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Pharmacogenomic insights into tuberculosis treatment shows the NAT2 genetic variants linked to hepatotoxicity risk: a systematic review and meta-analysis

Rashmi Mahajan[1] and Anuj Kumar Tyagi[1*]

Abstract

Background Tuberculosis (TB) patients undergoing anti-tuberculosis treatment often face serious adverse drug reactions, such as hepatotoxicity. Genetic variants of the N-acetyltransferase 2 (NAT2) gene have been linked to an increased risk of these toxic events.

Objective This study aims to provide a comprehensive evaluation of the evidence linking NAT2 genetic variants to anti-tuberculosis drug-related hepatotoxicity (ATDH).

Method A comprehensive review and meta-analysis was performed by accessing databases such as PubMed, Scopus, and Web of Science. A total of 24 articles were incorporated into the dataset. Meta-analyses were conducted to gather estimates of the association between the slow acetylators (SA) genotype and ATDH. The studies were stratified by ethnicity, regimen, genotyping methods, criteria for liver toxicity, and dosage. Also, meta-analysis for the specific SA type that was most likely responsible for the ATDH was also conducted.

Results The included studies showed individuals with a slow NAT2 acetylator had a significantly greater risk of experiencing hepatotoxicity ATDH (odds ratio [OR] 2.52 (95% CI: 1.95–3.27; p value < 0.001) compared to individuals with other types of acetylator (i.e., rapid and immediate). Among individuals with slow acetylator NAT2*5/7, NAT2*5/6, and NAT2*6/6 genotypes, there is a greater likelihood of association compared to other variations.

Conclusion Our meta-analysis confirms a significant association between slow NAT2 acetylator and increased hepatotoxicity risk. The findings from the present underscore the potential of pharmacogenomic testing to improve TB treatment outcomes. By identifying patients with the slow acetylator NAT2 genotype, healthcare providers can predict an increased risk of anti-tuberculosis drug-induced hepatotoxicity. This allows for personalized treatment strategies, such as adjusting drug dosages or selecting alternative therapies, to minimize adverse effects and optimize efficacy.

Keywords N-acetyltransferase2, NAT2, Isoniazid, INH, Tuberculosis, TB, Personalised therapy, Anti-tuberculosis drug induced hepatotoxicity, ATDH

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Introduction

Mycobacterium tuberculosis, the cause of tuberculosis (TB), continues to pose a significant global health concern, leading to substantial morbidity and mortality [1]. In 2022, TB was the second most common cause

of mortality worldwide, after COVID-19, and caused nearly twice as many deaths as HIV/AIDS, despite its preventable and curable nature [2]. In 2022, the World Health Organisation (WHO) reported that over 10 million individuals contracted TB, with 87% of cases occurring in thirty high-burden countries [2]. Eight countries accounted for two-thirds of the global TB cases: India (27%), Indonesia (10%), China (7.1%), the Philippines (7.0%), Pakistan (5.7%), Nigeria (4.5%), Bangladesh (3.6%), and the Democratic Republic of the Congo (3.0%) [2]. The disease disproportionately affected men (55%), followed by women (33%), and children (aged 0–14 years) (12%) [2].

Given the widespread impact of TB, particularly in high-burden countries where two-thirds of global cases were observed, a standardized six-month treatment regimen is employed; comprised of two-month course of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB), followed by a four-month course of INH and RMP [3]. This regimen is the standard treatment for tuberculosis. But there are some problems with treating TB, such as the rise of multidrug-resistant tuberculosis (MDR-TB), acquired immunodeficiency, and ATDH [4]. An estimated 410,000 individuals contracted MDR-TB in 2022 [2]. Adverse effects, such as ATDH, significantly influence non-adherence, leading to treatment failure, relapse, and the development of drug resistance [5]. It is essential to adhere to the prescribed treatment in order to cure TB; however, the extended treatment period frequently poses a challenge to patient motivation, particularly when they begin to feel better [3]. This leads to treatment interruptions, and the need to transition to second-line anti-tuberculosis drugs pharmaceuticals may result in suboptimal treatment responses [3]. These issues are compounded by various factors, including drug formulation, patient characteristics such as age, sex, and weight, and comorbidities, all of which influence the pharmacokinetic variability of INH and RMP [6, 7].

Furthermore, the pharmacogenetic variability in genes that encode drug metabolism and transport proteins further exacerbates this uncertainty [4, 8]. ATDH has been associated with drug-metabolising enzymes in research [5]. Genetically polymorphic enzymatic systems, including cytochrome P450 2E1 (CYP2E1), N-acetyltransferase 2 (NAT2), and glutathione S-transferase (GST), contribute to significant interindividual variations in drug metabolism and adverse effects [9]. (Fig. 1).

The NAT2 enzyme, characterised by significant variation among individuals due to genetic variability, primarily metabolises INH, an essential medicine in the TB treatment regimen with bactericidal characteristics [11]. Between 75 and 95% of the isoniazid (INH) is excreted by the kidneys within the first 24 h [12]. This excretion mainly occurs in the form of acetyl-isoniazid and isonicotinic acid, which are metabolic by-products. Isoniazid (INH) undergoes metabolic transformation by NAT2 within the liver, leading to the synthesis of acetylisoniazid (AcINH) [13]. Afterwards, AcINH undergoes hydrolysis to become acetylhydrazine (AcHZ), which is then oxidised by cytochrome CYP2E1 to generate hepatotoxic intermediates [14]. These metabolites can cause injury to liver cells, specifically hepatocytes, by disturbing their normal equilibrium or by triggering immunological responses [15]. During these immunological reactions, the metabolites that are connected to proteins in the plasma of hepatocytes can function as haptens [15]. Another metabolic pathway for the synthesis of detrimental metabolites involves the enzymatic conversion of INH to hydrazine, a highly toxic compound that has the potential to induce liver

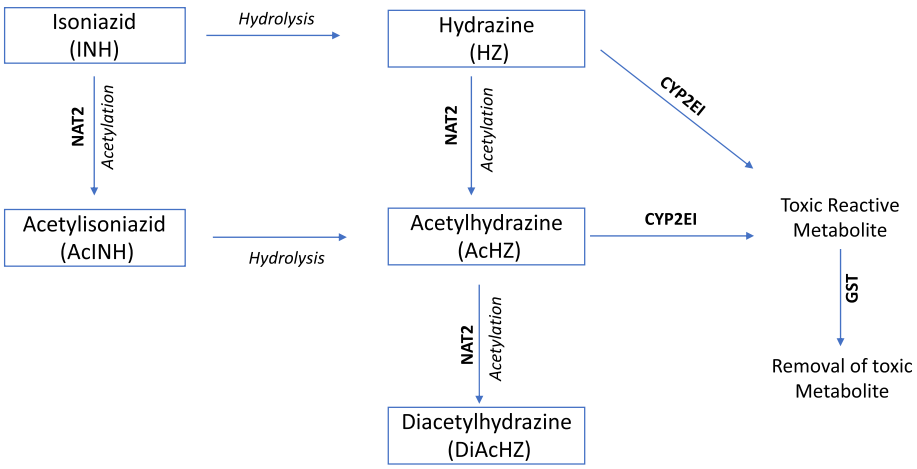

Fig. 1 Schematic representation of the INH metabolism and role of NAT2 enzymes [10]

injury [13]. NAT2 is responsible for the enzymatic conversion of AcHZ into diacetylhydrazine (DiAcHZ), a non-toxic compound [10]. GST, an essential phase II detoxifying enzyme, is thought to serve as an intracellular scavenger of free radicals, providing a protective role [10]. This is achieved by merging glutathione with detrimental metabolites generated by CYP2E1 [10]. Sulphydryl conjugation increases the elimination of metabolites from the body and reduces their detrimental effects [10]. Inadequate exposure to INH, which is directly linked to the concentration of medication, can lead to treatment failure and the emergence of drug resistance [13, 14].

Individuals can be classified as rapid, intermediate, or slow acetylators (SA) based on NAT2 mutations. SA break down isoniazid and acetylhydrazine, the immediate precursors of hazardous intermediates, more slowly, resulting in a slower rate of conversion to the harmless product diacetylhydrazine [13]. This protective acetylation process is further impeded by competition from INH [13]. Furthermore, direct hydrolysis of unacetylated INH produces hydrazine, which can similarly damage the liver, and is an important mechanism for producing hazardous intermediates [16]. Consequently, SA might be more likely to accumulate INH hazardous metabolites at a faster rate [13]. Pharmacokinetic studies also showed that the serum concentration of hydrazine was significantly higher in SA than in rapid acetylators, probably due to the high INH concentration [6, 8, 14] All of these drug-disposal processes may support the finding that SA are prone to INH-induced liver toxicity.

In this meta-analysis, our objective is to offer a comprehensive comprehension of the correlation between NAT2 genetic polymorphisms and INH-induced hepatotoxicity through the examination of data from studies conducted in diverse regions of the globe. This global perspective will improve our understanding of the pharmacogenetic variability in TB treatment and facilitate the development of personalised medicine approaches to reduce adverse effects and improve treatment outcomes.

Materials and methods

A comprehensive review of the literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. By employing a search strategy and study selection process, research studies examining the correlation between ATDH and any genetic variant were successfully identified. Nevertheless, the scope of this article is restricted to the subset of studies that examined NAT2 variants.

Search strategy

The search strategy involved utilizing the following terms and conditions to identify studies:

("N-acetyltransferase 2" OR "NAT 2" OR "NAT2" OR "N-acetyltransferase2").
AND ("Isoniazid" OR "INH").
AND ("Anti-tuberculosis" OR "Therapeutic" OR "Anti-tuberculosis treatment").
AND ("Personalized therapy" OR "Treatment" OR "Precision medicine" OR "Therapy").

The databases PubMed, Web of Science, and Scopus were searched queried for relevant articles. The search was performed in English and spanned the time period from the earliest study conducted in 2000 to February 2024.

Study selection

The search results were imported to Zotero. We removed duplicates, and both authors (R.M. and A.K.T.) evaluated the relevance of titles and abstracts and examined the complete texts to determine their suitability for inclusion in accordance with the selection criteria. Justifications were provided for the exclusion of studies. Manual searching was conducted independently by both the authors through the reference lists of pertinent review articles and additional studies that were not retrieved through the search strategy.

Selection criteria

Inclusion criteria

This study included the research with only case–control design where the cases consisted of tuberculosis patients with hepatotoxicity and the controls were tuberculosis patients without hepatotoxicity. The focus was exclusively on patients diagnosed with tuberculosis who had started anti-tuberculosis treatment. The studies were needed to involve the administration of INH alone or in combination with other drugs such as RMP, PZA, or EMB. Studies were considered if they assessed drug-related toxicity outcomes, with hepatotoxicity being the primary outcome. Additionally, studies also needed to include information on kidney profile tests such as AST, ALT, bilirubin, or other indicators of liver toxicity. Research papers that provided data on NAT2 variants, were included in the inclusion criteria for this study. Additionally, the studies needed to sufficient provide genotype distribution information sufficient to calculate the odds ratio (OR) and 95% confidence interval (CI). Almost all of the Studies included were with subjects were newly diagnosed and on treatment for pulmonary TB and all Patients were seen at regular intervals and

were questioned about their symptoms and adverse reactions to anti-tuberculosis drugs.

Exclusion criteria

Studies were excluded if they involved patients who received INH for conditions other than tuberculosis, such as other mycobacterial infections. Research focusing on infants and children was excluded. Children with tuberculosis often receive different dosing regimens compared to adults due to variations in drug metabolism and body size, which can impact the pharmacokinetics and toxicity profile of anti-TB medications. Since drug-induced hepatotoxicity may manifest differently in pediatric populations, we excluded child data to focus specifically on adult studies. This allowed us to analyze adult-specific risk factors and ensure the findings are more relevant to adult clinical practice. Additionally, studies that did not provide information on both kidney profile tests and NAT2 polymorphism variants were not considered. To avoid potential data duplication, reviews or systematic reviews were also excluded from the review.

Data extraction and quality assessment

We designed and piloted a data extraction form. We extracted data in accordance with the methods outlined in the Cochrane Handbook. We contacted study authors if outcome data necessary for inclusion in a meta-analysis were not published in the paper. All data were extracted independently by two investigators, and disagreements were resolved by discussion between the two investigators. The following information was extracted from each study: first author, year of publication, ethnicity, sample size, diagnosis criteria, anti-tuberculosis regimen, INH dosage and genotyping method. The eligibility/exclusion criteria mentioned above were used to assess the quality of the included studies, and study quality was assessed according to Newcastle–Ottawa quality assessment. The Newcastle–Ottawa quality assessment scale was used to evaluate the quality of each included study as follows: high quality 7–9, medium quality 4–6, and low quality < 4.

Statistical analysis

All statistical analyses were conducted using R version 4.4.1 (R Core Team, 2023), a software environment for statistical computing provided by the R Foundation for Statistical Computing, Vienna, Austria (URL: https://www.R-project.org/). The meta-analysis utilized the meta package (Rücker & Schwarzer, 2019). Pooled odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated and presented as forest plots to evaluate the strength of association based on comprehensive data on NAT2 polymorphism in cases and controls. Subgroup analyses were performed by ethnicity, regimen, dosage, genotyping method, and ATDH toxicity criteria to explore differences in the association between NAT2 genotype distribution and ATDH risk. Continuity correction has been implemented in the zero cases of the specific NAT2 2 slow variants. Depending on the heterogeneity among studies, either random effects or fixed effects models were employed. Heterogeneity was assessed using the standard Q-statistic test. Publication bias was evaluated using Begg's funnel plot test. A p value < 0.05 was considered statistically significant.

Results

Selection strategy

PRISMA flow chart showing the selection of studies during the literature search is provided in Fig. 2. An exhaustive compilation of four hundred thirty one papers was identified during this investigation; one hundred five of these were obtained from PubMed, one hundred ninety five from Scopus, and one hundred thirty one from Web of Science. A combination of manual and automated methods were employed to eliminate duplicate articles, leading in the removal of one hundred five cases of duplication.

Following this, the authors thoroughly inspected and evaluated the abstracts and titles of the remaining articles, classifying each one by type using Zotero. A detailed screening of the titles and abstracts of the papers resulted in the exclusion of two hundred fifty six research papers. Studies that failed to include human subjects, studies that made abstract references to isoniazid (INH) or N-acetyltransferase 2 (NAT2) without explicitly addressing their relevance to the specific objective of this comprehensive analysis, and studies that failed to specify the acetylator status of NAT2 were the main factors considered for exclusion. Book chapters, reviews, conference abstracts, editorials, and publications in languages other than English were excluded, leaving seventy items remaining for additional evaluation. In consequence, sixty three recordings were retained, and the complete articles were gathered for the ultimate assessment. After conducting an exhaustive review of the entire articles as part of the final screening process, it was determined that the lack of liver profile/ missing information in the studies was the main reason for exclusion. Infants and children were not subjects in any of the studies that were evaluated for potential inclusion. Ultimately, twenty-four papers were integrated into this inclusive review. [17–40]

Characteristics of included studies

Demographics characteristics

The 24 included studies varied in design, including cohort studies, case–control studies, and observational

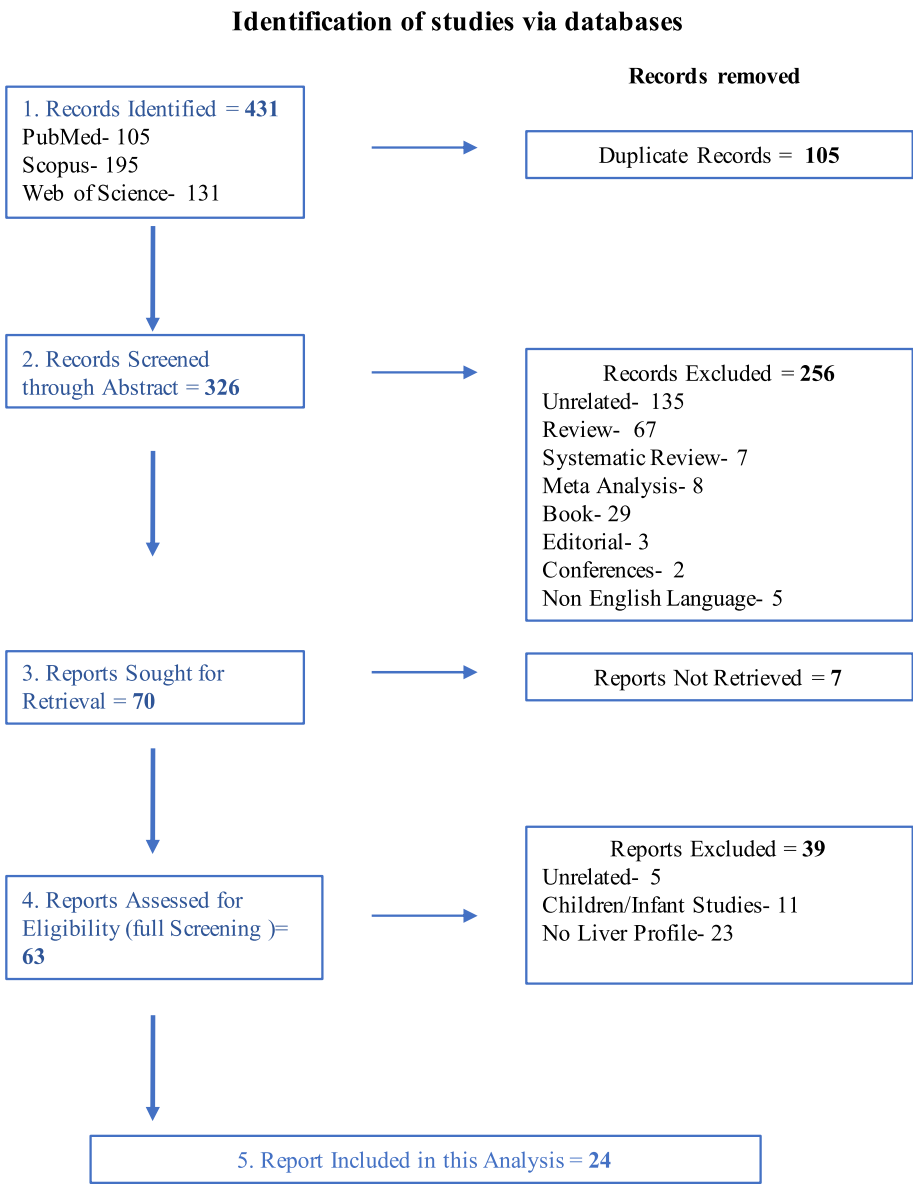

Fig. 2 Flowchart for identification of studies in the meta-analysis

studies. The studies were conducted across 13 countries, with the highest representation from India (n = 5), and Brazil (n = 4). The total number of patients across these studies was 6671 with a greater proportion of male patients (60%) compared to female participants. The research population was dispersed with the largest numbers from China (2130) and India (1405), and Brazil (869). The sample sizes of these 24 studies ranged from 66 to 1685. Significantly, countries like the UK, Canada, and Switzerland exhibited a substantial degree of demographic diversity, with almost half of their populations consisting of non-natives (Table 1).

It is worth mentioning that the median age and body mass index (BMI) of the participants were not provided in three and eleven of the publications, respectively (Table 1). The median age was determined to be 43 years on average. Nevertheless, it was noted that the median age of Indians diagnosed with tuberculosis was roughly 37 years, whereas for Taiwanese individuals, it was beyond 57 years. The BMI of the patients in all the studies found to be in normal range.

Table 1 Table describing the characteristics and data obtained from 24 studies

Sr. No	Study	Year	Ethnicity	Hepatotoxicity Criteria	Regimen	INH Dosage (mg)	Genotyping method	Median Age	BMI	Total Population	ATDH	SA	SA-ATDH
1	Huang, et al	2002	East Asian	ALT > 2 × ULN	INH, RMP, PZA, EMB	300	RFLP	68.5	Normal	224	33	53	14
2	Vuilleumier, et al	2006	Mixed	ALT > 4 × ULN	INH alone	300	q-PCR	31	n/a	89	8	35	3
3	Cho, et al	2007	East Asian	ALT > 2 × ULN	INH, RMP, PZA, EMB	300	Sequencing	48.95	Normal	132	18	19	7
4	Possuelo, et al	2008	Mixed	ALT > 2 × ULN	INH, RMP, PZA	n/a	Sequencing	36.5	n/a	254	14	69	9
5	Yamada, et al	2009	Mixed	ALT > 2 × ULN	INH alone	300	Sequencing	40.8	Normal	170	23	78	14
6	Bose, et al	2011	South Asian	ALT > 2 × ULN	INH, RMP, PZA, EMB	400	RFLP	37	Normal	218	41	108	29
7	Teixeira, et al	2011	South American	ALT > 3 × ULN	INH, RMP, PZA, EMB	400	Sequencing	45.28	n/a	149	26	82	18
8	Leiro-Fernandez, et al	2011	Caucasian	ALT > 3 × ULN	INH, RMP, PZA	300	RFLP	32.25	Normal	117	50	80	36
9	Sotsuka, et al	2011	East Asian	ALT > 2 × ULN	INH, RMP, PZA	300	RFLP	52.1	Normal	144	66	13	8
10	Mahmoud, et al	2012	Middle East	ALT > 2 × ULN	INH, RMP	n/a	RFLP	42	n/a	66	14	33	11
11	Lv, et al	2012	East Asian	ALT > 2 × ULN	INH, RMP, PZA, EMB	600	RFLP	42	Normal	445	89	92	18
12	Rana, et al	2012	South Asian	ALT > 2 × ULN	INH, RMP, PZA, EMB	300	RFLP	44.5	Normal	251	50	49	19
13	Gupta, et al	2013	South Asian	ALT > 2 × ULN	INH, RMP, PZA, EMB	300	RFLP	37.5	Normal	215	50	91	28
14	Ho, et al	2013	East Asian	ALT > 3 × ULN	INH, RMP, PZA, EMB	300	Mass Array	57	Normal	348	59	79	28
15	Santos, et al	2013	South American	ALT > 3 × ULN	INH, RMP, PZA	n/a	Sequencing	44.9	n/a	270	18	86	11
16	Ng, et al	2014	Mixed	ALT > 3 × ULN	INH, RMP, PZA, EMB	300	Sequencing	48.3	n/a	136	26	79	22
17	Singla, et al	2014	South Asian	ALT > 2 × ULN	n/a	n/a	RFLP	32.66	n/a	408	17	228	15
18	Xiang, et al	2014	East Asian	ALT > 2 × ULN	INH, RMP, PZA, EMB	600	LDR	n/a	n/a	1685	309	529	107
19	Mushiroda, et al	2016	East Asian	ALT > 3 × ULN	INH, RMP, PZA, EMB	n/a	Sequencing	n/a	n/a	366	73	27	13
20	Ben, et al	2017	Middle East	ALT > 2 × ULN	INH, RMP, PZA, EMB	300	RFLP	36	n/a	71	11	42	10
21	Araujo, et al	2020	South American	ALT > 3 × ULN	INH, RMP, PZA	n/a	Sequencing	n/a	Normal	173	53	11	5
22	Cavaco, et al	2022	Mixed	ALT > 2 × ULN	INH, RMP, PZA, EMB	n/a	Sequencing	49.6	n/a	233	103	126	68
23	Jaramillo, et al	2022	South American	ALT > 3 × ULN	INH, RMP, PZA, EMB	n/a	Sequencing	24.25	Normal	377	16	179	9
24	Thomas, et al	2024	South Asian	ALT > 3 × ULN	INH, RMP, PZA, EMB	n/a	q-PCR	47	Normal	130	17	40	9
Total										**6671**	**1184**	**2228**	**511**

NAT2 genotype distribution

The distribution of NAT2 genotypes was reported in all studies. NAT2*5, NAT2*6 and NAT2*7 and Nat2*14 were considered as slow Acetylator in our studies. The prevalence of slow acetylator ranged from 7 to 60%, with variations observed across different ethnic groups and geographic regions. The highest prevalence of slow acetylator was found in the Spanish, Tunisian, Indian and Brazilian populations. NAT2*5/5 (19%), NAT2*5/6 (18%), and NAT2*6/6 (16%) has shown the highest frequent among the SA.

Association with hepatotoxicity

In the meta-analysis, a significant association was observed between the slow NAT2 acetylator phenotype and the risk of hepatotoxicity. The pooled data revealed that slow NAT2 acetylator were significantly more likely to experience hepatotoxicity compared to other acetylator, with a random effects model yielding an odds ratio (OR) of 2.52 (95% CI: 1.95–3.27; p value < 0.001) and an I2 value of 58%, indicating moderate heterogeneity among studies (Fig. 3). Subgroup analyses were performed to explore variations in this association across different factors.

Ethnicity

The first subgroup analysis examined the impact of ethnicity on the association between slow NAT2 acetylator and hepatotoxicity. The analysis showed that slow NAT2 acetylator had a significantly increased risk of hepatotoxicity in several ethnic groups: Middle Eastern (OR 5.92; 95% CI: 1.85– 18.92), South Asian (OR 2.90; 95% CI: 2.02– 4.15), East Asian (OR 2.37; 95% CI: 1.37– 4.13), Mixed ethnicity (OR 2.34; 95% CI: 1.49– 3.68) and South American group (OR 2.19; 95% CI: 1.32–3.64) (Fig. 3).

Therapeutic drug combinations

The second subgroup analysis evaluated the effect of different therapeutic drug combinations on the association between slow NAT2 acetylator and hepatotoxicity. Among the 24 studies analyzed, 15 studies used the standard four-drug regimen of INH + RMP + PZA+ EMB, 5 studies used the three-drug regimen of INH + RMP + PZA, one of the studies (Mahmoud et al.) used INH + RMP, and two studies (Yamada et al. and Vuillemier et al.) used INH alone, with data missing for one study. The results demonstrated a positive association between the slow NAT2 genotype and the risk of hepatotoxicity for all regimens except for INH alone. The odds ratios for hepatotoxicity among slow acetylator compared to other acetylator were as follows: INH + RMP + PZA + EMB (OR 2.54; 95% CI: 1.83–3.52), INH + RMP + PZA (OR 2.41; 95% CI: 1.44–4.03), INH + RMP (OR 5.00; 95% CI: 1.25–20.08), and INH alone (OR 1.64; 95% CI: 0.76–3.54) (Fig. 4).

INH Dosage The third subgroup analysis examined the influence of INH dosage on the association between slow NAT2 acetylator and hepatotoxicity (Fig. 5). Interestingly, higher doses of INH showed a lower risk of hepatotoxicity (OR 1.15; 95% CI: 0.91–1.46) compared to the standard dose (OR 2.76; 95% CI: 2.03–3.74).

Criteria for liver toxicity

Another subgroup analysis based on different criteria for liver toxicity revealed that the association between slow NAT2 acetylator and hepatotoxicity was weaker when using criteria for severe liver damage compared to more inclusive definitions of liver toxicity. However, there was no significant difference observed between the categories of ALT = 2X Upper limit of normal (ULN) (2.64; 95% Cl: 1.88–3.72) and 3X ULN (2.53; 95% Cl: 1.95- 3.27) (Fig. 6).

Genotyping methods

Finally, a subgroup analysis of genotyping methods showed differences in the strength of the association between slow NAT2 acetylator and hepatotoxicity. The methods of RFLP (2.37; 95% Cl: 1.61–3.49) and Sequencing (2.87; 95% Cl: 2.16–3.80), showed a positive association, with hepatotoxicity (Fig. 7).

Additionally we have also performed metanalysis for the specific NAT2 SA. We have calculated OR, 95% Cl and p values for the NAT2*5/5, NAT2*5/6, NAT2*5/7, NAT2*6/6, NAT2*6/7 and NAT2*7/7. NAT2*5/6, NAT2*5/7 and NAT2*6/6 have showed the p values below 0.05 suggesting the significant association with ATDH (Table 2).

Sensitivity and quality assessment

The methodological quality of the included studies was assessed using the Newcastle–Ottawa Quality Assessment Scale (SI, Table 1). Only studies with a score of 7 or higher were included in this meta-analysis, ensuring a rigorous selection process focused on studies with robust design and minimized risk of bias.

Although available statistical approach for publication bias Begg's test did not indicate clear evidence of bias (P = 0.5190). The funnel plot (SI, Fig. 1) displayed some asymmetry pattern may indicate genuine variability in effect sizes across studies, possibly due to differences in population characteristics among studies. Study involved in the meta-analysis was deleted each time; the results remained similar, indicating the stability of our results. In conclusion, this meta-analysis showed that TB patients with a slow acetylator genotype had a higher

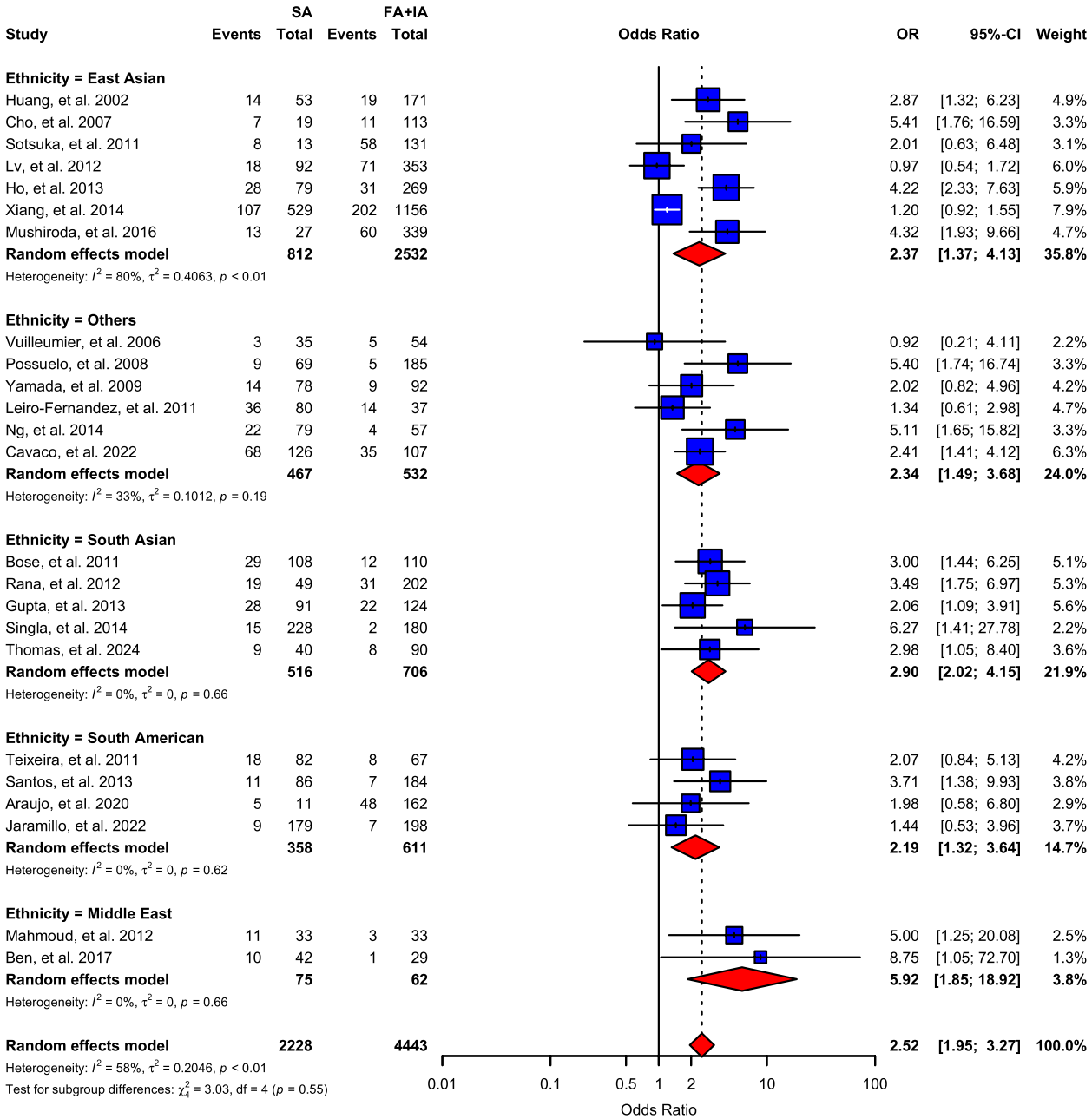

Fig. 3 Forest plot of ORs with 95% CI of INH-induced hepatotoxicity risk associated with NAT2 for the subgroup ethnicity

risk of ATDH than patients with rapid or intermediate acetylator.

Discussions

The relationship between NAT2 variations and the outcomes of anti-tuberculosis drug-associated toxicity is substantiated by substantial data, as has been previously established and confirmed by other systematic reviews and meta-analyses [8, 41–50]. Additionally, this meta-analysis provides robust evidence that the SA NAT2 acetylator phenotype is associated with an elevated risk of ATDH. The statistical analysis revealed a substantial correlation (p value < 0.001). In order to ensure a qualitative assessment, this meta-analysis excluded data that did not contain information on liver profile. Therefore, this meta-analysis is more comprehensive, as it includes all relevant information.

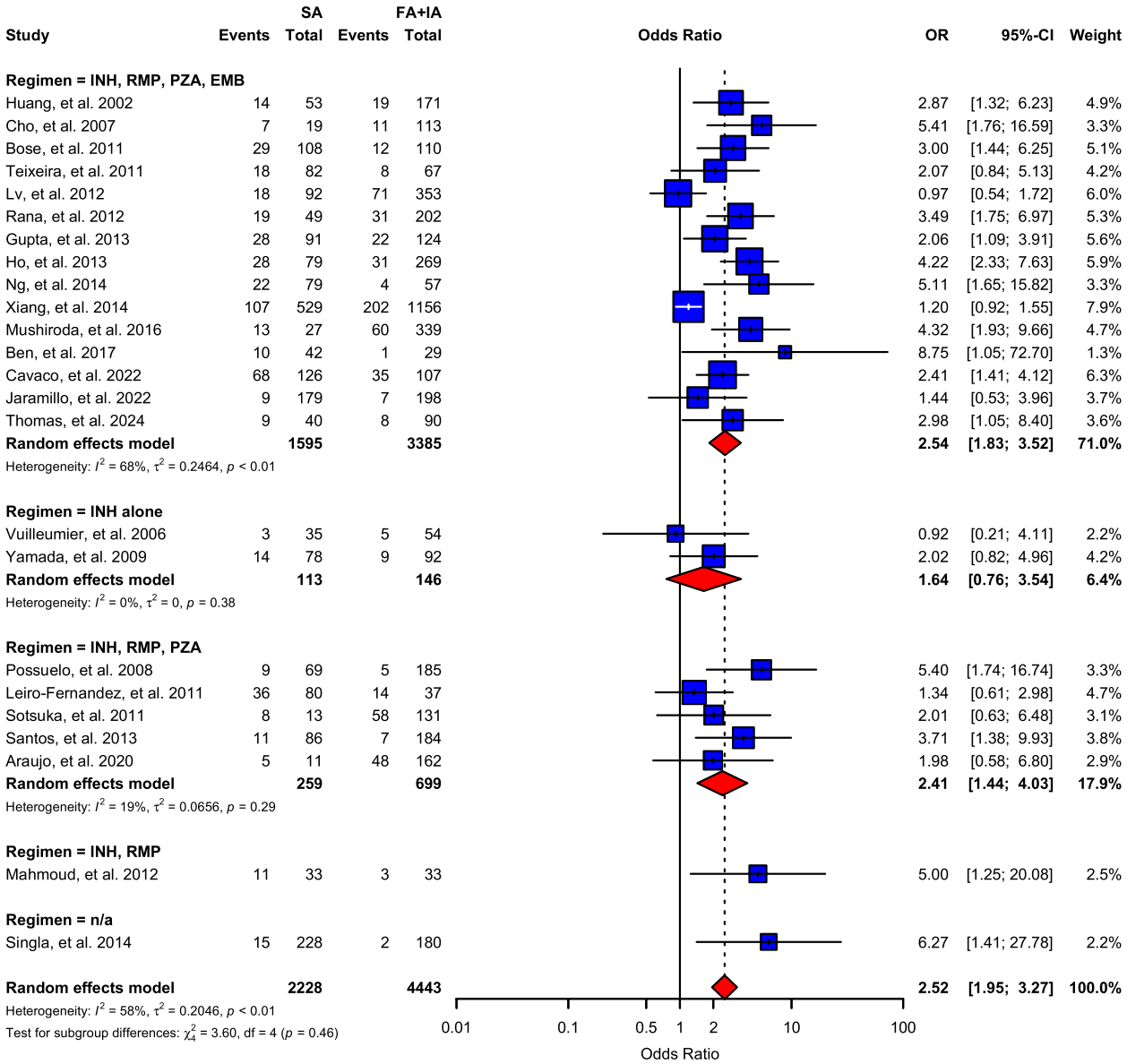

Fig. 4 Forest plot of ORs with 95% CI of INH-induced hepatotoxicity risk associated with NAT2 for the subgroup drug regimen

Primary findings

In order to enhance the accuracy of genetic effect estimations, meta-analyses were used. We have discovered that slow acetylators were substantially more susceptible to hepatotoxicity than other acetylators (rapid and immediate). This outcome is in accordance with the conclusions of numerous meta-analyses [41, 43, 44, 50]. 13 of the 24 studies included in our meta-analysis examined the relationship between susceptibility to ATDH and slow NAT2 acetylator [19–22, 24, 25, 27, 29, 30, 32, 33, 36, 37].

Previous meta-analyses on the association between NAT2 polymorphisms and anti-tuberculosis drug-induced hepatotoxicity (ATDH) have predominantly focused on overall NAT2 acetylator status, with limited attention given to individual single nucleotide polymorphisms within the NAT2 gene. This narrower approach has contributed to an incomplete understanding of how specific NAT2 alleles may influence susceptibility to ATDH. In contrast, the current meta-analysis provides a novel contribution by examining individual NAT2 polymorphisms—specifically NAT2*5/7, NAT2*5/6, and NAT2*6/6—in relation to ATDH risk. Our findings indicate a relatively elevated risk of ATDH among individuals with these polymorphisms, thereby offering a more detailed characterization

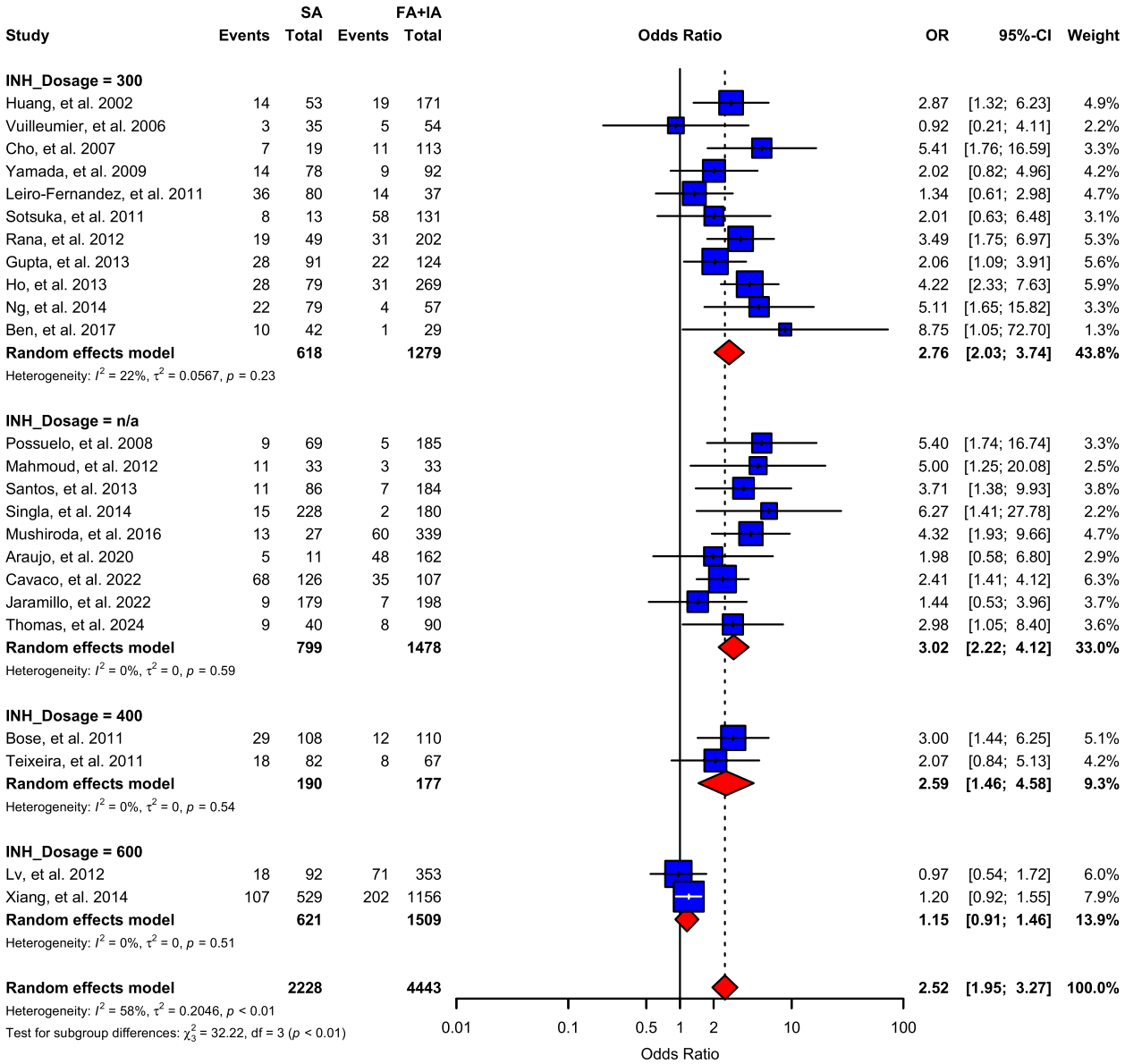

Fig. 5 Forest plot of ORs with 95% CI of INH-induced hepatotoxicity risk associated with NAT2 for the subgroup INH dosage

of genetic predisposition within the NAT2 slow acetylator group. The ethnic group, such as Asian countries, is the primary location of these polymorphisms.

In an effort to ascertain whether the NAT2 gene polymorphism was differentially associated with ATDH risk, we conducted a subgroup analysis for a variety of factors, including ethnicity, drug regimen, dosage, hepatotoxicity criteria, and genotyping methodologies.

The variation in odds ratios observed across ethnic groups—ranging from a high of 5.92 in Middle Eastern populations to 2.19 in South American populations. In the Middle-Eastern subgroup, the odds ratio for hepatotoxicity risk among NAT2 slow acetylator was notably high (OR 5.92; 95% CI: 1.85–18.92) as compared to other subgroups. However, this estimate is derived from two studies, both involving Tunisian populations, with a relatively small combined sample size compared to other ethnic groups [25, 36]. The limited sample size may have contributed to the higher odds ratio, as smaller studies are more susceptible to variability and may produce broader confidence intervals. Given the ethnic diversity in developed countries such as the United Kingdom, Canada, and those in Europe, demonstrating associations can be challenging [20, 28, 31]. Additional information

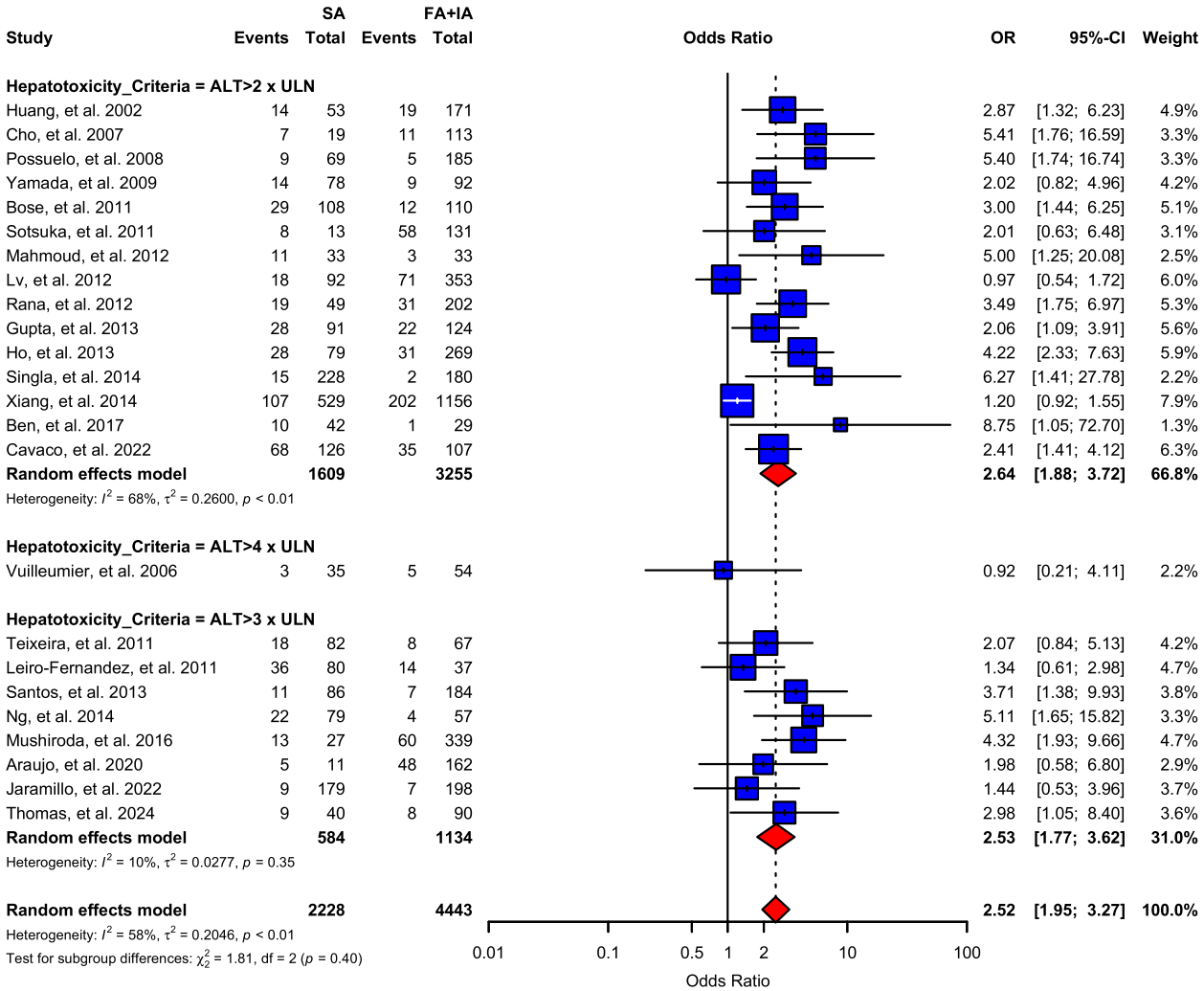

Fig. 6 Forest plot of ORs with 95% CI of INH-induced hepatotoxicity risk associated with NAT2 for the subgroup hepatotoxicity criteria

on the frequency of genetic variations and toxicity is necessary to accurately determine the impact on diverse populations. Additionally, it has been observed that NAT2 slow-acetylator alleles are associated with a higher risk of ATDH, particularly in TB patient from the South Asia and East Asia populations [19, 22–24, 27, 32, 33, 37].

In comparison to patients who received INH alone [28, 31], patients who received first-line combination drugs such as INH + RMP + PZB, INH + RMP, and INH + RMP + PZA + EMB exhibited significantly elevated risks in slow acetylators. This implies that various pharmacological treatments may induce distinct mechanisms.

Different countries adhere to distinct dosage regimens. A downward trend has been observed from a higher dose in comparison to the small amount of INH. In comparison to low doses, the risk association is smaller at higher doses. The Chinese population is administered with higher dose of 600 mg in the two investigations [38, 39]. More studies with various drug treatments may be required to make further development in this field, as the number of available studies is relatively limited. Also the dosage information is missing in nine out of twenty-four studies. The diagnosis of liver toxicity is based on a variety of criteria. This has the potential to significantly influence the association between the SA and toxicity. However, our findings did not reveal any distinction in the association between the mild and moderate forms of toxicity.

Various research groups employed a variety of molecular techniques for genotyping studies to investigate the correlation between polymorphisms in various drug-metabolizing enzymes and the risk of ATDH. Therefore, it is crucial to evaluate the precision of the

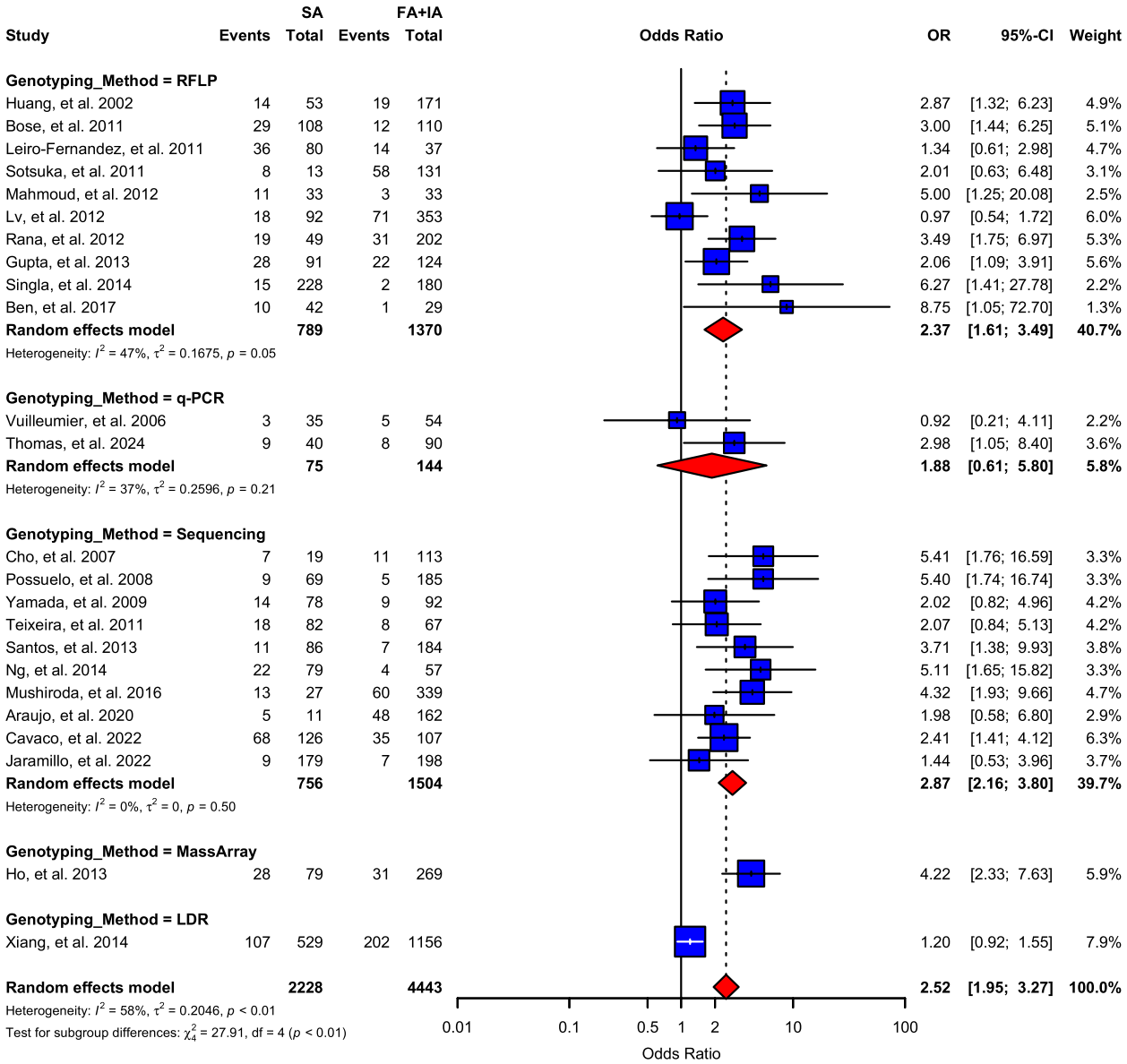

Fig. 7 Forest plot of ORs with 95% CI of INH-induced hepatotoxicity risk associated with NAT2 for the subgroup genotyping methods

genotyping techniques employed during the examination. The studies in this meta-analysis primarily utilised RFLP and sequencing. There was no discernible distinction observed between these two genotyping methodologies. Nevertheless, the limited number of studies used to determine the efficacy of alternative methods such as qPCR and LDR remains inconclusive. Our review and meta-analysis have produced relevant and reliable results and are statistically robust in sensitivity analyses, providing significant new information.

Limitations and future aspect of the studies

Our meta-analysis offers substantial evidence of a correlation between the slow NAT2 acetylator phenotype and an elevated risk of hepatotoxicity from anti-tuberculosis drug. Nevertheless, the interpretation of our findings may be influenced by a number of limitations.

Initially, the absence of comprehensive patient data in numerous studies imposed limitations on our analysis. In particular, the odds ratios for critical risk factors, including age, drug dosages, alcohol consumption,

Table 2 Comprises of the data on specific NAT2 slow variant which includes the pooled OR, 95% CI and *p* values

Study	NAT2*5/5		Nat2*5/6		NAT2*5/7		Nat2*6/6		NAT2*6/7		NAT2*7/7	
	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Huang, et al	0	1	0	6	0	2	6	10	7	12	1	8
Vuilleumier, et al	3	5	2	9	2	1	4	8	0	1	-	-
Cho, et al	-	-	-	-	0	1	3	2	4	7	0	2
Possuelo, et al	2	31	2	8	1	2	4	16	-	-	0	3
Bose, et al	2	8	7	42	8	12	1	3	8	9	2	3
Teixeira, et al	6	24	5	16	2	5	3	12	0	3	-	-
Leiro-Fernandez, et al	8	8	14	24	7	8	4	3	3	1	0	0
Mahmoud, et al	6	10	3	9	0	1	2	2	-	-	-	-
Lv, et al	0	0	3	8	2	2	7	27	5	29	1	8
Rana, et al	0	3	5	11	8	6	0	2	6	3	0	5
Gupta, et al	8	13	13	27	-	-	7	23	-	-	-	-
Ho, et al	0	4	4	14	4	4	15	31	14	50	3	15
Santos, et al	9	64	0	4	2	4	0	2	0	1	-	-
Xiang, et al	9	62	44	113	13	51	26	111	14	67	1	18
Mushiroda, et al	0	2	1	1	1	0	6	4	4	5	1	2
Ben, et al	2	8	6	15	0	3	2	4	0	2	-	-
Araujo, et al	-	-	-	-	-	-	5	6	-	-	-	-
Jaramillo, et al	7	101	1	13	-	-	-	-	1	53	-	-
Total	**62**	**344**	**110**	**320**	**50**	**102**	**95**	**266**	**66**	**243**	**9**	**64**
Pooled OR	**1.2954**		**1.5967**		**2.32**		**1.691**		**1.5883**		**0.7604**	
95% CI	**0.9186—1.8267**		**1.1976—2.1289**		**1.6112—3.3405**		**1.2725—2.2472**		**0.9813—2.5709**		**0.4072—1.4201**	
P (value)	**0.1399**		**0.0014***		**<0.0001***		**0.0003***		**0.0597**		**0.3902**	

Y = cases with the hepatotoxicity

N = absence of hepatotoxicity

* *p* value < 0.005, statistically significant

and smoking behaviours, were unable to be adjusted as a result of the inconsistent reporting across studies. The omission of these factors, which are recognised to affect drug metabolism and toxicity, has the potential to distort our assessments of the relationship between NAT2 acetylator status and hepatotoxicity. Secondly, our literature search was restricted to English publications only, which introduces a potential language bias. This limitation may have resulted in the exclusion of important studies published in other languages. Thirdly, the generalizability of our findings was restricted by the geographic variability in NAT2 polymorphism frequencies, particularly among developed countries with diverse ethnic populations. The applicability of our results to specific populations may be influenced by the variations in NAT2 allele distributions across regions, particularly in high-burden TB countries with significant ethnic diversity. Fourthly, the definitions of ATDH were not standardised, and the dosage information was missing in some studies included in our meta-analysis. Different studies employed varying definitions of elevated ALT levels, with some establishing specific thresholds while others utilized relative increases from baseline. This inconsistency complicates the interpretation of the aggregated findings and may lead to challenges in establishing a unified understanding of liver toxicity. Moreover, our capacity to undertake a comprehensive dose–response analysis and to evaluate the impact of various INH regimens on the risk of liver toxicity was impeded by the absence of treatment details.

Future research should address these limitations by standardising definitions and dosage information for ATDH, assuring comprehensive reporting of patient characteristics, including the ethnicity and including studies in a broader range of languages to minimise publication bias. Furthermore, in order to gain a more comprehensive understanding of NAT2 polymorphisms and their influence on drug-induced liver impairment, additional research should concentrate on finding the specific polymorphisms. A more comprehensive analysis of drug interactions, genetic factors, and administration regimens will be essential for the development of personalised treatment strategies for tuberculosis. These strategies can enhance treatment effectiveness and lower healthcare costs, particularly in high-burden areas where personalized therapeutic approaches are crucial for improving patient outcomes and reducing the incidence of adverse drug reactions.

Conclusion

Our meta-analysis confirms a significant association between slow NAT2 acetylators and increased hepatotoxicity risk with an observed OR 2.52 (95% CI: 1.95–3.27; p value < 0.001). Personalized TB drug therapy using NAT2 polymorphism data could reduce adverse drug reactions, particularly in South and East Asian populations with high ATDH incidence. Implementing a personalized clinical drug-dosage model may enhance treatment efficacy and reduce interruptions due to hepatotoxicity. This approach could also be cost-effective for high-burden TB countries, where treating ATDH is often more expensive than treating TB itself. Screening of patients for the NAT2 genetic polymorphisms can prove clinically useful for the prediction and prevention of ATDH.

Abbreviations

AcINH	Acetylisoniazid
AcHZ	Acetylhydrazine
ALT	Alanine aminotransferase
AST	Aspartate transaminase
ATDH	Anti-tuberculosis drug-related hepatotoxicity
CYP2E1	Cytochrome P450 2E1
DiAcHZ	Diacetylhydrazine
EMB	Ethambutol
GST	Glutathione S-transferase
INH	Isoniazid
NAT2	N-acetyltransferase 2
MDR-TB	Multidrug-resistant tuberculosis
RFLP	Restriction fragment length polymorphism
RMP	Rifampicin
SA	Slow acetylators
PZA	Pyrazinamide
TB	Tuberculosis
ULN	Upper limit of normal

Supplementary Information

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Supplementary Material 1.

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Clinical Trial Number

Not applicable.

Authors' contributions

RM and AKT designed the study and drafted the manuscript. RM and AKT screened the citations, assessed the eligibility of the articles and performed the quality assessment., RM and AKT extracted the data. RM ran the statistical analysis. RM, and AKT were involved in the interpretation of the data and critical revision of the manuscript.

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Data availability

The data sets from this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
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Competing interests
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