Original Article

The association between cytochrome P450 polymorphisms and anti-tuberculosis drug-induced liver injury: a systematic review and meta-analysis

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Background: Isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB) are the four most common drugs for the first-line treatment of tuberculosis (TB). Although chemotherapy drugs are widely used in the treatment of TB, and achieved good results, but the side effects, especially anti-tuberculosis drug-induced liver injury (ATDILI), cannot be overlooked. Many researchers have made efforts to uncover the association of cytochrome P450 (CYP) enzyme genetic polymorphisms with ATDILI. In this study, we systematically reviewed and meta-analyzed the relationship between CYP polymorphism and susceptibility to ATDILI.

Methods: We carried out literature searches of PubMed, Ovid, the Cochrane Library, Web of Science and Chinese National Knowledge Infrastructure (CNKI). Medical Subject Headings (MeSH) terms including "cytochrome P450 enzyme", "drug-induced liver injury", "polymorphism", "tuberculosis", and "hepatotoxicity" were used as keywords for our searches.

Results: The pooled odds ratio (OR) of all studies for CYP2E1 to the risk of ATDILI was 1.18 [95% confidence interval (CI): 0.82–1.71]. The articles in this meta-analysis were observed to be mildly heterogeneous. Further subgroup analysis revealed that the patients who receiving a four-drug protocol (INH + RIF + PZA + EMB) or three-drug protocol (INH + RIF + PZA) regimens showed a higher risk of ATDILI than those who receiving INH alone. However, subgroup analyses according to participants' ethnic origin, study type, and the definition of ATDILI produced no statistically significant results. Associations between other genes in the CYP family and ATDILI were indistinct and equivocal.

Discussion: Our meta-analysis has uncovered an association between CYP2E1 RsaI/PstI polymorphisms and ATDILI, especially among patients who receive a four-drug (INH + RIF + PZA + EMB) or three-drug (INH + RIF + PZA) anti-TB treatment regimen.

Keywords: Meta-analysis; cytochrome P450 enzyme (CYP enzyme); anti-tuberculosis drug-induced liver injury (ADTILI); genetic polymorphism; hepatoxicity

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Introduction

Tuberculosis (TB) is a worldwide infectious disease caused by *Mycobacterium tuberculosis*, which takes more lives than all other infectious diseases. Drug-resistant TB poses a serious threat to public health systems all over the world. Owing to the forward steps made in treating and preventing TB, in 2019, it is estimated that there will be 9.96 million new TB cases and 1.41 million deaths in the world. Since 2007, TB has been ranked as one of the top ten causes of death in the world and ranked first among all infectious diseases (1). Although novel diagnostic methods, medications, and vaccination for TB have been trialed, the most recommended drugs for the first-line treatment of TB are still isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB) with/without streptomycin. Chemotherapy drugs which can effectively treat TB are widely available, but their side effects cannot be overlooked, with the severest being anti-tuberculosis drug-induced liver injury (ADTILI). If the patient has ADTILI but fails to identify and stop treatment in time, the patient may have serious adverse reactions or even death.

N-acetyltransferase 2 (NAT2) initially metabolizes INH into acetylisoniazid, which is subsequently hydrolyzed to acetylhydrazine. NAT2 was further acetylated to produce a non-toxic metabolite diacetylhydrazine. Acetylhydrazine can also be oxidized by cytochrome P450 2E1 (*CYP2E1*), generating hepatotoxins including acetyldiazene, acetylonium ion, acetyl radical, and ketene. More than *NAT2* and *CYP2E1*, a relationship may potentially exist between polymorphisms in genes coding for the microsomal cytochrome P450 (CYP) enzymes, such as CYP3A4, and ATDILI. RMP induces CYP, resulting the level of toxic products increased after INH metabolism (2). The pregnane X receptor (*PXR*) closely modulates gene expression in the hepatic drug-clearance system, and its unwanted activation can contribute to ATDILI (3). RMP mediates the activation of *PXR*, which operates as a pivotal factor which controls xenobiotic and drug-mediated induction of the CYP3A, CYP2B, and CYP2C subfamilies (4). CYP enzymes may be of crucial importance to reactive metabolite synthesis and detoxification (5). Researchers have concentrated efforts toward depicting the association between ATDILI and CYP enzymes, such as CYP2B6 (6), CYP2C9, CYP2C19 (7), and CYP2D6 (8); however, their results have been controversial and contradictory.

To our knowledge, four meta-analyses regarding ATDILI's relationship with *CYP2E1* RsaI/PstI polymorphisms have been conducted previously (9-12). However, these studies have some inadequacies; for instance, none of them included studies published after 1st August, 2015, and none of them reviewed any other CYPs. In the present work, we systematically reviewed and meta-analyzed all published articles examining the extent of the supposed genetic relationship between CYP polymorphism and susceptibility to ATDILI.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1224).

Methods

Search strategy

We performed searches of Medline, Embase, the Cochrane Library, Web of Science, and Chinese National Knowledge Infrastructure (CNKI) to identify relevant studies written in Chinese or English and published before June 11, 2018. The following Medical Subject Headings (MeSH) terms were used as keywords for our searches: "cytochrome P450 enzyme", "drug-induced liver injury", "polymorphism", "tuberculosis", and "hepatotoxicity". We also manually screened the references from published meta-analyses to identify any other literature of potential interest.

Eligibility screening

To be included in the meta-analysis, studies needed to meet the following criteria: (I) the study was published in peer-reviewed journals and the original data were available; (II) the study included details of genotypic distribution of polymorphisms for the ATDILI groups and the control group; (III) the type of study design as a case-control or cohort study; and (IV) the details of the included studies included the definition of ATDILI and the detailed treatment plan of the patients. The exclusion criteria

were: (I) published literature repeatedly; (II) reviews and meta-analyses; (III) animal research; (IV) no association with CYPs.

Data extraction and assessment of study quality

Two authors extracted information from each article independently, including: the name of the first author; publication year; study participants' age, sex, and ethnicity; diagnostic criteria; genotyping method; numbers of participants in the case group and control group; and the frequency of genotypes among the ATDILI and control groups. We contacted the authors directly if the study participants' chemotherapy protocol were not mentioned in the studies. A response was received from one query, and the article was included (13). If there were differences on the included articles, the two authors discussed and decide whether to include. We assessed the quality of the studies based on the criteria revised by Deng (11).

Statistical analyses

CYP2E1 genotypes were analyzed according to the genetic model of proposed risk (C1/C1 *vs.* C1/C2 and C2/C2 for the RsaI/PstI polymorphism). All data were statistically analyzed with STATA version 14.0 (Stata, College Station, TX, USA) and Review Manager, version 5.3 (Revman, Cochrane Centre, The Cochrane Collaboration). The standard Q-statistic test was adopted to assess the studies for heterogeneity. Heterogeneity was evidenced by I^2>50%. If heterogeneity was present, we would employ the fixed-effects model; in its absence, the random-effects model would be adopted. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to analyze the correlation of genotypes with the risk of ATDILI in patients, with P<0.05 being an indication of statistical significance. We conducted subgroup analyses according to: (I) ethnicity (East Asian, South Asian, or South American); (II) chemotherapy protocol; (III) the study design: cohort or case-control; and (IV) the definition of ATDILI based on a minimum serum alanine aminotransferase (ALT) level the upper limit of normal (ULN). We tested the study results for stability by performing a sensitivity analysis, and Begg's funnel plot was used for publication bias detection.

Results

Study characteristics

From the 116 articles originally identified in our searches, 38 eligible studies were finally included. After reading these papers carefully, we found that 2 articles had duplicated data. Therefore, 37 studies described the relationship between CYP polymorphism and susceptibility to ATDILI, of which 30 studies were related to *CYP2E1* (2 focused on both *CYP2E1* and other CYPs), and 7 studies focused on the distribution of other CYPs. The selection process for the eligible studies is depicted in *Figure 1*. Among the 30 articles focusing on *CYP2E1*, 29 articles discussed *CYP2E1* RsaI/PstI polymorphisms and ATDILI, and 1 article discussed other tag single-nucleotide polymorphisms (SNPs) in *CYP2E1* (14). Further, 4 articles included participants with CYP3A4 (6,7,15,16), 2 articles included participants with, CYP2B6 (6,17), 2 articles with CYP2C9 (7,18), 2 articles with CYP2C19 (7,15,19), and 3 articles with CYPC3A5 (6,15,18) polymorphisms, respectively.

Eventually, 29 studies involving 7,526 patients (1,548 in the case group and 5,978 in the control group) satisfied the criteria for inclusion and were subsequently meta-analyzed. Among them, 11 articles included participants of Chinese ethnicity (8,14,20-29), 7 articles included Indian participants (30-35), 5 articles included Brazilian participants (2,13,36-38), 2 included Korean participants (39,40), 3 articles included participants of more than 1 ethnicity (41-43), 1 included Indonesian participants (44), 1 included Japanese participants (45), and 1 included Tunisian participants (46). Polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) was the method used most frequently to detect genotypes. Nine articles were case-control studies, and 19 were cohort studies (of which 1 was retrospective, and the others were prospective); the design method is not clear in one study

The main characteristics were summarized in *Table 1*. Of the patients who underwent the anti-TB treatment 1,548 case were with ADTIH, while 5,978 were not.

Association of CYP2E1 gene with ATDILI

A total of 28 studies reported an association between the *CYP2E1* gene and ATDILI, and there was obvious

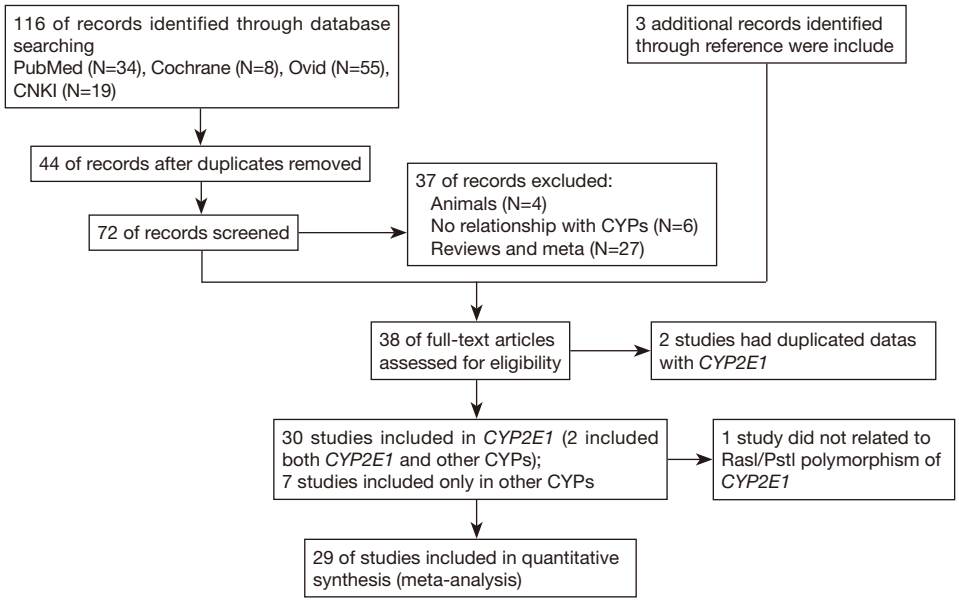

Figure 1 Flow chart of selecting studies for this meta-analysis. CNKI, Chinese National Knowledge Infrastructure; CYP, cytochrome P450; CYP2E1, cytochrome P450 2E1.

heterogeneity among the studies (χ^2=139.89, I^2=81%, P<0.05); consequently, we adopted the random-effects approach for the meta-analysis. The pooled OR of all studies for *CYP2E1* to the risk of ATDILI was 1.18 (95% CI: 0.82–1.71, P=0.37, *Figure 2*). This result showed that *CYP2E1* RsaI/PstI polymorphisms were not statistically associated with ATDILI. We further performed subgroup analysis according to ethnicity, with the ethnic groups in the studies mainly including East Asians, South Asians, and South Americans. However, There was no significant difference between subgroups (P=0.31, *Figure 3*). Subgroup analysis was performed according to the participants' drug protocol. The results showed that the patients who receiving a four-drug protocol (INH + RIF + PZA + EMB) or three-drug protocol (INH + RIF + PZA) regimens showed a higher risk of ATDILI than those who receiving INH alone (OR =1.33, 95% CI: 1.14–1.55; OR =2.32, 95% CI: 1.54–3.50) and OR =1.32, 95% CI: 0.64–2.76, respectively) (*Figure 4*). Additionally, we analyzed the subgroups according to study type (cohort design or case-control) and the definition of ATDILI (ALT >3 ULN or ALT >2 ULN); however, no significant difference was found between the subgroups (*Figures 5,6*).

Sensitivity analysis and publication bias

Low-quality studies were excluded in sensitivity analysis to determine whether the literature quality was the source of heterogeneity. Sensitivity analysis after the elimination of low quality literature (score <6) was carry out. We found that there was still extremely obvious heterogeneity between the studies, indicating that the source of heterogeneity was not the quality of the literature. Begg's funnel plot analysis of the 29 included studies concerning CYP1E2 and ATDILI suggested an acceptable level of publication bias (t=1.60, P=0.122) (*Figure 7*).

Associations of other genes in the CYP family with ATDILI

Nine articles focused on the relationships of other genes in the CYP family with ATDILI. Although the heterogeneity among the articles was significant, there was some consistency. For instance, the 516 TT homozygous mutant of *CYP2B6* was used for the risk analysis. One study base on Chinese population suggested male patients harboring the *CYP2B6* *6/*6 genotype to potentially have lower susceptibility to developing ATDILI than female (P=0.039,

Table 1 Characteristics of the studies included in the meta-analysis

Quality score	Study	Year	Population	Study design	Male (N)		Mean age (year)		Case* (N)		Control* (N)		Drug protocol	ATDILI definition	Genotyping method
					Case	Control	Case	Control	C1/C1	C1/C2 + C2/C2	C1/C1	C1/C2 + C2/C2			
7	Ben Fredj (46)	2017	Tunisian	Cohort	8	41	36	36	11	0	54	6	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP
6	Artini (44)	2017	Indonesia	Cohort	2	18	NA**	NA**	3	2	19	11	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP
7	Zhang (8)	2016	Chinese	Case -control	92	92	52.4	53.1	70	44	80	34	INH + RIF + PZA + EMB	ALT >3 ULN	PCR-RFLP
7	Heinrich (13)	2016	Brazilian	Cohort	NA**	NA**	NA**	NA**	14	9	69	24	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP
6	Feng (21)	2014	Chinese	Case -control	118	118	48.8	48.6	136	37	97	76	INH + RIF + PZA	ALT >3 ULN	PCR
6	Zaverucha-do-Valle (2)	2014	Brazilian	Cohort ($R^{\dagger}$)	NA**	NA**	NA**	NA**	48	3	74	4	INH + RIF + PZA	ALT >2 ULN	PCR-RFLP
7	Xiang (27)	2014	Chinese	Cohort	NA**	NA**	37	46	58	2	126	336	INH + RIF + PZA + EMB	AST >2 ULN	PCR
7	Sharma (35)	2014	Indian	Cohort	63	145	35.2	27.6	81	24	139	46	INH + RIF + PZA + EMB	ALT >3 ULN	PCR-RFLP
7	Singla (34)	2014	Indian	Cohort	11	241	48.8	32.7	15	2	375	16	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP
7	Rana (32)	2014	Indian	Cohort	33	152	43.6	42.3	28	27	150	95	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP
7	Brito (36)	2014	Brazilian	Cohort	7	NA	38.1	36.8	13	2	195	35	INH + RIF + PZA	ALT >3 ULN	PCR-RFLP
7	Santos (38)	2013	Brazilian	Cohort	10	124	47.7	45.6	15	3	173	56	INH + RIF + PZA	ALT >3 ULN	PCR
7	Gupta (30)	2013	Indian	Cohort	24	99	37	38	49	1	156	9	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP
7	Chamorro (41)	2013	Combined	Cohort	19	83	27	29	30	17	83	45	INH + RIF + PZA + EMB	ALT >3 ULN	PCR-RFLP
7	Mishra (31)	2013	Indian	Cohort	NA**	NA**	NA**	NA**	31	2	168	5	INH + RIF + PZA + EMB	ALT >3 ULN	PCR-RFLP
7	Tang (25)	2012	Chinese	Cohort	65	260	43.7	43.6	56	33	225	11	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP

Table 1 (*continued*)

Table 1 (*continued*)

Quality score	Study	Year	Population	Study design	Male (N)		Mean age (year)		Case* (N)		Control* (N)		Drug protocol	ATDILI definition	Genotyping method
					Case	Control	Case	Control	C1/C1	C1/C2 + C2/C2	C1/C1	C1/C2 + C2/C2			
7	An (20)	2012	Chinese	Case -control	56	75	34	28	72	29	64	43	INH + RIF + PZA + EMB	ALT >2 ULN	PCR
5	Zhou (23)	2012	Chinese	Case -control	NA**	NA**	NA**	NA**	65	35	51	49	INH + RIF + PZA + EMB	ALT >2 ULN	PCR
7	Teixeira (37)	2011	Brazilian	Case -control	16	74	47.58	42.99	23	3	128	13	At least INH	ALT >3 ULN	PCR-RFLP
6	Sotsuka (45)	2011	Japanese	Cohort	18	68	59.8	50.4	11	9	60	32	INH + RIF + PZA + EMB	ALT >3 ULN	PCR-RFLP
7	Wang (26)	2010	Chinese	Case -control	70	75	48.6	44.68	82	22	71	40	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP
6	Lee (29)	2010	Chinese	Cohort	70	75	58.4	54.9	26	19	55	40	INH + RIF + PZA + EMB	ALT >2 ULN	PCR
6	Chen (28)	2010	Chinese	Cohort	81	156	45.9	45.7	76	27	143	93	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP
7	Kim (40)	2009	Korean	Cohort	16	74	47.6	43	54	12	97	56	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP
7	Yamada (43)	2009	Combined	Cohort	3	63	NA**	NA**	17	6	107	40	INH	ALT >2 ULN	PCR-RFLP
7	Cho (39)	2007	Korean	Cohort	6	51	51.2	46.7	10	8	65	49	INH + RIF + PZA + EMB	ALT >2 ULN	PCR
6	Vuilleumier (42)	2006	Combined	Cohort	NA**	NA**	NA**	NA**	7	1	44	37	INH + B6	ALT >3 ULN	PCR-RFLP
5	Roy (33)	2006	Indian	NA	8	64	NA	NA	7	1	99	2	INH + RIF + PZA + EMB	NA**	PCR-RFLP
7	Huang (22)	2003	Chinese	Cohort	9	40	70	59	37	12	148	121	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP

*, cases were TB patients with ATDILI; controls were TB patients without ATDILI; **, no independent data available; †, retrospective cohort study, others were prospective cohort studies. ATDILI, anti-tuberculosis drug-induced liver injury; INH, isoniazid; RMP, rifampicin; PZA, pyrazinamide; EMB, ethambutol; ALT, alanine aminotransferase; ULN, upper limit of normal; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; TB, tuberculosis.

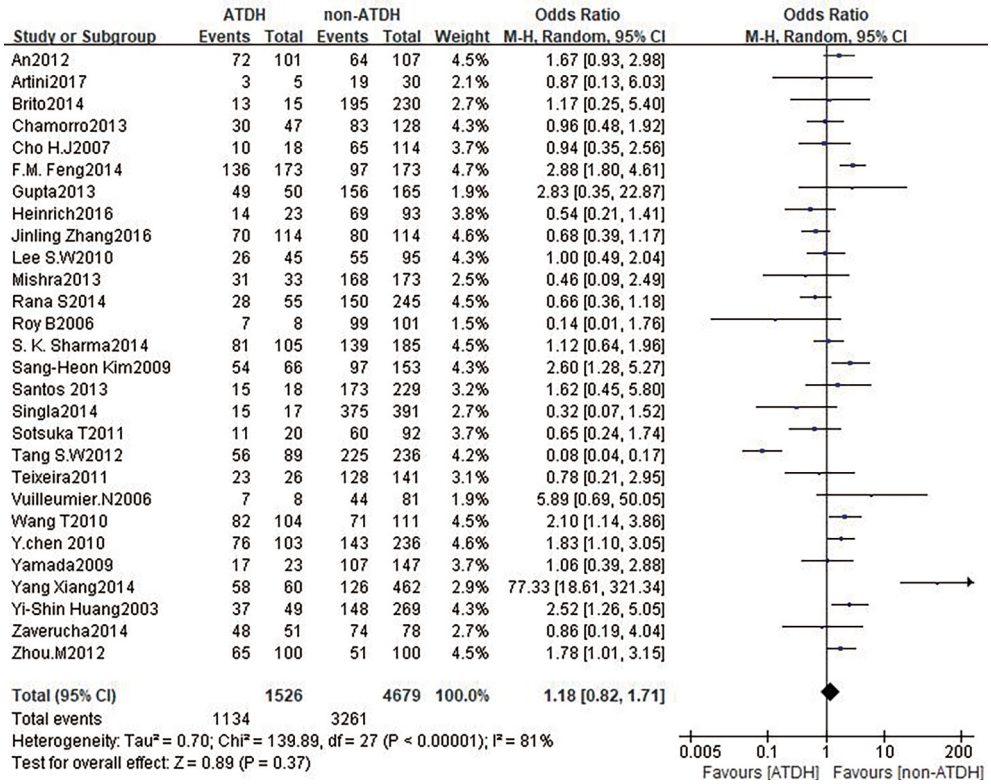

Figure 2 Forest plot of the association between *CYP2E1* RsaI/PstI polymorphisms and ADTILI risk in all 29 studies. CYP2E1, cytochrome P450 2E1; ATDILI, anti-tuberculosis drug-induced liver injury; ATDH, anti-tuberculosis drug-induced hepatotoxicity; CI, confidence interval.

OR =0.097, 95% CI: 0.011–0.885) (17). In Another study found the 516 TT homozygous mutant genotype of the *CYP2B6* gene to also carry significance (P=0.046; OR =0.063, 95% CI: 0.004–0.955) in a key variable analysis (6).

With respect to CYP3A4, the situation was even more indistinct. For the *CYP3A4* gene (c.-392 G>A) CYP3A4 genotypes were not significantly associated with ADTILI in Zaverucha-do-Valle's study (2), which was most likely attributable to most of the participants in the analysis carrying the homozygous wild-type genotype. Meanwhile, in Sun's study, the CYP3A4 18B20332G/A genotype was found to be a protective genotype against ADTILI (OR =0.088 95% CI: 0.027–0.291) (15). Moreover, in Guo's study, the CYP3A4 18B genotype elevated the risk of developing ADTILI (OR =1.196, 95% CI: 1.231–2.980) (16). The results were equivocal. The main characteristics and genotypes are summarized in *Tables 2,3*, respectively.

Discussion

In the present study, we meta-analyzed 29 studies involving 7,526 cases (1,548 with ATDILI, and 5,978 without ATDILI) which explored the association of *CYP2E1* RsaI/PstI gene polymorphism with ADTILI. Our study found that RsaI/PstI polymorphisms in the *CYP2E1* gene were associated with an increased risk of developing ATDILI among East Asian populations. This conclusion was in agreement with the results of three other meta-analyses (47). INH showed a reduced inhibitory effect on *CYP2E1* activity among patients carrying the *CYP2E1* RsaI/PstI c1/c1 genotype compared to patients with other genotypes. Thus, as a result of INH treatment, participants harboring the *CYP2E1* c1/c1 genotype display increased *CYP2E1* activity compared to patients carrying other genotypes; consequently, these patients may display elevated

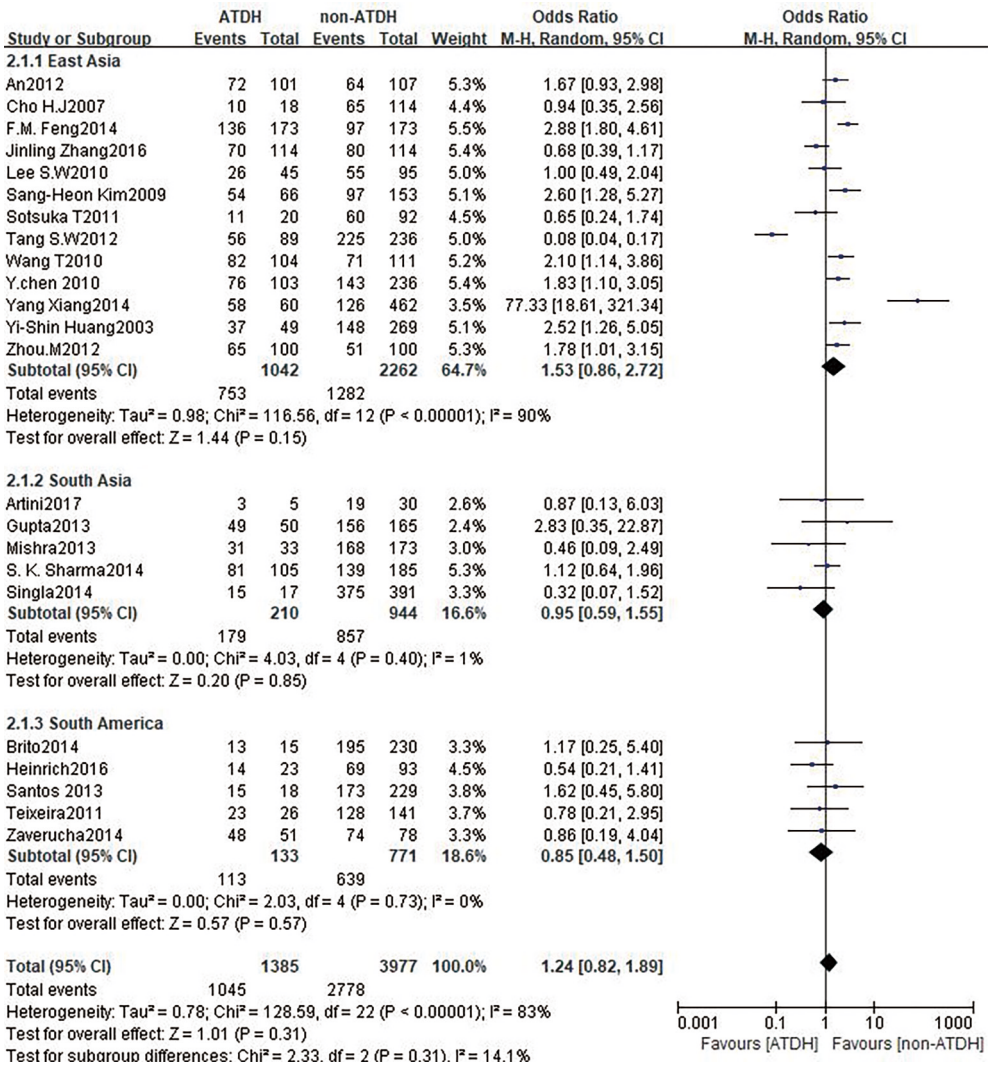

Figure 3 Forest plot of the association between *CYP2E1* RsaI/PstI polymorphisms and ADTILI risk in subgroups with different ethnic origins. CYP2E1, cytochrome P450 2E1; ATDILI, anti-tuberculosis drug-induced liver injury; ATDH, anti-tuberculosis drug-induced hepatotoxicity; CI, confidence interval.

hepatotoxin production, increasing their chances of sustaining liver injury (10).

The human derived *PXR*, also known as nuclear receptor 112, was initially considered as the main regulatory factor of exogenous detoxification. It regulates the expression of drug metabolizing enzymes and transporters to control the degradation and excretion of exogenous and endogenous substances (including therapeutic drugs). *PXR* gene polymorphism is considered to be related to adverse reactions and interactions of drugs (or exogenous drugs) (48). The polymorphism of *PXR* gene and anti-tuberculosis drug-induced hepatotoxicity (ATDH) susceptibility have attracted the attention of researchers. In 2015, Zazuli *et al.* analyzed the *PXR* gene polymorphism of 106 Indonesian people, and found that the T genotype of rs3814055 was related to high risk of ATDH, so it was considered that *PXR* gene polymorphism was one of the risk factors of ATDH (49). In the same year, Wang *et al.* analyzed the polymorphism of *PXR* combined *NAT* gene in 355 Taiwan people at the same time. It was found that *NAT2* and malnutrition were independent risk factors of ATDH in male and female patients, but AA genotype of rs2461823 and an allele of rs6785049 were only independent risk factors for female sex. The results show that SNP genotype

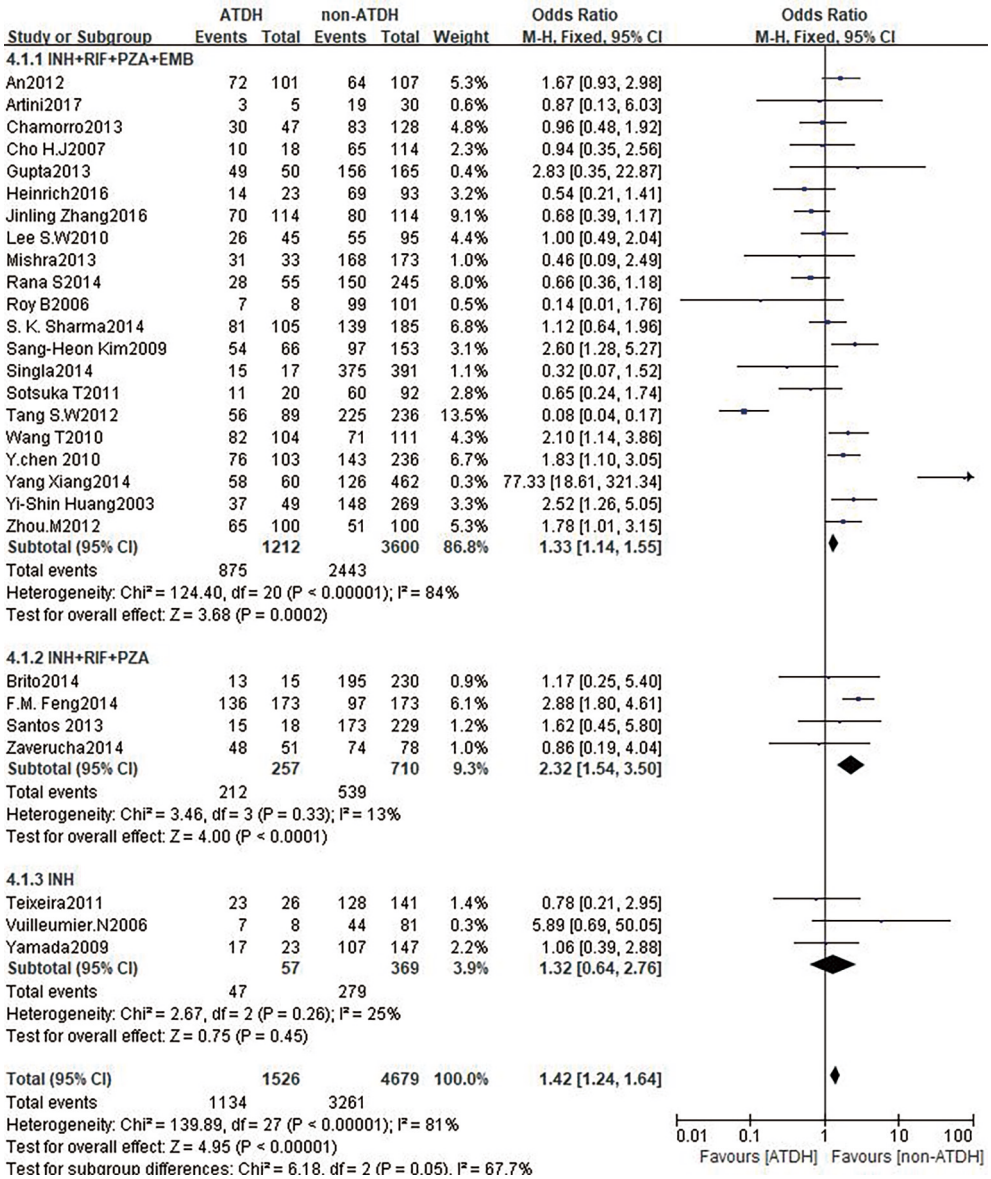

Figure 4 Forest plot of the association between *CYP2E1* RsaI/PstI polymorphisms and ADTILI risk in subgroups with different anti-TB combination regimens. CYP2E1, cytochrome P450 2E1; ATDILI, anti-tuberculosis drug-induced liver injury; TB, tuberculosis; ATDH, anti-tuberculosis drug-induced hepatotoxicity; CI, confidence interval.

and haplotype of PXR are still important risk factors of ATDH in Asian population, and show the characteristics of gender stratification (50). In 2019, Wang *et al.* studied 502 Chinese TB patients and found that the secondary allele and h0010001 haplotype of rs7643645 in PXR were related to reducing the risk of ATDH, and suggested that the drug metabolic enzyme regulated by PXR was related to the pathogenesis of ATDH (51). In 2019, Zhang *et al.* conducted allele frequency, genotype and genetic model of *PXR* gene in 746 patients with TB in Western China, and analyzed interaction with SNP. It was found that the risk of ATDH in T allele carriers of rs3814055 was lower than that of C allele carriers, the dominant and additive models in the main genetic models also suggested that the locus was related to the risk of ATDH susceptibility (52).

NAT2 and *CYP2E1* are the key enzymes for the

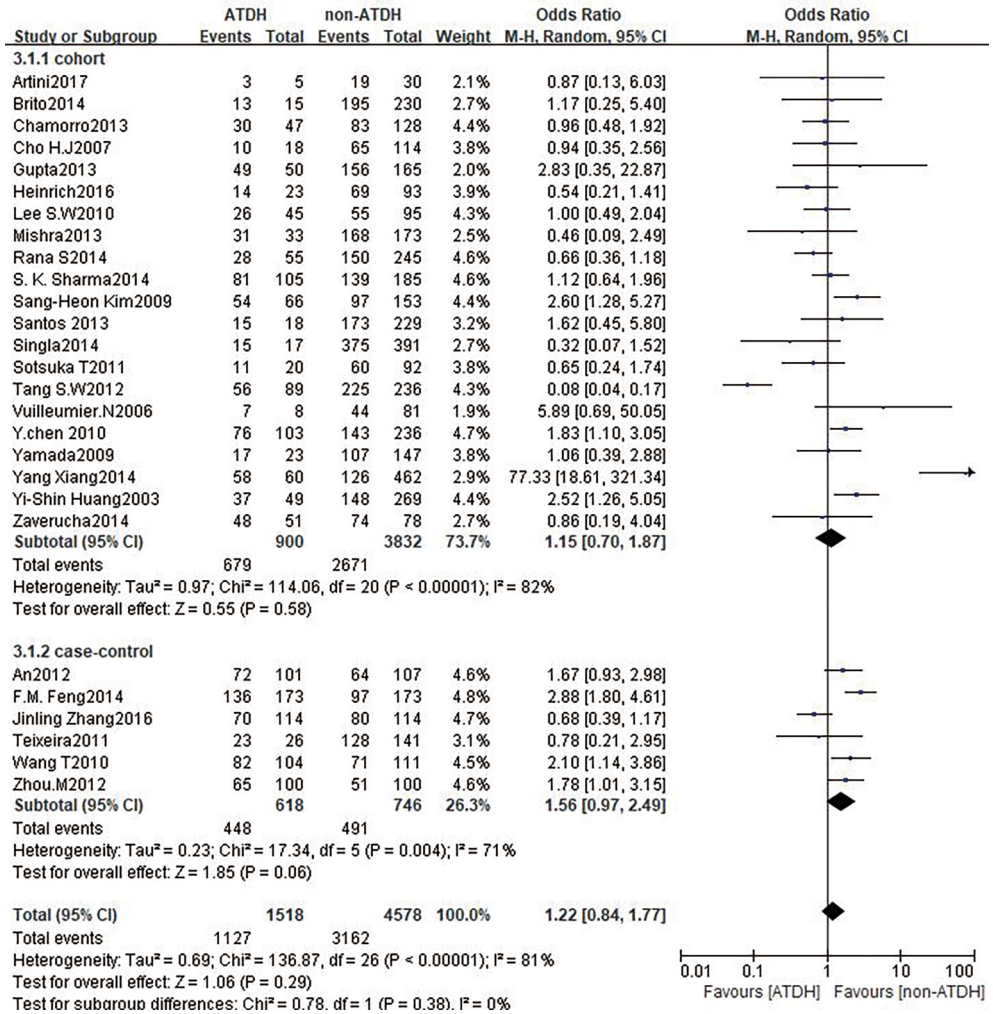

Figure 5 Forest plot of the association between *CYP2E1* RsaI/PstI polymorphisms and ADTILI risk in subgroups based on study type. CYP2E1, cytochrome P450 2E1; ATDILI, anti-tuberculosis drug-induced liver injury; ATDH, anti-tuberculosis drug-induced hepatotoxicity; CI, confidence interval.

detoxification of INH in liver (5). Due to the association between the "slow acetylation" phenotype of *NAT2* gene and the increased blood level and toxic reaction rate of INH, FDA has included the *NAT2* gene phenotype in the drug label of INH for the treatment of TB (53). PharmGKB database also uses important *NAT2* genetic variation as a clinical guideline to predict the risk of ATDH induced by INH in TB patients. Researchers have studied a large number of gene polymorphisms in drug metabolism, such as *CYP2E1*, glutathione S-transferase (GST), cholesterol 7α-hydroxylase gene, bile salt export pump (*BSEP*) gene, sodium ion sodium taurocholate cotransporter polypeptide gene and *PXR* gene. hydrazine (Hz), acetyldiazine (AC) and their metabolites, which are the toxic metabolites of INH, can cause liver injury, which is related to the metabolism of *NAT2*, *CYP2E1* and *GST* had correlation; RIF also has weak hepatotoxicity due to the enhancement of INH hydrolase activity and/or activation of *PXR*, such as CYP, glutathione, bile acid and lipid metabolism enzymes, with the incidence of less than 1.1% (3,54,55).

The occurrence and development of ATDH involves many complex links, such as drug metabolism, oxidative stress, mitochondrial dysfunction, immune regulation and inflammatory response. These links occur simultaneously or sequentially, and the interaction of each link determines the occurrence, outcome and prognosis of ATDH. Drug

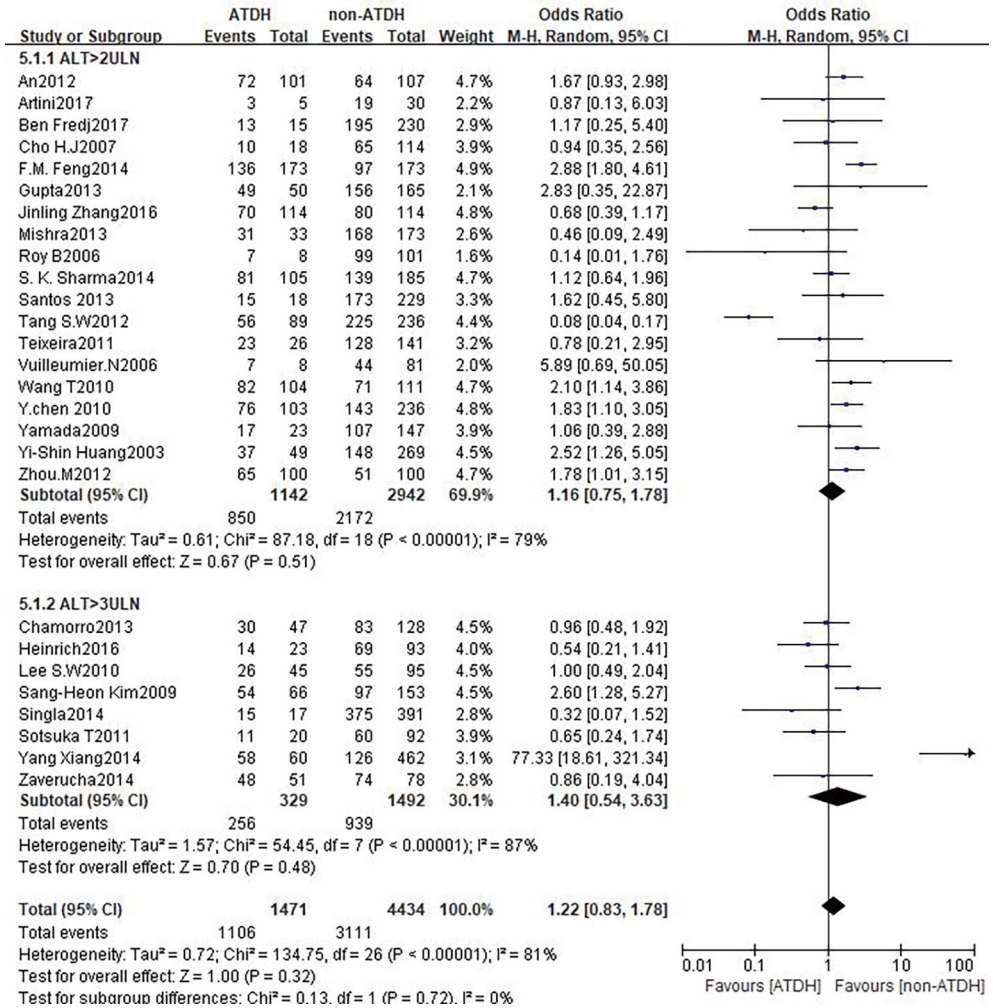

Figure 6 Forest plot of the association between *CYP2E1* RsaI/PstI polymorphisms and ADTILI risk in subgroups based on the definition of ATDILI. CYP2E1, cytochrome P450 2E1; ATDILI, anti-tuberculosis drug-induced liver injury; ATDH, anti-tuberculosis drug-induced hepatotoxicity; CI, confidence interval.

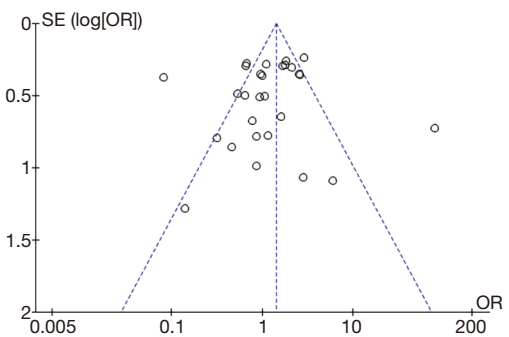

Figure 7 Begg's plot of publication bias among all 29 studies on the association of *CYP2E1* RsaI/PstI polymorphisms with ADTILI risk. CYP2E1, cytochrome P450 2E1; ATDILI, anti-tuberculosis drug-induced liver injury; OR, odds ratio.

metabolic transport is the initiation of ATDH, especially the metabolism of INH is related to the metabolic type of metabolic enzyme NAT (5,53,56).

Drug metabolizing enzyme gene polymorphism has always been the research direction of ATDH, but most of them are small sample and single ethnic analysis, and there is no recognized conclusion about the correlation between *NAT* gene polymorphism and ATDH (53).

Studies in the case-control design subgroup seemed to show high risks of ATDILI. To some degree, this result may be explained by the accurate matching in advance, which eliminated some mixed factors, such as age and sex.

Both epigenetic and genetic alterations may affect the

Table 2 Characteristics of studies on the association of other CYPs and ATDILI risk

Study	Year	Population	Study design	Case[a] (N)	Control[a] (N)	Male case (N)	Male control (N)	Mean case[a]	Mean control[a]	CYPs
Sun	2017	Chinese	Case control	207	207	NA[b]	NA[b]	NA[b]	NA[b]	CYP1A2, CYP3A4, CYP3A5, CYP2C19
Guo	2016	Chinese	Case control	175	185	127	139	47.5	47.1	CYP3A4, CYP3A5
Lei	2015	Chinese	Case control	179	179	134	134	46.8	47	CYP1A2, CYP2C19
Lei	2015	Chinese	Case control	127	127	94	94	48.98	49.1	CYP1A1
Zhang	2016	Chinese	Case control	114	114	92	92	52.4	53.1	CYP2D6
Wang	2017	Chinese	Case control	166	177	88	86	38.3	38.3	CYP2B6
Fernande	2015	Brazilian	Cohort	31	189	NA[b]	NA[b]	NA[b]	NA[b]	CYP2B6, CYP3A5
Zaverucha -do-Valle	2014	Brazilian	Case control	51	78	NA[b]	NA[b]	NA[b]	NA[b]	CYP3A4
Tang	2013	Chinese	Cohort	89	356	65	260	43.7	43.6	CYP3A4, CYP2C9, CYP2C19

[a], cases were TB patients with ATDILI; controls were TB patients without ATDILI; [b], no independent data available. CYP, cytochrome P450; ATDILI, anti-tuberculosis drug-induced liver injury; TB, tuberculosis.

expression of GSTP1 and CYP1A1, such as abnormal changes in CpG island methylation of the GSTP1 promoter. Gene promoter methylation is generally related to transcriptional repression via mechanisms such as direct prevention of transcription factor binding to DNA binding sites or via complex indirect mechanisms such as chromatin remodeling. Toxic metabolites of anti-TB drugs may induce the methylation of the promoter regions of GSTP1 or CYP1A1 (19).

Down-regulated expression of bile acid transporters, BSEP, and sodium taurocholate co-transporting polypeptide (NTCP) are found in mice co-treated with INH and RMP, which is associated with an increased risk of the ATDILI (28). Increased expression of CYP7A1 occurs in Wistar rats co-treated with INH and RMP, which results in excess bile acids based on histo-pathological studies (29). Therefore, alterations of CYP7A1 and BSEP in the accumulation of bile acids may contribute to ATDILI (53).

We also found that the risk of ATDILI varies with different treatment protocol for TB. Only three studies used INH as the sole anti-TB treatment, while most of the others used a three- or four-drug combination regimen. Thus, it was equivocal that INH alone seemed to have a lower risk (OR =0.97), while combination regimens seemed to have a higher risk. In most of the articles, the definition of ATDILI was an ALT level of at least two- or three-fold the ULN, with or without an elevated level of aspartate aminotransferase (AST), and with or without symptoms of hepatitis. We stratified ATDILI into subgroups only by levels of ALT, and found a statistical association between ATIDIL risk and the ALT >2 ULN subgroup (OR =1.35, 95% CI: 1.05–1.74, P=0.021); however, taking the heterogeneity into consideration (I^2=44.4%, P=0.02), the analysis maybe under power. It is worth mentioning that heterogeneity dramatically decreased from I^2=44% to I^2=23%, following the removal of Feng *et al.*'s article (21), with a seemingly stable association (OR =1.26, 95% CI: 1.01–1.58, P=0.04).

In our study, a total of 28 studies reported an association between the *CYP2E1* gene and ATDILI, and there was obvious heterogeneity among the studies (χ^2=139.89, I^2=81%, P<0.05); The pooled OR of all studies for *CYP2E1* to the risk of ATDILI was 1.18 (95% CI: 0.82–1.71, P=0.37, *Figure 2*). This result showed that *CYP2E1* RsaI/PstI polymorphisms were not statistically associated with ATDILI. Our meta-analysis has uncovered an association between *CYP2E1* RsaI/PstI polymorphisms and ATDILI, especially among patients who receive a four-drug (INH + RIF + PZA + EMB) or three-drug (INH + RIF + PZA) anti-TB treatment regimen.

The Begg's funnel plot (P=0.122) showed the included studies to have an acceptable level of publication bias. Compared with previous meta-analyses, there was a remarkable increase in articles with a larger number of

Table 3 Genotype distributions of the other CYP polymorphisms in each study

Study	CYPs	SNPs	Case[a]			Control[a]			Drug protocol	Definition of ATDILI	Genotype method
			11[b]	12[b]	22[b]	11[b]	12[b]	22[b]			
Sun (15)	CYP1A2	734C/A	34	84	89	49	59	99	INH + RIF + PZA + EMB	ALT >3 ULN	PCR-RFLP
	CYP3A4	20231G/A	91	95	21	116	69	14	–	–	–
	CYP3A5	6986A/G	51	72	84	11	67	129	–	–	–
	CYP2C19	681G/A	71	104	32	76	110	21	–	–	–
Guo (16)	CYP3A4	20231G/A	74	82	19	109	63	13	–	–	–
	CYP3A5	6986A/G	8	68	99	31	76	78	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP
Lei (18)	CYP1A2	734C/A	32	69	78	41	87	51	–	–	–
	CYP2C19	681G/A	62	90	27	66	93	20	–	–	–
Lei (19)	CYP1A1	mspI	65	62[c]		74	53[c]		INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP
Zhang (8)	CYP2D6	188C/T	74	40[c]		80	34[c]		INH + RIF + PZA + EMB	ALT >3 ULN	PCR-RFLP
Wang (17)	CYP2B6	rs3745274G/T	113	48	5	110	53	14	INH + RIF + PZA + EMB	ALT >2 ULN	PCR-RFLP
	CYP2B6	rs2279343A/G	94	58	12	95	61	21	–	–	–
Fernande (6)	CYP2B6	rs3745274G/T	12	18	1	90	86	13	INH + RIF + PZA	ALT >3 ULN	PCR-RFLP
	CYP3A5	6986A/G	11	20	0	95	94	0	–	–	–
Zaverucha-do-Valle (2)	CYP3A4	392 G/A	27	35[c]		25	44[c]		INH + RIF + PZA	ALT >2 ULN	PCR-RFLP
Tang (7)	CYP3A4	rs1233983T/A	36	42	11	166	146	38	INH + RIF + PZA + EMB	ALT >3 ULN	PCR-RFLP
	CYP2C9	rs4918758T/A	33	36	18	119	166	69	–	–	–
	CYP2C9	rs9334098G/A	86	2	0	330	24	0	–	–	–
	CYP2C19	rs1568732T/G	79	8	1	295	55	4	–	–	–
	CYP2C19	rs4986894T/C	36	36	12	147	155	44	–	–	–

[a], cases were TB patients with ATDILI; controls were TB patients without ATDILI; [b], wild homozygote (n=11); hybrid (n=12); mutant homozygote (n=22); [c], hybrid and mutant homozygote. CYP, cytochrome P450; ATDILI, anti-tuberculosis drug-induced liver injury; INH, isoniazid; RMP, rifampicin; PZA, pyrazinamide; EMB, ethambutol; ALT, alanine aminotransferase; ULN, upper limit of normal; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; TB, tuberculosis.

cases with different origins and over a long-time span. It is possible that studies based on smaller sample sizes could have tilted toward producing positive results. Second, as in Feng *et al.*'s study (21), liver function detection was done at 6 months after the end of therapy, which is a later point in time than in most of the reported studies (6,17,21). A large proportion of studies reported that ADTILI occurred within 2 months after the end of treatment, which suggests there was potential selection bias. Third, there were many case-control studies in this research, which may have contributed to selection bias. Finally, we only do meta-analysis on those published articles. Therefore, mild publication bias potentially existed.

There are also some limitations to our meta-analysis. First, we did not research DraI polymorphisms in the *CYP2E1* gene, as they have rarely been reported on since the publication of Wang's study (12); moreover, none of the existing meta-analyses declared any association between DraI polymorphism and ADTILI. Second, we did not evaluate the potential association between NATs and *CYP2E1*, and there may be combined effects of these two genes. Further analyses should be conducted to assess the combination of NAT statues and *CYP2E1* genotypes on the risk of ATDIL. Third, there are many other high-risk factors for ATIDLI, such as alcohol consumption, sex, diabetes, malnutrition, HIV infection and viral hepatitis (5). Although it is difficult to explore these underlying risk factors in a simple meta-analysis, the gene-to-gene, gene-to-environment, and gene phenotypes should not be neglected. Finally, there was a lack of evidence of other CYPs related to ATIDIL due to the limited number of studies, and even in the handful of studies available, the authors did not focus on the same tag SNPs.

In the transcription factor binding sites of the PXR regulatory region (the promoter and intron 1) have also been associated with PXR alteration and CYP3A4 expression, and drug-induced liver injury (50). As RIF is a human PXR–specific activator, it is reasonable to believe that the polymorphism of CYP3A4 may have an effect on RIF-induced liver injury, although to date, there have been no positive findings (7).

Notably, in Zhang's research (8), a correlation was identified between CpG island hypermethylation of the *CYP2E1* and *CYP2D6* genes and the development of ADTILI. This finding may bring new insight into the relationship between the epigenetic candidate genes with ADTILI.

In conclusion, the results of this meta-analysis indicate an association between *CYP2E1* genetic polymorphisms and ATDILI, especially in patients treated with a four-drug (INH + RIF + PZA + EMB) or three-drug (INH + RIF + PZA) anti-TB treatment regimen. Genetic mutations of CYP enzyme family members and alterations in DNA methylation levels are perhaps only two of many risk factors for ATDILI, with other extrinsic factors waiting to be discovered, including diet, alcohol consumption, smoking, existing liver disease, and other co-existing diseases. Furthermore, the gene-to-gene, gene-to-environment, and host immunity against varied strains of TB also need to be explored.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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