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Association of N-acetyltransferase 2 (*NAT2*) polymorphisms and elevated liver enzymes of Myanmar tuberculosis patients in Thailand

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ABSTRACT

Introduction: Isoniazid (INH) and its toxic metabolites are the major cause of anti-tuberculosis (TB) drug-induced liver injury (AT-DILI). N-acetyltransferase 2 (NAT2) is involved in many metabolic pathways of INH. Previous studies demonstrated the association of *NAT2* polymorphisms and AT-DILI. **Objectives:** This study aimed to determine *NAT2* gene polymorphisms in Myanmar TB patients and evaluate the association of *NAT2* polymorphisms with elevated liver enzymes. **Results:** In 59 patients, the most common alleles and genotypes were *NAT2**6A and *NAT2**4/*7B. A high ratio of slow acetylators (47%, n = 28) and intermediate acetylators (44%, n = 26) was observed. The CT genotype of *NAT2* single nucleotide polymorphisms (SNP) rs1799929 was frequently observed in patients with elevated aspartate aminotransferase (AST) levels. Slow acetylators with *NAT2**5B/*5B showed the highest AST and alanine aminotransferase (ALT) levels. Multiple linear regression showed the significant association of *NAT2* SNP rs1799929, INH dose, and age with a variation of AST levels (R^2 = 0.356), while NAT2 phenotype, INH dose, and age-linked with a variation of AST levels (R^2 = 0.222). *NAT2* SNP rs1799929 also exhibited 22% of ALT level variation. **Conclusion:** The *NAT2* genotype and phenotype distribution in the Myanmar population are similar to those in other Southeast Asian populations. A strong influence of *NAT2* polymorphisms on elevated liver enzymes suggests closely monitoring of AT-DILI in Myanmar TB patients.

Keywords: Isoniazid, liver enzyme, Myanmar, N-acetyltransferase 2 polymorphism, tuberculosis

INTRODUCTION

Tuberculosis (TB) affects approximately 10 million people worldwide.[1] Myanmar and Thailand were on the list of the 30 countries with a high TB burden.[1] According to the World Health Organization (WHO) global TB report 2019, the estimated TB incidence in Myanmar and Thailand in 2018 was 181,000 and 106,000 cases, respectively.[1] The 6-month standard treatment of TB consists of four first-line drugs; isoniazid (INH), rifampicin, pyrazinamide, and ethambutol.[2] Long-term treatment periods with complicated dosage regimens, as well as severe adverse drug reactions, lead to noncompliance and increase the risk of treatment failure.[3,4]

Hepatotoxicity is the most common adverse effect of first-line anti-TB drugs, including INH, rifampicin, and pyrazinamide.[5,6] Previous studies demonstrated that rifampicin and pyrazinamide disrupt the metabolic pathways of INH, resulting in anti-TB drug-induced liver injury (AT-DILI).[7,8] N-acetyltransferase (NAT2) has a major role in INH metabolism, as it involves the production and clearance of toxic INH metabolites.[9] *NAT2* polymorphisms have been previously reported among populations.[10,11] Moreover, the linkage of *NAT2* polymorphisms and AT-DILI has been increasingly reported in many populations.[12-15]

Many single nucleotide polymorphisms (SNPs) have been discovered in the *NAT2* coding exon and promoter.[16] These SNPs are combined and formed *NAT2* alleles or *NAT2* haplotypes.[16] This study determined four SNPs which are commonly found in Asian and Southeast Asian populations; rs1041983 (*NAT2* C282T), rs1799929 (*NAT2* C481T),

rs1799930 (*NAT2* G590A), and rs1799931 (*NAT2* G857A).[14] Then, *NAT2* haplotypes were determined based on *NAT2* SNPs.[14] Based on *NAT2* haplotypes or *NAT2* alleles, three phenotypes of acetylation; slow acetylator with two slow alleles, intermediate acetylator with one rapid and one slow alleles, and rapid acetylator with two rapid alleles were described.[17] The East Asian population showed a higher ratio of rapid acetylators,[18] whereas Southeast Asian populations have higher ratios of intermediate and slow acetylators.[14,19] The *NAT2* polymorphisms of the Myanmar population have not been reported. This study attempted to describe *NAT2* polymorphisms in the Myanmar population and to determine the association between *NAT2* polymorphisms and anti-TB-induced elevated liver enzyme levels. The data would help support appropriate pharmaceutical care to reduce adverse reactions, increase drug compliance, and promote successful TB treatment. Moreover, this study would provide genetic information to establish pharmacogenomics-based therapy in anti-TB treatment.

MATERIALS AND METHODS

Subjects

This study was a retrospective study which included 59 Myanmar TB patients from January 2017 to July 2019 at the TB clinic, Samut Sakhon Hospital, Thailand. This study was approved by the Research Ethics Review Committee for Research Involving Human Research Participants, Health Sciences Group, Chulalongkorn University, Thailand (COA No. 267/2018) and Samut Sakhon Hospital's Ethics Review Committee.

The inclusion criteria were (a) male and female Myanmar TB patients age more than 15 years old and (b) first-time treatment with either a standard 6-month TB regimen or shorter MDR-TB regimen or TB meningitis regimen. Then, the patients were excluded if they had the following criteria: (a) Non-tuberculous mycobacterial infection, (b) abnormal liver and kidney functions before treatment regimen, (c) alcoholism and alcoholic liver disease, (d) pregnancy and lactating mother, and (e) treatment with other potential hepatotoxic drugs.[20] Patients who fulfilled the described inclusion/exclusion criteria were enrolled in the study. The informed consent form was read and signed by all participants.

Levels of the liver enzymes AST and ALT were determined at 2 weeks after anti-TB treatment. Intravenous blood samples (5 mL) from each patient were collected and kept in a vacationer with ethylenediaminetetraacetic acid anticoagulant at 4°C for further gene sequencing.

NAT2 Genotyping

Genomic DNA was extracted from patients' blood by a QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The quality of DNA was determined by a NanoDrop spectrophotometer. In this study, the following SNPs which are commonly found in Asian and Southeast Asian population, rs1041983 (*NAT2* C282T), rs1799929 (*NAT2* C481T), rs1799930 (*NAT2* G590A), and rs1799931 (*NAT2* G857A), were sequenced using allele-specific polymerase chain reaction based on a previous study by Wattanapokayakit *et al*.[14]

Data Analysis

The haplotype was determined by the four SNPs. The slow acetylator phenotype was observed in patients with two slow *NAT2* alleles (*NAT2**5B, *NAT2**6A, *NAT2**7B), whereas patients with two rapid *NAT2* alleles (*NAT2**4) were rapid acetylators.[14] In addition, intermediate acetylators were the patients with one rapid *NAT2* allele and one slow *NAT2* allele.[14]

The expected allele and genotype frequencies were calculated from each single allele frequency. The Chi-square was used to test deviation from Hardy-Weinberg equilibrium.

According to normal liver enzyme levels[21] (AST 0–40 U/L [man], 0–32 U/L [woman], ALT 0–41 U/L [man], and 0–33 U/L [woman]), patients were stratified into two groups: Normal liver enzymes and elevated liver enzymes (from the upper limit of normal range). The continuous variables, age, BMI, and anti-TB doses, were firstly analyzed for their normal distribution using 5% trimmed mean, skewness, Q-Q plot, and Shapiro-Will test. Then, the differences between groups were compared by Student's *t*-test. The differences between groups of discrete variables were compared by either Chi-square or Fisher's exact test. Binary logistic regression was used to determine the association of *NAT2* SNPs and elevated AST and ALT liver enzymes. One-way analysis of variance (ANOVA) was used to determine the effects of *NAT2* SNPs, genotypes, and phenotypes on AST and ALT levels.

The relationship of genetic factors; *NAT2* SNPs, genotype and phenotype, and non-genetic factors; age, gender, BMI, TB types, and anti-TB doses, and elevated liver enzymes was examined using simple linear regression. Then, variables showing a $P < 0.15$ were entered into multiple linear regression analysis. Data were coded and analyzed with IBM SPSS version 22.

RESULTS AND DISCUSSION

Patients' Characteristics

In this study, all TB patients were first-time treated with the standard 6-month TB regimen. The anti-TB drugs INH,

Table 1: SNP-based allele distribution of *NAT2* gene polymorphisms in Myanmar TB patients (n=59)

SNP ID	Nucleotide change	Amino acid change	Allele 1/2	11 (n)	12 (n)	22 (n)	VAF	HWE	
								χ^2	*P*-value
rs1041983	*NAT2* C282T	-	C/T	11	30	18	0.56 (T)	0.058	0.81
rs1799929	*NAT2* C481T	-	C/T	46	10	3	0.14 (T)	4.526	0.03#
rs1799930	*NAT2* G590A	R197Q	G/A	26	24	9	0.36 (A)	0.750	0.39
rs1799931	*NAT2* G857A	G286E	G/A	36	22	1	0.20 (A)	1.340	0.25

HWE: Hardy-Weinberg equilibrium, VAF: Variance allele frequency, #P<0.05. TB: Tuberculosis

rifampicin, pyrazinamide, and ethambutol were given in the recommended dose ranges according to WHO guidelines.[2] The continuous data, including age, BMI, and anti-TB doses, are normal distribution. Patients from seven sub-ethnic groups in Myanmar were enrolled in this study [Table S1].

NAT2 gene Polymorphisms of Myanmar TB Patients

The highest *NAT2* SNP was *NAT2* SNP rs1041983 (56%). Interestingly, *NAT2* SNP rs1799929 was deviated from equilibrium [Table 1]. *NAT2**6A was the most common haplotype [Table 2]. The most common genotype was *NAT2**4/*7B [Table 3]. Most patients were slow acetylators (n = 28, 47.46%) and intermediate acetylators (n = 26, 44.07%). Five patients (8.47%) were rapid acetylators [Table 3].

Association of Non-genetic Factors of Myanmar TB Patients and Elevated Liver Enzymes during Anti-TB Treatment

Non-genetic factors of patients in the normal liver enzyme group and the elevated liver enzyme group were not significantly different [Table S2]. In the same way, anti-TB doses were not different between patient groups [Table S3].

Association of Genetic Factors of Myanmar TB Patients and Elevated Liver Enzymes During Anti-TB Treatment

NAT2 SNP rs1799929 had an impact on AST levels, as patients with CT and TT variances had significantly higher AST levels (P < 0.05 compared to the CC genotype) [Figure 1a]. With binary logistic regression, the association of *NAT2* SNP rs1799929 CT genotype with elevated AST liver enzymes in patients was found (odds ratio = 4.625, 95% confidence interval = 1.078–19.840, P = 0.039) [Table 4]. One-way ANOVA revealed a significant difference of AST levels among *NAT2* genotypes (P = 0.048), which *NAT2**5B/*5B had the highest liver AST levels [Table 5] However, one-way ANOVA showed no effect of NAT2 phenotypes on AST levels [Figure 2a].

Similarly, patients with TT variance exhibited significantly higher ALT levels (P < 0.05 compared to CC genotype) [Figure 1b]. In addition, the highest ALT values were found in *NAT2**5B/*5B [Table 5], and slow acetylator displayed significant ALT liver enzymes (P < 0.05 compared to rapid acetylator) [Figure 2b]. However, there is no significant association between *NAT2* SNPs and elevated ALT levels.

Table 2: *NAT2* haplotype distribution in Myanmar TB patients (n=59)

NAT2 allele	Haplotype†	2n=118	Frequency
*NAT2**4	C-C-G-G	36	0.305
*NAT2**5B	C-T-G-G	16	0.136
*NAT2**6A	T-C-A-G	42	0.356
*NAT2**7B	T-C-G-A	24	0.203

†Haplotype was determined from the four SNPs, including rs1041983, rs 1799929, rs 1799930, and rs1799931.
TB: Tuberculosis

Regression Analysis of Non-genetic and Genetic Factors of Myanmar TB Patients and Elevated Liver Enzymes during Anti-TB Treatment

Multiple linear regression analysis showed that *NAT2* SNP rs1799929, INH dose, and age of patients were associated with AST levels (B = 49.334, P < 0.001, B = 22.241, P = 0.007 and B = 1.991, P = 0.025, respectively) and explained 35.6% of the variation (R^2 = 0.356) [Table 6]. In addition, NAT2 phenotype, INH dose, and age also showed an association with AST liver enzymes in patients (B = 23.781, P = 0.038, B = 22.003, P = 0.016 ,and B = 2.581, P = 0.008, respectively) and explained 22.2% of the variation of AST liver enzymes in patients (R^2 = 0.222) [Table 6].

Similar to ALT levels, we detected an association of *NAT2* SNP rs1799929 and ALT liver enzymes of patients (B = 85.944, P < 0.001), and this regression explained 22.4% (R^2 = 0.224) of the variation in ALT levels of patients [Table 7].

DISCUSSION

This report is the first to investigate *NAT2* polymorphisms in the Myanmar population. *NAT2* SNP rs1041983 and *NAT2**6A, a slow *NAT2* allele, were highly observed in Myanmar TB patients. As a result, a high ratio of slow acetylators (47%) and

Table 3: *NAT2* phenotype and genotype distribution in Myanmar TB patients (n=59)

Phenotype	Genotype		*n*	*n* (%)	HWE	
					χ^2	P-value
Rapid acetylator	Rapid/rapid allele	*4/*4	5	5 (8.47)	0.091	0.763
Intermediate acetylator	Rapid/slow allele	*4/*5B	3	26 (44.07)		
		*4/*6A	11			
		*4/*7B	12			
Slow acetylator	Slow/slow allele	*5B/*5B	3	28 (47.46)		
		*5B/*6A	5			
		*5B/*7B	2			
		*6A/*6A	9			
		*6A/*7B	8			
		*7B/*7B	1			

HWE: Hardy-Weinberg equilibrium. TB: Tuberculosis

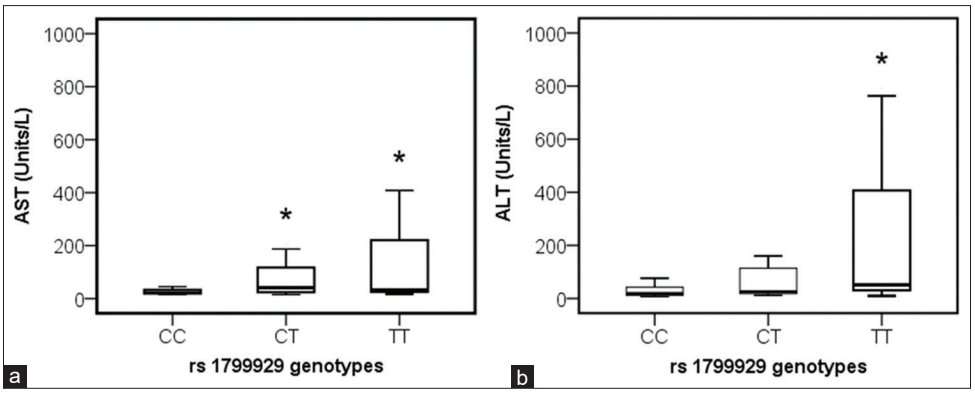

Figure 1: (a and b) Mean aspartate aminotransferase and alanine aminotransferase live enzymes of *NAT2* rs1799929 genotypes, CC (n = 46), CT (n = 10), and TT (n = 3),*P < 0.05 compared to CC genotype

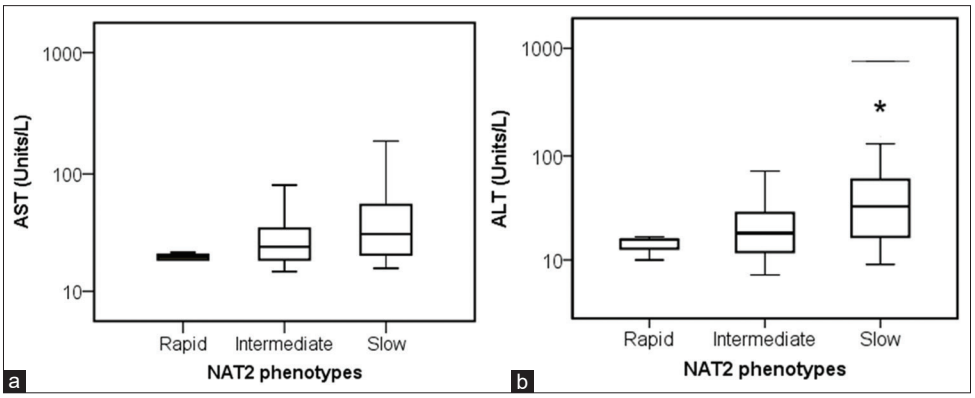

Figure 2: Mean aspartate aminotransferase and alanine aminotransferase live enzymes of NAT2 phenotypes, rapid (n = 5), intermediate (n = 26), and show (n = 28), P < 0.05 compared to NAT2 rapid acetylator

Table 4: Association of *NAT2* SNPs allele of patients and elevated AST liver enzyme ranges (n=59)

SNP	Genotype	*P*-value†	OR	C.I. (95%)	
				Lower	Upper
rs1041983	CC		reference		
	CT	0.860	1.174	0.199	6.935
	TT	0.382	2.250	0.365	13.870
rs1799929	CC		reference		
	CT	0.039#	4.625	1.078	19.840
	TT	0.514	2.312	0.186	28.717
rs1799930	GG		reference		
	GA	0.215	2.406	0.691	9.632
	AA	0.257	2.750	0.479	15.794
rs1799931	GG		reference		
	GA	0.799	0.850	0.243	2.973
	AA	1.000	0.000	0.000	NA

†Binary logistic regression for comparison between groups, P<0.05 considered significant, OR: Odds ratio, CI (95%): 95% confidence interval, #II<0.05. AST: Aspartate aminotransferase

intermediate acetylators (44%) was demonstrated in this study. *NAT2* polymorphism of the Myanmar population in this study is similar to previous studies in the Southeast Asian population, including Thai, Indonesian, and Buginese ethnicities of Indonesia.[14,19,22] In contrast, East Asian population, Chinese, Korean, and Japanese, are mostly rapid acetylators.[18,23]

A deviation from Hardy-Weinberg Equilibrium was found in *NAT2* SNP rs1799929. A small sample size together with seven sub-ethnic groups may explain this deviation. In Myanmar, ethnicity is highly diverse with eight main ethnicities and over 100 sub-ethnicities. This deviation suggests that ethnicity might be an important factor in genetic polymorphisms and that ethnicity should be an important inclusion criterion in future studies.

NAT2 SNP rs1799929 was highly associated with liver enzyme elevation in this study. *NAT2* SNP rs1799929 CT genotype was highly found in patients with elevated AST levels. In addition, multiple linear regression analyses suggested that *NAT2* SNP rs1799929 was the genetic determiner of elevated AST and ALT levels during anti-TB treatment. It is also noted that INH doses given to patients in normal and elevated liver enzyme groups were not significant different, even though the INH dose was close to the upper dosage range according to the WHO recommendations.[2] This study provides evidence of the influence of genetic factor, especially the *NAT2* SNP rs1799929, on anti-TB drugs induced liver enzyme elevation in the Myanmar population.

CT and TT genotypes of *NAT2* SNP rs1799929 are link to *NAT2**5, a slow *NAT2* allele. In the same way, this study

Table 5: Distribution of the NAT2 genotype, phenotype, and the respective liver enzymes in Myanmar TB patients (*n*=59)

Phenotype	Genotype	*n* (%)	AST, mean±SD	ALT, mean±SD
Rapid acetylator (*n*=5)	*4/*4	5 (8.5)	20.20±1.30	14.40±2.88
Intermediate acetylator (*n*=26)	*4/*5B	3 (5.1)	33.33±20.84	19.67±8.62
	*4/*6A	11 (18.6)	34.10±31.66	19.50±19.43
	*4/*7B	12 (20.3)	31.25±17.24	30.27±4.92
Slow acetylator (*n*=28)	*5B/*5B	3 (5.1)	152.67±221.27	274.67±423.41
	*5B/*6A	5 (8.5)	76.80±64.84	82.60±63.67
	*5B/*7B	2 (3.4)	108.50±11.02	66.00±67.88
	*6A/*6A	9 (15.3)	30.11±15.34	27.78±24.75
	*6A/*7B	8 (13.6)	38.00±21.99	46.75±17.59
	*7B/*7B	1 (1.7)	34.00	10.00
P-value[¶]			0.048[#]	0.02[#]

[¶]ANOVA for comparison between groups, $P<0.05$ considered significant, [#]$P<0.05$. TB: Tuberculosis, ALT: Alanine aminotransferase. ANOVA: Analysis of variance

Table 6: Multiple linear regression analysis between non-genetic and genetic factors and AST liver enzymes of patients (*n*=59)

Model		Unstandardized coefficients		Standardized coefficients	t	*P*-value[¶]	CI (95%)	
		B	SE	Beta			Lower	Upper
1	Constant	−165.545	60.794		−2.723	0.009	−287.429	−43.661
	rs1799929	49.334	12.066	0.459	4.089	<0.001[#]	25.143	73.525
	Isoniazid dose	22.241	7.992	0.315	2.783	0.007[#]	6.219	38.264
	Age	1.991	0.863	0.265	2.306	0.025[#]	0.260	3.722
R^2=0.356, Adjusted R^2= 0.320								
2	Constant	−226.037	73.839		−3.061	0.003	−374.076	−77.998
	NAT2 phenotype	23.781	11.187	0.258	2.126	0.038[#]	1.352	46.210
	Isoniazid dose	22.003	8.823	0.311	2.494	0.016[#]	4.314	39.692
	Age	2.581	0.932	0.344	2.771	0.008[#]	0.713	4.449
R^2=0.222, Adjusted R^2= 0.179								

B: Linear coefficient, S.E: Standard Error, C.I. (95%): 95% confidence interval. Model 1: Age, BMI, INH doses, rs1041983, rs1799929, rs1799930, and rs1799931 to multiple linear regression. Model 2: Age, INH doses, NAT2 phenotype to multiple linear regression. [¶]*P*-value was calculated by stepwise linear regression analysis, #$P<0.05$. AST: Aspartate aminotransferase

Table 7: Multiple linear regression analysis between non-genetic and genetic factors and ALT liver enzymes of patients (*n*=59)

Model		Unstandardized coefficients		Standardized coefficients	t	*P*-value[¶]	CI (95%)	
		B	SE	Beta			Lower	Upper
1	Constant	22.577	13.405		1.684	0.098	-4.288	49.442
	rs1799929	85.944	21.578	0.473	3.983	<0.001[#]	42.701	129.186
R^2=0.224, Adjusted R^2= 0.210								

B: Linear coefficient, SE: Standard Error, CI (95%): 95% confidence interval. Model 1: INH doses, rs1041983, rs1799929, rs1799930, and rs1799931 to multiple linear regression, [¶]*P*-value was calculated by stepwise linear regression analysis, [#]$P<0.05$. ALT: Alanine aminotransferase

revealed the highest AST and ALT levels in slow acetylators with *NAT2**5B/*5B. Furthermore, multiple linear regression analysis reported a significant association between the NAT2 phenotype and AST levels. This result is in agreement with the review article by Tostmann *et al*.[8] showing that advanced age and slow acetylator status were risk factors for AT-DILI.

CONCLUSION

The distribution of slow acetylators and intermediate acetylators is higher than that of rapid acetylators in this Myanmar population. *NAT2* polymorphism is an important factor in predicting elevated AST and ALT levels. The result suggests that the lower doses of anti-TB drugs would be appropriate for this population group. In addition, adverse drug reactions, especially AT-DILI, should be closely monitored in Myanmar patients. This study provides data to support adverse drug reaction management of Myanmar migrant workers to promote anti-TB drug compliance and consequently reduce the epidemic of TB infection in the Southeast Asia region.

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AUTHORS' CONTRIBUTIONS

Study design: RR, KST; Sample collection: KST, CC; DNA genotyping and analysis: KST, PK; Data analysis: RR, KST, PK; and Manuscript preparation: RR, KST, PK.

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SUPPLEMENTARY

Table S1: Demographic and clinical characteristics of Myanmar TB patients (n=59)

Patients' characteristics	n=59
Age, mean±S.D.	31.20±8.05
Gender, n (%)	
Male	24 (40.7%)
Female	35 (59.3%)
BMI (kg/m^2), mean±S.D.	19.89±3.16
Ethnicity, n (%)	
Burma	32 (54.2%)
Mon	16 (27.1%)
Da-wal	5 (8.5%)
Ka-yin	2 (3.4%)
Ya-khaing	2 (3.4%)
Shan	1 (1.7%)
Pa-O	1 (1.7%)
Types of TB, n (%)	
Pulmonary TB	51 (86.4%)
Extra-pulmonary TB	8 (13.6%)
INH (mg/kg) , mean±S.D.	5.60±0.86
RIF (mg/kg) , mean±S.D.	10.36±1.09
PZA (mg/kg) , mean±S.D.	24.52±3.64
ETB (mg/kg) , mean±S.D.	18.24±1.65
Type of TB regimen, n (%)	
First-time treatment with anti-TB drugs	59 (100%)
AST†, mean±S.D.	44.14±59.23
ALT†, mean±S.D.	46.51±99.97

BMI: Body Mass Index, TB: Tuberculosis, S.D.: Standard Deviation, INH: Isoniazid, RIF: Rifampicin, PZA: Pyrazinamide, ETB: Ethambutol, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, †AST and ALT liver enzymes are measured after 2-week of anti-TB treatment

Table S2: Association of non-genetic factors of patients and elevated liver enzyme ranges (n=59)

Variables	AST liver enzymes		*p*-value	ALT liver enzymes		*p*-value
	normal (n=45)	elevated (n=14)		normal (n=42)	elevated (n=17)	
Age (mean±S.D.)	31.11±7.98	31.50±8.56	>0.05†	30.83±8.17	32.12±7.91	>0.05†
BMI (mean±S.D.)	20.30±3.20	18.58±2.57	>0.05†	20.24±3.12	19.05±3.10	>0.05†
Gender (n)						
Male	20	4	>0.05†	17	7	>0.05†
Female	25	10		25	10	
Type of TB (n)						
P-TB	39	12	>0.05†	37	14	>0.05†
EP-TB	6	2		5	3	

BMI: body mass index, P-TB: pulmonary TB, EP-TB: extra-pulmonary TB, S.D.: standard deviation, †Students t-test, †χ^2 or Fisher's exact test for comparison of variables between groups

Table S3: Association of doses of anti-TB drugs of patients and elevated liver enzyme ranges (n=59)

Variables	AST liver enzymes		*p*-value	ALT liver enzymes		*p*-value
	normal (n=45)	elevated (n=14)		normal (n=42)	elevated (n=17)	
INH (mg/kg) mean±S.D.	5.88±0.87	6.38±0.70	>0.05†	5.93±0.88	6.16±0.81	>0.05†
RIF (mg/kg) mean±S.D.	10.35±1.08	10.38±1.04	>0.05†	10.36±0.18	10.36±1.03	>0.05†
PZA (mg/kg) mean±S.D.	24.70±3.72	23.97±3.45	>0.05†	24.74±3.53	24.00±3.99	>0.05†
ETB (mg/kg) mean±S.D.	18.28±1.69	18.10±1.54	>0.05†	18.38±1.43	17.89±2.10	>0.05†

INH: isoniazid, RIF: rifampicin, PZA: pyrazinamide, ETB: ethambutol, S.D.: standard deviation, †Students t-test for comparison of variables between groups

AQ1 **Table S4:** Association of *NAT2* SNPs allele of patients and elevated ALT liver enzyme ranges (n=59)

SNP	Genotype	B	S.E	Wald	*p*-value†	OR	C.I. 95%	
							lower	upper
rs1041983	CC				reference			
	CT	0.588	0.887	0.439	0.507	1.800	0.317	10.232
	TT	1.052	0.919	1.310	0.252	2.864	0.473	17.351
rs1799929	CC				reference			
	CT	0.693	0.733	0.893	0.345	2.000	0.475	8.420
	TT	1.792	1.273	1.980	0.159	6.000	0.495	72.771
rs1799930	GG				reference			
	GA	0.711	0.634	1.257	0.262	2.036	0.588	7.052
	AA	-0.100	0.929	0.012	0.914	0.905	0.147	5.583
rs1799931	GG				reference			
	GA	0.929	0.597	2.420	0.120	2.531	0.785	8.157
	AA	-19.986	40192.970	0.00	1.000	0.000	0.000	NA

†Binary logistic regression for comparison between groups, $P<0.05$ considered significant, OR: odds ratio, C.I. (95%): 95% confidence interval