited number of
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39 377 polymorphic genotypes were assessed for the association with the risk of ATDILI, particularly
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41 378 for *SLCO1B1*. In addition, only one genetic model was used for *CYP2E1*, *NAT2*, and *GST* when
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43 379 evaluating the association between genetic polymorphisms of these genes and the risk of
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45 380 ATDILI. Although we acknowledge dominant, recessive, and additive genomic models can be
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47 381 used for two alleles, it could not be applied to our meta-analysis because we compared patients
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49 382 with different genotype-based phenotype, i.e., slow acetylator vs. fast/intermediate acetylator and
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51 383 null vs. non-null *GSTs*. Multiple allelic variants or allele subgroups may represent the same
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4 384 phenotype (e.g., *NAT2**5B, *6A, and *7B all represent slow acetylator genotypes), and the
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6 385 genetic model selection can be varied depending on the specific allelic variant⁴⁷. Therefore, the
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8 386 genetic models used in previous original and meta-analysis studies were adopted for these
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11 387 polymorphic genes in our current study^{9 18 19}. Future studies are needed to comprehensively and
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13 388 adequately address the relationship between the ATDILI risk and various genetic polymorphisms
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16 389 by using different genetic risk models and including more polymorphic genotypes.

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18 390 In conclusion, the risk of ATDILI during TB therapy was significantly increased in
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20 391 tuberculosis patients carrying *NAT2* slow acetylator, *CYP2E1* *RsaI/PstI* c1/c1, or *GSTM1* null
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22 392 genotypes. Screening for these genetic polymorphisms, particularly for the *NAT2* slow acetylator
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24 393 genotype, may be of great clinical benefit to identify patients at high risk for ATDILI and
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27 394 minimize the risk of ATDILI. Future studies are pertinent to develop dose and/or treatment
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29 395 adjustment strategies, to evaluate the feasibility and cost-effectiveness of the genetic screening
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31 396 test, and to assess the effect of more genetic polymorphisms on the risk of ATDILI for optimal
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33 397 prevention and management of ATDILI.

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46 401 University.

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52 403 **Contributors**

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55 404 S.Y. devised and designed the study. S.Y., J.Y.P., and S.J.H. conducted the literature search,

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4 405 performed data extraction and analysis, and. interpreted the data. S.Y., E.K.C., and J.I.L.
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6 406 prepared and reviewed the manuscript. All authors reviewed, amended and approved the
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26 27 414 **Competing interests**

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35 36 417 **Patient consent**

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25 678 Enzyme Polymorphisms NAT2, CYP2E1, GSTM1 and GSTT1. *Plos One* 2014;9.
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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) *CYP2E1* *RsaI/PstI* polymorphism, (B) *CYP2E1* *DraI* polymorphism, (C) *NAT2* polymorphism, (D) *GSTM1* polymorphism, (E) *GSTT1* polymorphism, (F) *GSTT1/MI* 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

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4 702 **S10 Table. Subgroup analysis for the association between *NAT2* polymorphism and the risk**
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6 703 **of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug**
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8 704 **regimen, and study design**

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11 705 **S11 Table. Subgroup analysis for the association between *GST* polymorphisms and the risk**
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13 707 **regimen, and study design**

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5 709 **Figure legends**

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7 710 **Figure 1.** Study selection process flowchart.

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9 711 **Figure 2.** Risk of anti-tuberculosis drug-induced liver injury in patients with the *CYP2E1* (A)
10 712 *RsaI/PstI* c1/c1 genotype compared to c1/c2 + c2/c2 genotypes and (B) *DraI* D/D genotype
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14 713 compared to D/C + C/C genotypes.

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16 714 **Figure 3.** Risk of anti-tuberculosis drug-induced liver injury in patients with the *NAT2* slow
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19 715 acetylator genotype compared to those with the intermediate/fast acetylator genotypes.

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21 716 **Figure 4.** Risk of anti-tuberculosis drug-induced liver injury in patients with (A) the *GSTM1* null
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23 717 genotype compared to the non-null genotype, (B) the *GSTT1* null genotype compared to the non-
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26 718 null genotype, and (C) the *GSTM1/GSTT1* dual-null genotype compared to the one- and non-null
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28 719 genotypes.

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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	<i>CYP2E1</i>	Case-control	Chinese	173/173	48.8/48.6	68.0/68.0	INH, RIF, PZA	ALT > 3 × ULN	6
Kim, 2009 ⁴⁸	<i>CYP2E1</i>	Case-control	Korean	67/159	42.1/42.8	65.7/65.4	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Singh, 2014 ⁴⁹	<i>CYP2E1</i>	Cohort	Indian	50/135	NA/NA	NA/NA	NA	ALT > 2 × ULN	7
Tang, 2013 ⁵⁰	<i>CYP2E1</i>	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	<i>NAT2</i>	Cohort	Tunisian	14/52	42.4/42.1	42.8/48.1	INH, RIF containing regimen	ALT > 2 × ULN	7
Bozok Cetintas, 2008 ⁵²	<i>NAT2</i>	Case-control	Turkish	30/70	39.8/37.3	50.0/72.8	INH, RIF, PZA, EMB	ALT > 3 × ULN	6
Higuchi, 2007 ⁵³	<i>NAT2</i>	Cohort	Japanese	18/82	60.8/64.7	50.0/57.3	INH, RIF containing regimen	ALT > 2 × ULN	7
Ho, 2013 ⁵⁴	<i>NAT2</i>	Cohort	Taiwanese	20/328	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 5 × ULN	6
Huang, 2002 ⁵⁵	<i>NAT2</i>	Cohort	Taiwanese	33/191	73.3/63.7	87.9/88.5	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Khalili, 2011 ⁵⁶	<i>NAT2</i>	Case-control	Iranian	14/36	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 3 × ULN	6
Leiro-Fernandez, 2011 ⁵⁷	<i>NAT2</i>	Case-control	Caucasian	50/67	34.0/30.5 ^b	54.0/56.7	INH, RIF, PZA	ALT > 3 × ULN	7
Ly, 2012 ²⁴	<i>NAT2</i>	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	<i>NAT2</i>	Case-control	Mixed	26/101	48.3/NA	38.5/NA	INH containing regimen	ALT > 5 × ULN	7
Ohno, 2000 ⁵⁹	<i>NAT2</i>	Cohort	Japanese	14/63	NA/NA	NA/NA	INH, RIF	ALT > 1.5 × ULN	7
Possuelo, 2008 ⁶⁰	<i>NAT2</i>	Cohort	Brazilian	14/240	38.9/36.5	50.0/66.9	INH, RIF, PZA	ALT > 3 × ULN	7
Rana, 2012 ⁶¹	<i>NAT2</i>	Cohort	Indian	50/201	45.3/43.8	76.0/57.2	INH, RIF, PZA, EMB	ALT > 5 × ULN	7
Shimizu, 2006 ⁶²	<i>NAT2</i>	Case-control	Japanese	10/32	60.5/64.9	70.0/46.9	INH, RIF	ALT > 2 × ULN	6
Yuliwulandari, 2016 ⁶³	<i>NAT2</i>	Case-control	Indonesian	50/191	NA/NA	NA/NA	NA	ALT > 2 × ULN	7
Wattanapokayakit, 2016 ²⁵	<i>NAT2</i>	Case-control	Thai	53/85	51.4/50.2	58.5/60.0	INH containing regimen	ALT > 2 × ULN	7
Chatterjee, 2010 ⁶⁴	<i>GSTMI, GSTTI</i>	Case-control	Indian	51/100	37.2/33.2	49.0/63.0	INH, RIF, PZA	ALT > 3 × ULN	7
Gupta, 2013 ⁶⁵	<i>GSTMI, GSTTI</i>	Cohort	Indian	50/246	37.0/36.5 ^b	48.0/56.5	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Huang, 2007 ⁶⁶	<i>GSTMI, GSTTI</i>	Case-control	Taiwanese	63/63	62.0/NA	NA/NA	NA	ALT > 5 × ULN	6
Kim, 2010 ⁶⁷	<i>GSTMI, GSTTI</i>	Case-control	Korean	57/190	47.3/42.4	59.6/67.9	INH, RIF, PZA, EMB	ALT > 3 × ULN	7
Leiro, 2008 ⁶⁸	<i>GSTMI, GSTTI</i>	Case-control	Caucasian	35/60	34.0/31.0 ^b	40.0/41.7	INH, RIF, PZA	ALT > 3 × ULN	7
Liu, 2014 ⁶⁹	<i>GSTMI, GSTTI</i>	Case-control	Chinese	20/143	35.9/61.2	60.0/59.4	INH containing regimen	ALT > 2 × ULN	7
Monteiro, 2012 ⁷⁰	<i>GSTMI, GSTTI</i>	Cohort	Brazilian	59/118	37.0/38.0 ^b	76.0/61.0	NA	ALT > 2 × ULN	7

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

	<i>CYP2E1</i>	control							
Vuilleumier, 2006 ⁸¹	<i>NAT2, CYP2E1</i>	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	<i>NAT2, CYP2E1</i>	Case-control	Mixed	23/147	NA/NA	13.0/42.9	INH	ALT > 2 × ULN	7
Zaverucha-do-Valle, 2014 ⁸³	<i>NAT2, CYP2E1</i>	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	<i>CYP2E1, GSTM1</i>	Cohort	Indian	105/185	35.2/27.6	55.7/72.1	INH, RIF, PZA, EMB	ALT > 5 × ULN	7
Wang, 2010 ⁸⁵	<i>CYP2E1, GSTM1</i>	Case-control	Chinese	104/111	48.6/44.7	67.3/67.6	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Tang, 2012 ⁸⁶	<i>CYP2E1, GSTM1, GSTT1</i>	Case-control	Chinese	89/356	43.7/43.6	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Yimer, 2011 ⁴⁵	<i>NAT2, SLCO1B1</i>	Cohort	Ethiopian	41/160	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 2 × ULN	6
Brito, 2014 ⁸⁷	<i>NAT2, CYP2E1, GSTM1, GSTT1</i>	Cohort	Brazilian	15/230	38.1/36.8	46.7/NA	INH, RIF, PZA	ALT > 3 × ULN	7
Forestiero, 2013 ⁸⁸	<i>NAT2, CYP2E1, GSTM1, GSTT1</i>	Cohort	Brazilian	59/40	NA/NA	49.2/60.0	INH, RIF, PZA	ALT > 2.5 × ULN	6
Rana, 2014 ⁸⁹	<i>NAT2, CYP2E1, GSTM1, GSTT1</i>	Cohort	Indian	55/245	43.6/42.3	60.0/62.0	INH, RIF, PZA, EMB	ALT > 5 × ULN	6
Singla, 2014 ²⁶	<i>NAT2, CYP2E1, GSTM1,</i>	Case-control	Indian	17/391	48.2/32.7	64.7/61.4	INH, RIF, PZA, EMB, STM	ALT > 2 × ULN	7

	<i>GSTT1</i>								
Sotsuka, 2011 ⁹⁰	<i>NAT2</i> , <i>CYP2E1</i> , <i>GSTM1</i> , <i>GSTT1</i>	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	<i>NAT2</i> , <i>CYP2E1</i> , <i>GSTM1</i> , <i>GSTT1</i>	Case-control	Brazilian	26/141	47.6/43.0	61.5/52.5	INH containing regimen	ALT > 3 × ULN	7
Xiang, 2014 ⁹²	<i>NAT2</i> , <i>CYP2E1</i> , <i>GSTM1</i> , <i>GSTT1</i>	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

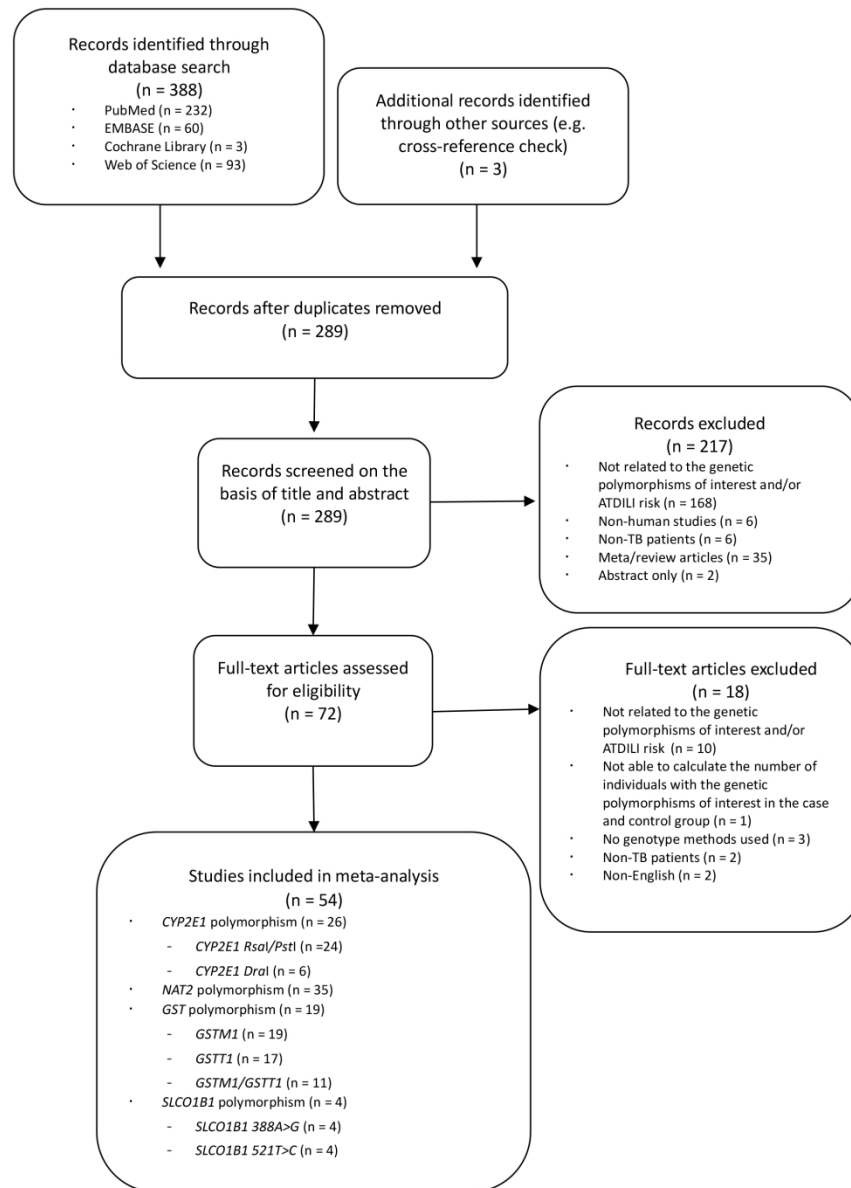
^c Number of individuals in the age ranges

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

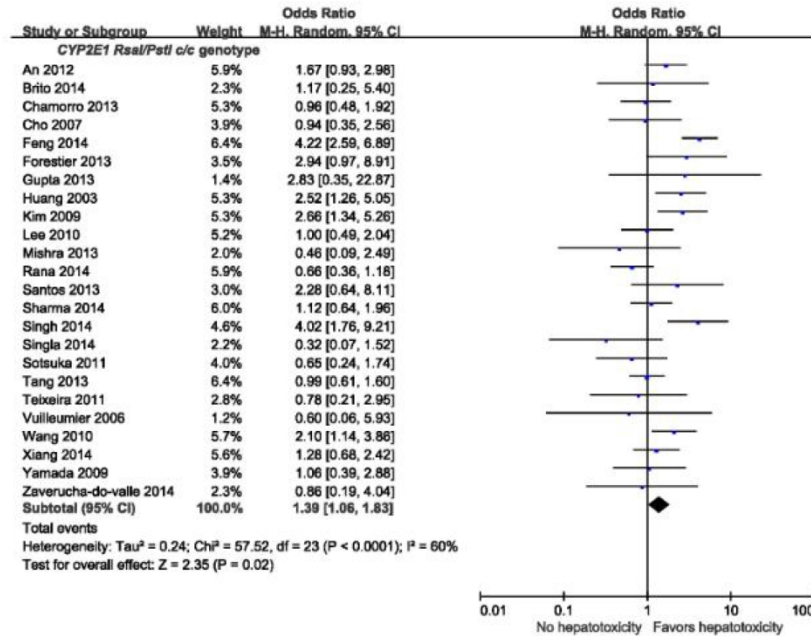
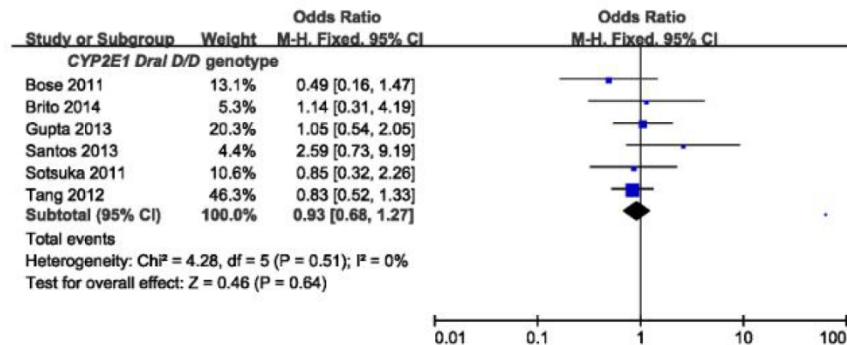
Table 2. Association between the *SLCO1B1* polymorphisms and the risk of anti-tuberculosis drug-induced liver injury

Polymorphism	Genetic model	Number of studies	OR (95% CI)	P value	I ² , %	P _{heterogeneity}	Model of meta-analysis
<i>SLCO1B1</i> 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
<i>SLCO1B1</i> 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

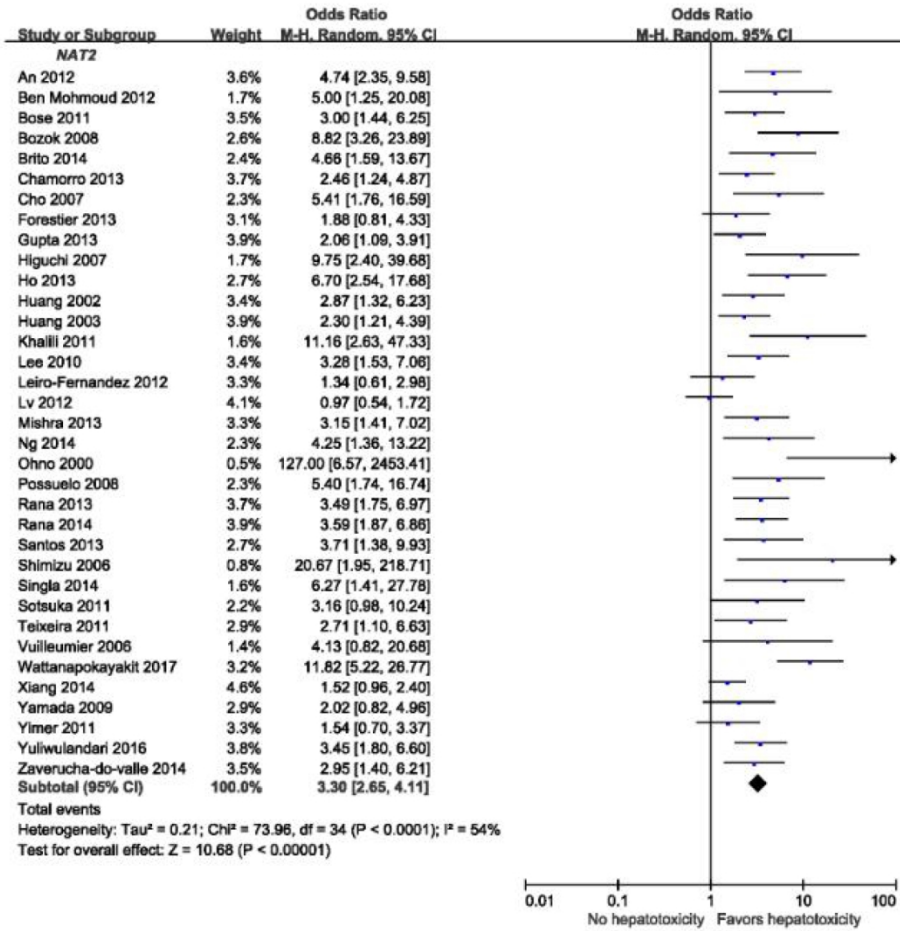
Abbreviations: **OR**, odds ratio; **CI**, confidence interval



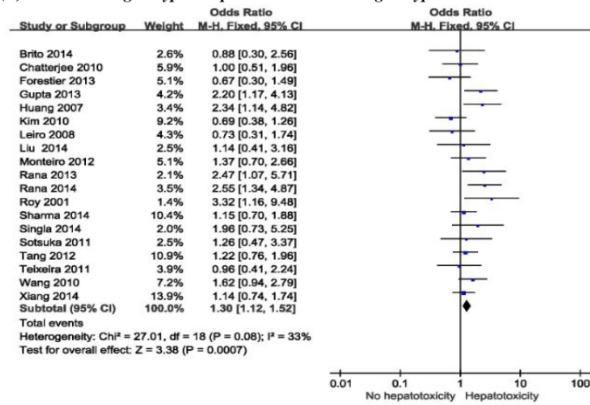
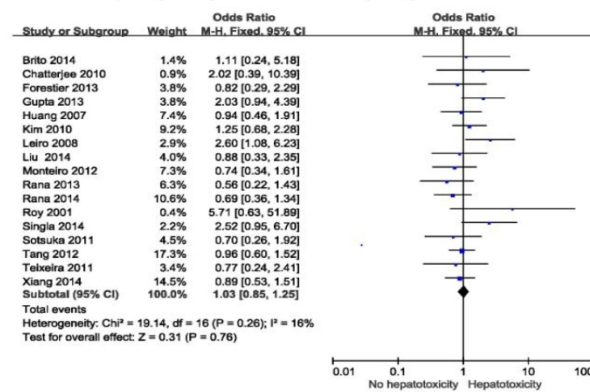
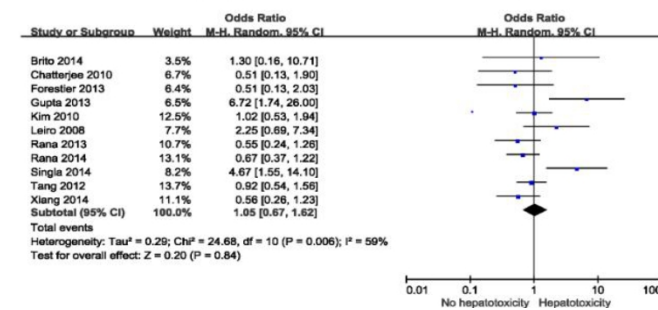
Study selection process flowchart.

(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.

(A) *GSTM1* null genotype compared to the non-null genotype(B) *GSTT1* null genotype compared to the non-null genotype(C) *GSTM1/GSTT1* dual-null genotype compared to the one- and non-null 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	-

For peer review only

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 "arylamineN 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	<i>RsaI/PstI</i> genotype (n = 24)				<i>DraI</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

1										
2										
3	Kim ²	54 (81.8)	12 (18.2)	97 (63.4)	56 (36.6)	NA	NA	NA	NA	SNP stream
4										
5										
6	Lee ⁵⁵	26 (57.8)	19 (42.2)	55 (57.9)	40 (42.1)	NA	NA	NA	NA	Taqman
7										
8	Mishra ³⁹	31 (93.9)	2 (6.1)	168 (97.1)	5 (2.9)	NA	NA	NA	NA	PCR-RFLP
9										
10										
11	Rana ⁵⁶	28 (50.9)	27 (49.1)	150 (61.2)	95 (38.8)	NA	NA	NA	NA	PCR-RFLP
12										
13										
14	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
15										
16	Sharma ⁴⁴	81 (77.1)	24 (22.9)	139 (75.1)	46 (24.9)	NA	NA	NA	NA	PCR-RFLP
17										
18										
19	Singh ³	42 (84.0)	8 (16.0)	77 (56.6)	59 (43.4)	NA	NA	NA	NA	PCR-RFLP
20										
21										
22	Singla ⁵¹	15 (88.0)	2 (12.0)	375 (96.0)	16 (4.0)	NA	NA	NA	NA	PCR-RFLP
23										
24										
25	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
26										
27										
28	Tang ⁴⁶	NA	NA	NA	NA	47 (52.8)	42 (47.2)	204 (57.3)	152 (42.7)	PCR-RFLP
29										
30	Tang ⁴	56 (62.9)	33 (37.1)	225 (63.2)	131 (36.8)	NA	NA	NA	NA	Taqman
31										
32										
33	Teixeira ⁵³	23 (88.5)	3 (11.5)	128 (90.8)	13 (9.2)	NA	NA	NA	NA	PCR-RFLP
34										
35										
36	Vuilleumier ⁴¹	7 (87.5)	1 (12.5)	58 (92.1)	5 (7.9)	NA	NA	NA	NA	PCR-RFLP
37										
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3	Wang ⁴⁵	82 (78.8)	22 (21.2)	71 (64.0)	40 (36.0)	NA	NA	NA	NA	PCR-RFLP
4										
5										
6	Xiang ⁵⁴	58 (82.9)	12 (17.1)	1264 (79.0)	336 (21.0)	NA	NA	NA	NA	PCR/ligase detection reaction assays
7										
8										
9	Yamada ⁴²	17 (73.9)	6 (26.1)	107 (72.8)	40 (27.2)	NA	NA	NA	NA	PCR-RFLP
10										
11										
12	Zaverucha-do-Valle ⁴³	48 (94.1)	3 (5.9)	74 (94.9)	4 (5.1)	NA	NA	NA	NA	PCR-RFLP
13										

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

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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	<i>GSTM1</i> genotype (n = 19)				<i>GSTT1</i> genotype (n = 17)				<i>GSTM1/GSTT1</i> 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

1														
2														
3	Monteiro	21	38	34	84	11	48	28	90	NA	NA	NA	NA	PCR
4	²⁶	(35.6)	(64.4)	(28.8)	(71.2)	(18.7)	(81.3)	(23.8)	(76.2)					
5														
6	Rana ²⁷	10	20	37	183	6	24	68	152	9	21	96	124	PCR
7		(41.6)	(58.4)	(18.5)	(81.5)	(25.0)	(75.0)	(33.8)	(66.2)	(37.5)	(62.5)	(47.7)	(52.3)	
8														
9	Rana ¹⁶	19	36	42	203	14	41	81	164	22	33	122	123	PCR
10		(34.5)	(65.5)	(17.1)	(82.9)	(25.5)	(74.5)	(33.1)	(66.9)	(40.0)	(60.0)	(49.8)	(50.2)	
11														
12	Roy ²⁸	17	15	8	25	5	28	1	32	NA	NA	NA	NA	PCR
13		(52.0)	(48.0)	(24.0)	(76.0)	(15.0)	(85.0)	(3.0)	(97.0)					
14														
15	Sharma ⁴⁴	42	63	68	117	NA	NA	NA	NA	NA	NA	NA	NA	PCR
16		(40.0)	(60.0)	(36.7)	(63.3)									
17														
18	Singla ⁵¹	10	7	165	226	8	9	102	289	5	12	32	359	Multiplex
19		(59.0)	(41.0)	(42.0)	(58.0)	(47.0)	(53.0)	(26.0)	(74.0)	(29.0)	(71.0)	(8.0)	(92.0)	PCR
20														
21	Sotsuka ⁵²	12	8	50	42	7	13	40	52	NA	NA	NA	NA	PCR
22		(60.0)	(40.0)	(54.3)	(45.7)	(35.0)	(65.0)	(43.5)	(56.5)					
23														
24	Tang ⁴⁶	55	34	203	153	40	49	164	192	22	67	94	262	Multiplex
25		(61.8)	(38.2)	(57.0)	(43.0)	(44.9)	(55.1)	(46.1)	(53.9)	(24.7)	(75.3)	(26.4)	(73.6)	PCR
26														
27	Teixeira ⁵³	11	15	61	80	4	22	27	114	NA	NA	NA	NA	Multiplex
28		(42.3)	(57.7)	(43.3)	(56.7)	(15.4)	(84.6)	(19.2)	(80.8)					PCR
29														
30	Wang ⁴⁵	63	41	54	57	NA	NA	NA	NA	NA	NA	NA	NA	PCR
31		(60.6)	(39.4)	(48.6)	(51.4)									
32														
33	Xiang ⁵⁴	41	48	925	1230	18	71	477	1678	7	68	283	1427	PCR
34		(46.1)	(53.9)	(42.9)	(57.1)	(20.2)	(79.8)	(22.1)	(77.9)	(9.3)	(90.7)	(16.5)	(83.5)	

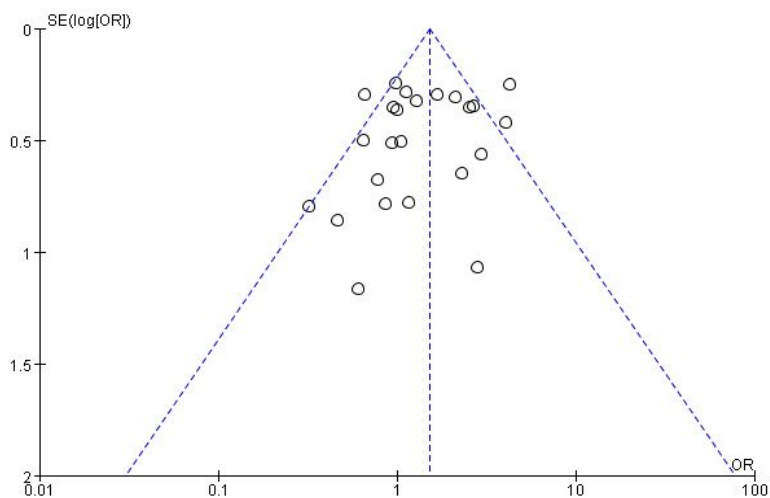
Abbreviations: *NA*, not available; *PCR*, polymerase chain reaction

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

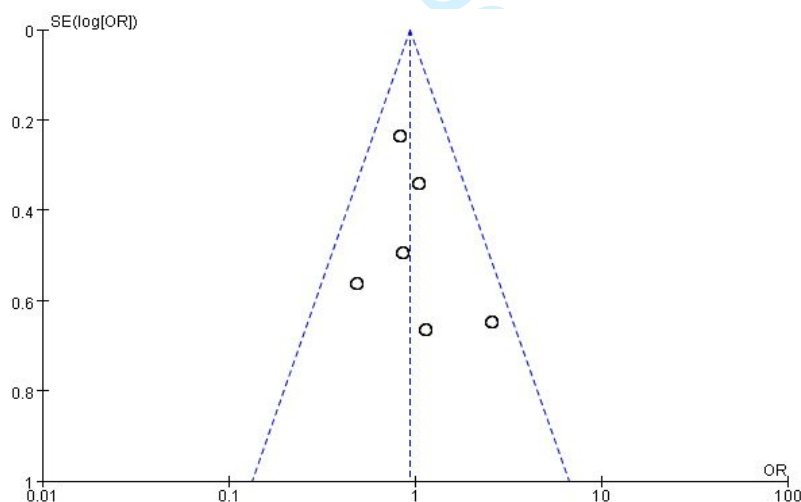
Abbreviations: *PCR*, polymerase chain reaction; *SNP*, single nucleotide polymorphism

Study	<i>SLCO1B1</i> 388A>G (rs2306283)						<i>SLCO1B1</i> 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

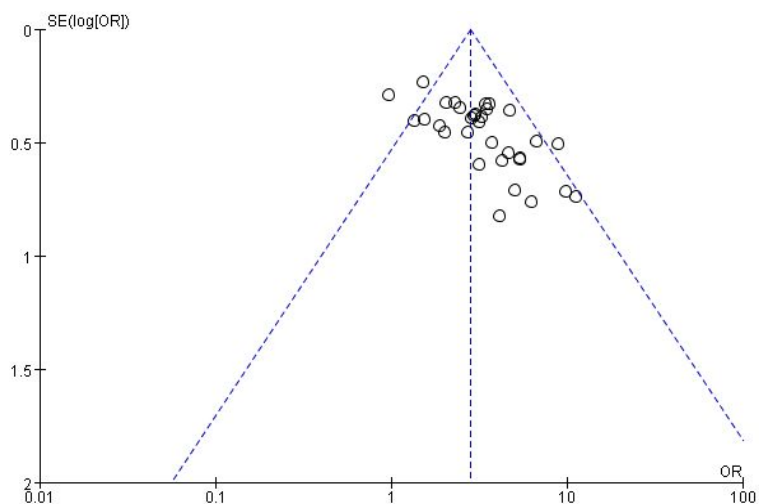
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3 **(A) *CYP2E1* *RsaI/PstI* polymorphism**
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22 **(B) *CYP2E1* *DraI* polymorphism**
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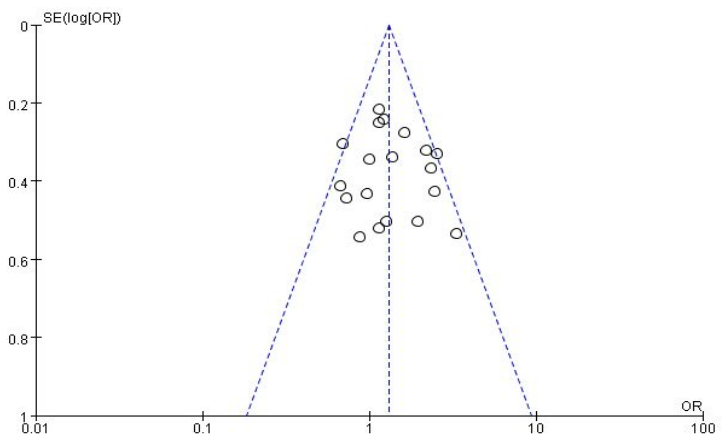


43 **(C) *NAT2* polymorphism**
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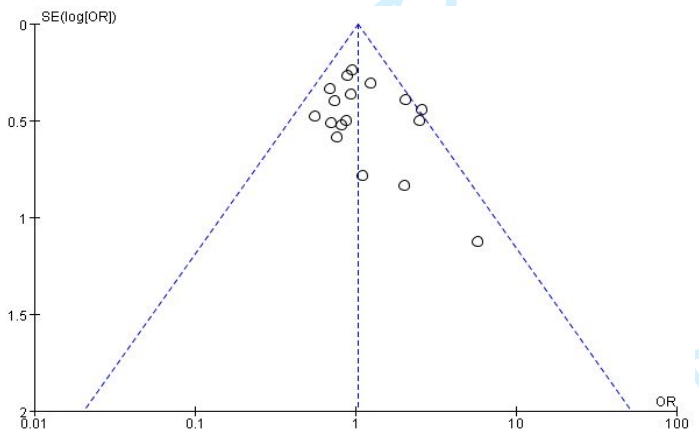


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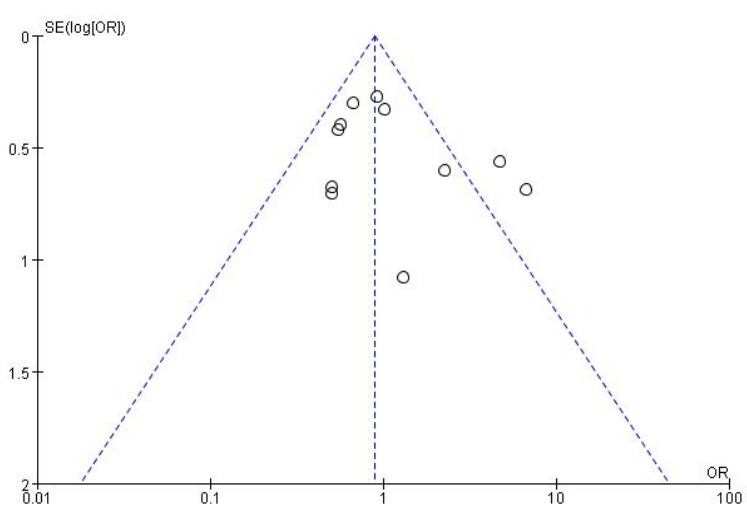
(D) *GSTM1* polymorphism



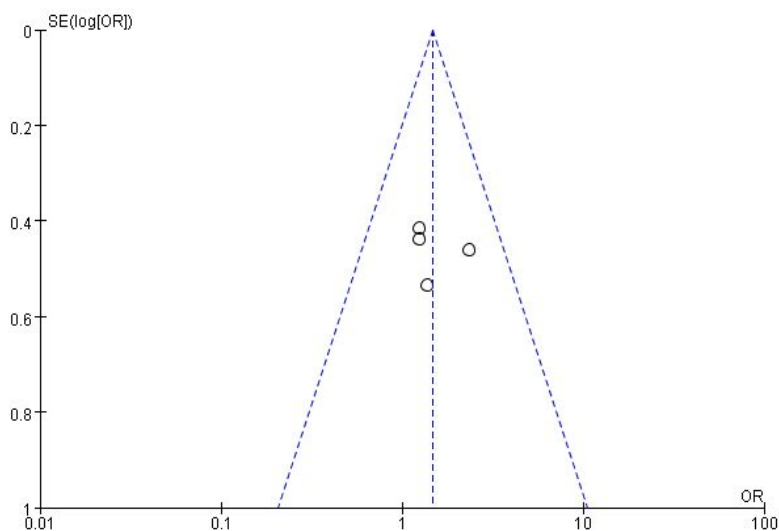
(E) *GSTT1* polymorphism



(F) *GSTT1/M1* polymorphism



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3 **(G) *SLCO1B1* 388A>G and 521T>C polymorphism**
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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) *CYP2E1* *RsaI/PstI* polymorphism, (B) *CYP2E1* *DraI* polymorphism, (C) *NAT2* polymorphism, (D) *GSTM1* polymorphism, (E) *GSTT1* polymorphism, (F) *GSTT1/MI* 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	
<i>CYP2E1 RsaI/PstI</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
	<i>CYP2E1 DraI^c</i> (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

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3 ^b P value from Cochran's Q test based on chi-square statistic

4 ^c Subgroup analysis based on anti-TB drug regimen could not be performed due to insufficient information provided.
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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	
<i>NAT2</i> (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	
<i>GSTM1</i> ^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	
<i>GSTT1</i> ^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	
<i>GSTM1/GSTT1</i> ^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

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^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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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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8 **Association of genetic polymorphisms of *CYP2E1*, *NAT2*, *GST*, and**
9 ***SLCO1B1* with the risk of anti-tuberculosis drug-induced liver**
10 **injury: a systematic review and meta-analysis**
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41 **Running head**

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44 Genetics of anti-tuberculosis liver injury
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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 RsaI/PstI* 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 DraI*, *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*

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4 *RsaI/PstI* c1/c1 genotype, and *GSTM1* null genotype. Close monitoring may be warranted for
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6 patients with these genotypes.
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11 **Strengths and limitations of this study**

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- 14 ● This is the first meta-analysis to evaluate the association between the risk of ATDILI
15 and *SLCO1B1* in patients with tuberculosis.
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- 18 ● We included most updated studies with the large sample sizes to better clarify the
19 association of genetic polymorphisms with the risk of ATDILI.
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- 22 ● The effect of anti-tuberculosis drug dosages on the risk of ATDILI could not be
23 accounted for in this study due to the lack of drug dosing information in the majority of
24 the included studies.
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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 2017¹. 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 therapy⁴. 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 detrimental⁵. 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 tuberculosis⁶. 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 ATDILI¹¹. 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 drug¹⁴. Among various drug transporters, organic

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4 anion transporting polypeptide 1B1 (OATP1B1), encoded by *SLCO1B1*, is the major influx
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6 transporter responsible for hepatic uptake of RIF¹⁵. Although several studies have previously
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8 examined the association between *SLCO1B1* polymorphisms and the risk of ATDILI, conflicting
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10 results have been reported regarding the effect of *SLCO1B1* polymorphisms on ATDILI risk.
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13 Therefore, an updated meta-analysis has been warranted to confirm the association between the
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15 ATDILI risk and genetic polymorphisms of DMEs. In our preliminary literature search, several
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17 polymorphic genes, including many DMEs, transporters, and other genes such as those involved
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19 in the immune system, were identified to have an association with the risk of ATDILI. Among
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21 these, sufficient, published information was available to confirm the effect of *CYP2E1*, *NAT2*,
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23 *GST*, and *SLCO1B1* genetic polymorphisms on the ATDILI risk through meta-analysis.
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28 **Objectives**

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

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

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

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31 Studies were considered eligible if they met all of the following inclusion criteria: (1) studies in
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33 patients with tuberculosis receiving anti-tuberculosis drug regimen; (2) studies with the control
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35 group of patients with tuberculosis, tolerant of anti-tuberculosis medications; (3) studies
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37 evaluating the association between the occurrence of ATDILI and genetic polymorphisms of
38
39 *CYP2E1*, *NAT2*, *GST*, and *SLCO1B1* 388A>G and 521T>C; and (4) case-control or cohort
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41 observational studies. Excluded studies were as follows: (1) studies available only in the form of
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43 abstracts or meeting posters; (2) review or meta-analysis articles; (3) studies providing
44
45 insufficient data necessary for the statistical data analysis; (4) studies in non-English language;
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47 (5) non-human studies including animal and *in vitro* studies; (6) studies with unpublished data;
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49 (7) studies providing insufficient information on genotyping methods; and (8) healthy controls.
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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 *RsaI/PstI* polymorphism, D/D vs. D/C and C/C for the *DraI* 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

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4 relevant genetic model for *SLCO1B1* 388A>G and 521T>C polymorphisms, all three genomic
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6 models including dominant, recessive, and additive models were evaluated. The Mantel-
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8 Haenszel or DerSimonian-Laird method based on fixed- or random-effects models, respectively,
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10 were used depending on the presence of heterogeneity^{20 21}. The random-effects model was used
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12 in the presence of significant heterogeneity; otherwise, the fixed-effects model was used to
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14 estimate the total effect of a polymorphic gene genotype on the risk of ATDILI. Heterogeneity of
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16 study outcomes among included studies was evaluated using Cochran's Q test (*Q*) and quantified
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18 using Higgin's *I*² test. Significant heterogeneity was defined as the *I*² score of > 40%
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20 accompanied by $P < 0.10$ from the Cochran's Q test²². The strength of the association between
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22 the genetic polymorphisms and the risk of ATDILI was estimated using pooled odds ratios (ORs)
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24 with the corresponding 95% confidence intervals (CIs). The statistical significance of an OR was
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26 defined as $P < 0.05$ from the Z test.
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32 Subgroup analysis was performed based on ethnicity, anti-tuberculosis drug regimen
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34 used, and the type of study design. Sensitivity analysis was conducted to assess the robustness of
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36 the results and to identify the source of heterogeneity using the leave-one-out method. In each
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38 analysis, one study was deleted, and with the one study left out, the meta-analysis was
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40 performed; this process was repeated until every study had been deleted from our included study
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42 pool for each tested polymorphic gene. Publication bias was evaluated with a symmetrical funnel
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44 plot. Statistical analyses were performed using Review Manager Software version 5.3 (Cochrane
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46 Collaboration, London, UK).
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53 Patient and public involvement

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4 Patients and public were not involved in the design of this study.
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8 9 **Results**

10 11 12 **Study selection and characteristics**

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15 Overall, 388 articles were identified through electronic database search and 3 articles through
16 manual search by reviewing the reference lists of retrieved articles. After removing 99
17 duplicates, 289 articles were screened for relevance based on the title and abstract. Among them,
18 72 relevant articles were assessed for eligibility through full-text evaluations. Finally, a total of
19 54 articles which met the inclusion criteria were included in our analysis (Figure 1). Among the
20 54 studies, 26 studies were included for *CYP2E1*, 35 studies for *NAT2*, 19 studies for *GST* (19
21 for *GSTM1*, 17 for *GSTT1*, and 11 for *GSTM1/GSTT1*), and 4 studies for *SLCO1B1* 388A>G and
22 521T>C.
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34 Table 1 summarizes the characteristics of the included studies. Across the included
35 studies, large variability in study population was observed in terms of ethnicity (Chinese,
36 Japanese, Korean, Indian, Taiwanese, Brazilian, Caucasian, Iranian, Tunisian, and Turkish), age
37 (mean or median age ranging from 27 to 70 years), and sex (the proportion of males ranging
38 from 13% to 90%). Patients in our included studies received either monotherapy with INH or
39 RIF or a combination therapy including a 4-drug regimen of INH, RIF, PZA, and EMB for the
40 treatment of tuberculosis. ATDILI was defined as an elevated serum alanine aminotransferase
41 (ALT) concentration by 1.5- to 5-fold or greater above the upper limit of normal (ULN)
42 depending on the study. The quality score of the included studies was 6 or greater based on the
43 revised Little's recommendation (Table 1, S3 Table)^{16,17}. Genotype distribution and genotyping
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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 RsaI/PstI* 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 RsaI/PstI* 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 RsaI/PstI* 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 RsaI/PstI* 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 DraI* 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 *DraI* 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

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4 Overall, 35 studies with 1323 cases and 7319 controls were included in our primary analysis for
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6 the *NAT2* polymorphism. Using the random-effects model, the pooled estimates of all included
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8 studies ($n = 35$) showed a significant association between the risk of ATDILI and the *NAT2*
9
10 polymorphism (OR for the slow acetylator genotype = 3.30, 95% CI 2.65–4.11, $P < 0.00001$; $I^2 =$
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12 54%, $P_{heterogeneity} < 0.0001$) (Figure 3). In the subgroup analysis based on ethnicity, anti-
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14 tuberculosis drug regimens used, and study design, the risk of ATDILI was significantly
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16 increased in slow acetylators compared to fast or intermediate acetylators in all subgroups (S10
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18 Table).

21 ***GST***

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25 For the *GSTM1* polymorphism, a total of 19 studies with 977 cases and 5119 controls were
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27 included in our primary analysis. Using the fixed-effects model, the pooled estimates of all
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29 included studies ($n = 19$) showed a significant association between the risk of ATDILI and the
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31 *GSTM1* polymorphism (OR for the *GSTM1* null genotype = 1.30, 95% CI 1.12–1.52, $P = 0.0007$;
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33 $I^2 = 33\%$, $P_{heterogeneity} = 0.08$) (Figure 4A). When studies were stratified for ethnicity, the risk of
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35 ATDILI was significantly increased for the *GSTM1* null genotype in Indians (OR = 1.68, 95% CI
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37 1.30–2.19, $P < 0.0001$; $I^2 = 36\%$, $P_{heterogeneity} = 0.15$) (S11 Table). In the subgroup analyses by
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39 study design, the estimated OR (95% CI, P -value; I^2 , $P_{heterogeneity}$) for the *GSTM1* null genotype
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41 relative to the non-null genotype was 1.41 (1.04-1.93, $P = 0.03$; $I^2 = 44\%$, $P_{heterogeneity} = 0.08$) in
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43 cohort studies and 1.25 (1.01-1.55, $P = 0.20$; $I^2 = 29\%$, $P_{heterogeneity} = 0.17$) in case-control studies,
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45 respectively (S11 Table).
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51 For the *GSTT1* and *GSTM1/GSTT1* polymorphisms, 17 studies (768 cases, 4823 controls)
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53 and 11 studies (547 cases, 4233 controls) were included in our primary analyses, respectively.
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4 The risk of ATDILI was not significantly associated with the *GSTT1* polymorphism (OR for the
5 null genotype = 1.03, 95% CI 0.85–1.25, $P = 0.76$; $I^2 = 16\%$, $P_{heterogeneity} = 0.26$) or the
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9 *GSTM1/GSTT1* polymorphism (OR for the dual-null genotype = 1.05, 95% CI 0.67–1.62, $P =$
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11 0.84; $I^2 = 59\%$, $P_{heterogeneity} = 0.006$) (Figures 4B and 4C). When studies were stratified for
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13 ethnicity, anti-tuberculosis drug regimens used, and study design, no subgroups showed
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15 significant association between the risk of ATDILI and the *GSTT1* and the *GSTM1/GSTT1*
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17 polymorphisms (S11 Table).

20 ***SLCO1B1***

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

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47 Our primary analysis results showed significantly high heterogeneity between studies for
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49 *CYP2E1* *RsaI/PstI* ($I^2 = 60\%$, $P < 0.0001$), *NAT2* ($I^2 = 54\%$, $P < 0.0001$), *GSTM1/GSTT1* ($I^2 =$
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51 59%, $P = 0.006$), and *SLCO1B1* 521T>C (dominant genetic model: $I^2 = 66\%$, $P = 0.03$)
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53 polymorphisms. This high heterogeneity between studies may be due to substantial differences in
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4 ethnicity, anti-tuberculosis drug regimen, the genotyping method used, study design, and
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6 diagnostic criteria of ATDILI among the included studies (Table 1). Through the sensitivity
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8 analyses, outlier studies were identified as the major source of heterogeneity. After removing
9
10 these outlier studies, heterogeneity was substantially reduced ($I^2 = 60\%$ to 42% for *CYP2E1*
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12 *RsaI/PstI*²³, $I^2 = 54\%$ to 34% for *NAT2*^{24 25}, $I^2 = 59\%$ to 0% for *GSTM1/GSTT1*^{26 27}, and $I^2 =$
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14 66% to 0% for *SLCO1B1* 521T>C dominant genetic model²⁸). The overall results for the
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16 association between the risk of ATDILI and these genetic polymorphisms after excluding the
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18 outlier studies stayed the same as those from our primary analysis results.
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25 Discussion

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28 In this study, we conducted a large-scale meta-analysis evaluating the association between the
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30 risk of ATDILI and genetic polymorphisms of *SLCO1B1* as well as various DMEs including
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32 *CYP2E1*, *NAT2*, and *GST* to provide more updated, comprehensive, and compelling evidence.
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34 Compared with previous meta-analyses, our present study included a larger number of studies,
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36 which may sufficiently increase the statistical power compared to individual studies. However,
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38 a limited number of studies for the *SLCO1B1* genetic polymorphisms were included ($n = 4$).
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40 Consistently with previous studies, our current study suggested a significantly increased risk of
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42 ATDILI in patients with the *CYP2E1 RsaI/PstI* c1/c1 genotype (OR = 1.39, 95% CI 1.06–1.83),
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44 the *NAT2* slow acetylator genotype (OR = 3.30, 95% CI 2.65–4.11), and the *GSTM1* null
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46 genotype (OR = 1.30, 95% CI 1.12–1.52)^{9 12 29}. Among these genotypes, the largest increase in
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48 the risk of ATDILI was shown in patients with the *NAT2* slow acetylator genotype. In contrast,
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50 no significant association was observed between the risk of ATDILI and the genetic
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4 polymorphisms of *CYP2E1 DraI*, *GSTT1*, *GSTM1/GSTT1*, *SLCO1B1 388A>G*, and *SLCO1B1*
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6 *521T>C*. Caution needs to be exercised when interpreting this study finding because the lack of
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8 significant association between these polymorphisms and the risk of ATDILI might be due to
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10 small sample sizes and the low frequency of ATDILI reported in patients with these genetic
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12 polymorphisms.
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16 When evaluating the impact of the *CYP2E1 RsaI/PstI* and *DraI* genetic polymorphisms
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18 on the risk of ATDILI in our study, patients with the *RsaI/PstI* c1/c1 genotype were 1.39-times
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20 more likely to develop ATDILI. Similarly, in a previous meta-analysis by Deng and colleagues,
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22 the risk of ATDILI was 1.4-times higher in patients with the *RsaI/PstI* c1/c1 genotype compared
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24 to other genotypes³⁰. In the liver, INH is metabolized by NAT2 to acetylisoniazid which is
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26 consequently oxidized by CYP2E1 to reactive hepatotoxic intermediates^{31 32}. The increased
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28 inducibility or greater activity of CYP2E1 in patients with the *CYP2E1 RsaI/PstI* c1/c1 genotype
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30 may result in the production of more intermediate hepatotoxins, ultimately leading to the
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32 increased risk of ATDILI^{31 32}. Our subgroup analysis showed a significantly increased risk of
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34 ATDILI in the *CYP2E1 RsaI/PstI* c1/c1 genotype carriers of East Asian ethnicity (S9 Table),
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36 suggesting a potential gene-ethnicity interaction³³. A previous study identified age, female sex,
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38 white race, non-Hispanic ethnicity, lower body mass index, elevated plasma aspartate
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40 transaminase concentrations at baseline, and nine months of daily INH use as risk factors for
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42 ATDILI³⁴. Considering their race, ethnicity, and relatively lower body mass index compared to
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44 other ethnicities, East Asians may be at an increased risk of ATDILI. As the *CYP2E1 RsaI/PstI*
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46 c1 allele frequency is relatively low in this population (79.8% vs. 88.5% to 99.8% in other
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48 ethnicities), the ethnicity itself might play an important role in developing hepatotoxicity through
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50 gene-ethnicity interaction³⁵. Furthermore, the relatively high frequency of c2 allele in this
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4 population might serve as a good control to estimate the effect of c1 allele on the risk of
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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 polymorphism³⁵. In addition to ethnicity,
combination anti-tuberculosis therapy was shown to significantly increase the risk of ATDILI in
patients with the *CYP2E1* *RsaI/PstI* 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 ATDILI⁷.

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 Caucasians³⁶. 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

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4 through the binding of INH to liver proteins³⁹. Therefore, clinicians should closely monitor
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6 patients with tuberculosis carrying the *NAT2* slow acetylator genotype for hepatotoxicity when
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8 INH-based treatment is administered to these patients.
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11 According to previous studies, GST enzymes, particularly those coded by *GSTM1* and
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13 *GSTT1* loci, are associated with the risk of drug-induced hepatotoxicity^{9 40}. Similar to previous
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15 studies, our current study demonstrated a significantly increased risk of ATDILI in individuals
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17 with the *GSTM1* null genotype compared to those with the non-null genotype; however, the risk
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19 of ATDILI was not affected by the *GSTT1* or *GSTM1/GSTT1* genetic polymorphisms. GSTs are
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21 important enzymes to detoxify various xenobiotics and play an essential role in INH metabolism
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23 by eliminating acetyldiazene ketene acetylonium ion, which is a possibly hepatotoxic free radical
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25 metabolite of INH, from the body through *GSTM1*. This may account for the significant
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27 association of the ATDILI risk with the *GSTM1* genotype, but not with the *GSTT1* or
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29 *GSTM1/GSTT1* genotypes^{9 40}. Our subgroup analysis showed a significantly increased risk of
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31 ATDILI in the *GSTM1* null genotype carriers of Indian ethnicity; although not statistically
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33 significant, the risk of ATDILI was relatively high in the East Asian population with the *GSTM1*
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35 null genotype (S11 Table). Considering the substantial difference in the *GSTM1* null allele
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37 frequency between Indians (29.6%) and East Asians (52.1%), a potential gene-ethnicity
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39 interaction may exist based on their race, ethnicity, and body size as aforementioned^{34 41}. Other
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41 characteristics than the *GSTM1* polymorphism in these ethnicities may play a more important
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43 role in the development of ATDILI. In addition, when studies were stratified by study design, the
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45 risk of ATDILI was significantly increased in patients with the *GSTM1* null genotype for cohort
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47 studies only, but not for case-control studies, probably due to a relatively larger sample size with
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49 cohort studies compared to case-control studies.
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4 *SLCO1B1* encodes organic anion transporting polypeptide 1B1 (OATP1B1) which is a
5 major influx drug transporter responsible for the hepatic uptake of various endogenous and
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7 exogenous substances including RIF⁴². Previous studies showed significantly altered systemic
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9 exposure of RIF in carriers of the *SLCO1B1* polymorphism^{43 44}. To our knowledge, only four
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11 studies have been conducted to examine the association between the ATDILI risk and the
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13 *SLCO1B1* genetic polymorphisms^{10 28 42 45}. Various single nucleotide polymorphisms (SNPs) of
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15 *SLCO1B1* were evaluated in these studies; however, *SLCO1B1* 388A>G (rs2306283) and
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17 521T>C (rs4149056) were the only polymorphisms assessed in common^{10 28 42 45}. Therefore, to
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19 maximize the sample size in our current meta-analysis, we examined the association between the
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21 risk of ATDILI and the polymorphic genotypes of *SLCO1B1* 388A>G and 521T>C. Similar to
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23 each of the included studies, we did not find significant difference in the risk of ATDILI among
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25 patients with different *SLCO1B1* 388A>G and 521T>C genotypes.
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32 There are limitations to this study. First, due to the lack of information regarding other
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34 patient characteristics potentially associated with ATDILI, our estimated ORs were not adjusted
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36 based on the potential risk factors such as age, anti-tuberculosis drug dosages, alcohol
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38 consumption, cigarette smoking, and other lifestyle characteristics^{7 46}. Second, our literature
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40 search limited to the articles published in English may lead to language bias. Third, a specific
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42 causative agent of ATDILI could not be identified in our analysis because most patients in our
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44 included studies received a combination regimen of anti-tuberculosis drugs. Fourth, only the
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46 limited number of polymorphic genotypes were assessed for the association with the risk of
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48 ATDILI, particularly for *SLCO1B1*. In addition, only one genetic model was used for *CYP2E1*,
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50 *NAT2*, and *GST* when evaluating the association between genetic polymorphisms of these genes
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52 and the risk of ATDILI. Although we acknowledge dominant, recessive, and additive genomic
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4 models can be used for two alleles, it could not be applied to our meta-analysis because we
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6 compared patients with different genotype-based phenotype, i.e., slow acetylator vs.
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8 fast/intermediate acetylator and null vs. non-null *GSTs*. Multiple allelic variants or allele
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10 subgroups may represent the same phenotype (e.g., *NAT2**5B, *6A, and *7B all represent slow
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12 acetylator genotypes), and the genetic model selection can be varied depending on the specific
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14 allelic variant⁴⁷. Therefore, the genetic models used in previous original and meta-analysis
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16 studies were adopted for these polymorphic genes in our current study^{9 18 19}. Future studies are
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18 needed to comprehensively and adequately address the relationship between the ATDILI risk and
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20 various genetic polymorphisms by using different genetic risk models and including more
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22 polymorphic genotypes.
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27 In conclusion, the risk of ATDILI during tuberculosis therapy was significantly increased
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29 in patients with tuberculosis carrying *NAT2* slow acetylator, *CYP2E1* *RsaI/PstI* c1/c1, or *GSTM1*
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31 null genotypes. Screening for these genetic polymorphisms, particularly for the *NAT2* slow
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33 acetylator genotype, may be of great clinical benefit to identify patients at high risk for ATDILI
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35 and minimize the risk of ATDILI. Future studies are pertinent to develop dose and/or treatment
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37 adjustment strategies, to evaluate the feasibility and cost-effectiveness of the genetic screening
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39 test, and to assess the effect of more genetic polymorphisms on the risk of ATDILI for optimal
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41 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

Provenance and peer review

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No additional unpublished data are available

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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) *CYP2E1* *RsaI/PstI* polymorphism, (B) *CYP2E1* *DraI* polymorphism, (C) *NAT2* polymorphism, (D) *GSTM1* polymorphism, (E) *GSTT1* polymorphism, (F) *GSTT1/MI* 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

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4 **S10 Table. Subgroup analysis for the association between *NAT2* polymorphism and the risk**
5 **of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug**
6 **regimen, and study design**
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11 **S11 Table. Subgroup analysis for the association between *GST* polymorphisms and the risk**
12 **of anti-tuberculosis drug-induced liver injury based on ethnicity, anti-tuberculosis drug**
13 **regimen, and study design**
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Figure legends

Figure 1. Study selection process flowchart.

Figure 2. 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.

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	<i>CYP2E1</i>	Case-control	Chinese	173/173	48.8/48.6	68.0/68.0	INH, RIF, PZA	ALT > 3 × ULN	6
Kim, 2009 ⁴⁸	<i>CYP2E1</i>	Case-control	Korean	67/159	42.1/42.8	65.7/65.4	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Singh, 2014 ⁴⁹	<i>CYP2E1</i>	Cohort	Indian	50/135	NA/NA	NA/NA	NA	ALT > 2 × ULN	7
Tang, 2013 ⁵⁰	<i>CYP2E1</i>	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	<i>NAT2</i>	Cohort	Tunisian	14/52	42.4/42.1	42.8/48.1	INH, RIF containing regimen	ALT > 2 × ULN	7
Bozok Cetintas, 2008 ⁵²	<i>NAT2</i>	Case-control	Turkish	30/70	39.8/37.3	50.0/72.8	INH, RIF, PZA, EMB	ALT > 3 × ULN	6
Higuchi, 2007 ⁵³	<i>NAT2</i>	Cohort	Japanese	18/82	60.8/64.7	50.0/57.3	INH, RIF containing regimen	ALT > 2 × ULN	7
Ho, 2013 ⁵⁴	<i>NAT2</i>	Cohort	Taiwanese	20/328	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 5 × ULN	6
Huang, 2002 ⁵⁵	<i>NAT2</i>	Cohort	Taiwanese	33/191	73.3/63.7	87.9/88.5	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Khalili, 2011 ⁵⁶	<i>NAT2</i>	Case-control	Iranian	14/36	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 3 × ULN	6
Leiro-Fernandez, 2011 ⁵⁷	<i>NAT2</i>	Case-control	Caucasian	50/67	34.0/30.5 ^b	54.0/56.7	INH, RIF, PZA	ALT > 3 × ULN	7
Ly, 2012 ²⁴	<i>NAT2</i>	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	<i>NAT2</i>	Case-control	Mixed	26/101	48.3/NA	38.5/NA	INH containing regimen	ALT > 5 × ULN	7
Ohno, 2000 ⁵⁹	<i>NAT2</i>	Cohort	Japanese	14/63	NA/NA	NA/NA	INH, RIF	ALT > 1.5 × ULN	7
Possuelo, 2008 ⁶⁰	<i>NAT2</i>	Cohort	Brazilian	14/240	38.9/36.5	50.0/66.9	INH, RIF, PZA	ALT > 3 × ULN	7
Rana, 2012 ⁶¹	<i>NAT2</i>	Cohort	Indian	50/201	45.3/43.8	76.0/57.2	INH, RIF, PZA, EMB	ALT > 5 × ULN	7
Shimizu, 2006 ⁶²	<i>NAT2</i>	Case-control	Japanese	10/32	60.5/64.9	70.0/46.9	INH, RIF	ALT > 2 × ULN	6
Yuliwulandari, 2016 ⁶³	<i>NAT2</i>	Case-control	Indonesian	50/191	NA/NA	NA/NA	NA	ALT > 2 × ULN	7
Wattanapokayakit, 2016 ²⁵	<i>NAT2</i>	Case-control	Thai	53/85	51.4/50.2	58.5/60.0	INH containing regimen	ALT > 2 × ULN	7
Chatterjee, 2010 ⁶⁴	<i>GSTMI, GSTTI</i>	Case-control	Indian	51/100	37.2/33.2	49.0/63.0	INH, RIF, PZA	ALT > 3 × ULN	7
Gupta, 2013 ⁶⁵	<i>GSTMI, GSTTI</i>	Cohort	Indian	50/246	37.0/36.5 ^b	48.0/56.5	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Huang, 2007 ⁶⁶	<i>GSTMI, GSTTI</i>	Case-control	Taiwanese	63/63	62.0/NA	NA/NA	NA	ALT > 5 × ULN	6
Kim, 2010 ⁶⁷	<i>GSTMI, GSTTI</i>	Case-control	Korean	57/190	47.3/42.4	59.6/67.9	INH, RIF, PZA, EMB	ALT > 3 × ULN	7
Leiro, 2008 ⁶⁸	<i>GSTMI, GSTTI</i>	Case-control	Caucasian	35/60	34.0/31.0 ^b	40.0/41.7	INH, RIF, PZA	ALT > 3 × ULN	7
Liu, 2014 ⁶⁹	<i>GSTMI, GSTTI</i>	Case-control	Chinese	20/143	35.9/61.2	60.0/59.4	INH containing regimen	ALT > 2 × ULN	7
Monteiro, 2012 ⁷⁰	<i>GSTMI, GSTTI</i>	Cohort	Brazilian	59/118	37.0/38.0 ^b	76.0/61.0	NA	ALT > 2 × ULN	7

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

	<i>CYP2E1</i>	control							
Vuilleumier, 2006 ⁸¹	<i>NAT2, CYP2E1</i>	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	<i>NAT2, CYP2E1</i>	Case-control	Mixed	23/147	NA/NA	13.0/42.9	INH	ALT > 2 × ULN	7
Zaverucha-do-Valle, 2014 ⁸³	<i>NAT2, CYP2E1</i>	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	<i>CYP2E1, GSTM1</i>	Cohort	Indian	105/185	35.2/27.6	55.7/72.1	INH, RIF, PZA, EMB	ALT > 5 × ULN	7
Wang, 2010 ⁸⁵	<i>CYP2E1, GSTM1</i>	Case-control	Chinese	104/111	48.6/44.7	67.3/67.6	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Tang, 2012 ⁸⁶	<i>CYP2E1, GSTM1, GSTT1</i>	Case-control	Chinese	89/356	43.7/43.6	73.0/73.0	INH, RIF, PZA, EMB	ALT > 2 × ULN	7
Yimer, 2011 ⁴⁵	<i>NAT2, SLCO1B1</i>	Cohort	Ethiopian	41/160	NA/NA	NA/NA	INH, RIF, PZA, EMB	ALT > 2 × ULN	6
Brito, 2014 ⁸⁷	<i>NAT2, CYP2E1, GSTM1, GSTT1</i>	Cohort	Brazilian	15/230	38.1/36.8	46.7/NA	INH, RIF, PZA	ALT > 3 × ULN	7
Forestiero, 2013 ⁸⁸	<i>NAT2, CYP2E1, GSTM1, GSTT1</i>	Cohort	Brazilian	59/40	NA/NA	49.2/60.0	INH, RIF, PZA	ALT > 2.5 × ULN	6
Rana, 2014 ⁸⁹	<i>NAT2, CYP2E1, GSTM1, GSTT1</i>	Cohort	Indian	55/245	43.6/42.3	60.0/62.0	INH, RIF, PZA, EMB	ALT > 5 × ULN	6
Singla, 2014 ²⁶	<i>NAT2, CYP2E1, GSTM1,</i>	Case-control	Indian	17/391	48.2/32.7	64.7/61.4	INH, RIF, PZA, EMB, STM	ALT > 2 × ULN	7

	<i>GSTT1</i>								
Sotsuka, 2011 ⁹⁰	<i>NAT2</i> , <i>CYP2E1</i> , <i>GSTM1</i> , <i>GSTT1</i>	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	<i>NAT2</i> , <i>CYP2E1</i> , <i>GSTM1</i> , <i>GSTT1</i>	Case-control	Brazilian	26/141	47.6/43.0	61.5/52.5	INH containing regimen	ALT > 3 × ULN	7
Xiang, 2014 ⁹²	<i>NAT2</i> , <i>CYP2E1</i> , <i>GSTM1</i> , <i>GSTT1</i>	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

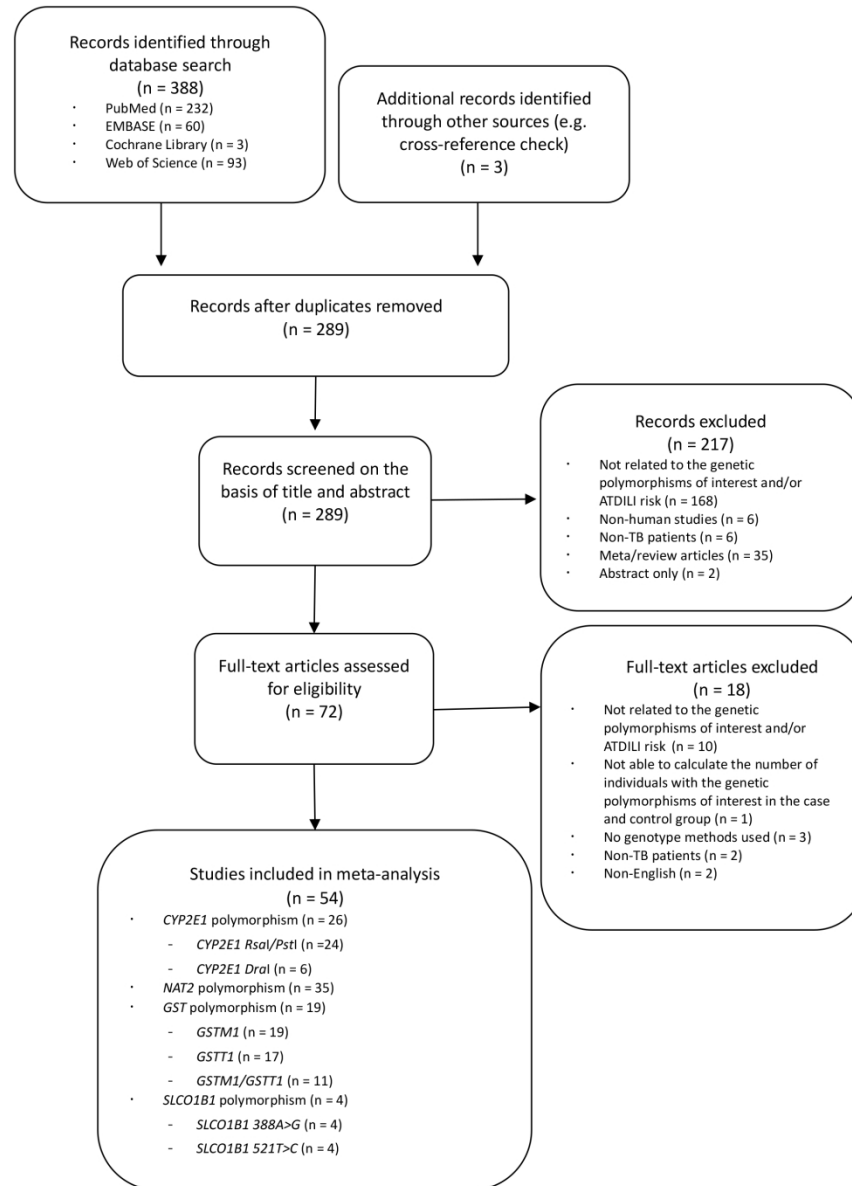
^d Detailed scoring for each quality assessment criterion based on the revised Little's recommendation in supplementary data S2 Table.

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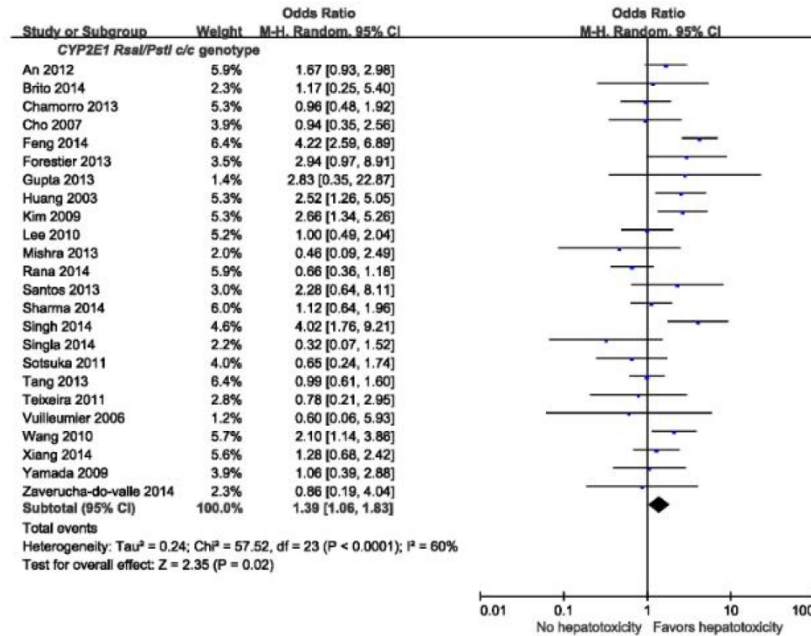
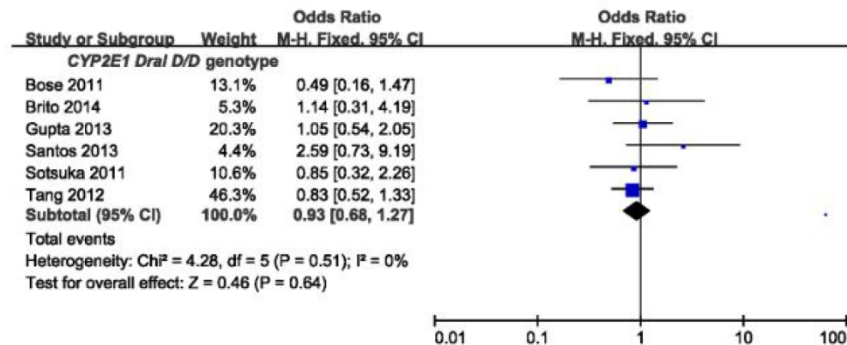
Table 2. Association between the *SLCO1B1* polymorphisms and the risk of anti-tuberculosis drug-induced liver injury

Polymorphism	Genetic model	Number of studies	OR (95% CI)	P value	I ² , %	P _{heterogeneity}	Model of meta-analysis
<i>SLCO1B1</i> 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
<i>SLCO1B1</i> 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

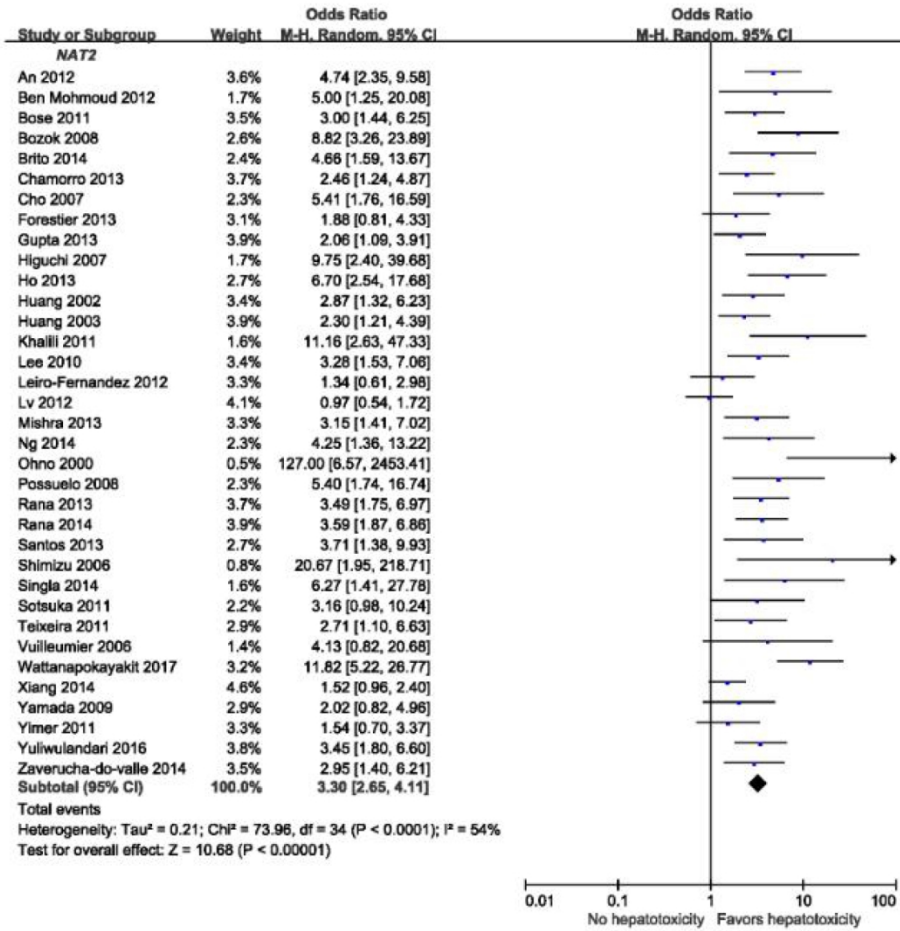
Abbreviations: **OR**, odds ratio; **CI**, confidence interval



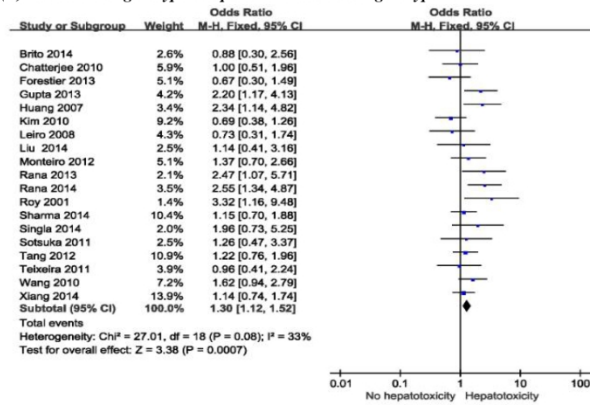
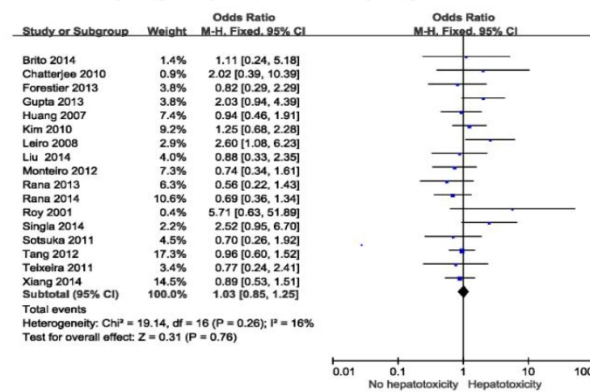
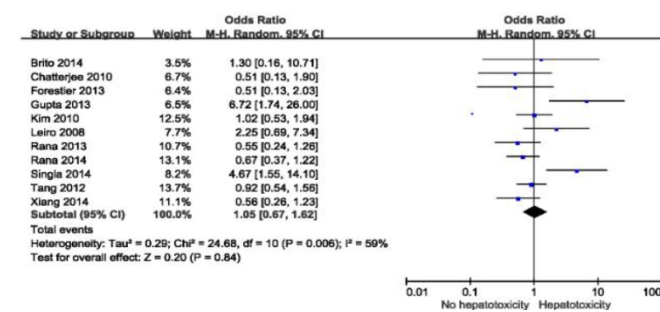
Study selection process flowchart.

(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.

(A) *GSTM1* null genotype compared to the non-null genotype(B) *GSTT1* null genotype compared to the non-null genotype(C) *GSTM1/GSTT1* dual-null genotype compared to the one- and non-null 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	-

For peer review only

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 "arylamineN acetyltransferase") OR N acetyltransferase*) OR ((drug metaboli#er*) OR (drug metaboli#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	<i>RsaI/PstI</i> genotype (n = 24)				<i>DraI</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

1										
2										
3	Kim ²	54 (81.8)	12 (18.2)	97 (63.4)	56 (36.6)	NA	NA	NA	NA	SNP stream
4										
5	Lee ⁵⁵	26 (57.8)	19 (42.2)	55 (57.9)	40 (42.1)	NA	NA	NA	NA	Taqman
6										
7										
8	Mishra ³⁹	31 (93.9)	2 (6.1)	168 (97.1)	5 (2.9)	NA	NA	NA	NA	PCR-RFLP
9										
10										
11	Rana ⁵⁶	28 (50.9)	27 (49.1)	150 (61.2)	95 (38.8)	NA	NA	NA	NA	PCR-RFLP
12										
13	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
14										
15										
16	Sharma ⁴⁴	81 (77.1)	24 (22.9)	139 (75.1)	46 (24.9)	NA	NA	NA	NA	PCR-RFLP
17										
18										
19	Singh ³	42 (84.0)	8 (16.0)	77 (56.6)	59 (43.4)	NA	NA	NA	NA	PCR-RFLP
20										
21										
22	Singla ⁵¹	15 (88.0)	2 (12.0)	375 (96.0)	16 (4.0)	NA	NA	NA	NA	PCR-RFLP
23										
24										
25	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
26										
27										
28	Tang ⁴⁶	NA	NA	NA	NA	47 (52.8)	42 (47.2)	204 (57.3)	152 (42.7)	PCR-RFLP
29										
30	Tang ⁴	56 (62.9)	33 (37.1)	225 (63.2)	131 (36.8)	NA	NA	NA	NA	Taqman
31										
32										
33	Teixeira ⁵³	23 (88.5)	3 (11.5)	128 (90.8)	13 (9.2)	NA	NA	NA	NA	PCR-RFLP
34										
35										
36	Vuilleumier ⁴¹	7 (87.5)	1 (12.5)	58 (92.1)	5 (7.9)	NA	NA	NA	NA	PCR-RFLP
37										
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3	Wang ⁴⁵	82 (78.8)	22 (21.2)	71 (64.0)	40 (36.0)	NA	NA	NA	NA	PCR-RFLP
4										
5										
6	Xiang ⁵⁴	58 (82.9)	12 (17.1)	1264 (79.0)	336 (21.0)	NA	NA	NA	NA	PCR/ligase detection reaction assays
7										
8										
9	Yamada ⁴²	17 (73.9)	6 (26.1)	107 (72.8)	40 (27.2)	NA	NA	NA	NA	PCR-RFLP
10										
11										
12	Zaverucha-do-Valle ⁴³	48 (94.1)	3 (5.9)	74 (94.9)	4 (5.1)	NA	NA	NA	NA	PCR-RFLP
13										

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

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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	<i>GSTM1</i> genotype (n = 19)				<i>GSTT1</i> genotype (n = 17)				<i>GSTM1/GSTT1</i> 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

1														
2														
3	Monteiro	21	38	34	84	11	48	28	90	NA	NA	NA	NA	PCR
4	²⁶	(35.6)	(64.4)	(28.8)	(71.2)	(18.7)	(81.3)	(23.8)	(76.2)					
5														
6	Rana ²⁷	10	20	37	183	6	24	68	152	9	21	96	124	PCR
7		(41.6)	(58.4)	(18.5)	(81.5)	(25.0)	(75.0)	(33.8)	(66.2)	(37.5)	(62.5)	(47.7)	(52.3)	
8														
9	Rana ¹⁶	19	36	42	203	14	41	81	164	22	33	122	123	PCR
10		(34.5)	(65.5)	(17.1)	(82.9)	(25.5)	(74.5)	(33.1)	(66.9)	(40.0)	(60.0)	(49.8)	(50.2)	
11														
12	Roy ²⁸	17	15	8	25	5	28	1	32	NA	NA	NA	NA	PCR
13		(52.0)	(48.0)	(24.0)	(76.0)	(15.0)	(85.0)	(3.0)	(97.0)					
14														
15	Sharma ⁴⁴	42	63	68	117	NA	NA	NA	NA	NA	NA	NA	NA	PCR
16		(40.0)	(60.0)	(36.7)	(63.3)									
17														
18	Singla ⁵¹	10	7	165	226	8	9	102	289	5	12	32	359	Multiplex
19		(59.0)	(41.0)	(42.0)	(58.0)	(47.0)	(53.0)	(26.0)	(74.0)	(29.0)	(71.0)	(8.0)	(92.0)	PCR
20														
21	Sotsuka ⁵²	12	8	50	42	7	13	40	52	NA	NA	NA	NA	PCR
22		(60.0)	(40.0)	(54.3)	(45.7)	(35.0)	(65.0)	(43.5)	(56.5)					
23														
24	Tang ⁴⁶	55	34	203	153	40	49	164	192	22	67	94	262	Multiplex
25		(61.8)	(38.2)	(57.0)	(43.0)	(44.9)	(55.1)	(46.1)	(53.9)	(24.7)	(75.3)	(26.4)	(73.6)	PCR
26														
27	Teixeira ⁵³	11	15	61	80	4	22	27	114	NA	NA	NA	NA	Multiplex
28		(42.3)	(57.7)	(43.3)	(56.7)	(15.4)	(84.6)	(19.2)	(80.8)					PCR
29														
30	Wang ⁴⁵	63	41	54	57	NA	NA	NA	NA	NA	NA	NA	NA	PCR
31		(60.6)	(39.4)	(48.6)	(51.4)									
32														
33	Xiang ⁵⁴	41	48	925	1230	18	71	477	1678	7	68	283	1427	PCR
34		(46.1)	(53.9)	(42.9)	(57.1)	(20.2)	(79.8)	(22.1)	(77.9)	(9.3)	(90.7)	(16.5)	(83.5)	

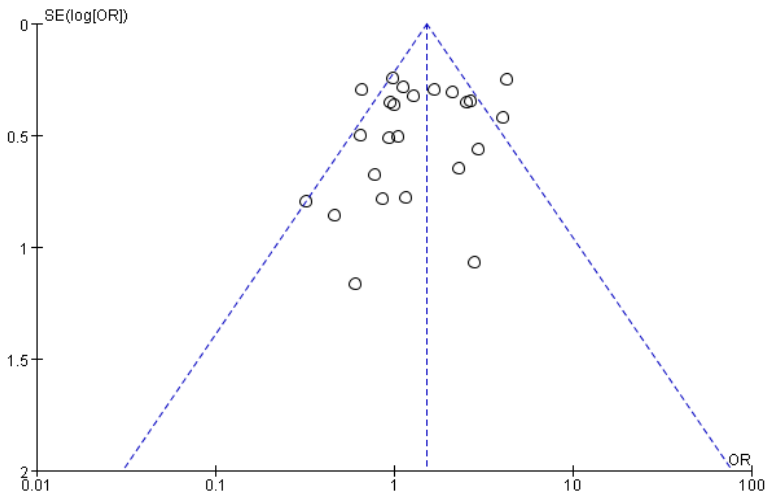
Abbreviations: *NA*, not available; *PCR*, polymerase chain reaction

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

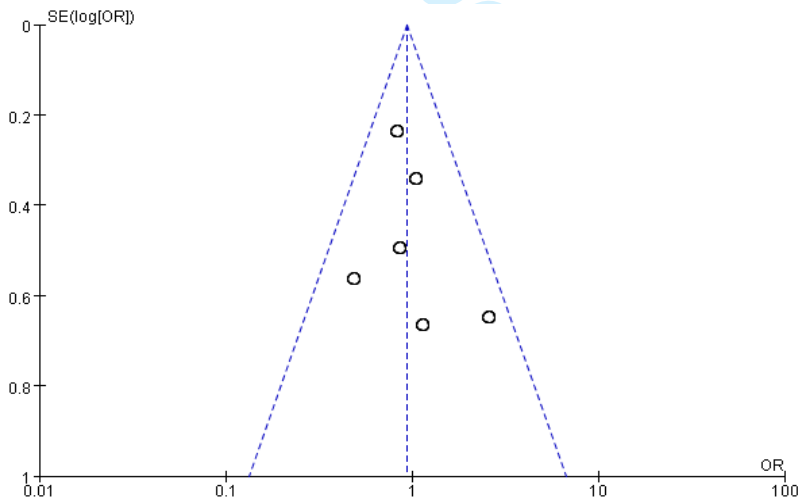
Study	<i>SLCO1B1</i> 388A>G (rs2306283)						<i>SLCO1B1</i> 521T>C (rs4149056)						Genotyping method
	Case (number of individuals [%])			Control (number of individuals [%])			Case (number of individuals [%])			Control (number of individuals [%])			
	AA	AG	GG	AA	AG	GG	TT	CT	CC	TT	CT	CC	
Chen ²⁹	8 (9.0)	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

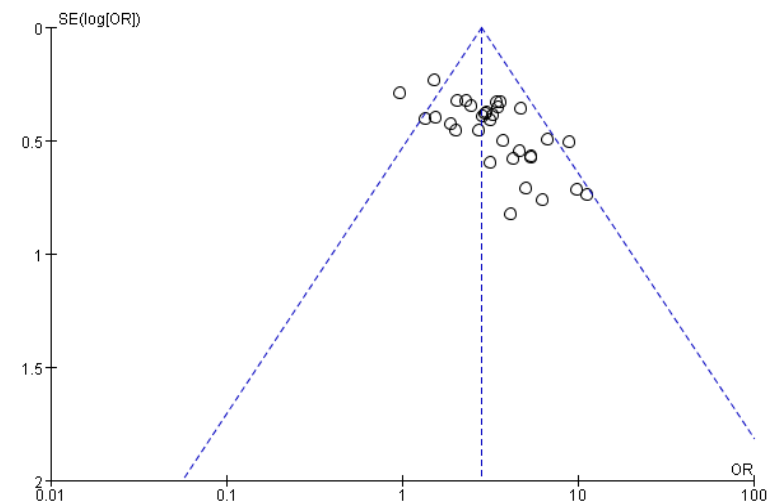
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3 **(A) *CYP2E1* *RsaI/PstI* polymorphism**
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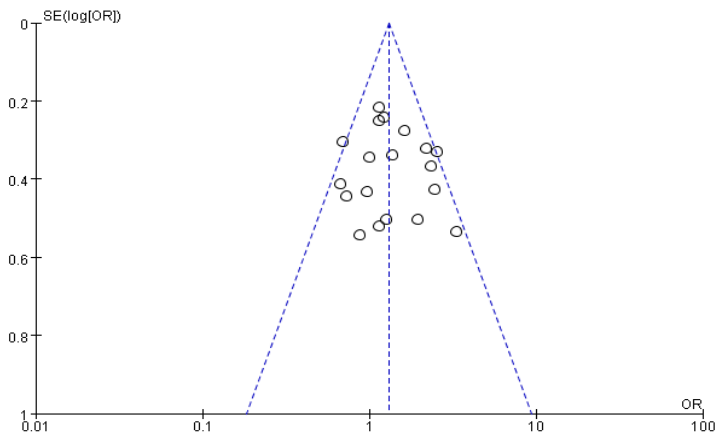
22 **(B) *CYP2E1* *DraI* polymorphism**
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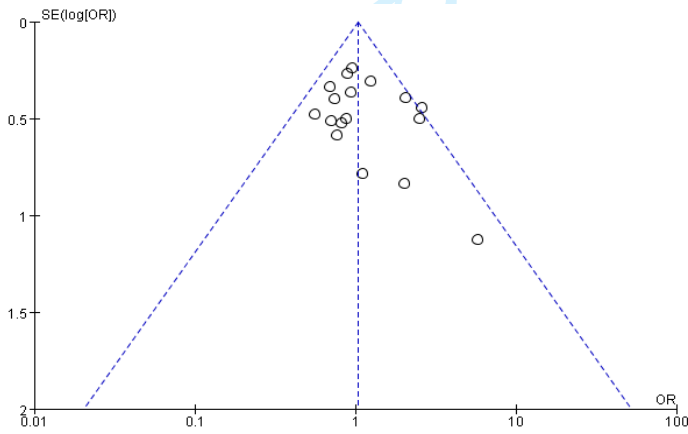
42 **(C) *NAT2* polymorphism**
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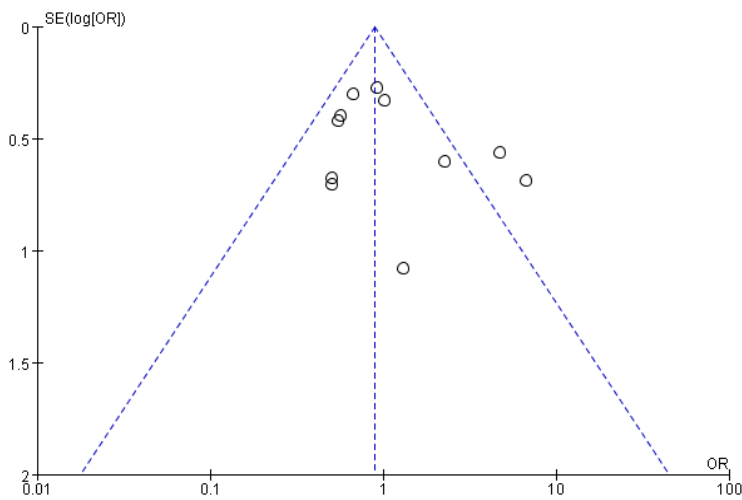
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4 **(D) *GSTM1* polymorphism**



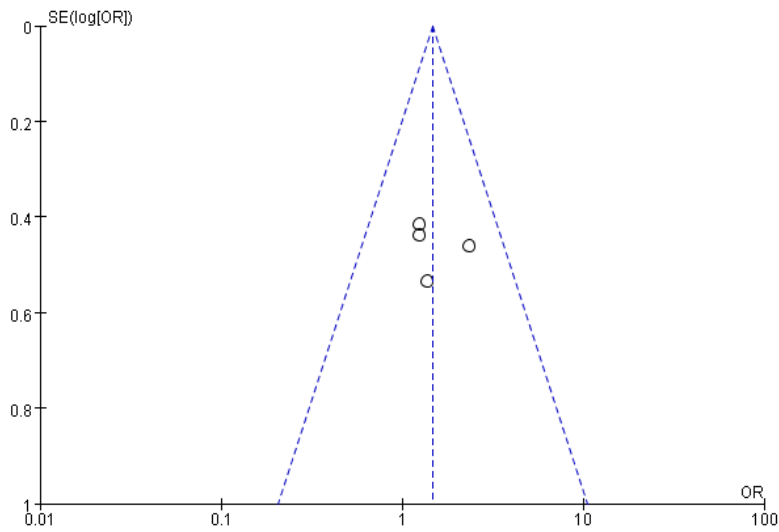
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22 **(E) *GSTT1* polymorphism**



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40 **(F) *GSTT1/M1* polymorphism**



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3 **(G) *SLCO1B1* 388A>G and 521T>C polymorphism**
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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) *CYP2E1* *RsaI/PstI* polymorphism, (B) *CYP2E1* *DraI* 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	
<i>CYP2E1 RsaI/PstI</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
	<i>CYP2E1 DraI^c</i> (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

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3 ^b P value from Cochran's Q test based on chi-square statistic

4 ^c Subgroup analysis based on anti-TB drug regimen could not be performed due to insufficient information provided.
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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	
<i>NAT2</i> (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	
<i>GSTM1</i> ^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
<i>GSTT1</i> ^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
<i>GSTM1/GSTT1</i> ^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

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^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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