

**Original Article**

**DECREASE OF LIVER FUNCTION AFTER TREATMENT OF ANTITUBERCULOSIS DRUGS IN TUBERCULOSIS PATIENTS WITH MALNUTRITION AND ALCOHOL CONSUMPTION**

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**ABSTRACT**

**Objective:** To evaluate the decrease of liver function after treatment of antituberculosis drugs-fixed doses combination (ATD-FDC) category 1 in tuberculosis patients with malnutrition and alcohol consumption.

**Methods:** This was an experimental study, with a quasi-experimental pretest and posttest design, to evaluate the increase in SGPT in pulmonary TB patients with malnutrition, treated with ATD-FDC for 8 w. Inclusion criteria were: pulmonary TB patients, aged  $\geq 18$  y old, who would receive ATD-FDC category 1 treatment, did not have an increase in SGPT level at the beginning of the treatment and were willing to join the study. This study was conducted in all community health centers in Kupang, Indonesia.

**Results:** The result of this study showed that percentage of SGPT level is increased after treatment of ATD-FDC compared with before treatment in TB patient with malnutrition compared with TB patients without malnutrition (135.1% vs. 54.7%;  $p < 0.001$ ). The difference of SGPT level in TB patients  $\geq 40$  y versus  $< 40$  y was 15.5 IU/l versus 9.1 IU/l ( $p < 0.05$ ). The difference of SGPT level in TB patient  $\geq 40$  y with routine alcohol consumption habit compared with non-routine alcohol consumption was 29.3 IU/l vs. 12.8 IU/l ( $p < 0.01$ ).

**Conclusion:** Pulmonary TB patients with malnutrition had a larger decrease in liver function after treatment with ATD-FDC category 1 for 8 w, compared to those without malnutrition. Routine alcohol consumption had an effect on the increase in SGPT level in older patients.

**Keywords:** ATD-FDC-malnutrition-alcohol consumption.

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**INTRODUCTION**

Tuberculosis (TB) is an important global public health problem, and until recently, it has become the attention of various countries in the world. In Indonesia, TB is a major problem in public health. A total number of TB patients in Indonesia is on the highest five in the world, after India, China, South Africa and Nigeria [1].

The effectivity of TB drugs is the main health issue in various countries in the world. It is affected mainly by the adherence of the patients, multidrug resistance, and unfavorable drug adverse effects [2]. Antituberculosis drugs (ATD) have adequately high affectivity, with acceptable toxicity level; however, these drugs given in combination may lead to serious adverse effects. Possible adverse effects include hepatitis (jaundice) without other causes, pruritus and skin redness, balance disorder, deafness, gastrointestinal disorder, eye disorder, purpura and shock [3-4].

Three drugs in the treatment of TB, namely, isoniazid, pyrazinamide, and rifampicin, have the potential to cause hepatotoxicity, which can progress into drug-associated hepatitis. Hepatotoxicity interaction between isoniazid and rifampicin may be associated with the additive or synergistic effects [5-6].

Villar *et al.* reported that the risk of drug-induced hepatitis was 18.2% in patients who had risk factors for old age, chronic liver disease, alcohol/other drugs abuse, or malnutrition, and 5.8% in patients without the risk factors [7]. Incidence of antituberculosis drug-induced hepatitis (anti-TB-DIH) is the most serious adverse effect and has a potential to be fatal, particularly with the risk factors such as age, female gender, slow acetylation status, alcohol consumption habit, malnutrition, hypoalbuminemia, human immunodeficiency virus (HIV) positive patients and previous liver diseases [5, 8-10]. Several other studies reported that malnutrition did not affect the occurrence of anti-TB-DIH, and did not affect the metabolism of isoniazid and rifampicin in the body [11-12].

Nusa Tenggara Timur (NTT) Province is an area with a relatively high TB prevalence. A total number of pulmonary TB with acid-fast bacilli (+) detected in 2010 in NTT Province was 3,708 cases, of which there were 3,222 cases treated, with the cure rate was up to 70.7%. Data from Indonesian Ministry of Health in 2013 showed that TB case notification rate per 100,000 people in NTT was 90, with a success rate of 94.56% [13].

Prevalence of malnutrition among TB patients in NTT is very high. There are 87% TB patients in NTT who have malnutrition, and average body mass index (BMI) of TB patients were 16.1, lower than the average BMI in healthy people [14]. The prevalence of malnutrition in TB patients in Yogyakarta were only 41.9%, with the average BMI of 18.4 [12]. A study in Jakarta also showed the prevalence of malnutrition in TB patients were 66% [15].

Malnutrition increases the risk of TB, and in turn, TB causes malnutrition. Malnutrition is commonly found in people with TB and a predictor of mortality and TB recurrence [16].

Half of the NTT population also had alcohol consumption habit. This habit has an unfavorable effect on the body. It may cause malnutrition, as well as increases the risk of hepatotoxicity in TB patients who were treated with the antituberculosis drugs-fixed dose combination (ATD-FDC) [17]. Therefore, this study was aimed to evaluate the decrease of liver function after treatment of antituberculosis drugs-fixed doses combination (ATD-FDC) category 1 in tuberculosis patients with malnutrition and alcohol consumption.

**MATERIALS AND METHODS**

This was an experimental study, with a quasi-experimental pretest and posttest design, to evaluate the increase in SGPT in pulmonary TB patients with malnutrition, treated with ATD-FDC for 8 w. This study protocol has received ethical clearance from the ethics committee in Biomedical Research on Human in GadjahMada University.

Cases were collected with consecutive sampling technique, which means that all cases satisfied the inclusion and exclusion criteria may be included as samples in this study until sample size needed was fulfilled. The sample size was calculated with Lemeshow formula, and we need a minimum of 72 patients. Inclusion criteria were: pulmonary TB patients, aged  $\geq 18$  y old, who would receive ATD-FDC category 1 treatment, did not have an increase in SGPT level at the beginning of the treatment and were willing to join the study. This study was conducted in all community health centers in Kupang district, NTT province, Indonesia.

History taking, physical examination and laboratory examination (SGPT and bilirubin) were conducted to each subject at the beginning before the treatment, and after 8 w treatment. Estimation was made by enzymatic and spectrophotometric methods, respectively. A decrease in liver function was shown when the patients had the symptoms of nausea, vomiting, or abdominal pain, with jaundiced sclera, or an

increase in SGPT over the upper limit of normal value, or urinary bilirubin positive. Malnutrition was assessed by the measurement of body mass index (BMI)  $< 18.5$  kg/m<sup>2</sup>. BMI was calculated by dividing the body weight (kg) by the square of body height (m<sup>2</sup>). Statistical analysis was done by independent t-test and paired t-test.

## RESULTS

TB patients who fulfilled the inclusion criteria and included as the subjects of this study were 74 patients, but only 72 patients who completed the study and could be analyzed. Two of them died during treatment.

The average age of subjects was 35.1 y, with a minimum age of 18 y and maximum age of 70 y. The proportion of the older patients ( $\geq 40$  y) was 33.3% (24 patients) and the younger patients ( $< 40$  y) was 66.7% (48 patients).

**Table 1: Characteristics of all pulmonary TB patients who received ATD-FDC category 1 for 8 w**

Variables		n (%)
Age (years)	35.1 $\pm$ 14.81	24/72 (33.3)
- Older ( $\geq 40$ y)		48/72 (66.7)
- Younger ( $< 40$ y)		
Gender (%)		
- Male		46/72 (63.9)
- Female		26/72 (36.1)
Body weight (kg)	42.54 $\pm$ 6.74	
Body height (cm)	160.22 $\pm$ 7.47	
Body mass index (mean $\pm$ SD)	16.53 $\pm$ 2.07	
Nutritional status based on BMI		
- No malnutrition		10/72 (13.9)
- Malnutrition		62/72 (86.1)
Alcohol consumption habit:		
- Yes		31/72 (43.06)
- No		41/72 (56.94)
Routine alcohol consumption habit:		
- Yes		14/72 (19.44)
- No		58/72 (80.56)
Drug dose		
- 2 tablets		14/72 (19.44)
- 3 tablets or more		58/72 (80.56)

Value are expressed as mean $\pm$ SD

The proportion of male subjects was 63.9% (46 patients), and that of a female was 36.1% (26 patients). The average BMI was low, around 16.5, and the proportion of subjects with malnutrition was 86.1%. The proportion of subjects with alcohol consumption habit was 43.06% while those with routine alcohol consumption habit were

19.44%. There were 19.44% subjects who received 2 tablets, and 80.56% who received 3 tablets or more. In this study, total patients who were older  $\geq 40$  y) and had malnutrition were 18. Out of 18 patients, those who had alcohol consumption habit was 38.89% (7 patients).

**Table 2: SGPT level before and after receiving ATD-FDC treatment for 8 w in pulmonary TB patients**

Variables	SGPT before treatment (IU/l)	SGPT after treatment (IU/l)
Age		
- All (n=72)	19.8 $\pm$ 8.2***	31.1 $\pm$ 11.3***
- Older ( $\geq 40$ y) (n=24)	19.5 $\pm$ 9.2***	35.1 $\pm$ 10.3***
- Younger ( $< 40$ y) (n=48)	19.9 $\pm$ 7.7***	29.0 $\pm$ 11.3***
Gender		
- Male (n=46)	19.6 $\pm$ 8.6***	30.9 $\pm$ 12.0***
- Female (n=26)	20.2 $\pm$ 7.6***	31.3 $\pm$ 10.1***
Malnutrition		
- Yes (n=62)	18.7 $\pm$ 7.8***	30.0 $\pm$ 10.5***
- No (n=10)	26.9 $\pm$ 6.6*	37.9 $\pm$ 13.9*
Alcohol consumption habit:		
- Yes (n=31)	20.8 $\pm$ 9.73***	30.9 $\pm$ 13.5***
- No (n=41)	19.0 $\pm$ 6.8***	31.2 $\pm$ 9.4***
Routine alcohol consumption		
- Yes (n=14)	21.4 $\pm$ 8.9*	32.8 $\pm$ 15.6*
- No (n=58)	19.4 $\pm$ 8.0***	30.6 $\pm$ 10.1***
Drug dose		
- 3 tablets or more (n=58)	20.1 $\pm$ 8.3***	31.6 $\pm$ 11.2***
- 2 tablets (n=14)	18.7 $\pm$ 7.9*	28.6 $\pm$ 11.9*

The analysis was conducted with paired T-test. Value are expressed as mean $\pm$ SD, \* p $<$ 0.05, \*\*\* p $<$ 0.001.

In this study, there was a statistically significant difference in average SGPT level before and after ATD-FDC category 1 treatment in all subjects.

**Table 3: Increase in SGPT level in TB patients treated with ATD-FDC category 1 for 8 w**

Variables	Increase in SGPT level (IU/l)
Age	
- Older ( $\geq 40$ y) (n=24)	15.5 $\pm$ 12.6*
- Younger (<40 y) (n=48)	9.1 $\pm$ 12.7*
Gender	
- Male (n=46)	11.4 $\pm$ 13.0
- Female (n=26)	11.1 $\pm$ 13.3
Malnutrition	
- Yes (n=62)	11.3 $\pm$ 13.2
- No (n=10)	11.0 $\pm$ 12.0
Alcohol consumption habit:	
- Yes (n=31)	10.1 $\pm$ 14.0
- No (n=41)	12.1 $\pm$ 12.2
Routine alcohol consumption	
- Yes (n=14)	11.4 $\pm$ 18.2
- No (n=58)	11.2 $\pm$ 11.6
Drug dose	
- 3 tablets or more (n=58)	11.6 $\pm$ 12.5
- 2 tablets (n=14)	9.9 $\pm$ 15.2

The analysis was conducted with independent T-test. Value are expressed as mean $\pm$ SD,  $p^* < 0.05$ .

The average increase in SGPT level in older subjects was 15.5 while that in the younger subjects was 9.1. In older patients, average first SGPT level was 19.5 and average second SGPT level was 35.1. In younger patients, average first SGPT level was 19.9 and average second SGPT

level was 29.0. Analysis showed that there was an age effect on the increase in SGPT level in TB patients treated with ATD-FDC category 1 for 8 w because there was a statistically significant difference in the average increase in SGPT level between the older and younger age.

**Table 4: Difference in SGPT level stratified by age in patients with malnutrition and without malnutrition**

Variables	Difference in SGPT level (IU/l)
TB patients with malnutrition	
• Older ( $\geq 40$ y) (n=14)	17.3 $\pm$ 12.2*
• Younger (<40 y) (n=44)	8.8 $\pm$ 13.0*
TB patients without malnutrition	
• Older ( $\geq 40$ y) (n=6)	10.2 $\pm$ 13.6
• Younger (<40 y) (n=4)	12.3 $\pm$ 11.0

The analysis was conducted with independent T-test. Value are expressed as mean $\pm$ SD,  $*p < 0.05$ .

In malnutrition-patients, the average increase in SGPT level for older patients ( $\geq 40$  y) was 17.3, while that for younger patients (<40 y) was 8.8. This difference was statistically significant. In patients without malnutrition, the average increase in SGPT level in older patients ( $\geq 40$  y) was 10.2, while that in younger patients (<40 y) was 12.3, but there was no statistically significant difference. Average increase in SGPT level in male subjects was 11.4 while that in female subjects was 11.1. Analysis showed that gender did not affect the average increase in SGPT level because there was no

statistically significant difference in the average increase of SGPT level between males and females.

In this study, most subjects had malnutrition (86.1%). The average increase in SGPT level in patients with malnutrition was 11.3 while the average increase in SGPT level in patients without malnutrition was lower (11.0). Analysis showed that the average increase in SGPT level was higher in malnutrition-patients, but this difference was not statistically significant.

**Table 5: Percentage of increase in SGPT level compared to the SGPT level before treatment with ATD-FDC category 1 for 8 w in TB patients with malnutrition and without malnutrition**

Variables	% increase SGPT level compared with initial SGPT level
TB patients	
- With malnutrition (n=62)	135.05 $\pm$ 117.45***
- Without malnutrition (n=10)	54.69 $\pm$ 37.66***

The analysis was conducted with independent T-test. \*\*\*  $p < 0.001$ .

The average percentage of the increase in SGPT level compared to the initial SGPT level in patients with malnutrition was 135.1%, and that in patients without malnutrition was 54.7%. This difference was statistically significant. The average difference in SGPT level in patients who had alcohol consumption habit was 10.1 while the average in

patients who did not have alcohol consumption habit was 12.1. This difference was not statistically significant. The average of the difference in SGPT level in patients who had routine alcohol consumption habit was 11.4, while that for patients who did not have the habit was 11.2. This difference was not statistically significant.

**Table 6: Difference in SGPT level before and after treatment with ATD-FDC category 1 for 8 w in older ( $\geq 40$  y) TB patients stratified by alcohol consumption habit**

Variables	Difference in SGPT level (IU/l)
Older ( $\geq 40$ y) TB patients	
• Alcohol consumption (+) (n=11)	14.7 $\pm$ 15.4
• Alcohol consumption (-) (n=13)	16.2 $\pm$ 10.4
Older ( $\geq 40$ y) TB patients	
• Routine alcohol consumption (+) (n=4)	29.3 $\pm$ 10.6**
• Routine alcohol consumption (-) (n=20)	12.8 $\pm$ 11.3**

The analysis was conducted with independent T-test. Value are expressed as mean $\pm$ SD, \*\* $p < 0.01$

In older patients, the average increase in SGPT level in patients who had alcohol consumption habit was 14.7, and in those without the habit was 16.2. In older patients who had routine alcohol consumption habit, the average increase in SGPT level was 29.3, and in those without the habit 12.8. From the analysis, routine alcohol consumption had an effect on the increase in SGPT level in older patients, because there was a significant difference between older patients who had routine alcohol consumption habit and those without the habit.

In this study, most patients took 3 ATD-FDC tablets or more. In those patients who took 3 ATD-FDC tablets or more, the average difference in SGPT level was 11.6, while in those who took 2 tablets, the average difference was 9.9. There was no statistically significant difference in the average of the difference in SGPT level in patients who took 2 tablets or 3 tablets or more.

From urinary bilirubin examination, the results were negative in all subjects, both before treatment with ATD-FDC category 1 and after the treatment for 8 w. Based on these results, there was an increase in SGPT level before and after the treatment with ATD-FDC category 1 for 8 w, but this did not increase the urinary bilirubin level.

## DISCUSSION

In this study, there was an increase in SGPT level after the treatment with ATD-FDC category 1 for 8 w, because there was a statistically significant difference in SGPT level before and after the treatment. This is in line with the previous study that showed a decrease in liver function after ATD drugs treatment [3, 18].

Analysis showed that gender did not affect the increase in SGPT level in this study, because there was no statistically significant difference between the average in the increase of SGPT level between males and females, although there was a significant difference between the average SGPT level before and after the treatment in the whole subjects. These results are consistent with several previous studies which showed that there was no difference in the increase in serum transaminase level between male and female subjects [5, 9, 12]. However, these results are different from the study by Shakya, which suggested that female gender was a predisposing factor of hepatotoxicity induced by ATD [19].

The study by Makhoul in Mesir included more females (56%) than males. This case-control study had a sample size of 100 patients [9]. Meanwhile, the study by Shakya was conducted in Nepal, using cohort study design with 50 subjects [19].

The results are consistent with previous studies which showed that the proportion of male TB patients were larger than females [5, 19-20].

Analysis showed that age had an effect on the increase in SGPT level in TB patients who were treated with ATD-FDC category 1 for 8 w. This is similar to the previous studies which suggested that there was an effect of age on the increase in serum transaminase level [10-11]. Meanwhile, a study by Febrinasari showed that age did not affect the increase in serum transaminase level [12].

The results are in line with several previous studies which showed that there was no difference in the increase in transaminase level between male and female subjects [5, 9, 12]. However, this is different from the study by Shakya, which stated that female gender was the predisposing factor of hepatotoxicity induced by ATD [20].

Analysis showed that malnutrition affected the decrease in liver function in TB patients treated with ATD-FDC category 1 for 8 w. This is consistent with the previous studies which suggested that malnutrition was a risk factor of hepatotoxicity in TB patients who were treated with ATD drugs [5, 10, 21]. However, this is contrasted with the study by Febrinasari, who showed that malnutrition did not affect the increase in serum transaminase level [12].

The results are similar with the previous study that suggested that high dose alcohol consumption affected hepatotoxicity in TB patients who were treated with ATD drugs [7, 11]. Nevertheless, the results differ from the results of the study by Singh *et al.* who stated that alcohol consumption habit was not a risk factor of hepatotoxicity in TB patients who were treated with ATD [5].

From the analysis, it was shown that drug dose did not affect the increase in SGPT level. This is in line with the study by Febrinasari in Yogyakarta, which showed that there was no effect of drug dose on the increase in SGPT level in TB patients who were treated with ATD-FDC category 1 [12].

Analysis showed that there was an effect of malnutrition on the decrease in liver function in TB patients who were treated with ATD-FDC category 1 for 8 w. This is in line with the previous studies which showed that malnutrition was a risk factor of hepatotoxicity in TB patients who were treated with ATD [5, 10, 21]. This differs from the results from Febrinasari study that suggested that malnutrition did not affect the increase in serum transaminase level [12].

A study by Singh was conducted in India. India is a country with a high prevalence rate of TB. In the study, malnutrition was measured similarly as the measurement in this study, namely, using BMI $<$ 18.5. Average BMI of subjects in Singh study was 17.2. It was a case-control study conducted on 120 TB patients [5].

The result of this study was similar with that of Singh study in India. This is likely due to the similarity in locations of the study, which have high TB prevalence with a low average of BMI. Therefore, there is a possibility that there has been a decrease in liver function caused by malnutrition [5]. Limitations of this study were not conducted screening pre-albumin levels to see malnutrition in early studies

## CONCLUSION

Pulmonary TB patients with malnutrition had a larger decrease in liver function after treatment with ATD-FDC category 1 for 8 w, compared to those without malnutrition. Routine alcohol consumption had an effect on the increase in SGPT level in older patients

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## CONFLICT OF INTERESTS

Declared none

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