Abstract. Antituberculosis (anti-TB) drugs are the most common cause of drug-induced liver injury (DILI). There are numerous studies revealing the associations between the polymorphisms of pharmacogenes and the risk of anti-TB DILI (ATDILI). In the present study, relevant studies regarding the pharmacogenes associated with ATDILI were systematically searched in PubMed and Scopus. A total of 24 genes associated with ATDILI were reported on and the top five reported genes in terms of frequency were revealed to be N-acetyltransferase 2, cytochrome P450 family 2 subfamily E member 1, glutathione S-transferases [glutathione S-transferase mu 1 (GSTM1) and glutathione S-transferase theta 1 (GSTT1)] and solute carrier organic anion transporter family member 1B1. As ATDILI may be the result of direct and indirect interactions, the encoded proteins were further analysed using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) to observe the protein-protein interactions and the associations amongst these proteins. The results suggested that only GSTT1 and GSTM1 were central proteins associated with all the other analysed proteins. Therefore, the association between GSTT1 or GSTM1 and the risk of developing ATDILI were further analysed. The results revealed that a GSTM1 deletion genotype was significantly associated with risk of ATDILI (odds ratio (OR), 1.28; 95% confidence interval (CI), 1.08-1.51; P=0.004), whereas the GSTT1 deletion genotype and GSTM1/GSTT1 dual-deletion genotype were not significantly associated with risk of ATDILI. Subgroup analysis based on ethnicity was performed and the results demonstrated a significant association between GSTM1 and ATDILI in South Asian individuals (OR, 1.48; 95% CI, 1.12-1.95; P=0.005), which has not been reported previously, to the best of our knowledge. In conclusion, GSTM1 was associated with ATDILI in South Asian individuals.

Introduction

Antituberculosis drug-induced liver injury (ATDILI) is one of the most common adverse reactions to drugs used to treat tuberculosis (TB), frequently resulting in the discontinued or interrupted use of drugs, and thus contributing to the socio-economic burden of the disease (1). The majority of patients with TB with DILI develop irreversible liver failure and eventually require a liver transplant due to a poorly defined pathogenesis and delayed diagnosis (2). Therefore, an improved understanding of the causes underlying hepatotoxicity induced by anti-TB drugs may result in the identification of novel markers and novel therapeutic targets for preventing and slowing the progression of DILI. Although the exact aetiology of DILI is not completely understood, it is considered a multifactorial disease which stems from a range of risk factors, including drugs used for treatment of TB and the dose, duration, hepatic metabolism and lipophilicity of those drugs, and other factors including sex, age and metabolism (2). Genetics has been proposed as a critical contributor to the pathogenesis of DILI (3). Thus, a focus has been placed on the potential influence of genetic factors in the development of ATDILI, in which a variety of genetic polymorphisms including in N-acetyltransferase 2 (NAT2), cytochrome P450 family 2 subfamily E member 1 (CYP2E1) and glutathione S-transferases [glutathione S-transferase mu 1 (GSTM1) and glutathione S-transferase theta 1 (GSTT1)] have been reported to be associated with an increased risk of ATDILI (4).

Of the various genes known to be associated with ATDILI, GSTs are gaining increasing interest as potential mediators of hepatotoxicity. GSTs are essential phase II metabolizing enzymes for detoxification, which are responsible for mitigating the cellular damage resulting from oxidative stress via...
conjuring glutathione to substrates including reactive oxygen species (ROS) in response to liver injury, and have been implicated in hepatotoxicity (5). Thus, they exert a protective effect against cellular damage, and one study revealed that gene deletions caused by the homozygous null mutations of GSTM1 and GSTT1, which are two major GSTIs involved in the isoniazid metabolism pathway, were significantly associated with an elevated risk of DILI in patients with TB (6). A number of clinical studies have demonstrated a potential significant association between GSTM1 or GSTT1 and susceptibility to ATDILI and DILI (7-21); however, the results obtained from these studies are inconsistent. For example, Rana et al (14) revealed that GSTM1 was associated with an increased risk of ATDILI; however, in a study by Chatterjee et al (7), an association was not observed. A meta-analysis is a valuable tool for deriving meaningful conclusions from data and may help resolve inconsistencies in research, and may thus assist in clarifying the association between polymorphisms of GSTM1 or GSTT1 and ATDILI.

Numerous meta-analyses have revealed an association between GSTM1 and GSTT1 null genotypes and susceptibility to ATDILI (6,22-24); nevertheless, there remain important gaps in our knowledge. Firstly, previous meta-analyses have included publications with confounding factors, including patients with hepatitis virus infection or human immunodeficiency virus (HIV) (23,25). Furthermore, since a large number of studies have been published, it is necessary to perform an updated meta-analysis to assess the association of genetic polymorphisms with ATDILI. Additionally, although genetic data derived from numerous meta-analyses are based on a large multi-ethnic population, the association between polymorphisms and individuals of South Asian descent require further validation. To address the aforementioned limitations of previous meta-analyses, the present meta-analysis was designed with a more stringent selection criteria to verify the precise associations between GSTM1 and GSTT1 with susceptibility to ATDILI. Therefore, the aim of the present analysis was to summarize and analyse the body of available data regarding the pharmacogenomics associated with ATDILI using a systematic review and meta-analysis approach, along with network analysis in order to gain insight into the molecular interactions between these pharmacogenes, their genetic polymorphisms and association with a susceptibility to ATDILI based on genetics and ethnicity.

Materials and methods

Identification of genes associated with ATDILI. The PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and Scopus (https://www.scopus.com/) databases were searched using the following terms: ‘drug-induced liver injury’ OR ‘hepatitis’ OR ‘drug-induced hepatitis’ OR ‘drug-induced hepatotoxicity’ OR ‘hepatotoxicity’ OR ‘liver injury’ AND ‘pharmacogenomic OR pharmacogenetic’ OR ‘genetic polymorphism’ OR ‘polymorphism’ AND ‘antituberculosis OR antitubercular’ OR ‘tuberculosis treatment’. Original articles examining the association between genetic polymorphisms and ATDILI with a cut-off date of October 30, 2018, were gathered. The frequencies of each gene associated with ATDILI were counted and the top five most frequent genes were and analysed using the STRING online software (26). STRING integrated and ranked protein/gene associations were benchmarked based on reference data which consisted of experimental and predicted interactions between each protein. The interaction network was considered relevant if the confidence score was >0.7 (26). In the protein-protein interaction (PPI) network, each node represented a protein, and each edge indicated a physical or theoretical interaction between two proteins in the network.

Search strategy for literature on GSTM1 and GSTT1. Searches for original publications were performed in PubMed, Scopus and Web of Science (https://www.webofknowledge.com/) databases with a cut-off date of December 25, 2018. The process was performed using the PICO strategy (27). The PICO in this study was set as follows: Population (P), tuberculosis patient; Intervention (I), GSTM1 or GSTT1 polymorphisms; Comparator (C), gene deletion and wild type; and Outcomes (O), liver injury or hepatotoxicity. The search strategies were constructed by combining search terms using Boolean operators, including ‘OR’ within the same domain and ‘AND’ amongst domains (28).

Study selection for meta-analysis of GSTM1 and GSTT1. For inclusion of a study, it had to satisfy the specific inclusion and exclusion criteria. The inclusion criteria were: i) case-control or cohort study investigating the association between GSTM1 or GSTT1 and susceptibility to ATDILI susceptibility; and ii) study participants were patients with TB receiving isoniazid, rifampicin, pyrazinamide or ethambutol. The exclusion criteria were: i) case report, secondary or tertiary publications including reviews, systematic review and meta-analysis; ii) articles not available in English; iii) studies using healthy volunteers as the control group; iv) studies using a duplicated set of subjects and/or data; and v) studies which included participants with confounding factors of hepatotoxicity, including those co-infected with hepatitis virus or human immunodeficiency virus, excessive consumption of alcoholic beverages or concomitant administration of other potential hepatotoxic medication.

Assessment of the quality of the study. To assess the quality of each study, two reviewers independently evaluated the quality of the publications according to the Newcastle-Ottawa scale (29). The score from the Newcastle-Ottawa scale ranges from 0-9. Publications were included and designated as ’pass’ if the publication assessment score was >5.

Data extraction for meta-analysis. Data from all the eligible studies were extracted into a data sheet. The following data were extracted: First author, publication year, study design, ethnicity, sample size, sex, age, body mass index (BMI), observed medication and the number of cases/controls for each GST (M1, T1 and M1/T1) genotype with their odds ratio (OR) and 95% confidence intervals (CI). If any disagreement between data extraction results by two reviewers were revealed, it was resolved by discussion and consensus with a third reviewer.

Statistical analysis. The extracted data such as age and BMI are presented as the mean. Meta-analysis of the effects of
**Results**

**Genes associated with ATDILI.** A total of 973 studies were obtained from PubMed and Scopus databases based on the aforementioned search criteria. Of these, 91 were duplicates and excluded. Subsequent to refining the data using the exclusion criteria, 788 publications were excluded as follows: irrelevant (n=695); studies in non-human models (n=54); secondary publications (n=30); and studies where healthy volunteers were used as the control group (n=9). Therefore, 94 publications were included in this analysis. However, only 77 publications identified a statistically significant gene associated with ATDILI. There were 94 reports of genes in the 77 publications. The top five most frequently reported genes were NAT2 (35 reports), CYP2E1 (14 reports), GSTM1 (10 reports), GSTT1 (4 reports) and solute carrier organic anion transporter family member 1B1 (SLCO1B1; 4 reports) (Fig. 1).

The PPI analysis of these five genes revealed interactions amongst GSTM1, GSTT1, CYP2E1 and NAT2. Interestingly, according to STRING analysis, associations between GSTM1 or GSTT1 with CYP2E1 or NAT2 enzymes were observed in the PPI network (Fig. 2).

**Study selection for meta-analysis of the association between GSTM1 or GSTT1 with ATDILI.** The selection process of the included studies is illustrated in Fig. 3. Initially, a total of 278 publications were used, and 15 publications were selected with 905 cases of ATDILI from a total of 3,785 patients with...
TB. All included publications were qualified according to the Newcastle-Ottawa scale for case-control and cohort studies.

**Study characteristics of the meta-analyses.** The studies used were published between 2001 and 2018 and are presented in Table I. The majority of the studies were performed on East Asian (9,12,18,20,21) and South Asian (7,8,10,14-17) patients. Other studies were performed on South East Asian (13), South American (19) and European patients (11).

**Meta-analysis of results.** The associations between GSTM1, GSTT1 and GSTM1/GSTT1 dual-deletions with the susceptibility of ATDILI in patients with TB are summarized in Figs. 4–6. The results suggested that GSTM1 was significantly associated with a susceptibility of ATDILI with an OR of 1.28 (95% CI, 1.08-1.51; P<0.05; Fig. 4). However, there was no significant difference between the cases and controls on the influence of the dual gene deletions, the deletion of GSTT1 (Fig. 5) or GSTM1/GSTT1 (Fig. 6).

**Meta-analysis sensitivity, heterogeneity and publication bias analyses.** Sensitivity analysis was performed by removing a single study at a time to assess the effect of each study on the overall estimate. The results demonstrated that the meta-analysis of the GSTM1 deletion genotype passed the sensitivity analysis. Heterogeneity was not observed in the GSTM1 deletion genotype studies (data not shown). Subgroup analysis was used to explain the heterogeneity by subgrouping the studies according to ethnicity as follows; East Asian, South Asian and South East Asian (Fig. 7). Publication bias
Table I. Main characteristics of the eligible publications in the present updated meta-analysis.

| Author, year | Ethnicity          | Study design | Sample size case/control | Sex (male/female) | Age (mean) | BMI (mean) | (Refs.) |
|--------------|--------------------|--------------|--------------------------|-------------------|------------|------------|---------|
|              |                    |              | Case | Control | Total | Case | Control | Case | Control | Case | Control | (Refs.) |
| Perwitasari et al 2018 | South East Asian | Cohort | 136 | 71 | 207 | NA | NA | NA | NA | (13) |
| Xiang et al 2014 | East Asian | Cohort | 89 | 1,858 | 1,947 | 60/29 | 1,012/846 | 37 | 46 | 20.3 | 21.4 | (21) |
| Singla et al 2014 | South Asian | Cohort | 17 | 391 | 408 | 11/7 | 241/150 | 48 | 33 | NA | NA | (17) |
| Sharma et al 2014 | South Asian | Cohort | 113 | 201 | 314 | 63/50 | 145/56 | 28 | 35 | 17.1 | 17.1 | (16) |
| Rana et al 2014 | South Asian | Case-control | 50 | 245 | 295 | 33/22 | 152/93 | 44 | 42 | 19.23 | 23.1 | (14) |
| Liu et al 2014 | East Asian | Case-control | 20 | 143 | 163 | 12/8 | 85/58 | 4 | 6 | NA | NA | (12) |
| Gupta et al 2013 | South Asian | Case-control | 50 | 246 | 296 | 24/26 | 139/107 | 37 | 37 | 21.0 | 21.0 | (8) |
| Tang et al 2012 | East Asian | Case-control | 89 | 356 | 445 | 65/24 | 260/96 | 44 | 44 | 19.5 | 19.4 | (18) |
| Teixeira et al 2011 | South American | Case-control | 26 | 141 | 167 | 16/10 | 74/67 | 48 | 43 | NA | NA | (19) |
| Wang et al 2010 | East Asian | Case-control | 104 | 111 | 215 | 70/34 | 75/36 | 49 | 45 | 19.8 | 20.2 | (20) |
| Kim et al 2010 | East Asian | Case-control | 57 | 190 | 247 | 34/27 | 129/61 | 47 | 42 | NA | NA | (10) |
| Chatterjee et al 2010 | South Asian | Case-control | 51 | 100 | 151 | 25/26 | 63/37 | 37 | 33 | 16.2 | 17.5 | (7) |
| Leiro et al 2008 | European | Case-control | 35 | 60 | 95 | 14/21 | 25/35 | 34 | 31 | 23.1 | 22.1 | (11) |
| Huang et al 2007 | East Asian | Case-control | 63 | 63 | 126 | 42/22 | NA | 62 | NA | NA | NA | (9) |
| Roy et al 2001 | South Asian | Case-control | 33 | 33 | 66 | 15/18 | NA | 30 | NA | NA | NA | (15) |

NA, Not Available; BMI, body mass index.
was investigated using a funnel plot. In the funnel plots, a condensed plot presented at the top of the 95% CI triangle indicated a publication bias for studies with a large number of enrolled patients. However, the plots were symmetrical between each of the sides within the triangle which demonstrated that publication bias was not revealed to be a negative or positive result.

Results of subgroup meta-analysis. The subgroup analyses based on the ethnicity of patients with TB were performed for the \textit{GSTM1} gene deletion (Fig. 7). The results demonstrated that the \textit{GSTM1} deletion was significantly associated with ATDILI in South Asian patients with an OR of 1.48 (95% CI, 1.12-1.95; P<0.01). On the contrary, there was no significant association between \textit{GSTM1} with ATDILI in any of the other ethnicities.

Discussion

Despite extensive research efforts, current understanding of the mechanisms which regulate the progression of hepatotoxicity progression during the treatment of TB remains unclear. As such, the majority of the patients with hepatotoxicity induced by anti-TB drugs will develop end-stage liver injury due to a lack of reliable and specific biomarkers for ATDILI (32). Genetic variations associated with ATDILI have been extensively studied, and may be used as genetic biomarkers for identifying patients who may be at increased risk of ATDILI, prior to the prescription of therapeutics which may aggravate the risk (33). In the present analysis, previous studies on the association of genetic variations in patients with ATDILI were analysed and the top five most frequently reported genes were \textit{NAT2}, \textit{CYP2E1}, \textit{GSTM1}, \textit{GSTT1} and \textit{SLCO1B1}.
In addition, PPI network analysis of these genes illustrated that there were direct links between NAT2, CYP2E1, GSTM1 and GSTT1 enzymes, and GSTs were indicated as serving as a key molecule in this PPI network. Supporting this hypothesis, alternative results from a PPI network delineated that GSTM1 was functionally associated with CYP2E1 and GSTT1 in drug metabolism in Kyoto Encyclopedia of Genes and Genomes pathway analysis (34) and was frequently reported alongside the NAT2 enzyme in numerous studies (8,14,17). Based on the metabolism pathway of isoniazid, NAT2, CYP2E1, GSTM1 and GSTT1 enzymes functionally associate with each other to metabolize isoniazid, and GSTM1 and GSTT1 enzymes

Figure 6. Forest plot comparison between GSTM1/GSTT1 dual-deletion and presence and the susceptibility of ATDILI from 8 publications. CI, confidential interval; M-H, Mantel-Haenszel; ATDILI, antituberculosis drug-induced liver injury; GSTM1, glutathione S-transferase μ1; GSTT1, glutathione S-transferase 01.

Figure 7. Asian ethnicity subgroup analysis forest plot comparison between GSTM1 deletion and normal and the susceptibility of ATDILI from 13 publications and 3 Asian ethnicities. CI, confidential interval; M-H, Mantel-Haenszel; ATDILI, antituberculosis drug-induced liver injury; GSTM1, glutathione S-transferase μ1.
function to detoxify the toxic metabolites formed following the metabolism of isoniazid by NAT2 and CYP2E1 (35). Based on the data on the genes associated with ATDILI NAT2, CYP2E1, GSTM1 and GSTT1, polymorphisms of these genes may together contribute to the risk of ATDILI. Thus, further investigation is required to determine the effects of polymorphisms of these genes, and how they may contribute to the risk of ATDILI. To the best of our knowledge, there are no publications which have investigated the influence of the multi-genetic contribution on the risk of ATDILI. Therefore, the present study was not able to perform a meta-analysis to demonstrate the association of the multi-gene effect on the risk of ATDILI. A meta-analysis was performed to verify the association between polymorphisms of GSTM1 and GSTT1 and ATDILI risk. There was an association between a GSTM1 null genotype with an increased risk of ATDILI in patients with TB. This result supports the hypothesis that genetic variation in genes encoding proteins responsible for managing oxidation may increase the risk of ATDILI, and genetic polymorphisms of GSTM1 and GSTT1 may serve as novel genetic markers for predicting which patients with TB are at a higher risk of ATDILI.

As the GST enzymes are fundamental for the elimination of ROS through the conjugation of glutathione to substrates including xenobiotics and ROS (4), it is not surprising that they exert protective effects on numerous different types of cells from the oxidative stress induced by anti-TB drugs, and an absence of GST activity leaves the liver more susceptible to ATDILI (2). The two major GST enzymes which conjugate isoniazid metabolites are GSTM1 and GSTT1, and an absence of their activity caused by homozygous null mutations has been implicated in liver injury owing to a lack of protection from oxidant species (5). Supporting this, the results of the present meta-analysis revealed that a null GSTM1 genotype was significantly associated with a higher risk of ATDILI (P<0.05), in agreement with a number of previous meta-analyses (5,6,21-23). Previously, GSTM1 was reported to be significantly correlated with a susceptibility to develop ATDILI only in East Asian individuals, although in the present analysis, an association between GSTM1 polymorphisms and South Asian individuals was observed. The reason for this inconsistency is unknown, but may be attributed to the lesser number of included publications due to the more stringent inclusion and exclusion criteria. Therefore, further investigation is required to determine the association between GSTM1 deletion and ATDILI risk in East Asian, South East Asian, Caucasian and African individuals.

It has been demonstrated that the homozygous null mutation of GSTT1 may result in the loss of detoxification activity of hepatotoxic reactive metabolites in hepatocytes (36). Thus, it seems plausible that a GSTT1 null genotype may result in an increased risk of ATDILI. Nonetheless, in the present study, no significant association between a null GSTT1 genotype and ATDILI was observed, consistent with previous meta-analyses (6,22-24). A potential explanation for this result may be due to the small sample sizes. In the present study, although 905 ATDILI cases and 2,880 controls were pooled, the number of subjects was still insufficient. Tang et al (6) suggested that a cohort of >10,000 patients is required to determine the significance of a polymorphism when the risk of a polymorphism is moderate (37). Alternatively, Bao et al (4) illustrated that there are multiple factors, including genetic and environmental factors, which influence the pathogenesis of ATDILI. In the present analysis, confounding environmental factors including viral hepatitis, HIV infection and alcohol consumption were excluded, but other factors including age, sex and BMI were included, which may have thus resulted in an inaccurate association. Altogether, it was not possible to ascertain whether a null GSTT1 genotype was associated with the risk of ATDILI, for which a multi-centre genetic association study with larger sample sizes and well-characterized subjects is required.

Whether combined GSTM1 and GSTT1 null genotypes are associated with an elevated risk of ATDILI remains yet to be determined. Lucena et al (38) focused on investigating the potential association between a combination of GSTM1 and GSTT1 polymorphisms with DILI and demonstrated a significant association between GSTM1 and GSTT1 dual-null polymorphisms and an increased risk of ATDILI. In the present analysis, no significant association between GSTM1/GSTT1 dual-null genotypes and ATDILI risk was observed. This contrasting result may be attributable to differences in the pathophysiology of hepatotoxicity, ethnicity and the type of drugs prescribed between studies. Supporting the observation that there was no association between GSTM1/GSTT1 dual-null genotypes and ATDILI risk, Ginsberg et al (39) investigated the genotypic frequency and distribution of GSTM1 and GSTT1 null genotypes in a wide spectrum of the human populations, and they revealed that GSTM1 or GSTT1 null genotypes were highly prevalent in Asian patients compared with GSTM1/GSTT1 dual-null polymorphisms.

If there is a direct link between a null GSTM1 genotype and an increased risk of ATDILI in patients with TB, it may be hypothesized that a homozygous deletion of GSTM1 results in a loss of GSTM1 enzyme activity contributing to the pathogenesis of hepatotoxicity influenced by anti-TB drugs. Hepatotoxicity induced by anti-TB drugs, particularly isoniazid, is mediated through toxic intermediaries, including hydrazine and acetyldiazine, in addition to ROS (40,41). An increase in ROS production results in increased oxidative stress, which in turn induces organ failure, particularly of the liver (40), in which NAT2 and CYP2E1 have been revealed to be responsible for a biotransformation pathway of isoniazid-induced increased ROS generation (34). In a NAT2- and CYP2E1-mediated detoxification of an isoniazid-mediated increase in ROS levels, GST enzymes are known to serve a protective function against oxidative stress-induced cellular injury (4), suggesting that GSTs may serve a function in the detoxification of anti-TB drugs. This hypothesis is supported by the results from the PPI network analysis, in which a functional association between GSTs with NAT2 and CYP2E1 was observed, and the centrality of GST enzymes in the interactions between molecules was established. Although results from the present meta-analysis along with PPI network analysis provide support for an association between GSTM1 deletion and an increased risk of ATDILI in patients with TB, the function of genetic variations of GSTs genes and the risk of ATDILI remains yet to be determined, and additional research is required to determine their function in the detoxification of oxidative intermediates which results from the metabolism of anti-TB drugs.
There are certain limitations in the present study. The major limitation of the present study is that it only illustrated the association of ATDILI with GSTT1 polymorphisms using the previous case-control and cohort study results; however, the exact function of GSTT1 in the pathogenesis of ATDILI was unable to be determined. To address the cause and effect association, further experimental studies using in vivo models need to be performed. Another limitation is that the present study only included publications which were published in the English language, thus a language bias was unavoidable. In addition, pooling data from different types of study designs, including case-controlled and cohort studies, may provide a higher number of studies compared with previous meta-analyses; however, these may contribute to significant heterogeneity. On the other hand, the strength of the present study is that all publications with confounding factors were excluded to better mitigate the effect of the confounding factors, providing more reliable results.

In conclusion, the meta-analysis revealed that a GSTM1 null genotype was significantly associated with the susceptibility of ATDILI, particularly in South Asian individuals. However, there was no association between a null GSTT1 or a dual-null GSTM1/GSTT1 genotype and risk of ATDILI. STRING analysis revealed that GSTs interact with other proteins associated with ATDILI, including NAT2 and CYP2E1, and thus may exert a protective function. Additional studies are required with larger sample sizes, well-characterized subjects and various ethnicities including South East Asian, Caucasian and African individuals to draw a more precise conclusion and support the use of these genetic markers for predicting the risk of ATDILI in patients with TB.

Acknowledgements

The authors would like to thank The International Research Network team for their grant, encouragement, and technical support and Dr Supharat Suvichapanich (Department of Biochemistry, Faculty of Pharmacy, Mahidol University) and Mrs. Saowalak Turongkaravee (Department of Pharmacy, Faculty of Pharmacy, Mahidol University) for their constructive comments and suggestions.

Funding

The present study was supported by The International Research Network of The Thailand Research Fund (grant no. IRN60W003) and Medical Scholar Program of Mahidol University (Thailand).

Availability of data and materials

The data analysed and generated during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JJ, UC, SM and SW conceived and designed the study. NC and WU performed literature review. NC retrieved the data. JJ and NC reviewed the assessment of the quality of the study. NC performed the meta-analyses. NC, JJ, and WU wrote the manuscript. All authors edited and revised the manuscript. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Tothmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ and Dekhuijzen R: Antituberculosis drug-induced hepatotoxicity: Concise up-to-date review. J Gastroenterol Hepatol 23: 192-202, 2008.
2. Ramappa V and Aithal GP: Hepatotoxicity related to anti-tuberculosis drugs: Mechanisms and management. J Clin Exp Hepatol 3: 37-49, 2013.
3. Clare KE, Miller MH and Dillon JF: Genetic factors influencing drug-induced liver injury: Do they have a role in prevention and diagnosis? Curr Hepatol Rep 16: 258-264, 2017.
4. Bao Y, Ma X, Rasmussen TP and Zhong XB: Genetic variations associated with anti-tuberculosis drug-induced liver injury. Curr Pharmaco Rep 4: 171-181, 2018.
5. Eaton DL and Bammler TK: Concise review of the glutathione S-transferases and their significance to toxicology. Toxicol Sci 49: 156-164, 1999.
6. Tang N, Deng R, Wang Y, Lin M, Li H, Qiu Y, Hong M and Zhou G: GSTM1 and GSTT1 null polymorphisms and susceptibility to anti-tuberculosis drug-induced liver injury: A meta-analysis. Int J Tuberc Lung Dis 17: 17-25, 2013.
7. Chatterjee S, Lyle N, Mandal A and Kundu S: GSTT1 and GSTM1 gene deletions are not associated with hepatotoxicity caused by antitubercular drugs. J Clin Pharm Ther 35: 465-470, 2010.
8. Gupta VH, Singh M, Amarapurkar DN, Sasi P, Joshi JM, Bajjal R, H R PK, Amarapurkar AD, Joshi K and Wangikar PK: Association of GST null genotypes with anti-tuberculosis drug induced hepatotoxicity in western Indian population. Ann Hepatol 12: 959-965, 2013.
9. Huang YS, Su WJ, Huang YH, Chen CY, Chang FY, Lin HC and Lee SD: Genetic polymorphisms of manganese superoxide-dismutase, NAD(P)H: Quinone oxidoreductase, glutathione S-transferase M1 and T1, and the susceptibility to drug-induced liver injury. J Hepatol 47: 128-134, 2007.
10. Kim SH, Kim SH, Yoon HJ, Shin DH, Park SS, Kim YS, Park JS and Jee YK: GSTT1 and GSTM1 null mutations and adverse reactions induced by antituberculosis drugs in Koreans. Tuberculosis (Edinb) 90: 39-43, 2010.
11. Leiro V, Fernandez-Villar A, Valverde D, Constenla L, Vázquez R, Piñeiro L and Gonzalez-Quintela A: Influence of glutathione S-transferase M1 and T1 homozygous null mutations on the risk of antituberculosis drug-induced hepatotoxicity in a Caucasian population. Liver Int 28: 835-839, 2008.
12. Liu P, Jian AX, Wu XR, Zhao W, Yin QQ, Qi H, Jiao WW, Xiao J, Sun L, Shen C, et al: Impact of glutathione S-transferase M1 and T1 on anti-tuberculosis drug-induced hepatotoxicity in Chinese pediatric patients. PLoS One 9: e135410, 2014.
13. Perwitasari DA, Darmawan E, Mulyani UA, Vlies PV, Alfenaar JC, Anthobar J and Willfert B: Polymorphisms of NAT2, CYP2E1, GST, and HLA related to drug-induced liver injury in Indonesian tuberculosis patients. Int J Mycobacteriology 7: 380-386, 2018.
14. Rana SV, Sharma SK, Ola RP, Kamboj JK, Malik A, Morya KK and Sinha SK: N-Acetyltransferase 2, cytochrome P4502E1, and glutathione S-transferase genotypes in antitubercular treatment-induced hepatotoxicity in North Indians. J Clin Pharm Ther 39: 91-96, 2014.
15. Roy B, Chowdhury A, Kundu S, Santra A, Dey B, Chakraborty M and Majumder PP: Increased risk of antituberculosis drug-induced hepatotoxicity in individuals with glutathione S-transferase M1 'null' mutation. J Gastroenterol Hepatol 16: 1033-1037, 2001.

16. Sharma SK, Jha BK, Sharma A, Sreenivas V, Upadhyay V, Jaisinghani C, Singla R, Mishra HK and Soneja M: Genetic polymorphisms of CYP2E1 and GSTM1 loci and susceptibility to anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 18: 588-593, 2014.

17. Singla N, Gupta D, Birbhan N and Singh J: Association of NAT2, GST and CYP2E1 polymorphisms and anti-tuberculosis drug-induced hepatotoxicity. Tuberculosis (Edinb) 94: 293-298, 2014.

18. Tang SW, Lv XZ, Zhang Y, Wu SS, Yang ZR, Xia YY, Tu DH, Deng PY, Ma Y, Chen DF and Zhan S: CYP2E1, GSTM1 and GSTT1 genetic polymorphisms and susceptibility to antituberculosis drug-induced hepatotoxicity: A nested case-control study. J Clin Pharm Ther 37: 588-593, 2012.

19. Teixeira RL, Morato RG, Cabello PH, Muniz LM, Moreira Ada S, Kritski AL, Mello FC, Safiys PN, Miranda AB and Santos AR: Genetic polymorphisms of NAT2, CYP2E1 and GST enzymes and the occurrence of antituberculosis drug-induced hepatitis in Brazilian TB patients. Mem Inst Oswaldo Cruz 106: 716-724, 2011.

20. Wang T, Yu HT, Wang W, Pan YY, He LX and Wang ZY: Genetic polymorphisms of cytochrome P450 and glutathione S-transferase associated with antituberculosis drug-induced hepatotoxicity in Chinese tuberculosis patients. J Int Med Res 38: 977-986, 2010.

21. Xiang Y, Ma L, Wu W, Liu Y, Li Y, Zhu X, Wang Q, Ma J, Cao M, Wang Q, et al: The incidence of liver injury in uygur patients treated for TB in xinjiang uygur autonomous region, China, and its association with hepatic enzyme polymorphisms NAT2, CYP2E1, GSTM1 and GSTT1. PLoS One 9: e85905, 2014.

22. Cai Y, Yi J, Zhou C and Shen X: Pharmacogenetic study of drug-metabolising enzyme polymorphisms on the risk of anti-tuberculosis drug-induced liver injury: A meta-analysis. PLoS One 7: e47769, 2012.

23. Li C, Long J, Hu X and Zhou Y: GSTM1 and GSTT1 genetic polymorphisms and risk of anti-tuberculosis drug-induced hepatotoxicity: An updated meta-analysis. Eur J Clin Microbiol Infect Dis 32: 859-863, 2013.

24. Sun F, Chen Y, Xiang Y and Zhan S: Drug-metabolising enzyme polymorphisms and predisposition to anti-tuberculosis drug-induced liver injury: A meta-analysis. Int J Tuberc Lung Dis 12: 994-1002, 2008.

25. Cai L, Cai MH, Wang MY, Xu XY, Chen WZ, Qin SY, Wan CL and He L: Meta-analysis-based preliminary exploration of the connection between ATDIII and schizophrenia by GSTM1/T1 gene polymorphisms. PLoS One 10: e0128643, 2015.

26. Szklarczyk D, Franceschini A, Wyder S, Forslund K, Heller D, Huerta-Cepas J, Simonovic M, Roth A, Santos A, Tsafou KP, et al: STRING v10: Protein-protein interaction networks, integrated over the tree of life. Nucleic Acids Res 43: D447-D452, 2015.

27. Aslam S and Emmanuel P: Formulating a researchable question: A critical step for facilitating good clinical research. Indian J Sex Transm Dis AIDS 31: 47-50, 2010.

28. Grewal A, Kataria H and Dhawan I: Literature search for research planning and identification of research problem. Indian J Anaesth 60: 635-639, 2016.

29. Wells G, Shea B, O’Connell D, Robertson J, Peterson J, Welch V, Losos M and Tugwell P: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute, 2019.

30. Higgins JP and Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med 21: 1539-1558, 2002.

31. Higgins JP, Thompson SG, Deeks JJ and Altman DG: Measuring inconsistency in meta-analyses. BMJ 327: 557-560, 2003.

32. McGill MR and Jaeschke H: Biomarkers of drug-induced liver injury: Progress and utility in research, medicine, and regulation. Expert Rev Mol Diagn 18: 797-807, 2018.

33. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, Pelouquin CA, Gordin FM, Nunes D, Strader DB, et al: An official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 174: 935-952, 2006.

34. Kanehsa M and Goto S: KEGG: Kyoto encyclopedia of genes and genomes. Nucleic Acids Res 28: 27-30, 2000.

35. Wang P, Pradhan K, Zhong XB and Ma X: Isoniazid metabolism and hepatotoxicity. Acta Pharm Sin B 6: 384-392, 2016.

36. Roy PD, Majumder M and Roy B: Pharmacogenomics of anti-TB drugs-related hepatotoxicity. Pharmacogenomics 9: 311-321, 2008.

37. Ioannidis JP, Trikalinos TA and Khoury MJ: Implications of small effect sizes of individual genetic variants on the design and interpretation of genetic association studies of complex diseases. Am J Epidemiol 164: 609-614, 2006.

38. Lucena MI, Andrade RJ, Martínez C, Ullzurrun E, García-Martín E, Borraz Y, Fernández MC, Romero-Gomez M, Castiella A, Planas R, et al: Glutathione S-transferase ml and t1 null genotypes increase susceptibility to idiosyncratic drug-induced liver injury. Hepatology 48: 588-596, 2008.

39. Ginsberg G, Smolenski S, Hattis D, Guyton KZ, Johns DO and Sonawane B: Genetic polymorphism in glutathione transferases (GST): Population distribution of GSTM1, T1, and P1 conjugating activity. J Toxicol Environ Health B Crit Rev 12: 389-439, 2009.

40. Chowdhury A, Santra A, Bhattacharjee K, Ghatak S, Saha DR and Dhali GK: Mitochondrial oxidative stress and permeability transition in isoniazid and rifampicin induced liver injury in mice. J Hepatol 45: 117-126, 2006.

41. Zhai Q, Lu SR, Lin Y, Yang QL and Yu B: Oxidative stress potentiated by diallylsulfide, a selective CYP2E1 inhibitor, in isoniazid toxic effect on rat primary hepatocytes. Toxicol Lett 183: 95-98, 2008.