

## Evaluation of The Risk Factors of Anti-Tuberculosis Drugs Induced Liver Injury from Multiple Hospitals in Thailand

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### ABSTRACT

Although the risk factors of anti-tuberculosis drugs induced liver injury (AT-DILI) was published in several countries, Thai patients have been limited to knowledge. A retrospective case-control study design was performed between May, 2013 and July, 2015. The TB patients from Ramathibodi Hospital and case record form collected from the Department of Medical Sciences were enrolled and received first line treatment which consisted of isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin. The aim was to determine odds ratio (OR) of risk factors for developing AT-DILI and pattern of DILI. Control group was defined as non-liver injury occurring whereas case group was liver injury occurring. Statistical Package for Social Science (SPSS) version 21 was used. A total of 60 and 78 patients were included in the case group and control group, respectively. Four risk factors were found to be statistically significant associated with AT-DILI including severity of TB (OR = 2.32, 95% CI = 1.03 - 5.20, p-value = 0.038), extrapulmonary TB (OR = 3.18, 95% CI = 1.26 - 8.05, p-value = 0.012), receiving dose of isoniazid higher than normal (OR = 2.36, 95% CI = 1.10 - 5.03, p-value = 0.025), and receiving dose of ethambutol higher than normal (OR = 3.55, 95% CI = 1.38 - 9.14, p-value = 0.009). Adjusted OR of extrapulmonary TB was significantly increased risk of AT-DILI (OR adjusted = 3.91, 95%CI = 1.41-10.89, p-value = 0.009). The patterns of AT-DILI in cases were almost the symptoms were unexplained jaundice and the most anti-TB drugs were pyrazinamide. The prevention of AT-DILI should concern for these risk factors.

**Keywords:** Anti-Tuberculosis Drugs, Liver Injury, Risk Factors

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## Introduction

Tuberculosis (TB) is an important infectious disease, transmitted through respiratory route. TB is a contagious and a severe airborne disease that causes infection by *Mycobacterium tuberculosis* (*M. tuberculosis*) bacteria. Normally, TB affects the lungs; however, it may also affect any other organs of the body. Pharmacological treatment of TB ranges from six months to two years, depending on types of infection. Global burden of TB infection has been declining for the past several years such as the incidence declining at a rate of 1.5 % between 2000 and 2013. However, the global burden of TB remains enormous. In 2013, there were an estimated 5.7 million new cases of TB (48% co-infected with HIV) and 1.5 million people died from TB, including almost deaths among 400,000 HIV-negative individuals and 1.1 million among people who were HIV-positive (World Health Organization [WHO], 2012). Using anti-TB drugs, the mortality rates are dramatically reduced. The first line anti-TB drug therapy consists of isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin.

Anti-TB drugs induced liver injury (AT-DILI) is the importance of public health problems. This often results in discontinuation of the first-line anti-TB drugs and has a negative impact on patient compliance and treatment failure and death. The first line drugs consist of isoniazid (H), rifampicin (R), pyrazinamide (P), ethambutol (E) and streptomycin (S). Combination therapy leads to higher rate of AT-DILI. Worldwide, the incidence of AT-DILI in diverse studies ranged from 5% to as high as 33% (Jittimanee *et al.*, 2009; Gholami *et al.*, 2006; Yee *et al.*, 2003; Teleman *et al.*, 2002; Marzuki *et al.*, 2008; Schaberg *et al.*, 1996; Khalili *et al.*, 2009; Lee *et al.*, 2010; Steele *et al.*, 1991; Thongraung *et al.*, 2012). Determination of the risk factors for AT-DILI can play an important role in minimizing its occurrence. As a result, this retrospective case-control study shall provide more understanding of AT-DILI in Thai population. In this study, the twelve risk factors were studied for their association with AT-DILI; 1) age ☐ 35 year old, 2) female gender, 3) malnutrition, 4) HIV co-infection, 5) hepatitis B virus/hepatitis C virus infection, 6) *NAT2* and other genetic factors, 7) severity of TB, 8) concomitant diseases, 9) alcohol consumption, 10) sites of TB infection, 11) concomitant drugs and 12) receiving dose of the first line anti-TB drugs higher than normal (Singla *et al.*, 2010; Pande *et al.*, 1996; Jittimanee *et al.*, 2009; Gholami *et al.*, 2006; Yee *et al.*, 2003; Teleman *et al.*, 2002; Marzuki *et al.*, 2008; Schaberg *et al.*, 1996; Khalili *et al.*, 2009; Lee *et al.*, 2010; Steele *et al.*, 1991; Thongraung *et al.*, 2012; Chamorro *et al.*, 2013; Makhoul *et al.*, 2008; Krittiyanunt *et al.*, 2002).

As a result, this study is retrospective case-control study. The present study aims to evaluate the pattern of AT-DILI and determined the odds ratio of potential risk factors of AT-DILI in Thai patients. From the available researches, this study tries to find the large number patients. The present study was conducted in multiple hospitals. In the future, the potential risk factor of AT-DILI in Thai patients will be evaluated, which will create a considerable impact on widespread areas, such as development algorithms, center TB care etc. The rational of risk factors of AT-DILI will also lead to a better therapeutic outcome and prevention

## Objective of the study

1. To evaluate the pattern of AT-DILI in Thai TB patients.
2. To determine the odds ratio of potential risk factors of AT-DILI in Thai TB patients.

## Materials and Methods

### Study design and population

This study is a retrospective case-control study design. The data compares the difference between cases and controls in multihospital. The twelve risk factors were studied to associate with AT-DILI; 1) age  $\geq$  35 year old, 2) female gender, 3) malnutrition, 4) HIV co-infection, 5) hepatitis B virus/hepatitis C virus infection, 6) *NAT2* and other genetic factors, 7) severity of TB, 8) concomitant diseases, 9) alcohol consumption, 10) sites of TB infection, 11) concomitant drugs and 12) receiving dose of the first line anti-TB drugs higher than normal.

The conceptualized framework of the components for evaluating the risk factors of AT-DILI is composing of: 1) the research pharmacist reviewed the literature related to the risk factors and AT-DILI, 2) evaluation the potential risk factors of AT-DILI, 3) development of the data collection forms, 4) verification of the data collection forms with Case report forms (CRFs) from The Pharmacogenomic study of anti-TB drugs side effects Thailand project, 5) process of data collection (The source of data collection was enrolled 2 sources as following: the first source, patients were recruited and assigned into case group or control group and at Ramathibodi Hospital and the second source, patients were collected by CRFs in the collaboration of the collaboration of Department of Medical Sciences (DMSc) in Chiangrai Prachanukroh Hospital, Bureau of AIDS, and TB and STI and Central Chest Institute of Thailand). and 6) data and statistical analysis. The materials of the study are divided into 3 categories as follows: 1) Medical chart and other materials for Ramathibodi Hospital 2) CRFs for the DMSc and 3) Data collection forms

Population is the patients who are diagnosed as tuberculosis disease. Control group was defined as non-liver injury occurring whereas case group was liver injury occurring. AT-DILI was defined as serum alanine transaminase (ALT) and/or aspartate aminotransferase (AST) elevation more than three times the upper limit of normal (ULN) and/or symptoms of hepatitis (abdominal pain, nausea, vomiting, unexplained fatigue or jaundice), or A rise in the level of serum total bilirubin over 1.5 mg/dl. The patients fulfilled following inclusion criteria: they were diagnosed of TB disease, received the first-line anti-TB drug, and older than 18 years old. Patients receiving other potential liver injury drugs in addition to anti-TB drugs and theme were causing of DILI by evaluating with physician diagnosis or occurring DILI before regimen of starting the first line anti-TB drugs were excluded.

The protocol of this study was approved by the Human Research Ethics Committee of Ministry of public in September 2012 and the Human Research Ethics Committee of Faculty of Medicine, Ramathibodi Hospital, Mahidol University in June 2014. The subject in each group should be at least 51 patients in case group and 101 patients in control group. Sample size calculated by minimum of the odds ratio. Previously in Malaysia, Marzuki (2008) described the minimum of OR was 2.33 from extrapulmonary TB.

Formula in case control study;

$$n = \left( \frac{r+1}{r} \right) \frac{(\bar{p})(1-\bar{p})(Z_{\beta} + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

### Statistical Analyses

The data were analyzed by using the SPSS version 21. Descriptive data including demographic data and characteristics of AT-DILI in case and control group were presented and compared. The risk factors between cases and controls were analyzed by odd ratio (OR) and 95%confidence interval (95%CI). All significant OR were converted into categorical variables while performing logistic regression by binary logistic regression. Multivariate analysis was presented with 95% CI and p-value <0.05. The chi-square test or Fisher's exact test was used to find the significant risk factors. The level of statistical significance was specified at  $p < 0.05$ .

## Results

### Demographic data

One hundred and eighty-one patients were enrolled in the study. Forty three TB patients of this group did not complete the entire study. So, they were excluded from this study. Finally, a total of 138 patients were compared 60 case and 78 control groups. The majority of them were male (control group vs. case group; 62.8% vs. 55.0%). The mean age of both groups was age higher than 35 years old. Patient's characteristics were statistically significant different between two groups, including dose of isoniazide, dose of ethambutol, The mean  $\pm$  SD of ALP and AST of baseline. Characteristics of these are presented in Table 1.

**Table 1** Demographic data of control and case groups.

Characteristics	Controls (n = 78) (%)	Cases (n = 60) (%)	p-value*
1. Gender			
Male	49(62.8)	33(55.0)	0.354
Female	29(37.2)	27(45.0)	
2. Age (years) Mean $\pm$ SD	52.1 $\pm$ 16.2	52.4 $\pm$ 14.6	0.928
3. BMI (kg/m <sup>2</sup> ) Mean $\pm$ SD	19.9 $\pm$ 4.1	19.6 $\pm$ 4.2	0.755
4. Dose of the first line anti-TB drugs (mg/day) Mean $\pm$ SD	5.2 $\pm$ 1.2	5.9 $\pm$ 1.4	0.005*
Isoniazid	9.5 $\pm$ 1.7	9.9 $\pm$ 1.3	0.107
Rifampicin	16.6 $\pm$ 2.8	18.6 $\pm$ 4.4	0.004*
Ethambutol	25.6 $\pm$ 4.9	26.2 $\pm$ 6.8	0.631
Pyrazinamide			
5. HIV Status			
Positive	2(25.6)	4(6.7)	0.403
Negative	76(97.4)	56(93.3)	
6. Severity of TB			
Normal	65(83.3)	41(68.3)	0.075
1 cavity	10(12.8)	17(28.3)	
□ 1 cavity	3(3.9)	2(3.4)	
7. Alcohol Consumption			
Yes	7(9.0)	5(9.3)	1.000
No	71(91.0)	49(90.7)	
8. Sites of TB Infection			
Pulmonary TB	70(89.7)	44(73.3)	0.010*
Extrapulmonary TB	8(10.3)	11(18.3)	
Both	0(0.0)	5(8.3)	
9. Genetic Susceptibility Factors**			
fast acetylators	38 (95.0)	32 (80.0)	0.087
slow acetylators	2 (5.0)	8 (20.0)	

\*\* slow acetylators (Alleles without any defective forms were defined as functional allele NAT2\*4)

### Characteristics of anti-TB regimens for the patient treatment

According to the recommendation of the WHO guideline as followings; 1<sup>st</sup> regimen (2HRE/7HR), 2<sup>nd</sup> regimen (2HRZE/4HR), 3<sup>rd</sup> regimen (2HRZS/4HR) and 4<sup>th</sup> regimen (2HRZ/4HR), almost patients received 2HREZ/4HR for the beginning and the end regimens in both groups. Approximately, patients who received anti-TB drug at the beginning regimens were similar between the control and the case group, as shown in Table 2.

**Table 2** Characteristics of anti-TB regimens for the patient treatment

Regimens	No. of patients who revived type of regimens			
	Controls (n = 78) (%)		Cases (n = 60) (%)	
	At beginning	At the end	At beginning	At the end
1. 2HRZE/4HR	77(98.7)	65(83.3)	60(100)	38(63.3)
2. Other*	1(1.3)	13(16.7)	0(0.0)	22(36.7)
Total	78		60	
* The classification of other regimens were various type of regimens e.g. 3HRE/6HR, 2HRZE/6E(Ofloxacin) S, 2HRE/6HE(Ofloxacin), etc.				

### Characteristics of anti-TB drugs induced liver injury

Sixty patients were AT-DILI in the present study. Characteristics of AT-DILI in case group will present as follows: 1) Patterns of symptoms for AT-DILI, 2) Patterns of abnormal laboratory liver function test for AT-DILI and 3) Patterns of AT-DILI. For details of characteristics of AT-DILI in cases show in Table 3.

**Table 3** Characteristics of anti-TB drugs induced liver injury

Characteristics of AT-DILI	No. of patients	Percentage
1. Patterns of symptoms for AT-DILI		
1.1 a symptomatic	4	6.7
1.2 Nausea and vomiting	18	30.0
1.3 Jaundice	17	28.3
1.4 Nausea and vomiting with jaundice	9	15.0
1.5 Nausea and vomiting with fatigue	4	6.7
1.6 Nausea and vomiting with fatigue with jaundice	3	5.0
1.7 Abdominal pain	2	3.3
1.8 Fatigue	2	3.3
1.9 Fatigue with jaundice	1	1.7
2. Patterns of abnormal laboratory liver function test for AT-DILI		
2.1 Laboratory		
- ALT+AST	37	61.6
- ALT+AST+TBIL	21	35.0
- ALT	1	1.7
- AST	1	1.7
2.2 Severity of AT-DILI		
- Grade 1 (mild)	2	3.3
- Grade 2 (mild)	38	63.3
- Grade 3 (moderate)	13	21.7
- Grade 4 (severe)	7	11.7
3. Patterns of AT-DILI		
3.1 Drug type caused liver injury		
Pyrazinamide	27	45.0
Isoniazid plus rifampicin plus pyrazinamide	17	28.3
Isoniazid plus pyrazinamide	8	13.3
Rifampicin plus pyrazinamide	5	8.3
Rifampicin	2	3.3
Isoniazid	1	1.7
Total	60	100
ALT = alanine aminotransaminase, AST = aspartate aminotransaminase, TBIL = total bilirubin		

### The risk factors of anti-TB drugs induced liver injury

Table 4 shows detail of the univariate analysis of potential factors influencing for AT-DILI by OR. The results showed four risk factors were an increased risk of AT-DILI that include; 1) Severity of TB, 2) Sites of TB infection, 3) Receiving dose of isoniazid higher than normal and 4) Receiving dose of ethambutol higher than normal.

**Table 4** Univariate analysis of risk factors for AT-DILI.

	Risk factors	Cases (n) (%)	Controls (n) (%)	OR <sup>1</sup>	95% CI <sup>2</sup>	p-value
1.	Age					
	□35 years old	52(86.7)	62(79.5)	1.67	0.67-4.23	0.270
	<35 years old	8 (13.3)	16 (20.5)	1		
2.	Gender					
	Female	27(45.0)	29 (37.2)	1.38	0.70-2.74	0.354
	Male	33 (55.0)	49 (62.8)	1		
3.	Malnutrition					
	Yes	24(54.5)	46(59.0)	0.84	0.40-1.76	0.635
	No	20 (45.5)	32(41.0)	1		
4.	HIV co-infection					
	Positive test	4(6.7)	2(2.6)	2.71	0.48-15.34	0.403
	Negative test	56 (93.3)	76 (97.4)	1		
5.	Hepatitis B virus/hepatitis C virus co-infection					
	Yes	5(13.2)	4(6.9)	2.05	0.51-8.17	0.476
	No	33 (86.8)	54(93.1)	1		
6.	Severity of TB					
	Yes	19(31.7)	13(16.7)	2.32	1.03-5.20	0.038*
	No	41 (68.3)	65 (83.3)	1		
7.	Concomitant diseases					
	Yes	7(11.7)	7(9.0)	1.34	0.44-4.05	0.604
	No	53 (88.3)	71 (91.0)	1		
8.	Co-medicine					
	Yes	7(11.7)	3(3.8)	3.30	0.82-13.36	0.102
	No	53 (88.3)	75 (96.2)	1		
9.	Alcohol consumption					
	Yes	5 (9.3)	7 (9.0)	1.04	0.31 -3.45	1.000
	No	49 (90.7)	71 (91.0)	1		
10.	NAT2 genetic factor					
	Slow acetylators	8 (20.0)	2 (5.0)	4.75	0.94-23.99	0.087
	Fast acetylators	32 (80.0)	38 (95.0)	1		
11.	Sites of TB infection					
	Extrapulmonary TB	16(26.7)	8(10.3)	3.18	1.26-8.05	0.012*
	Pulmonary TB	44 (73.3)	70 (89.7)	1		
12.	Receiving dose of the first line anti-TB drugs higher than normal					
	12.1 Isoniazid					
	Yes	22(43.1)	19(24.4)	2.36	1.10-5.03	0.025*
	No	29(56.9)	59(75.6)	1		
	12.2 Rifampicin					
	Yes	3 (5.9)	4 (5.1)	1.16	0.25 -5.40	1.000
	No	33 (55.0)	33 (55.0)	1		
	12.3 Ethambutol					
	Yes	15 (28.8)	8 (10.3)	3.55	1.38 -9.14	0.009*
	No	37 (71.2)	70 (89.7)	1		
	12.4 Pyrazinamide					
	Yes	12 (23.5)	15 (19.2)	1.29	0.55 -3.05	0.557
	No	39 (76.5)	63 (80.8)	1		



The most potent risk factors of AT-DILI were extrapulmonary TB. In the present study, conditional binary logistic regression was used to identify the association between the potential risk factors and AT-DILI for adjusting the confounder. It was matched the significant risk factors for case and control groups. Multivariate analysis was presented with 95% CI and p-value < 0.05. Patients with extrapulmonary TB were at an increased the risk for AT-DILI (OR adjusted= 3.91, 95%CI = 1.41 – 10.89, p-value = 0.009) (Table 5).

**Table 5** Multivariate analysis for adjusted OR of risk factors for AT-DILI.

Risk factors	OR adjusted <sup>3</sup>	95% CI <sup>2</sup>	p-value*
Severity of TB			
Yes	2.24	0.91-5.50	0.078
No	1		
Sites of TB infection			
Extrapulmonary TB	3.91	1.41 - 10.89	0.009*
Pulmonary TB	1		
Receiving dose of isoniazid higher than normal			
Yes	2.20	0.95 - 5.12	0.068
No	1		
Receiving dose of ethambutol higher than normal			
Yes	2.78	0.99 - 7.79	0.051
No	1		

## Discussion

In the present study, the univariate analysis of risk factors for AT-DILI were used by OR. The results showed four risk factors were an increased risk of AT-DILI, i.e., severity of TB, sites of TB infection, receiving dose of isoniazid higher than normal and receiving dose of ethambutol higher than normal. The present study, as compared to previous studies (Singla *et al.*, 2010; Pande *et al.*, 1996; Jittimanee *et al.*, 2009; Gholami *et al.*, 2006; Yee *et al.*, 2003; Teleman *et al.*, 2002; Marzuki *et al.*, 2008; Schaberg *et al.*, 1996; Khalili *et al.*, 2009; Lee *et al.*, 2010; Steele *et al.*, 1991; Thongraung *et al.*, 2012; Chamorro *et al.*, 2013; Makhoul *et al.*, 2008; Krittiyanunt *et al.*, 2002), has tried to observe the role of the risk factors in predicting the occurrence of AT-DILI in a fairly large number of patients who have other confounding risk factors, i.e., alcoholism, hepatitis B virus/hepatitis C virus co-infection, HIV infection, chronic liver disease and concomitant drugs of other hepatotoxic drugs. This study reduced the potential confounding variables by multivariate analysis which used adjusted OR. Globally, many studies found the potential risk factors of AT-DILI. The previous study reported significantly extrapulmonary TB is at higher risk of AT-DILI (OR = 2.33, 95%CI = 1.16-4.67). This study was the same study design which retrospectively case control study. This study

carried out with 473 TB patients, 46 developed AT-DILI and 138 selected as controls in Malaysia. To summarize, the OR in the present study was higher than the previous studies. This also found that extrapulmonary TB was a significant risk factor by multivariate logistic regression analysis ( $p$ -value = 0.009). This finding is rather interesting, since there are not many published reports importance these apart from a few reports. Owing to population in both studies were in the South Asia. Birthplace in Asia were associated with increased occurrence of AT-DILI in term of similarly ethnic. The previous study supports high risk of AT-DILI in patients who was extrapulmonary TB (Marzuki *et al.*, 2008).

Approximately 15% in control group and 20% in case group switched to another regimen at the end treatment. However, most treatment at the ending regimens received 2HRZE/4HR for treatment in the both groups. The reason of this was not only AT-DILI occurring but it was many reasons, i.e., treatment failure, MDR-TB, and other ADRs etc. The present study reported the first-line anti-TB drugs for the standard regimen is the most important cause of AT-DILI after treatment but most of them could continuous anti-TB drugs.

Data from the present study showed that 1.7% of the patients did not meet The American Thoracic Society guideline because only AST increase greater than three times. However, among patients who are ALP were not more than three times of the ULN, their bilirubin levels and/or AST were higher than the normal value. Similarly, Singla (2010) defined AT-DILI as symptoms with serum total bilirubin increasing greater than 1.5 mg/dl plus elevated level of transaminase. However, twenty one patients (35.0%) were serum total bilirubin increasing greater than 1.5 mg/dl plus ALT plus AST.

The abnormal symptoms for AT-DILI in the present study was nausea and vomiting (30.0%), jaundice (28.3%), fatigue with jaundice (15.0%), nausea and vomiting with fatigue (6.7%), nausea and vomiting with fatigue with jaundice (5.0%), fatigue (3.3%) and fatigue with jaundice(1.7%), respectively. However, 4 (6.7%) patients were not abnormal symptoms for AT-DILI. Consequently, follow up of patients based on clinical sings was considered to be sufficient by WHO and routine laboratory follow up was not recommended unless past history of liver disease, regular alcohol consumption or immunodeficiency disorders (WHO, 2012). So, when starting anti-TB drugs there should be awareness of signs and symptoms of AT-DILI because the rate of severity level was high and harmful to life.

Limitations of this a retrospective case-control study should be noted. Firstly, this study was retrospective and the researcher had to rely on the data available in its current information. So, these were barely enough to see the complete outcome and/or some information, for example the duration of DILI in cases, the episodes of DILI, the patients not yet recovered (15% in the present study). Second, the explanation of these situations might result from the period of data collection was also too short and small sample size to see the impact of some the risk factor and pattern of AT-DILI. Although the number of enrolled control group was less than the sample size calculation because they missed relevant information. So, the small number of these may lack statistical power. Third, the low number of patients with risk of *NAT2* genetic factor could be affect in OR analysis. Accordingly, the process of collecting data in this study may be very difficult due to the limitation of the budget. Moreover, the study has some limitation, for example, laboratory investigations to determine plasma or tissue drug concentration, liver function tests, acetylator

status, etc. of the patients were not done because of high cost and data obtained from interview of the patients and patients' family sometimes may not be complete. Finally, the present study suspected only the risk of *NAT2* genetic factor. However, any complex disease cannot be explained only by a variation in one genes alone because the variation in many genes, i.e., patients were genotype of the human leukocyte antigen (HLA) which was presence of HLA-DQB1\*0201 or absence of HLA-DQA1\*0102, patients were genotype of wild type CYP2E1 c1/c1, and patients were genotype of Glutathione S Transferase M1(GSTM1) null and combined GSTM1 and T1 null genotypes, where the effect of any single variant is expected to be small. The corroboration between AT-DILI and other genetic susceptibility factors should be study in the future. It may also be helpful to know the reality genetic susceptibility factors for AT-DILI.

### Conclusions

The present study was performed with a retrospective case-control study. Four risk factors were found to be statistically significant associated with AT-DILI including severity of TB (OR = 2.32, 95% CI = 1.03 - 5.20, p-value = 0.038), extrapulmonary TB (OR = 3.18, 95% CI = 1.26 - 8.05, p-value = 0.012), receiving dose of isoniazid higher than normal (OR = 2.36, 95% CI = 1.10 - 5.03, p-value = 0.025), and receiving dose of ethambutol higher than normal (OR = 3.55, 95% CI = 1.38 - 9.14, p-value = 0.009). Adjusted OR of extrapulmonary TB was significantly increased risk of AT-DILI (OR adjusted = 3.91, 95%CI = 1.41-10.89, p-value = 0.009). The patterns of AT-DILI in cases shown the most symptoms of DILI in cases was nausea and vomiting (30.0%), almost patients were rising in ALT with AST (61.6%), the most severity were grade 2 (63.3%) base on WHO definition criteria and the most drugs caused liver injury were pyrazinamide (45.0 %). Furthermore, this result suggests that the protocol of anti-TB therapy for Thai population may need some revision to prevent fatal hepatotoxicity. To confirm this hypothesis many more studies with larger number of sample size is needed.

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