

# Increasing serum transaminase is not associated with the serum isoniazid and rifampicin levels in tuberculosis patients treated with fixed-dose combination antituberculosis in Yogyakarta

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## ABSTRACT

Tuberculosis (TB) remains a major health problem in the world. Isoniazid (INH) and rifampicin are first-line antituberculosis that can cause hepatotoxicity characterized by an increase of serum transaminase level. Previous study showed the increase in transaminase level of TB patients due to INH and rifampicin. However, it did not explain about its correlation with the drugs concentration. The aim of this study was to evaluate the relationship between the increase of serum INH and rifampicin concentrations and the increase of serum transaminase level in TB patients. This was a cross sectional study involving 31 TB patients who underwent intensive phase of treatment with fixed-dose combination antituberculosis therapy (FDC-ATT) in Yogyakarta. Serum transaminase levels i.e. AST and ALT before and at the end of the intensive phase of treatment were determined by an automatic chemical analyzer. Serum INH and rifampicin concentrations at the end of the intensive phase of treatment were measured by HPLC. t- test, Mann Whitney, Fisher and Spearman tests were used to analyze the data. Mean of INH and rifampicin concentrations were  $2.72 \pm 0.46 \mu\text{g/mL}$  and  $4.12 \pm 0.42 \mu\text{g/mL}$ , respectively. Mean of INH and rifampicin concentrations of TB patients with high AST level ( $5.03 \pm 4.14 \mu\text{g/mL}$  and  $8.52 \pm 3.06 \mu\text{g/mL}$ ) tended to be higher than those with normal AST level ( $2.47 \pm 0.27 \mu\text{g/mL}$  and  $3.64 \pm 0.32 \mu\text{g/mL}$ ). However, they were not significantly difference ( $p > 0.05$ ). Furthermore, mean of INH and rifampicin concentrations of TB patients with high ALT level ( $7.07 \pm 6.24 \mu\text{g/mL}$  and  $10.67 \pm 3.76 \mu\text{g/mL}$ ) also tended to be higher than those with normal AST level ( $2.42 \pm 0.26 \mu\text{g/mL}$  and  $3.66 \pm 0.30 \mu\text{g/mL}$ ). However, they were not also significantly difference ( $p > 0.05$ ). In conclusion, there are no correlation between INH and rifampicin concentrations and the increase of transaminase level in TB patients after intensive phase of treatment.

## ABSTRAK

Tuberkulosis (TB) masih menjadi masalah kesehatan utama di dunia. Isoniasid (INH) dan rifampisin adalah antituberkulosis lini pertaman yang dapat menyebabkan hepatotoksik yang ditandai dengan kenaikan kadar transaminase serum. Penelitian sebelumnya

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menunjukkan kenaikan transaminase serum pasien TB disebabkan INH dan rifampisin. Namun demikian tidak dijelaskan hubungannya dengan kadar obat dalam tubuh. Tujuan penelitian ini adalah untuk mengkaji hubungan antaran kenaikan kadar INH dan rifampicin serum dengan kenaikan transaminase pada pasien TB. Penelitian ini merupakan penelitian potong lintang yang melibatkan 31 penderita TB yang menjalani pengobatan fase intensif dengan obat antituberkulosis kombinasi dosis tetap di Yogyakarta. Kadar transaminase serum yaitu SGPT dan SGOT sebelum dan setelah pengobatan fase intensif diukur *automatic chemical analyzer*. Kadar INH dan rifampicin serum pada akhir pengobatan fase intensif diukur dengan HPLC. Uji t, Mann-Whitney, Fisher dan Spearman digunakan dalam analisis data. Rerata kadar INH dan rifampisin berturut-turut adalah  $2,72 \pm 0,46 \mu\text{g}/\text{mL}$  dan  $4,12 \pm 0,42 \mu\text{g}/\text{mL}$ . Rerata kadar INH dan rifampisin serum pasien TB dengan kadar SGPT tinggi ( $5,03 \pm 4,14 \mu\text{g}/\text{mL}$  dan  $8,52 \pm 3,06 \mu\text{g}/\text{mL}$ ) cenderung lebih tinggi dibandingkan pasien dengan SGPT rendah ( $2,47 \pm 0,27 \mu\text{g}/\text{mL}$  dan  $3,64 \pm 0,32 \mu\text{g}/\text{mL}$ ). Namun demikian perbedaan ini tidak bermakna secara signifikan ( $p > 0,05$ ). Demikian juga rerata kadar INH dan rifampisin serum pasien TB dengan kadar SGOT tinggi ( $7,07 \pm 6,24 \mu\text{g}/\text{mL}$  dan  $10,67 \pm 3,76 \mu\text{g}/\text{mL}$ ) cenderung lebih tinggi dibandingkan pasien dengan SGOT rendah ( $2,42 \pm 0,26 \mu\text{g}/\text{mL}$  dan  $3,66 \pm 0,30 \mu\text{g}/\text{mL}$ ). Namun demikian perbedaan ini juga tidak bermakna secara signifikan ( $p > 0,05$ ). Dapat disimpulkan tidak terdapat hubungan antara kadar INH dan rifampisin serum dengan kenaikan kadar transaminase pada pasien TB setelah pengobatan fase intensif.

**Keywords** : serum transaminase – isoniazid – rifampicin - fixed dose combination – hepatotoxics

## INTRODUCTION

Tuberculosis (TB) remains a major health problem in the world including in Indonesia. In 2007, an estimated 9.27 million new cases of tuberculosis in the world was reported with the incidence was approximately 140 cases per 100,000 population. This incidence increased from the previous report of 9.24 million new cases in 2006 and 8.3 million new cases in 2000.<sup>1</sup> Indonesia is the third highest number of TB cases in the world after India and China. It is estimated that the number of TB patients in Indonesia around 10% of the total number of TB patients in world.<sup>2</sup> According to the World Health Organization (WHO) the number of TB cases in Indonesia around 566,000 or 244/100,000/year, with the death cases reached 91,000 person/year.<sup>3</sup>

Rifampicin, isoniazid (INH), pyrazinamide, ethambutol and streptomycin are the first-line drugs for TB. They are available in the form of a package of fixed-dose

combinations (FDCs) consisting of a combination of 2 or 4 drugs in one tablets.<sup>2</sup> The advantages of the FDC antituberculosis therapy (FDC-ATT) include better patient compliance, simplification of prescription, easier management of drug supply, reduced cost and less chances of developing drug resistance, whereas the disadvantages include prescribing errors, development of side effects, trust excessive of the treatment observer and decrease of rifampicin bioavailability.<sup>3-5</sup>

Drug-induced hepatotoxicity caused by isoniazid (INH), rifampicin, and pyrazinamide is commonly observed in patients receiving antituberculosis treatment.<sup>6</sup> In clinical practice, hepatotoxicity is characterized by the increase of serum transaminase levels more than three times the upper limit of normal, accompanied by symptoms such as anorexia, nausea, vomiting or abdominal pain or those more than five times the normal limit without symptoms.<sup>7</sup>

Rifampicin is well known as a potent cytochrome P450 (CYP) inducer. It has been known to markedly decrease serum concentrations of various drugs, which are concomitantly administered treatment.<sup>8</sup> Administration of rifampicin along with INH in FDC-ATT may increase serum concentration of toxic metabolite of INH such as mono acetylhydrazine lead to increase hepatotoxicity.<sup>9-11</sup> This study was conducted to evaluate the association between serum concentrations of INH and rifampicin and serum transaminase in tuberculosis patients treated with fixed-dose combinations antituberculosis in Yogyakarta.

## **SUBJECTS AND METHODS**

### **Subjects**

This cross sectional study was performed from August 2009 to January 2010 in Yogyakarta. The pulmonary tuberculosis patients who underwent the intensive phase of tuberculosis treatment in the Community Health Care and Center for Pulmonary Disease Treatment (BP4) in Yogyakarta were selected. The inclusion criteria were smear positive pulmonary tuberculosis, aged more than 18 years, had never received antituberculosis drugs, currently received FDC-ATT category 1 and willing to participate in the study by signing a written informed consent. The exclusion criteria were had diabetes mellitus, disturbed liver function, could not well communicate and not willingness to follow the tuberculosis treatment program with DOTS (direct observed treatment, short course). The protocol of this study has been approved by the Medical Health Research Ethics Committee, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta.

### **Procedure**

On the day that had been agreed, patients were gathered to be selected. An explanation concerning the background, objectives, benefit of the study was given. Patients who fulfilled the criteria were given an informed consent to be signed. Demographics data of patients include name, age, gender, weight, height and body mass index (BMI) were then recorded. Data of medical history, physical examination and nutritional status were obtained from medical records or questionnaires. Before the intensive phase of treatment initiated (day 0), the blood sample were taken from the median cubital vein of patients and serum transaminase levels i.e. aspartate aminotransferase (AST/GOT) and alanin aminotransferase (ALT/GPT) were determined. During the intensive of treatment, patient's clinical symptoms include nausea, vomiting and jaundice were monitored and recorded. In case of jaundice observed during the intensive of treatment, serum transaminase of the patients was determined. At the end of the intensive of treatment (day 56), the blood sample were taken again and serum transaminase, INH as well as rifampicin levels were determined. The serum INH and rifampicin levels were determined by using high-performance liquid chromatography (HPLC) method in the Integrated Research and Testing Laboratory, Universitas Gadjah Mada, Yogyakarta.

### **Statistical analysis**

Data were presented as mean  $\pm$  standard deviation (SD) or percentage. Numerical data were compared by using t-test or Mann-Whitney U test., whereas categorical data were compared by using Chi-square test or Fisher exact test. Correlation between serum isoniazid, rifampicin and transaminase levels were analyzed by using Spearman test.

**RESULTS**

**Characteristics of subjects**

Thirty one pulmonary tuberculosis patients who meet the inclusion and exclusion criteria were enrolled in this study. The characteristics of patients were presented in TABLE 1. The age of subjects varied from 21 to 71 years with the mean of  $44.2 \pm 13.7$  years. In addition, based on the nutritional status the majority of subjects were under weight (58.1%) with the mean of BMI value was  $18.4 \pm 2.0$ .

TABLE 1. Characteristics of subjects (n=31)

Characteristics	Value
Age (mean±SD year)	$44.2 \pm 13.7$
Sex [n (%)]	
• Male	24 (77.4)
• Female	7 (22.6)
Weight (mean±SD kg)	$49.5 \pm 5.8$
Height (mean±SD m)	$1.64 \pm 0.06$
Body Mass Index (mean±SD)	$18.4 \pm 2.0$
Nutritional Status [n (%)]	
• Normal	13 (41.9)
• Low	18 (58.1)

**Serum INH, rifampicin, AST and ALT levels**

The serum INH level of subjects after intensive phase of treatment (day 56) wide varied from 0.53 to 13.32 µg/mL with the average of  $2.72 \pm 0.46$  µg/mL, while those serum rifampicin level also wide varied from 0.49 to 14.43 µg/mL with the average of  $4.12 \pm 0.42$  µg/mL. Serum AST level after intensive phase of treatment showed that 3 (9.6%) subjects had high serum AST level (>37 mg/dL) whereas most of subjects had

normal serum AST level (15-37 mg/dL). Furthermore, serum ALT level after intensive of treatment showed that 2 (6.5%) subjects had high serum ALT level (>40 mg/dL), whereas most of subjects had normal serum ALT level (5-40 mg/dL).

**Gender, nutritional status, age and dose in relations to AST and ALT levels**

Based on the AST level showed that most of subjects were male (24 subjects or 77.4%), only 7 (22.6%) subjects were female (TABLE 1). Subjects with high AST level were dominated by male (2 subjects or 66.7%) and only 1 subject or 33.3% was female. Similarly result was observed in the subjects with normal AST levels. Twenty two or 78.6% subjects were male and only 6 or 21.4% were female (TABLE 2).

Although the serum INH level in subjects with high AST level ( $5.03 \pm 4.14$  µg/mL) was two time higher than it in subjects with normal AST level ( $2.47 \pm 0.27$  µg/mL). However, it was not significantly different ( $p = 0.05$ ). Similarly result was observed in the serum rifampicin level. The serum rifampicin level in subjects with high AST level ( $8.52 \pm 3.06$  µg/mL) was also higher than it in subjects with normal AST level ( $3.64 \pm 0.32$  µg/mL). However, it was not significantly different ( $p = 0.25$ ) (TABLE 2).

Most of subjects with high AST level (2 of 3 subjects or 66.7%) and those with normal AST level (22 of 28 subjects or 78.6%) were given 3 tablets of FDC-ATT. Only 1 subject (33.3%) with high AST level and 6 subjects (21.4%) with normal AST level were given 4 tablets of FDC-ATT (TABLE 2).

TABLE 2. Characteristics of subjects based on AST (n=31)

Characteristic	AST level		p
	High (n=3)	Normal (n=28)	
Age (mean ± SD year)	39.3 ± 3.5	45.5 ± 13.7	0.08 <sup>a</sup>
Sex [n (%)]			
• Male	2 (66.7)	22 (78.6)	0.55 <sup>b</sup>
• Female	1 (33.3)	6 (21.4)	
Weight (mean ± SD kg)	49.0 ± 6.6	50.0 ± 6.6	0.80 <sup>a</sup>
Height (mean ± SD m)	1.64 ± 0.12	1.64 ± 0.06	0.88 <sup>a</sup>
Body Mass Index (mean ± SD)	18.1 ± 0.3	18.7 ± 2.4	0.68 <sup>a</sup>
Nutritional status (%)			
• Normal	0/3 (0)	13/28 (46.4)	0.24 <sup>b</sup>
• Low	3/3 (100)	15/28 (53.6)	
Isoniazid level (mean ± SEM µg/mL)	5.03 ± 4.14	2.47 ± 0.27	0.05 <sup>c</sup>
Rifampicin level (mean ± SEM µg/mL)	8.52 ± 3.06	3.64 ± 0.32	0.25 <sup>a</sup>
Dose FDC-ATT [n (%)]			
• 4 tablets	1 (33.3)	6 (21.4)	0.55 <sup>b</sup>
• 3 tablets	2 (66.7)	22 (78.6)	

<sup>a</sup>Independent t-test; <sup>b</sup>Fisher's exact test; <sup>c</sup>Mann-Whitney U test

Based on ALT level showed that most of subjects were also male (24 subjects or 77.4%), only 7 (22.6%) subjects were female (TABLE 1). Subjects with high ALT level were similar between male and female, whereas subjects with normal ALT level were dominated by male 23 (79.3%) and only 6 or 20.7% subjects were female.

Similar result was observed between serum INH and rifampicin levels in relation with AST level and with ALT level. Although the serum INH level in subjects with high ALT level ( $7.07 \pm 6.24$  µg/mL) was almost three time higher than it in subjects with normal ALT level ( $2.42 \pm 0.26$  µg/mL). However,

it was not significantly different ( $p = 0.05$ ). Similarly result was observed in the serum rifampicin level. The serum rifampicin level in subjects with high ALT level ( $10.67 \pm 3.76$  µg/mL) was also higher than it in subjects with normal ALT level ( $3.66 \pm 0.30$  µg/mL). However, it was not significantly different ( $p = 0.25$ ) (TABLE 3).

One (50%) subjects with high ALT level and 23 (79.3%) subjects with normal ALT were given 3 tablets of FDC-ATT and 1 (50.0%) subjects with high ALT level and 6 (20.7%) subjects with normal AST level were given 4 tablets of FDC-ATT (TABLE 3).

TABLE 3. Characteristics of subjects based on ALT (n=31)

Characteristic	ALT level		p
	High (n=2)	Normal (n=29)	
Age (mean ± SD year)	37.5 ± 2.1	45.4 ± 13.5	0.42 <sup>a</sup>
Sex [n (%)]			
Male	1 (50.0)	23 (79.3)	0.40 <sup>b</sup>
Female	1 (50.0)	6 (20.7)	
Weight (mean ± SD kg)	49.5 ± 9.2	50.0 ± 6.5	0.75 <sup>a</sup>
Height (mean ± SD m)	1.63 ± 0.12	1.64 ± 0.06	0.95 <sup>a</sup>
Body Mass Index (mean ± SD)	18.2 ± 0.1	18.6 ± 2.3	0.78 <sup>a</sup>
Nutritional status (%)			
Normal	0/2 (0)	13/29 (46.4)	0.49 <sup>b</sup>
Low	2/2 (100)	16/29 (53.6)	
Isoniazid level (mean ± SEM µg/mL)	7.07 ± 6.24	2.42 ± 0.26	0.81 <sup>c</sup>
Rifampicin level (mean ± SEM µg/mL)	10.67 ± 3.76	3.66 ± 0.30	0.31 <sup>a</sup>
Dose FDC-ATT [n (%)]			
4 tablets	1 (50.0)	6 (20.7)	0.40 <sup>b</sup>
3 tablets	1 (50.0)	23 (79.3)	

<sup>a</sup>Independent t-test; <sup>b</sup>Fisher’s exact test; <sup>c</sup>Mann-Whitney U test

**Correlation between isoniazid and rifampicin levels and AST and ALT levels**

No significant correlation between the serum INH and rifampicin levels, dose of

FDC-ATT as well as nutritional status and the difference in the ALT and AST levels were observed in thi study (TABLE 4).

TABLE 4. Correlation between isoniazid, rifampicin levels, dose of FDC-ATT and nutritional status with ALT and AST levels

Characteristic	difference AST p value	difference ALT p value
Isoniazid level	0.431	0.782
Rifampicin level	0.529	0.890
Dose of FDC-ATT	0.329	0.820
Nutritional status	0.135	0.800

Analysis with Spearman test

To evaluate the influence of the INH and rifampicin levels, dose of FDC-ATT and age on the serum AST level, the Fisher’s exact test was performed (TABLE 5). Subjects with high serum INH level ( $\geq 5 \mu\text{g/mL}$ ) had risk

of high serum AST level 13.5 greater than those with low serum INH level ( $< 5 \mu\text{g/mL}$ ). However, it was not statistically significant (OR=13.5;95% CI: 0.0-924.6).

TABLE 5. Influence of serum INH and rifampicin levels, dose of FDC-ATT as well as age on the risk of increase in serum AST level

Variabel	AST		x <sup>2</sup> , p	OR (95% CI)
	High	Normal		
Isoniazid level				
High	1	1	0.18	13.5 (0.0-924.6)
Normal	2	27		
Rifampisin level				
Normal	1	0	0.97	—
Low	2	28		
FDC-ATT				
4 tablets	1	6	0.55	1.83 (0.0-35.4)
3 tablets	2	22		
Age				
Old	1	16	0.57	0.38 (0.01-6.37)
Young	2	12		

Analysis with Fisher's Exact Test

Furthermore, the risk of developing high serum AST levels in subjects with dose of 4 tablets FDC-ATT was 1.83 times greater than those with dose of 3 tablets FDC-ATT. However, it was not also statistically significant (OR = 1.83; 95 % CI: 0.0-35.4). Age had no effect on the increase in serum AST level (OR = 0.38; 95% CI: 0.01 to 6.37).

To evaluate the influence of the INH and rifampicin levels, dose of FDC-ATT and age on the serum ALT level, the Fisher's exact test was performed (TABLE 5). Subjects with high serum INH level ( $\geq 5 \mu\text{g/mL}$ ) had risk of high serum AST level 28.0 greater than those with low serum INH level ( $< 5 \mu\text{g/mL}$ ). However, it was not statistically significant (OR=28.0;95% CI: 0.0-6844.55).

TABLE 6. Influence of serum INH and rifampicin levels, dose of FDC-ATT as well as age on the risk of increase in serum ALT level

Variabel	ALT		x <sup>2</sup> , p	OR (95% CI)
	High	Normal		
Isoniazid level				
High	1	1	0.13	28.0 (0.0-6844.55)
Normal	2	28		
Rifampisin level				
Normal	1	0	0.65	—
Low	1	29		
FDC-ATT				
4 tablets	1	6	0.55	3.83 (0.0-171.00)
3 tablets	2	22		

Analysis with Fisher's Exact Test

Furthermore, the risk of developing high serum ALT levels in subjects with dose of 4 tablets FDC-ATT was 3.83 times greater than those with dose of 3 tablets FDC-ATT. However, it was not also statistically significant (OR = 3.83; 95 % CI: 0.0-171.00).

### **Characteristics of subjects who have extreme data**

One of the subjects in this study had the highest serum drugs level compared to other subjects. Serum INH and rifampicin levels of this subject were 13.32 µg/mL and 14.43 µg/mL, respectively. Characteristics of this subject was a man with 39 years old, 55 kg body weight and low nutritional status (BMI of 17.9). He received 4 tablets FDC-ATT containing INH 300 mg and rifampicin 600 mg daily during the intensive phase of treatment. The serum AST and ALT levels of this subject before the intensive of treatment were normal. However, this serum AST and ALT levels increased five time at the end of the intensive of treatment, whereas his serum urea level (13 mg/dL) and serum creatinine level (0.96 mg/dL) were normal. This subject underwent intensive phase compliance of treatment, therefore he underwent continuous phase of treatment with drug-induced hepatotoxicity monitoring.

## **DISCUSSION**

### **Effect of serum INH concentration on serum transaminase**

The mean serum INH concentration two hours after FDC-ATT on 31 subjects was  $2.72 \pm 0.46$  µg/mL varied from 0.53 to 13.32 µg/mL with the median of 2.21 µg/mL. McIlleron *et al.*<sup>12</sup> reported that two hours after INH ingestion the median serum INH concentration was 5.0 µg/mL with the lowest concentration was 0.4 µg/mL and the highest

concentration was 13.6 µg/mL. Although the median of serum INH concentration in this study was different compare to that reported McIlleron *et al.*,<sup>12</sup> however the range of serum INH concentration was similar.

The mean serum INH concentration of subjects with high ALT level was almost three time higher than it in subjects with normal ALT level although it was not significantly different. The increase of ALT level until five times of normal was found in one (3.3%) subject in this study. The increase of ALT level of patients who underwent tuberculosis treatment was reported in previous studies. An increase of ALT level until five times on 0.56% of tuberculosis patients who treated with single dose of INH was reported.<sup>13</sup> An another study also reported an increase of serum transaminases until three times of normal on 0.3% of latent tuberculosis patients after treatment.<sup>14</sup>

Previous studies reported that INH hepatotoxicity was associated with the patient acetylator status in the *N*-acetyltransferase 2 (*NAT2*) genotype.<sup>15-18</sup> Slow acetylator status was a significant risk factor for drug-induced liver injury (DILI) in TB patients.<sup>19-22</sup> Isoniazid is metabolized to acetylisoniazid by NAT, which is then hydrolyzed to acetylhydrazine. Acetylhydrazine can be transformed into diacetylhydrazine by acetylation process and oxidized by CYP2E1 to form hepatotoxic metabolites. Low NAT activity in slow acetylator status will increase the risk of hepatotoxicity due to the majority acetylhydrazine is oxidized.<sup>23</sup>

### **Effect of serum rifampicin concentration on serum transaminase**

The mean serum rifampicin concentration two hours after FDC-ATT on 31 subjects was  $4.12 \pm 0.46$  µg/mL varied from 0.49 to 14.43 µg/mL. This serum rifampicin concentration



was relatively low therefore it did not influence serum transaminase of the patients. Van Crevel *et al.*<sup>24</sup> reported that serum rifampicin concentration two hours after ingestion can be categorized into subtherapeutic levels (<4 µg/mL), low concentration (4-8 µg/mL), therapeutic levels (8- 20 µg/mL), and toxic levels (> 20 µg/mL). Furthermore, it was also reported that 70% of the TB patients had subtherapeutic rifampicin concentrations (<4 µg/mL) and no toxic rifampicin concentration in serum was observed.<sup>24</sup> Another study reported 64% of TB patients had plasma rifampicin concentration less than 8 µg/mL after rifampicin treatment.<sup>25</sup> In this study, 55% of the TB patients had subtherapeutic, 40% of those had low therapeutic and only 3% of those had therapeutic level. The different in drug preparation may influence the serum rifampicin of TB patients. In this study rifampicin were given in FDC-ATT.

The mean serum rifampicin concentration of subjects with high ALT level was also almost three time higher than it in subjects with normal ALT level although it was not significantly different. It was indicated that serum rifampicin level did not affect the increase in serum transaminase. Previous studies conducted on TB patients showed the increase of serum transaminase level was not associated with the serum rifampicin level.<sup>26,27</sup>

#### **Effect of age, gender and nutritional status on serum transaminases**

No association between age and serum transaminase level was observed in this study. The serum transaminase level of the younger TB patients (18-40 years) was not significantly different compare to those older patients (>40 years). Previous studies also showed that the age was not associated with the incidence of hepatotoxicity.<sup>6,28,29</sup> Conversely, Mahmood

*et al.*<sup>30</sup> reported that serum transaminase increased in older TB patient (>35 years).

Gender was not also associated with the increase of serum transaminase in this study. The serum transaminase level of male TB patients was not significantly different compare to female TB patients. However, previous studies reported that the increase of serum transaminase was more frequent in female TB patients.<sup>30,31</sup> Similar with this study, the nutritional status was reported not associated with the serum transaminase.<sup>17,30,31</sup>

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#### **CONCLUSION**

In conclusion, the increase of serum transaminase is not associated with serum INH and rifampicin levels in pulmonary tuberculosis patients receiving FDC-ATT.

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