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Research Report

THE RISK FACTORS FOR DRUG INDUCED HEPATITIS IN PULMONARY TUBERCULOSIS PATIENTS IN DR. SOETOMO HOSPITAL

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ABSTRACT

Tuberculosis (TB) is still a major public health problem in Indonesia. Anti-tuberculosis drug-induced hepatotoxicity (DIH) is common side effect leading to changes in treatment regimens, and the less effective second-line treatments. Several risk factors such as age, sex, body mass index (BMI) and acetylization status for hepatotoxicity were suggested in previous studies but in the fact, those are often not related to DIH incidence after receiving standard TB treatment regimen. The aim of this study was to asses the role of risk factors in the DIH incidence in pulmonary TB patients receiving standard TB treatment regimen in Dr. Soetomo Hospital, Surabaya. Study design was analytic observational with case control. The subjects were 30 TB DIH patients and 31 TB non-DIH patients receiving standard national TB program therapy. DIH severity was divided based on International DIH Expert Working Group. Demographic data and BMI status were taken from medical records. The age classification are ≥35 years old and <35 years old as one of the risk factors studied. DNA sequencing was used to assess single-nucleotide polymorphisms in NAT2 coding region to evaluate acetylator status from blood samples. The risk factors were evaluated using chi-square test and Mantel-Haenszel test. Significant association between low BMI and DIH in general was identified (OR=3.017; 95% CI=1.029-8.845) and more significant association between low BMI and moderate DIH (OR=15.833; 95% CI=1.792-139.922). Age, sex, and acetylization status has no significant correlation with DIH incidence in general. Significant association between slow acetylator phenotype and incidence of moderate DIH was identified (OR=7.125; 95% CI= 1.309-38.711). In conclusion, some risk factors were correlated to DIH incidence in pulmonary TB patients receiving standart TB treatment regimen.

Keywords: *Tuberculosis, Drug-Induced Hepatitis, Anti-TB Drugs*

ABSTRAK

Tuberkulosis (TB) masih merupakan masalah besar di Indonesia. Hepatitis Imbas Obat (HIO) TB merupakan efek samping yang banyak terjadi dan dapat menyebabkan perubahan regimen pengobatan, dan penggunaan obat TB lini kedua yang kurang efektif. Beberapa faktor risiko timbulnya hepatotoksitas seperti umur, jenis kelamin, Indeks Massa Tubuh (IMT) dan status asetilator telah diteliti pada penelitian-penelitian sebelumnya, namun pada kenyataannya, kadang faktor risiko tersebut tidak terbukti berhubungan dengan kejadian HIO setelah mendapat pengobatan dengan regimen standar TB. Studi ini dilakukan untuk menilai peranan faktor risiko tersebut terhadap insidensi HIO pada pasien TB paru yang mendapat pengobatan regimen standar obat TB di RS Dr. Soetomo, Surabaya. Desain studi adalah observasi analitik dengan case control. Subjek terdiri dari 30 pasien TB HIO dan 31 pasien TB tanpa HIO yang mendapatkan terapi standar obat anti tuberkulosis (OAT) sesuai program nasional TB. Derajat keparahan HIO dibuat berdasarkan International DIH Expert Working Group. Data demografi dan IMT dikumpulkan dari rekam medik. Kami membagi usia menjadi ≥35 tahun dan <35 tahun sebagai salah satu faktor risiko yang diamati. Sekuensing DNA single-nucleotide polymorphism regio NAT2 dilakukan untuk menentukan status asetilator dari sampel darah. Evaluasi faktor risiko dilakukan dengan menggunakan uji chi-square dan uji Mantel-Haenszel. Korelasi signifikan terjadi antara IMT rendah dengan timbulnya HIO secara umum (OR=3.017; 95% CI=1.029-8.845) dan antara IMT rendah dengan timbulnya HIO derajat sedang (OR=15.833; 95% CI=1.792-139.922). Usia,

jenis kelamin dan status asetilator tidak berkorelasi signifikan terhadap timbulnya HIO secara umum. Korelasi signifikan terjadi antara asetilator lambat dengan kejadian HIO derajat sedang (OR=7.125; 95% CI=1.309-38.711). Kesimpulan pada penelitian ini adalah beberapa faktor risiko berhubungan dengan terjadinya HIO pada pasien TB paru yang mendapatkan terapi regimen standar.

Kata Kunci: *Tuberkulosis, Hepatitis Imbas Obat, Obat Anti TB*

INTRODUCTION

Drug Induced Hepatitis (DIH) is a severe side effect of oral anti tuberculosis. Anti tuberculosis drugs are metabolized mainly by the liver, and therefore, are potentially hepatotoxic. In DIH, there is an elevated liver enzyme, such as *aspartate amino transaminase* (AST), *alanin transaminase serum* (ALT), and total bilirubin increase as much as 3 times from their normal ranges.[1] DIH due to anti tuberculosis drugs, not only causing morbidity and mortality, but also changes the regimen and the less effective second-line treatment which eventually causing drugs resistance.

TB DIH is generally unpredictable and happens to a small number of patients, even after the patients received the standard dose. There are several factors which play roles in the susceptibility of a patient to develop DIH such as age, sex, body mass index (BMI), and genetic like acetylator status of NAT2 phenotype. The prevalence of DIH is much higher in developing countries owing to several factors such as acute or chronic liver disease, alcoholism, malnutrition, indiscriminate drug use, advanced TB, and other co-existing chronic illness. Anti tuberculosis drugs may cause hepatotoxicity ranging from a transient asymptomatic rise in liver enzymes to acute liver failure. The reported mortality from DIH after the development of jaundice varies from 4% to 12%. It is noted that the frequency of DIH in different countries varies widely from 2% to 39%.[2]

Advanced age has been noticed to be associated with increased risk of DIH after receiving anti TB drugs.[3] A case control study is showed increased incidence of DIH in the age group of 35-65 as opposed to the younger population.[4] Naqvi, et al[5] has reported that age >35 years is one of important risk factors for TB DIH.

Some studies have implicated female sex to be at increased risk for TB DIH which were also shown from data analysis of various international registries.[4,6] A few studies showed female patients were significantly higher than male patients.[7,8]

Malnutrition contributes to increased incidence of DIH after receiving anti TB drugs. Malnutrition which measured in terms of hypoalbuminemia (serum albumin levels <3.5 g/dl) is predicted two-fold higher incidence of DIH.[4] Makhlouf[9] also reported that lower Body Mass Index (BMI) of 20 kg/m^2 or less were independent predictors of TB DIH.

Isoniazid (INH) is one of hepatotoxic drugs in the standard TB treatment regimen. One of the gene which is important in the metabolism of isoniazid is NAT2 (*N-Acetyltransferase 2*) gene. NAT2 codes the *Acetyltransferase* enzyme which has part in the process of Isoniazid acetylization by the hepatic enzyme. Polymorphism in the different metabolism locus could cause a different pharmacologic response towards every individuals. Pharmacogenetics and N-acetyltransferase are historically related, and in vivo variation in NAT activity is one of the pharmacokinetics patterns, which is first recognized. The first action of NAT2 enzyme was identified as the advanced step, generally controlled for isoniazid metabolism. The slow decay of acetylhidrazin, a toxic substance, from patients who are affected is known as the slow acetylator.[10] The study based on genotyping of NAT2 showed that slow acetylators had increased the risk of hepatotoxicity than rapid acetylators. Furthermore, slow acetylators had more severe hepatotoxicity in comparison with rapid acetylators. This basis can be explained by the fact that slow acetylators also convert the toxic intermediate monoacetyl hydrazine to diacetyl hydrazine slowly which increases the risk of hepatotoxicity.[11]

A reviewed article written by Saha et al[12] was stated that isoniazid (INH), pyrazinamide (PZA), and rifampicin (RIF) used in TB DOTS (Directly Observed Treatment Short-course) as the main drugs are potentially hepatotoxic and may lead to DIH. INH mechanism has been known in the incidence of DIH through acetylator status, while the toxicity mechanism of RIF and PZA are still unknown. An article reviewed by Tostmann et al[2] stated that the enzymes involved PZA-toxicity is not exactly known. A study reported that the risk of hepatotoxicity increases during the addition PZA to INH and RIF.[13]

In this perspective, we designed this study to know the possible risk factors such as age, sex, BMI, and acetylator status for the development of DIH in patients receiving anti-tubercular treatment as per National TB Control Programme (NTP) strategy in Dr. Soetomo General Hospital, one of the top referral in East Indonesia.

MATERIAL AND METHOD

The study was an analytical observational, using the case control design. Samples were collected from all of Pulmonary TB patients who suffered from DIH, as well as those who did not have DIH which had been treated with full term of standard regimen in Dr. Soetomo General Hospital Surabaya. All of pulmonary TB patients were tested for blood plasma, liver and kidney function as a

baseline test to make sure that there was no liver function impairment in all patients before receiving standard TB treatment regimen.

According to the following biochemical criteria, hepatitis was defined as: 1) elevation of serum alanine transaminase (ALT) and/or aspartate transaminase (AST) 3 times the upper limit of normal (ULN), or 2) elevation of serum bilirubin ULN and ALT and/ or AST 2 ULN (the ULN was defined as 41 U/L for AST, 50 U/L for ALT in men and 35 U/L in women, and 1.0 mg/dL for bilirubin in our laboratory) with hepatitis signs and symptoms. Patients were not categorized as DIH if during the whole TB treatment, there was no hepatitis occurred. Pulmonary TB patients which have Hepatitis A, B, and C, liver cirrhosis, hepatoma, cholelithiasis, and also HIV were not included in this study. DIH Pulmonary TB Patients were divided into Mild DIH and Moderate DIH, based on the severity. The severity of DIH was graded in accordance with *International DIH Expert Working Group*,[1] where severity of DIH was graded as followed: Mild (elevated alanine amino transferase or alkaline phosphatase concentration reaching criteria for DIH but bilirubin concentration <2 upper limit of normal (ULN) and Moderate (elevated alanine amino transferase or alkaline phosphatase concentration reaching criteria for DIH and bilirubin concentration ≥2 ULN, or symptomatic hepatitis).

Demographic data such as age, sex, weight and height on the initial treatment were collected from the medical records. Liver function laboratory tests were done when the symptoms occurred such as nausea, and or followed by jaundice and an impaired liver function according to the DIH criteria. Blood serum from Pulmonary TB patients who suffered from DIH was sent to the biomolecular laboratory in Yarsi Research Center Jakarta to examine the NAT2 genotype sequencing. This examination aim is to evaluate single-nucleotide polymorphism. Non DIH Pulmonary TB patients were collected from the Pulmonary TB patients who had been on full term of standard regimen and did not have DIH. In the end of TB treatment, the blood serum was taken to examine the NAT2 genotype sequencing.

Statistic test used in this research was *Chi-Square* test to analyze the significance of variables on DIH occurrence.

RESULT AND DISCUSSION

The number of sample collected was 30 pulmonary TB patients with DIH and 31 patients without DIH. Based on the sex, number DIH and non DIH pulmonary TB patients were found a bit higher in men than women, that were 17 (56.7%) and 19 (61.3%) for men, respectively. The average age and weight in pulmonary TB patients with DIH were slightly higher compared than non DIH pulmonary TB patients. The pulmonary TB patients with DIH were averagely 45.10±14.31 years old, while non DIH pulmonary TB patients were averagely 49.84±12.85 years old. The height of the pulmonary TB patients with DIH was averagely 1.59±0.08 m and the non DIH pulmonary TB patient's height were 1.57±0.08 m in average. The average weight of DIH pulmonary TB patients (43.83±6.65 kg) was lower than the patients without DIH (47.83±8.77 kg). From the body mass index (BMI), the DIH pulmonary TB patients were 17.24±2.73 kg/cm^2, including 23.3% patients with low BMI, 43.3% with severely low BMI, and 33.3%with normal BMI. While, non DIH pulmonary TB patients were 19.24±2.83 kg/cm^2 in average, including 12.9% of the patients with low BMI, 25.8% with severely low BMI, and 61.3% with normal BMI (Table 1).

Based on the NAT2 haplotype reconstruction, 9 NAT2 haplotype could be identified in which each of them consisted of 6 SNP. Each were suitable with several studies,

Table 1. Demography profile and BMI status of DIH and Non DIH TB Patients

Character	DIH (n=30)	Non DIH (n=31)
Sex (Men/Women)	17/13	19/12
Age (Year)	45.10 ± 14.31 (17-66)*	49.84 ± 12.85 (26-68)*
Height (Meters)	1.59 ± 0.08 (1.45-1.9)*	1.57 ± 0.08 (1.45-1.75)*
Weight (Kg)	43.83 ± 6.65 (30-58)*	47.83 ± 8.77 (33-65)*
BMI (Kg/m^2)	17.24 ± 2.73 (10.53-22.66)*	19.24 ± 2.83 (13.28-25.11)*

* Mean ± SD (range)

Table 2. Slow and Rapid Allele Frequency

No	Haplotype	Nomenclature	Code	Cases	Control	Case Frequency	Control Frequency	p Value	Allele Prediction
1	Ttcaag	NAT2*6A	*6A	16	11	0.27	0.18	0.2816	Slow allele
2	Ttcagg	NAT2*6C	*6C	12	10	0.20	0.16	0.6441	Slow allele
3	Ttcgaa	NAT2*7B	*7B	10	10	0.17	0.16	1	Slow allele
4	Ttcgag	NAT2*13	*13	0	1	0.00	0.02	1	Rapid allele
5	Ttcgga	NAT2*7C	*7C	0	1	0.00	0.02	1	Slow allele
6	Ctcagg	NAT2*6F	*6F	1	1	0.02	0.02	1	Slow allele
7	Ctcgag	NAT2*4	*4	5	5	0.08	0.08	1	Rapid allele
8	Ctcggg	NAT2*12A	*12A	9	19	0.15	0.31	0.0514	Rapid allele
9	Cctggg	NAT2*5B	*5B	7	4	0.12	0.06	0.3625	Slow allele
TOTAL				60	62	1	1		

were enough to predict the NAT2 phenotype based on the database[14] among all patients. The determination of slow and rapid acetylator was based on several references, it is known that NAT2* 6A, NAT2*6B, NAT2*6C, NAT2*6J, NAT2*7B, NAT2*5B, NAT2*5C, NAT2*5D, NAT2*5J were slow acetylators, while NAT2*4A, NAT2*12A, NAT2*12B, NAT2*12C, NAT2*13B, NAT2*11A and NAT2*13A were rapid acetylator.[14,15] The frequent each haplotype was shown in table 2. The NAT2*6A frequency was higher but not significant (p 0.2816). As well as NAT2* 12A which was higher in non DIH pulmonary TB patients, compared to the DIH pulmonary TB patients (p 0.0514) as shown at Table 2.

In distribution bimodal model, the frequency of NAT2 phenotype in DIH pulmonary TB patients was 63.3% slow acetylator and 36.7% rapid acetylator. The NAT2 frequency in non DIH pulmonary TB patients was 38.7% slow acetylator and 61.3% rapid acetylator.

AST profile in DIH pulmonary TB patients were averagely 141.69±96.023 U/L, while the ones without DIH were 33.67±12.95 U/L in average, in which statistically showed a significant difference with p=0.001. ALT profile in DIH pulmonary TB patients were averagely 101.02±129.329, while the ones without DIH were averagely 28.8±18.68 with p=0.004. Total bilirubin in DIH pulmonary TB patients were 5.17±18.97 in average, while the non DIH were 0.37±0.15 in average with p=0.005. AST, ALT, and total bilirubin value were the criteria to define hepatitis.

From the age and sex, statistically, there was no significance between DIH and non DIH pulmonary TB patients. But from AST, ALT, and total bilirubin, there were significance with each p value as many as 0.001, 0.004, and 0.005. While from the acetylator status, there was also no significance between DIH and non DIH pulmonary TB patients. The data analysis above is revealed in Table 3.

A few studies showed the same result, such as where men were higher than women in getting DIH, although it was not significant.[5,16] Several different studies reported that female sex were observed to be independent risk factors for the development of DIH after receiving anti TB drugs.[3,7,8] One study is showed that patient's sex was not significantly associated with anti-TB-DIH.[17] Review article written by Devarbhavi[18] stated that women had a generally higher risk for DIH. Studies from Japan and Sweden found women contributed to the number of DIH cases as much as 58% and 56% respectively and may indicate demographic peculiarity of those countries. This was not corroborated by studies which are conducted from Spain (49%), USA (48%) and India (42%).[18] However, women have a higher risk for DIH in most studies. The study which conducted by Kumar et al[19] stated that there is an unclear reason for female preponderance, but another epidemiological study reported that compared with age-matched men, reproductive-aged women had a faster progression of tuberculosis, from infection into active disease. Other than that, females' activity of CYP3A was higher compared with males, which could explain why females were more susceptible to anti tuberculosis drug induced hepatitis (ATDH).[2] In Indonesia, TB is significantly more common among men than among women.[20] Therefore the susceptibility of TB DIH in men was higher than woman in this study, although it was statistically not significant, suggesting that different sex was not correlated with the incidence of DIH in this study.

Reviewed article written by Ramappa and Aithal[21] showed that age has been associated with an increased risk of DIH. Age over 60 years was associated with a 3.5 fold risk of DIH due to the anti TB drugs. In a case control study, patients who developed DIH on anti-TB drugs were older (39 years) compared to those who did not (32 years). The incidence of hepatotoxicity was 17% in patients below 35 years of age and 33% in age above 35 years; in a multivariate analysis, age >35 years was the only independent variable for predicting anti-TB DIH.[21] Elderly is associated with decreased liver blood flow, drug distribution and metabolism by CYP450 enzymes changes, resulting in a potentially lower effective clearance of the drugs.[2] However, the susceptibility of elderly to adverse events and drug-induced liver disease is highly variable and could be different from the younger people.[22] The difference between patients who were above and below 35 years old was not significant in the incidence of DIH in general as well as in groups in mild or moderate DIH. We suggest that the incidence of DIH in this study may be correlated with other factors than age.

Table 3. Statistic Analysis of Demography, BMI, Laboratory Liver Function and Acetylator Status Profile between DIH and Non DIH Pulmonary TB Patients

Variables	DIH (n=30)	Non DIH (n=31)	p value
Sex (women/men)	13/17	12/19	0.714
Age (≥ 35 y.o/<35 y.o)	22/8	27/4	0.176
BMI (low/normal)	20/10	12/19	0.029
AST*	141.69 ± 96.023*	33.67 ± 12.95*	0.001
ALT*	101.02 ± 129.329*	28.8 ± 18.68*	0.004
Direct Bilirubin*	2.04 ± 5.68*	0.62 ± 0.25*	0.079
Total Bilirubin*	5.17 ± 18.97*	0.37 ± 0.15*	0.005
Acetylator status (SA/RA)	19/11	12/19	0.054

* Mean ± SD ; SA = Slow Acetylator; RA = Rapid Acetylator ; *p* value based on *chi-square* test

Based on BMI status as stated in Table 3, incidence of DIH was associated with low BMI with p-value 0.029. Other studies also collected the same data, where the low BMI subjects[5] and those who had malnutrition[2,8] were on the higher risk of getting DIH after receiving standard TB treatment regimen. Decreased xenobiotic clearance and higher plasma levels are the results of malnutrition or lower BMI results.[2] Besides, this might be due to glutathione stores depletion, which causes patients to be more vulnerable to oxidative injuries.[16]

INH has been known as one of the anti TB drugs which can cause DIH through its acetylization metabolism. The study which was conducted by Sistanizad et al[11] showed that there was a different response in several individuals to the INH acetylization process, DIH incidence was more frequent in patients who has slow acetylator than rapid acetylator. Individuals who were categorized as slow acetylators in fact had a very slow N-acetyltransferase enzyme activity, caused by the genetic variation from the gene coding the expression of N-acetyltransferase enzyme. For individuals who had the abnormality caused by autosomal recessive allele, manifested as the polymorphic variation, the NAT enzyme activity became very slow. Thus, the ability for INH to be excreted in the form of inactive acetyl-INH was slow, making the INH had a long term of work, with the risk of an impaired function.[4] Previous reported studies showed that NAT2 slow acetylator phenotypes are associated with disease risks and drug toxicity.[23] The NAT2 slow acetylator phenotypes have been investigated to have association with isoniazid-induced hepatotoxicity in tuberculosis treatment.[24,25] In this study, the most NAT2 of DIH pulmonary TB patients had was NAT2*6A, which was the slow acetylators haplotype, but statistically, there was no significant difference compared to the rapid acetylators with the incidence of DIH. There were 11 of DIH pulmonary TB patients who have rapid asetylator, assumed that other TB drug like Pirazinamide (PZA), Rifampicin (RIF) may played role in the incidence of DIH. According to the previous research, RIF plasma levels were higher in cases with DIH than in controls and independently predicted subsequent development of DIH compared with INH and PZA.[26] In this study, there was no measurement of the RIF concentration in DIH patient's blood plasma after receiving the standard TB regimen. Review article written by Tostmann et al[2] stated that the mechanism of rifampicin-induced hepatotoxicity is unknown and unpredictable. There is also no evidence for the toxic metabolite presence. Rifampicin is a dominant inducer of the hepatic CYP450 system in the liver and intestine, by that, it increases metabolism of many other compounds. The usage of rifampicin and isoniazid combination has been correlated with a higher risk of hepatotoxicity. Rifampicin induces isoniazid hydrolase, causing an increased hydrazine production when rifampicin is combined with isoniazid (especially in slow acetylators), which may explain the higher toxicity of the combination.

PZA has been shown to increase the risk of hepatotoxicity, adding PZA to INH and RIF increased the risk of hepatotoxicity appreciably.[13] A study reported that among the 17 patients with hepatotoxicity, 12 patients are showed anti-TB DIH. Ten patients showed PZA-related hepatotoxicity and 2 showed INH- or RIF-related hepatotoxicity.[27] Although, review article written by Tostmann et al[2] stated that PZA is converted to pyrazinoic acid and further oxidized to 5hydroxypyrazinoic acid by xanthine oxidase. The serum half-life of pyrazinamide is not related to the length of treatment, indicating that pyrazinamide does not induce the enzymes responsible for its metabolism. The mechanism of pyrazinamide-induced toxicity is unknown; it is unknown whether enzymes are involved in pyrazinamide-toxicity and whether toxicity is caused by pyrazinamide or its metabolites. In a rat study, pyrazinamide inhibited the activity of several CYP450 isoenzymes (2B, 2C, 2E1, 3A), but a study in human liver microsomes showed that pyrazinamide has no inhibitory effect on the CYP450 isoenzymes.

DIH as the side effect of PZA and RIF cannot be avoided, but it was difficult to decide which drug causing the incidence of DIH because all TB patients who were included in this study were taking a combination of four anti-TB drugs: INH, RIF, PZA, and EMB. Therefore, we exclude the role of RIF and PZA, and focused on gene NAT2 which is important in the metabolism of INH. The role of BMI, sex and ages which from several studies are known as the factors causing DIH in patients receiving standard TB treatment regimen, even though it is still controversial and not one of them mentioned the specific correlation with one of the TB drugs.

Based on the severity, pulmonary TB patients with mild DIH is higher than moderate DIH, that are 19 patients (63.3%) and 11 patients (36.7%), respectively, shown in Table 4.

Table 4. Characteristic of and Non DIH and Mild/Moderate DIH Pulmonary TB Patients based on Demography, BMI and Acetylator Status Profiles

Variables	Non DIH (n=31)	Mild DIH (n=19)		Moderate DIH (n=11)	
			P value		P value
Sex (women/men)	12/19	10/9	0.336	3/8	0.496
Age (≥ 35 years old/< 35 years old)	27/4	14/5	0.231	8/3	0.272
BMI (low/normal)	12/19	10/9	0.336	10/1	0.003
Acetylators (slow/rapid)	12/19	10/9	0.336	9/2	0.014

Table 5. Analysis of Risk Factors for DIH

	P value (DIH vs Non DIH)	OR	95% CI	*P* value (Moderate DIH vs Non DIH)	OR	95% CI
Low BMI	0.029	3.017	1.029-8.845	0.003	15.833	1.792-139.922
Slow Acetylators	0.054	2.587	1.884-7.568	0.014	7.125	1.309-38.771

* Odd Ratio Based on *Chi-square* test with Cochran's and Mantel-Haenszel Statistics

Based on the DIH severity, there was still no significant difference between age and sex in both mild and moderate. But acetylator status showed a significance in moderate DIH, while low BMI showed a more significance compared to DIH in general with p 0.029 (table 3 and 5). According to mantel-Haenszel test low BMI has a significant correlation in the incidence of moderate DIH with p 0.003<0.05 (OR=15.833; 95% CI: 1.792-139.922). Likewise with the acetylator status and the incidence of moderate DIH with p 0.014<0.05 (OR=7.125; 95% CI: 1.309-38.711) as shown in Table 5.

The different study results with the previous study[24] which confirms the significance of the association between slow-acetylator *NAT2* variants and susceptibility to ATDH generally in an Indonesian population may be caused by a greater number of samples used in previous study. While the study by Lv et al[28] did not find significant association between NAT2 genotype and ATDH in community-based Chinese population, and based on Sistanizad et al[11] study also showed that slow acetylators are prone to develop more severe hepatotoxicity than rapid acetylators.

This study has limited information data. There were no other risk factors which could affect the incidence of DIH after standard TB treatment regimen, such as smoker, alcoholic, and the albumin level in each individual. Also, as mentioned above, there was no measurement of RIF concentration in patient's blood plasma, as well as the PZA metabolism measurement which was suspected as toxic to the liver.

CONCLUSION

From this study, it was concluded that the low BMI rate is the factor which affects the most in the incidence of DIH after receiving standard TB regimen. Acetylization status in INH metabolism pathway, as in INH, which is one of the standard TB regimen in this study does not affect the DIH in general, but still plays role in the incidence of moderate DIH. Further studies with a higher number of hepatotoxicity cases and simultaneous analysis of more risk factors factors such as smoking, alcohol consumption, and albumin levels, RIF concentration measurement and PZA metabolites in patient's blood plasma should be carried out in different ethnic populations and in different regions of Indonesia. From this study, we suggest that at least the practical aspect of TB treatment are used with regular monitoring of liver function on TB patients receiving standard TB regimen especially in patients with low BMI.

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