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SLOW N-ACETYL TRANSFERASE-2 (NAT-2) GENETIC VARIANT ASSOCIATION WITH ISONIAZID INDUCED HEPATOTOXICITY – A META-ANALYSIS

Samuel Jirom Wolday*[1], Aron Yohannes Abraha[2], Henok Mhreteab[2], Kisanet Fitwi[2], Samsom Habtemariam[2]

[1]*Department of Nursing, Ministry of Health, Keren Sub Zone, Anseba Region, Eritrea.
[2] Department of Pharmacy, Asmara College of Health Sciences, Asmara, Eritrea.

ABSTRACT

Background: The first line anti-tuberculosis drugs are known to cause dose related adverse drug reactions like peripheral neuritis and hepatotoxicity. The risk of getting peripheral neuritis have been avoided through a concomitant administration of pyridoxine; while hepatotoxicity remains to be a major adverse effect of anti-tuberculosis therapy. Many studies are working on finding ways to decrease the incidence of hepatotoxicity by making a link between pharmacokinetics pattern of anti-tuberculosis drugs and genetic polymorphism of the enzymes metabolizing them. One group of studies has reported a significant correlation and other group has reported the opposite. This study is aimed to solve the controversy by pooling the results of these two groups of studies, through a meta-analysis. **Methods:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. Prospective trials that reported isoniazid acetylation status and hepatotoxicity were selected. Effect size was expressed as pooled risk ratios (RRs) comparing slow with fast acetylators. **Results:** Ten prospective studies with 1147 slow acetylators and 1083 fast acetylators met inclusion and exclusion criteria. Slow acetylators were more likely than fast acetylators to have anti-tuberculosis drug induced liver injury (ATLI) [RR, 1.72(95% CI: 1.42-2.09)]. **Conclusions:** This meta-analysis showed that tuberculosis patients with a slow acetylator genotype had a higher risk of ATLI than patients with rapid acetylator genotype. Screening of patients for the NAT2 genetic polymorphisms may prove clinically useful for the prediction and prevention of ATLI.

KEYWORDS

Meta-analysis, Tuberculosis, Isoniazid and Pharmacogenomics.

Author for Correspondence:
Samuel Jirom Wolday,
Department of Nursing,
MOH Keren Sub Zone, Eritrea.
Email: samitusamitu234@gmail.com

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis, the organism is spread by inhaling the mycobacterium containing droplet nuclei that circulate in the air. It is a major global health concern. In 2014, there were 9.6 million new

cases of active TB worldwide and 12% of these cases involved co-infection with HIV and 1.5 million deaths, including 400,000 deaths among patients infected with HIV[1].

The first line drugs used in the treatment of tuberculosis are Isoniazid (INH), Rifampin (RIF), Pyrazinamide (PZA) and Ethambutol (EMB). Isoniazid has been an important drug since its introduction in 1952. Isoniazid is metabolized by the enzyme N-acetyl transferase-2 (NAT2). All the metabolites of isoniazid are devoid of any tuberculous activity.

Adverse effects of Isoniazid include peripheral neuropathy (due to a relative pyridoxine deficiency), Hepatitis and idiosyncratic hepatotoxicity (suggested to be caused by a toxic metabolite of monoacetylhydrazine, formed during the metabolism of Isoniazid) and Other adverse effects like mental abnormalities, Convulsions, Optic neuritis, Hypersensitivity reactions(rashes and fever). Except for hypersensitivity, adverse effects are related to the dosage and duration of administration.

Pharmacogenomics is defined as the study of the genetically determined molecular basis of drug treatment outcomes, and has evolved over the past 20 years. Inter-individual differences in response to the same drugs are known to occur; these differences are higher among individuals belonging to the same population than within the same individual at different times[2]. Inheritance as a determinant of drug response can be explained by the fact that huge population variations with minimal within-subject variations exist.

Inter-individual variations in drug response are known to occur due to sequence variants in genes coding for drug-metabolizing enzymes, drug transporters, or targets[3]. Non-genetic factors, such as age, organ function, concomitant therapy, nutritional status, drug interactions, and nature of the disease can also impact drug effects; however, inherited determinants remain constant throughout a lifetime of an individual. Pharmacogenomics has wide applications in several diseases, including cancer, cardiovascular diseases, depression, bipolar disorder and attention deficit hypersensitivity disorder.

Many studies have been working to find a connection between pharmacogenomics and TB; the study by Azuma *et al* in 2012[4] reported genetic polymorphisms in isoniazid metabolism, and they classified individuals in to Fast, Intermediate and Slow metabolizers (Acetylators); the studies by Ewa and Zofya in 2002[5] and Azuma *et al* in 2012[4] found a significant correlation between having slow acetylation and hepatotoxicity due to isoniazid; in contrast the studies by Surendra *et al* in 2016[6] and Xiaozhen *et al* in 2012[7] reported the absence of correlation. The table below a summary of some other studies worked in the association of pharmacogenomics and TB, with their conclusions.

RESEARCH PROBLEM

Isoniazid is the most effective and, at the same time, the most hepatotoxic drug given in the anti-TB regimen. Although hepatotoxicity is dose related adverse drug reaction, its incidence is reported even in highly controlled (except for genetic differences) trials that treat patients in the ideal way.

Many studies have reported the presence of an association between having some genetic variants and hepatotoxicity; while others have reported absence of any association; thus presence of contradictory evidence has made pharmacogenomics application, to minimize hepatotoxicity incidence, controversial.

RESEARCH HYPOTHESIS

Null hypothesis

There is no association between slow acetylation status and hepatotoxicity due to isoniazid.

Alternative Hypothesis

Having slow acetylation status results in increased risk of Hepatotoxicity due to isoniazid.

RESEARCH OBJECTIVES

General objective

Assessing if there is interrelation between hereditary constitution and unwanted response to anti T.B. drugs; so as to enable application of pharmacogenomics, if a significant interrelation can be made.

Specific objective

To show if slow acetylation status of a patient can significantly correlates to isoniazid induced hepatotoxicity.

METHODOLOGIES

Population size and data collection Procedure

Data containing total sample size of 7826 was obtained by searching through different data bases including; MEDLINE, PubMed, Cochrane CINAHL and EMBASE. The subject heading terms and strategies, "hepatotoxicity" OR "Treatment failure" OR "Blood Isoniazid concentration" AND "tuberculosis" AND "aryl amine N-acetyl transferase" OR "isoniazid N-acetyl transferase" OR "isoniazid acetyl transferase" OR "hydrazine acetyl transferase" OR "acetylation status" AND "treatment outcomes", were used.

Inclusion criteria

Studies which are prospective, examine tuberculosis treatment outcomes and correlate acetylation status of individuals with isoniazid induced hepatotoxicity were included in the analysis.

Exclusion criteria

Studies for primary drug-resistant tuberculosis, with extra-pulmonary tuberculosis, with vulnerable groups (those with comorbidities like HIV/AIDS, with prior hepatic disorders...etc.), with abstracts only, articles in languages other than English, review papers, and studies with incomplete data were excluded.

Operational definition of terms

Anti-tuberculosis drug induced liver injury (ATLI) was defined as an increase in liver biochemical parameters more than two times the upper limit of normal during anti-tuberculosis treatment, according to the international consensus meeting organized by the Council for International Organizations of Medical Sciences (CIOMS)[14].

Fastacetylators (FA) were Patients who had homozygote wild-type alleles of NAT*2gene; intermediate acetylators (IA) were those with heterozygote wild-type and mutant alleles and Slow acetylators (SA) were those who had homozygote mutant alleles.

Studies with small sample size were those with sample size of less than 200.

Quantitative data synthesis and statistical analysis

Data from each trial was entered according to the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Based on the incidence of hepatotoxicity in fast and slow acetylators, RRs (Mantel Haenszel (MH) RRs) with 95% confidence intervals (CIs) was computed for each included study.

Heterogeneity of the study results was explored using both the Cochrane Q statistic and estimating the I^2 test. In case of heterogeneity ($P < 0.05$ for the Q-test, $I^2 > 50\%$), the random-effects model which incorporates between- and within-study variance, was chosen. Otherwise, the fixed effect model was used to calculate the pooled RR. Pooled risk ratios with their 95% confidence intervals (CIs) were then calculated and displayed as forest plots to assess the strength of association between NAT2 genetic polymorphisms and susceptibility to ATLI in pulmonary TB patients. Subgroup analysis was done, by stratification with sample size, to assess the effect of studies with small sample size;

Finally, sensitivity analysis was done by sequential removal of each study included in the meta-analysis to reflect its influence on the overall RR.

RESULTS AND DISCUSSION

Sensitivity Analyses

Sensitivity analyses were performed to assess the influence of each individual study on the pooled RR by sequential removal of individual studies.

The results suggested that no individual study significantly affected the pooled RR, thus suggesting that the results of this meta-analysis are stable.

Publication Bias

A funnel plot of these 10 included studies concerning NAT2 and ATLI suggested a possibility of preferential publication of positive findings in smaller studies.

Discussion

Reduction or disturbance of NAT2 activity could result in the accumulation of intermediate

metabolites in the liver, leading to hepatotoxicity; the efficiency of this process depends partially on the polymorphic alleles present in the individual[23].

Slow acetylators not only acetylate the parent component (isoniazid) more slowly but also immediate precursors of toxic intermediates (monoacetylhydrazine to the harmless diacetylhydrazine)[24]; this protective acetylation is further suppressed by isoniazid. Therefore, slow acetylators may critically increase the accumulation of toxic metabolites indirectly.

Various similar studies in this field have reported results supporting the genetic based pharmacokinetic variability hypothesis for anti-TB drugs. Pasipanodya *et al*[25] have worked on association of rapid (fast) acetylators with microbiological failure, Acquired drug resistance, and relapse. Individualized drug regimens incorporating genetic factors, thus, may be needed to avoid these undesired outcomes.

Few studies incorporating pharmacogenomics in anti-TB therapy have shown reduced incidence of these undesirable events; In the study by Azuma *et al* INH-ATLI occurred in 78% of the slow acetylators in the standard treatment, while none of the slow acetylators in the pharmacogenomics based treatment experienced either INH-ATLI or early treatment failure; among the rapid acetylators, early treatment failure was observed with a significantly lower incidence rate in the pharmacogenomics based-treatment than in the standard treatment (15.0 % vs. 38%).

Association of pharmacogenomics and TB, with their conclusions

S.No	Country	Study	Study population	Conclusion
1	Brazil	Teixeria *et al*, 2011[8]	Brazilian population	Slow acetylators had a higher incidence of hepatitis than intermediate /rapid acetylators
2	Morocco	Guaoua *et al*, 2016[9]	Moroccan population	Slow acetylator phenotype may contribute to the development of TB treatment hepatotoxicity.
3	Colombia	Arias *et al* 2014[10]	Colombian -coast region population	Because of the high prevalence of slow acetylators, a greater incidence of tuberculosis (TB) drug-induced hepatotoxicity was predicted in these populations, with a higher frequency in the “Wiwa” group.
4	UK	Ching-Soon *et al*, 2014[11]	European or South Asian	The NAT2 slow acetylator genotype appears to be a significant risk factor for moderate and severe drug induced liver injury.
5	Tunisia	Ghozzi *et al*, 2012[12]	Tunisian patients with tuberculosis	Results suggest that the slow acetylator status of NAT2 is risk factor for INH-induced hepatotoxicity
6	Spain	Fernandez V, *et al*, 2011[13]	Caucasian patients with tuberculosis	Increased risk of ATLI related to the presence of slow NAT2polymorphismswas not demonstrated among a Caucasian TBcohort

Characteristics of included Studies

S.No	Study ID	country	Sample size	Outcome (Risk Ratio)
1	Bose 2011[15]	India	218	2.46 [1.33, 4.57]
2	Cho 2007[16]	Korea	132	2.74 [1.11, 6.77]
3	Huang 2002[17]	Taiwan	224	2.38 [1.28, 4.41]
4	Lee 2010[18]	Taiwan	140	2.01 [1.26, 3.22]
5	Sistanizad 2011[19]	Iran	50	2.70 [1.06, 6.88]
6	Sotsuka2011[20]	Japan	144	1.90 [1.09, 3.32]
7	Sharma 2016[6]	India	290	1.05 [0.70, 1.58]
8	Xiang 2014[21]	China	2244	1.98 [0.95, 4.15]
9	Xiaozhen 2012[7]	China	4304	0.99 [0.59, 1.67]
10	Cetintas 2008[22]	Turkey	100	3.10 [1.07, 8.98]

Publication Bias: Interpretation

S.No		Heterogeneity	Pooling model	Risk Ratio	Interpretation
1	All studies	Not significant	Fixed effects	1.72 95 %CI: (1.42 - 2.09)	Null hypothesis rejected; SA are 1.72 times more prone to ATLI than FA.
2	Studies with large sample size	Significant	Random effects	1.57 95% CI: (1.04 -2.37)	Null hypothesis rejected; SA are 1.57 times more prone to ATLI than FA.
3	Studies with small sample size	Not significant	Fixed effects	2.30 95% CI: (1.68 -3.15)	Null hypothesis rejected; SA are 2.30 times more prone to ATLI than FA.

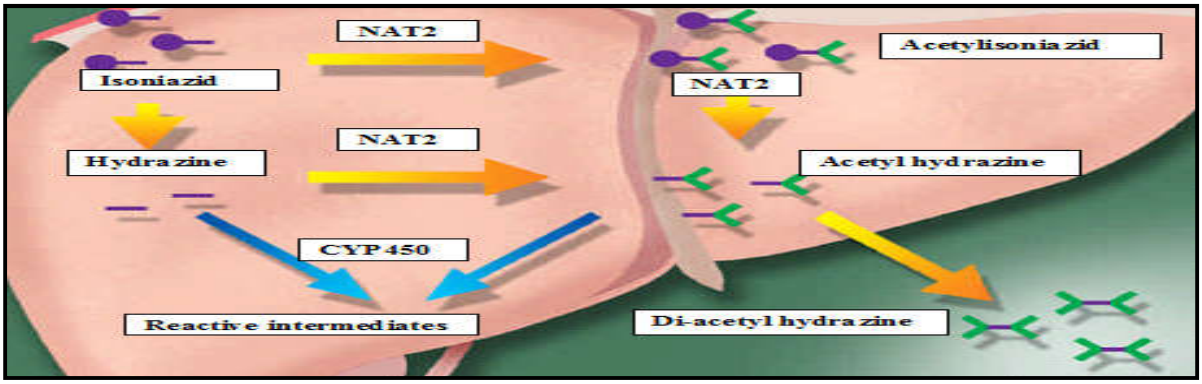


Figure No.1: Schematic representation of isoniazid metabolism

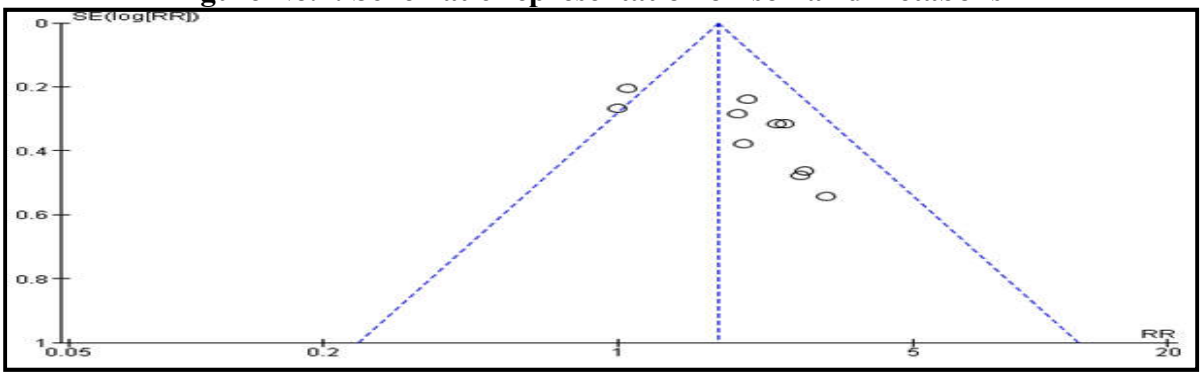
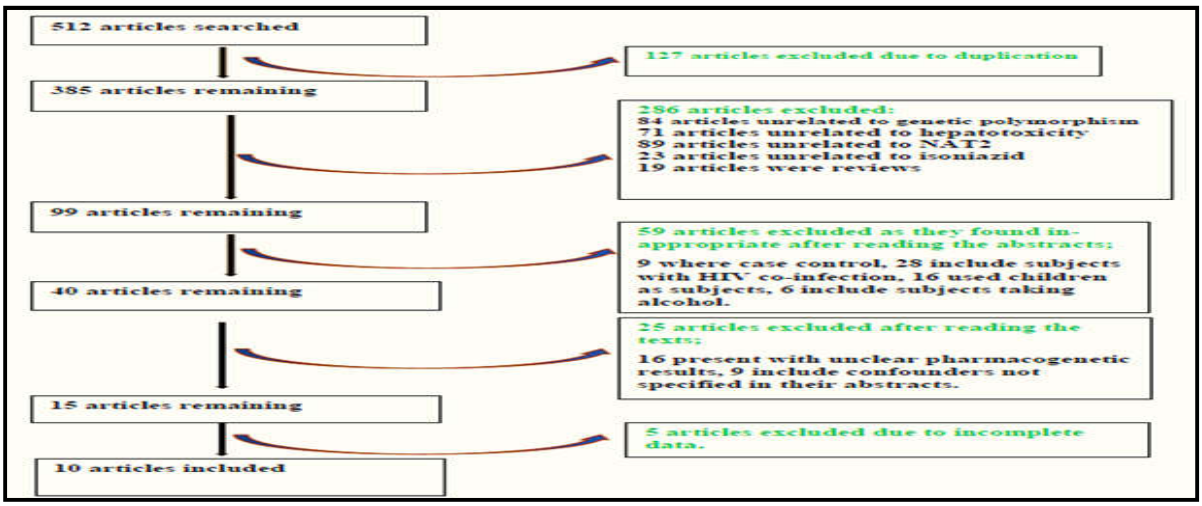
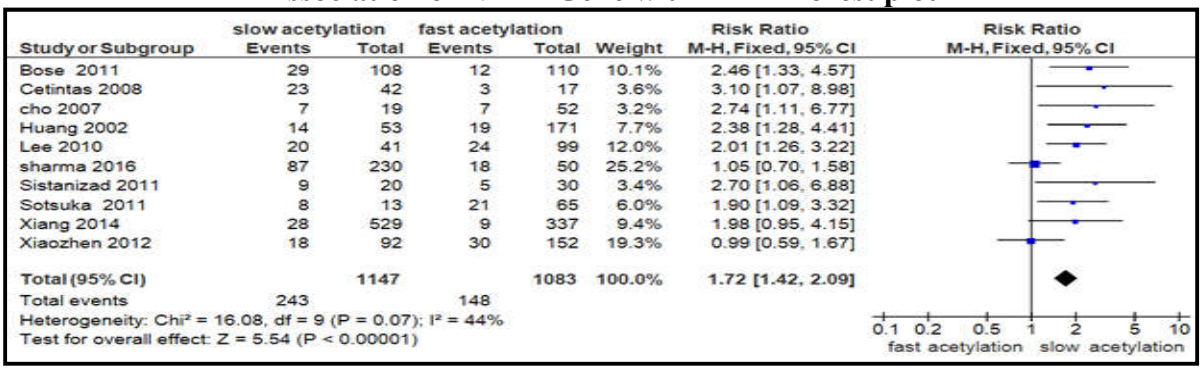


Figure No.2: Funnel plot of comparison: Fast versus slow acetylation for hepatotoxicity outcome

Data selection flow chart



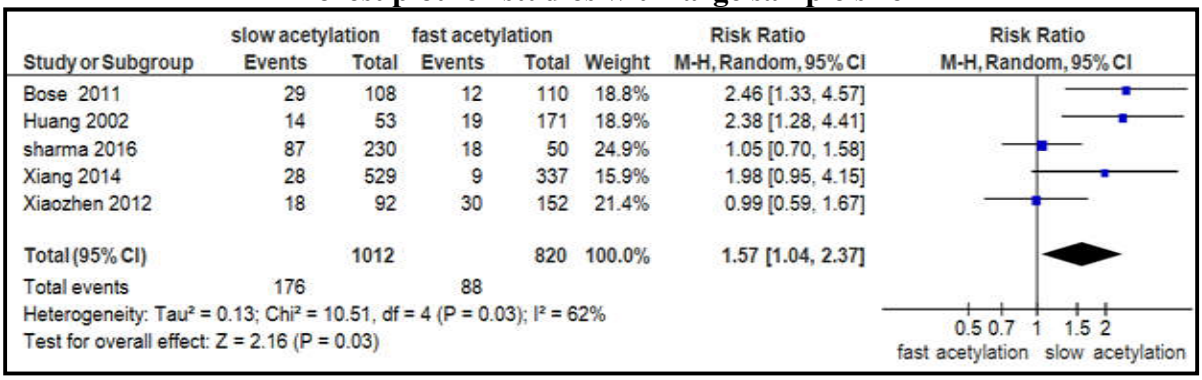
Association of NAT2 Gene with ATLI Forest plot



Study or Subgroup	slow acetylation Events	Total	fast acetylation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bose 2011	29	108	12	110	10.1%	2.46 [1.33, 4.57]
Cetintas 2008	23	42	3	17	3.6%	3.10 [1.07, 8.98]
cho 2007	7	19	7	52	3.2%	2.74 [1.11, 6.77]
Huang 2002	14	53	19	171	7.7%	2.38 [1.28, 4.41]
Lee 2010	20	41	24	99	12.0%	2.01 [1.26, 3.22]
sharma 2016	87	230	18	50	25.2%	1.05 [0.70, 1.58]
Sistanizad 2011	9	20	5	30	3.4%	2.70 [1.06, 6.88]
Sotsuka 2011	8	13	21	65	6.0%	1.90 [1.09, 3.32]
Xiang 2014	28	529	9	337	9.4%	1.98 [0.95, 4.15]
Xiaozhen 2012	18	92	30	152	19.3%	0.99 [0.59, 1.67]
Total (95% CI)		**1147**		**1083**	**100.0%**	**1.72 [1.42, 2.09]**
Total events	243		148			

Heterogeneity: Chi² = 16.08, df = 9 (P = 0.07); I² = 44%
Test for overall effect: Z = 5.54 (P < 0.00001)

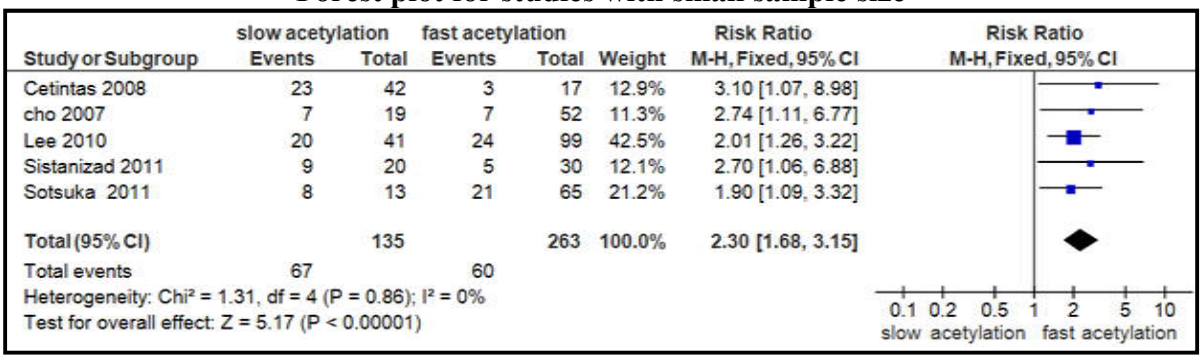
Forest plot for studies with large sample size



Study or Subgroup	slow acetylation Events	Total	fast acetylation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bose 2011	29	108	12	110	18.8%	2.46 [1.33, 4.57]
Huang 2002	14	53	19	171	18.9%	2.38 [1.28, 4.41]
sharma 2016	87	230	18	50	24.9%	1.05 [0.70, 1.58]
Xiang 2014	28	529	9	337	15.9%	1.98 [0.95, 4.15]
Xiaozhen 2012	18	92	30	152	21.4%	0.99 [0.59, 1.67]
Total (95% CI)		**1012**		**820**	**100.0%**	**1.57 [1.04, 2.37]**
Total events	176		88			

Heterogeneity: Tau² = 0.13; Chi² = 10.51, df = 4 (P = 0.03); I² = 62%
Test for overall effect: Z = 2.16 (P = 0.03)

Forest plot for studies with small sample size



Study or Subgroup	slow acetylation Events	Total	fast acetylation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cetintas 2008	23	42	3	17	12.9%	3.10 [1.07, 8.98]
cho 2007	7	19	7	52	11.3%	2.74 [1.11, 6.77]
Lee 2010	20	41	24	99	42.5%	2.01 [1.26, 3.22]
Sistanizad 2011	9	20	5	30	12.1%	2.70 [1.06, 6.88]
Sotsuka 2011	8	13	21	65	21.2%	1.90 [1.09, 3.32]
Total (95% CI)		**135**		**263**	**100.0%**	**2.30 [1.68, 3.15]**
Total events	67		60			

Heterogeneity: Chi² = 1.31, df = 4 (P = 0.86); I² = 0%
Test for overall effect: Z = 5.17 (P < 0.00001)

CONCLUSION

This meta-analysis showed that TB patients with a slow acetylator genotype had a higher risk of ATLI than patients with a rapid acetylator genotype. Screening of patients for the NAT2 genetic polymorphisms may prove clinically useful for the prediction and prevention of ATLI.

RECOMMENDATIONS

Although this meta-analysis have showed that slow acetylators are more susceptible to anti-tuberculosis drugs induced liver injury, a lot more trials incorporating pharmacogenomics based regimens should be conducted to see if the incidence of hepatotoxicity is reduced compared with those not applying pharmacogenomics.

At present, at least, routine monitoring for hepatotoxicity should be done for patients in anti–TB regimen, especially to those who are at increased risk like individuals co-infected with HIV, those with liver diseases and the elderly.

LIMITATIONS OF THE STUDY

Although comprehensive search was conducted to include as many articles as possible, still, there may be studies that are not included in this analysis.

This meta-analysis has included only published research works; inclusion of unpublished researches might give different weight; the greatest concern is in publication bias; it may be expected that unpublished researches, both, those reporting conclusions supporting and not supporting pharmacogenomics are missed; but, studies with no significant results often have a lower likelihood of being published; the overall result, thus, might be biased towards the significant result. Despite the limitations, we are confident that our findings provide useful information for clinical practice and public health policy decisions.

ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome; ATLI: Anti-tuberculosis drug induced liver injury; HIV: CI: Confidence Interval; INH: Isoniazid; Human Immune deficiency Virus; NAT-2: N-acetyl transferase; RR: Relative Risk; TB: Tuberculosis.

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AVAILABILITY OF DATA AND MATERIALS

The complete data set supporting the conclusions of this article is available from the corresponding author and can be accessed upon reasonable request.

AUTHORS' CONTRIBUTIONS

All authors participated in all phases of the study including topic selection, design, data collection, data analysis and interpretation. Samuel and Aron contributes to write this manuscript.

CONSENT FOR PUBLICATION

This manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the final manuscript and agreed for its publication.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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BIBLIOGRAPHY

1. WHO. Global tuberculosis report 2016. WHO/HTM/TB/2015.22, *World Health Organization, Geneva,* 2016, 142.
2. Vesell E S. Pharmacokinetic perspectives gained from twin and family studies, *Pharmacol Ther,* 41(3), 1989, 535-552.

3. McLeod H L, Evans W E. Pharmacogenomics: Unlocking the human genome for better drug therapy, *Annu Rev Pharmacol Toxicol,* 41, 2001, 101-121
4. Junichi Azuma, Masako Ohno, Ryuji Kubota, Soichiro Yokota, Kazunari Tsuyuguchi, Yasuhisa Okuda, Tetsuya Takashima, Sayaka Kamimura, Yasushi Fujio and Ichiro Kawase. NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: A randomized controlled trial for pharmacogenetics-based therapy, *Eur J Clin Pharmacol,* 69(5), 2013, 1091-1101.
5. Ewa Augustynowiczkopec, Zofia Zwolskay. The type of isoniazid acetylation in tuberculosis patients treated at National Tuberculosis and Lung Diseases research Institute, *Acta Pol Pharm,* 59(6), 2002, 443-447.
6. Surendra K. Sharma, Brajesh Kumar Jha, Abhishek Sharma, Sreenivas V, Vishwanath Upadhyay, Chandrita Jaisinghani, Rohit Singla, Hemant Kumar Mishra and Manish Soneja. Genetic polymorphisms of N-acetyltranseferase and susceptibility to antituberculosis drug-induced hepatotoxicity, *Indian J Med Res,* 144(6), 2016, 924-928.
7. Xiaozhen L V, Shaowen Tang, Yinyin Xia, Yuan Zhang, Shanshan Wu, Zhirong Yang *et al*. NAT2 genetic polymorphisms and anti-tuberculosis drug induced hepatotoxicity in chines community population, *Annals of Hepatology,* 11(5), 2012, 700-707.
8. Raquel Lima De Figueiredo Teixeira, Renata Gomes Morato, Pedro Hernan Cabello, Ligia Mayumi Kitada Muniz, Adriana Da Silva Rezende Moreira, Philip Noel Suffys, Antonio Basilio De Miranda, Adalberto Rezende Santos. Genetic polymorphisms of NAT2, CYP2E1 and GST enzymes and the occurrence of antituberculosis drug-induced hepatitis in Brazilian TB patients, *Memorias Do Instituto Oswaldo Cruz,* 106(6), 2011, 716-724.
9. Guaoua S, Ratbi I, Bencheikh R S, Sefiani A. NAT2 genotypes in moroccan patients with hepatotoxicity due to antituberculosis drugs, *Genet Test Mol Biomarkers,* 20(11), 2016, 680-684.
10. Arias I, Lecompte N, Visbal L, Curiel I, Hernández E, Garavito P, Silvera-Redondo C. NAT2 gene polymorphisms in three indigenous groups in the colombian caribbean coast region, *Colomb Med (Cali),* 45(4), 2014, 148-153.
11. Ching-Soon Ng, Abul Hasnat, Abdullah Al Maruf, Maizbha Uddin Ahmed, Munir Pirmohamed, Christopher P. Day, Guruprasad P. Aithal, Ann K. Daly. N-acetyltransferase 2 (NAT2) genotype as a risk factor for development of drug-induced liver injury relating to antituberculosis drug treatment in a mixed-ethnicity patient group, *Eur J Clin Pharmacol,* 70(9), 2014, 1079-1086.
12. Ghozzi H, Kamoun A, Hammami S, Zalila N, Makni H, Zeghal K. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatotoxicity in Tunisian patients with tuberculosis, *Pathologie Biologie,* 60(5), 2012, 324-330.
13. Leiro-Fernandez V, Agundez J A, Fernandez-Villar A. N-acetyltransferase 2 polymorphisms and risk of anti-tuberculosis drug-induced hepatotoxicity in Caucasians, *Int J Tuberc Lung Dis,* 15(10), 2011, 1403-1408.
14. Benichou C. Criteria of drug-induced liver disorders, Report of an international consensus meeting, *J Hepatol,* 11(2), 1990, 272-276.
15. Bose P D, Kar P. Role of polymorphic N-acetyl transferase2 and cytochrome P4502E1 gene in antituberculosis treatment-induced hepatitis, *J Gastroenterol Hepatol,* 26(2), 2011, 312-318.
16. Hyung Jung Cho, Jong Won Kim, Soo Youn Lee. Genetic polymorphisms of NAT2 and CYP2E1 associated with antituberculosis drug-induced hepatotoxicity in Korean patients with pulmonary tuberculosis, *Tuberculosis,* 87(6), 2007, 551-556.

17. Yi-Shin Huang, Herng-Der Chern, Wei-Juin Su, Jaw-Ching Wu, Shinn-Liang Lai, Shi-Yi Yang, Full-Young Chang, Shou-Dong Lee. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis, *Hepatology,* 35(4), 2002, 883-889.
18. Lee S W. Chung H H, Huang, Chuang T Y, Liou, Y H, Wu S H. NAT2 and CYP2E1 polymorphisms and susceptibility to first-line anti-tuberculosis drug-induced hepatitis, *Int J Tuberc Lung Dis,* 14(5), 2010, 622-626.
19. Mohammad Sistanizad, Ebrahim Azizi,Hosein Khalili, Mahboobeh Hajiabdolbaghi, Kheirollah Gholami, Reza Mahjub. Antituberculosis drug-induced hepatotoxicity in iranian tuberculosis patients: Role of isoniazid metabolic polymorphism, *Iran J Pharm Res,* 10(3), 2011, 633-639.
20. Takayo Sotsuka, Yuka Sasaki, Shigekazu Hirai, Fumio Yamagishi, Koichi Ueno. Association of isoniazid-metabolizing enzyme genotypes, *In Vivo,* 25(5), 2011, 803-812.
21. Yang Xiang, Long Ma, Weidong Wu, Wei Liu, Yongguang Li, Xia Zhu, Qian Wang, Jinfeng Ma, Mingqin Cao, Qian Wang, Xuemei Yao, Lei Yang, Atikaimu Wubuli, Corinne Merle, Paul Milligan, Ying Mao, Jiayi Gu, Xiumei Xin. The Incidence of Liver Injury in uyghur patients treated for TB in Xinjiang Uyghur autonomous region, China, and its association with hepatic enzyme polymorphisms NAT2, CYP2E1, GSTM1 and GSTT1, *Plos One,* 9(1), 2014, e85905.
22. Vildan Bozok Cetintas, Onur Fevzi Erer, Buket Kosova, Ilker Ozdemir, Nejat Topcuoglu, Serir Aktogu, Zuhal Eroglu. Determining the relation between N-acetyltransferase-2 acetylator phenotype and antituberculosis drug induced hepatitis by molecular biologic tests, *Tuberkuloz Ve Toraks Dergisi,* 56(1), 2008, 81-86.
23. Roy B. Anti-tuberculosis drug induced hepatotoxicity and genetic polymorphisms in drug-metabolizing genes, *Curr Pharmacogenomics,* 1(2), 2003, 101-109.
24. Lauterburg B H, Smith C V, Todd E L, Mitchell J R. Pharmacokinetics of the toxic hydrazine metabolites formed from isoniazid in humans, *J. Pharmacol. Exp. Ther,* 235(3), 1985, 566-570.
25. Jotam G. Pasipanodya, Shashikant Srivastava, Tawanda Gumbo. Meta-analysis of clinical studies support the pharmacokinetic variability hypothesis for acquired drug resistance and failure of antituberculosis therapy, *Clinical Infectious Diseases,* 55(2), 2012, 169-177.

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