Original Article

Prevalence and Risk Factors Associated with First-Line Anti-Tuberculosis Induced Hepatotoxicity in Suratthani Hospital, Thailand

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Background: Tuberculosis (TB) is a major public health problem, including Thailand. Anti-TB drugs are very effective treatment, but they can cause hepatotoxicity. Data on the prevalence of anti-TB drug-induced hepatotoxicity (DIH), as well as the contributing risk factors, are scarce in Thailand.

Objective: To measure the prevalence and identify risk factors associated with first-line drugs (FLD) induced hepatoxicity in TB patients.

Materials and Methods: The present study was a retrospective study design in TB clinic of Suratthani Hospital, in Southern Thailand. All patients diagnosed with TB and received FLD between January and December 2017, were eligible for the study. Hepatoxicity defined as the following criteria: serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >5x upper limit of normal (ULN) without symptoms, or AST or ALT >3x ULN with clinical symptoms.

Results: Of all the 198 TB cases, 18 were identified as DIH. Prevalence of DIH was 9.1%. Hepatitis after FLD was independently associated with age >60 years (adjusted OR [aOR] 28.49, 95% CI 2.68 to 302.95, p=0.005) and serum albumin <3.5 g/dL (aOR 20.97, 95% CI 2.11 to 208.51, p=0.009).

Conclusion: Age of more than 60 years and low serum albumin of less than 3.5 g/dL were significant risk factors associated with first-line anti-TB drugs induced hepatoxicity.

Keywords: Hepatoxicity, Anti-tuberculosis drug, Risk factor, Thailand

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Tuberculosis (TB) is a major public health problem in Thailand and many developing countries[1,2]. Thailand is one of fourteen TB high burdened countries with the incidence of 172/100,000 population by estimated in 2015[1]. TB can be found in multiple sites in the body, especially in the lungs. The patients with TB may have mild to severe symptoms[3,4].

Multiple drugs are the primary treatment for TB[5]. The first-line quadruple therapy drugs are isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB). Three of them include INH, RMP, and PZA are metabolized mainly by the liver, and therefore, are potentially hepatotoxic[5]. Drug-induced hepatotoxicity (DIH) is one of the most common and severe adverse effects of anti-TB medications, which may reduce treatment effectiveness by compromising treatment regimens. The phenotype of drug-induced liver injury of INH, RMP, and PZA were idiosyncratic pattern[6]. Hepatitis may present as asymptomatic increase aminotransferases in nearly 20% of patients who treated with the standard first-line anti-TB drugs (FLD)[7]. Furthermore, anti-TB drugs contribute to 5.7% of acute liver failure patients and even death in 67% of them[8].

There are several well-known risk factors associated with hepatitis after receiving TB treatment, including elderly patients age more than 60 years[9-13], regularly drink alcohol[9-15], have a history of liver disease or chronic hepatitis[16], human immunodeficiency virus (HIV) infection[17], malnutrition[18-20], and pregnant women[9-20].

However, the prevalence of anti-TB drug-induced hepatitis, as well as the contributing risk factors, are scarcely studied in Thailand. Therefore, the present study aimed to identify the factors associated with

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the occurrence of hepatitis in patients receiving FLD. Thus, the authors can closely monitor and prevent the occurrence of hepatitis in high-risk patients.

Materials and Methods

Setting

Suratthani Hospital (SH) is a tertiary care medical centre in the South of Thailand. TB clinic of SH is operated weekly as a one-stop service. The multidisciplinary TB care team includes pulmonologists, public health nurses, and pharmacists serve approximately 40 patients per week.

Design and participants

The authors conducted a retrospective cohort study to identify the prevalence and risk factors associated with hepatitis secondary to the FLD in TB clinic of SH. All naïve case of pulmonary, extrapulmonary and disseminated TB received standard quadruple FLD regimen in SH's TB clinic between January and December 2017 were included. The diagnosis of TB was considered by pulmonologists in TB clinic, based on clinical findings, sputum smear, culture, molecular testing (Xpert MTB/RIF or Line probe assays) and histopathological study results. The exclusion criteria were lost to follow-up, transferred out or died before receiving FLD for less than eight weeks.

Data collection

Demographic data, clinical, and laboratory investigation were retrieved from the electronic medical record. Demographic and clinical characteristic data included age, body weight, height, comorbidities (airway disease, liver disease, diabetes mellitus, HIV, hepatitis B virus [HBV] infection, hepatitis C virus [HCV] infection), alcohol consumption, smoking status, anti-TB dosage, serum creatinine (SCr), serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, total bilirubin. During the early medical chart review, the authors excluded there was excessive missing information about the concurrent use of over-the-counter medicine and herbal. Thus, the present decided to drop these variables from the data collection process.

Definition and pattern of drug-induced hepatotoxicity

For the present study, hepatotoxicity due to treatment with anti-TB drugs was defined as one of the following criteria: 1) AST or ALT levels >5 times of the upper limit of normal (ULN; 40 IU/L), 2) >3 times of ULN with clinical symptoms such as nausea, vomiting, abdominal pain, jaundice, or unexplained fatigue, 3) total bilirubin >3 mg/dL[21]. Non-hepatitis was defined by the absence of clinical symptoms or abnormal liver test described above during the course of anti-TB medication. Three patterns of idiosyncratic DIH were determined using the "R" ratio of ALT activity (patients ALT/ULN of ALT) to ALP activity (patients ALP/ULN of ALP [120 IU/L]). Those 3 patterns included the following: 1) hepatocellular pattern if ALT alone was elevated ≥5 times of ULN or R ratio ≥5, 2) cholestatic pattern if ALP alone was elevated ≥2 times of ULN or R ratio ≤2, mixed pattern if ration >2 to <5[6].

Statistical analysis

To measure prevalence, the authors analyzed the characteristics of all those eligibles and compared hepatitis with non-hepatitis cases. Categorical variables were presented as the percentage and compared using Fisher's exact test. Continuous variables were presented as mean ± standard deviation (SD) and compared using Two-sample t-test. Non-parametric continuous variables were presented as median and the interquartile range (IQR) and compared using Wilcoxon rank sum (Mann-Whitney) test. All proportion and p-value were calculated among non-missing data.

Logistic regression analysis was used to determine factors associated with hepatoxicity. Odds ratio (OR) and its 95% confidence interval (CI) were estimated. Variables that were selected by univariable analyses at p-value less than 0.1 were included in the final multivariable logistic regression model. A p-value of less than 0.05 considered to be statistically significant.

Ethics approval

The study protocol was approved by the Ethical Committee of Suratthani Hospital, Thailand (Approval ID: 16/2563).

Results

A total of 213 patients were eligible and treated with FLD during the study period. Of this number, 15 patients were excluded (12 patients lost to follow-up, and 3 died of other causes before 8 weeks of FLD). Finally, 198 patients were included in the final analysis. Eighteen patients developed hepatoxicity, thus, the prevalence of DIH was 9.1% (18/198). The patients were predominantly male (70%). The mean age was 41.4±15.6 years. The TB-HIV co-infection rate was 8.1% (16/198). Almost 80% of patients were

Table 1. Clinical characteristics of all type of TB patients with hepatitis and non-hepatitis after receiving first-line anti-TB drugs (n=198)

Characteristics	Overall; n (%)	Hepatitis; n (%)	Non-hepatitis; n (%)	p-value
Total	198 (100)	18 (9.1)	180 (90.9)	
Age (years)				
Mean±SD	41.4±15.6	40.8±15.1	47.4±20.1	0.087
>60 years	27 (13.6)	7 (38.9)	20 (11.1)	0.005
Sex: male	138 (69.7)	124 (68.9)	14 (77.8)	0.590
Body weight (kg); mean±SD	55.0±10.4	52.4±6.5	55.3±10.7	0.270
BMI (kg/m^2); mean±SD	20.3±3.6	18.8±2.7	20.4±3.7	0.073
Malnutrition (BMI <1.85 kg/m^2)	59 (29.8)	9 (50.0)	50 (27.8)	0.060
Underlying diseases				
Airway disease	9 (4.6)	2 (11.1)	7 (3.9)	0.190
Liver disease	8 (4.0)	3 (16.7)	5 (2.8)	0.027
Diabetes mellitus	13 (6.6)	1 (5.6)	12 (6.7)	1.000
Human immunodeficiency virus	16 (8.1)	13 (7.2)	3 (16.7)	0.170
• CD_4 level ($cell/mm^3$); median (IQR)	150 (32, 507)	42.0 (6, 494)	189 (69, 526)	0.310
Hepatitis B carrier	5 (2.5)	1 (5.6)	4 (2.2)	0.380
Hepatitis C carrier	2 (1.0)	0 (0.0)	2 (1.1)	1.000
Current alcohol consumption	87 (43.9)	12 (66.7)	75 (41.7)	0.049
Current smoker	85 (42.9)	12 (66.7)	73 (40.6)	0.045
Pulmonary TB	154 (77.8)	13 (72.2)	141 (78.3)	0.560
Bacteriologically confirmed*	105 (68.2)	10 (76.9)	95 (67.4)	0.829
Missing*	4 (2.6)	0 (0.0)	4 (2.84)	
Extra-pulmonary TB	55 (27.8)	5 (27.8)	50 (27.8)	1.000
Disseminated TB	18 (9.1)	1 (5.6)	17 (9.4)	1.000
Serum creatinine (mg/dL); median (IQR)	0.79 (0.64, 0.89)	0.80 (0.64, 1.07)	0.79 (0.64, 0.87)	0.290
Liver test level				
Initial; median (IQR)				
• AST (U/L)	23 (18, 41)	26 (15, 51)	23 (18, 37)	0.840
• ALT (U/L)	22 (12, 33)	25 (12, 38)	22 (13, 32)	0.830
• Albumin (g/dL); mean±SD	3.66±0.70	3.05±0.82	3.74±0.65	0.003
• Total bilirubin (mg/dL)	0.43 (34, 0.61)	0.48 (0.40, 0.64)	0.43 (0.33, 0.60)	0.360
After received anti-TB drugs; median (IQR)				
• AST (U/L)	29 (20, 42)	223 (148, 386)	25 (19, 32)	<0.001
• ALT (U/L)	23 (15, 40)	155 (102, 225)	19 (14, 30)	<0.001
• Albumin (g/dL); mean±SD	3.75±0.69	3.07±0.73	3.91±0.57	<0.001
• Total bilirubin (mg/dL)	0.45 (0.32, 0.77)	3.2 (1.7, 4.8)	0.4 (0.3, 0.6)	<0.001
• Timing of liver test after anti-TB (day)	15 (13, 24)	14 (9, 18)	16 (13, 24)	0.120

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; IQR=interquartile range; SD=standard deviation; TB=tuberculosis

* Percentage were calculated among pulmonary TB patients (n=154)

pulmonary TB, 68% of them were bacteriologically confirmed. The comparison between baseline characteristics, treatment and outcomes with hepatitis and non-hepatitis were shown in Table 1 and 2. The median duration between the initiation of anti-TB drugs and the onset of hepatitis was 15 days (IQR 13 to 24). In comparison with non-hepatitis cases, hepatitis cases were more likely to be aged >60 years (38.9% vs. 11.1%, p=0.005), had underlying liver disease (16.7% vs. 2.8%, p=0.027), current alcohol consumption (66.7% vs. 41.7%, p=0.049), current smoker (66.7% vs. 40.6%, p=0.045), and

Table 2. Treatment and outcomes of all type of TB patients with hepatitis and non-hepatitis after receiving first-line anti-TB drugs (n=198)

Variables	Overall	Hepatitis	Non-hepatitis	p-value
Anti-TB dosage; mean±SD				
Isoniazid (mg)	298.1±11.2	294.4±23.6	298.5±9.2	0.150
• Dose in mg/kg	5.6±1.0	5.6±0.8	5.6±1.0	0.980
Rifampicin	559.1±67.0	558.3±69.1	559.2±67.0	0.960
• Dose in mg/kg	10.4±1.7	10.6±1.6	10.4±1.8	0.640
Pyrazinamide (mg)	1287.9±249.0	1250.0±226.9	1291.7±251.4	0.500
• Dose in mg/kg	23.7±4.0	23.4±3.5	23.7±4.1	0.800
Ethambutol (mg)	971.5±177.9	966.7±171.5	971.9±179.0	0.900
• Dose in mg/kg	17.9±3.3	18.2±3.1	17.9±3.3	0.720
Outcomes; n (%)				0.410
Cured	94 (47.5)	9 (50.0)	85 (47.2)	
Treatment completed	83 (41.9)	7 (38.8)	76 (42.2)	
Treatment failed	0 (0.0)	0 (0.0)	0 (0.0)	
Died	2 (1.0)	1 (5.6)	1 (0.6)	
Lost to follow-up	15 (7.6)	1 (5.6)	14 (7.8)	
Not evaluated	4 (2.0)	0 (0.0)	4 (2.2)	

SD=standard deviation; TB=tuberculosis

had lower serum albumin (3.05 g/dL vs. 3.74 g/dL, p=0.003). However, there were no significant difference in gender, body weight, body mass index (BMI), underlying diseases (except liver diseases), type of TB, initial SCr, AST, ALT, and total bilirubin level, anti-TB dosage received and treatment outcomes (Table 1, 2). Of the 18 patients with DIH, 8 (44.4%) were hepatocellular pattern, 3 (16.7%) were cholestatic pattern and 7 (38.9%) were mixed pattern.

On univariable analysis, the following parameter were considered to be significant risk factors for developing hepatitis after anti-TB treatment: age >60 years (OR 5.09, 95% CI 1.77 to 14.63, p=0.003), current alcohol consumption (OR 2.80, 95% CI 1.01 to 7.79, p=0.049), current smoker (OR 2.93, 95% CI 1.05 to 8.16, p=0.040), history of liver disease (OR 7.00, 95% CI 1.52 to 32.18, p=0.012), and serum albumin <3.5 g/dL (OR 9.98, 95% CI 2.35 to 42.41, p=0.002) (Table 3). On multivariable analysis, hepatitis remained statistically associated with the age >60 years (adjusted OR [aOR] 28.49, 95% CI 2.68 to 302.95, p=0.005) and serum albumin <3.5 g/dL (aOR 20.97, 95% CI 2.11 to 208.51, p=0.009) (Table 4).

Table 3. Factors associated with hepatitis among all type of TB patients after receiving first-line anti-TB drugs by univariable logistic regression analysis

Factors	Univariable analysis		p-value
	OR	95% CI	
Age (years)			
≤60	1	Reference	
>60	5.09	1.77 to 14.63	0.003
Test for trend (every 1 year increased)	1.03	0.99 to 1.06	0.090
Sex			
Female	1	Reference	
Male	1.58	0.50 to 5.02	0.437
BMI (kg/m^2)			
≥18.5	1	Reference	
<18.5	2.60	0.98 to 6.93	0.056
Test for trend (every 1 kg/m^2 increased)	0.87	0.74 to 1.01	0.071
Current alcohol consumption			
No	1	Reference	
Yes	2.80	1.01 to 7.79	0.049
Current smoker			
No	1	Reference	
Yes	2.93	1.05 to 8.16	0.040
History of liver disease			
No	1	Reference	
Yes	7.00	1.52 to 32.18	0.012
Serum albumin level (g/dL)			
≥3.5	1	Reference	
<3.5	9.98	2.35 to 42.41	0.002
Test for trend (every 1 g/dL increased)	0.25	0.09 to 0.68	0.007

BMI=body mass index; CI=confidence interval; OR=odds ratio; TB=tuberculosis

Table 4. Factors associated with hepatitis among all type of TB patients received first-line anti-TB drugs by multivariable logistic regression analysis

Factors	Multivariable analysis		p-value
	aOR	95% CI	
Age >60 years	28.49	2.68 to 302.95	0.005
Current alcohol consumption	16.53	0.56 to 487.57	0.104
Current smoking	0.17	0.01 to 4.03	0.272
History of liver disease	5.10	0.36 to 72.19	0.229
BMI <18.5 kg/m^2	2.08	0.31 to 14.09	0.455
Serum albumin <3.5 g/dL	20.97	2.11 to 208.51	0.009

aOR=adjusted odds ratio; BMI=body mass index; CI=confidence interval; TB=tuberculosis

Discussion

In the present study, the prevalence of anti-TB DIH was 9.1%, similar to many developing countries which reported vary from 8% to 10%[22,23], but higher than the developed countries which reported vary from

1% to 3%[24]. The explanation of this difference could be due to the relatively higher incidence of alcohol consumption, malnutrition, chronic liver disease and viral hepatitis in the developing countries[25].

Similar to the previous study finding, the patient age more than 60 years[4], and the serum albumin of less than 3.5 g/dL[18,26,27], were independent risk factors associated with DIH. Some studies showed that patients with pre-treatment hypoalbuminemia had a twofold or threefold higher risk of developing anti-TB drug-induced hepatitis[22,23]. Hypoalbuminemia is more common in the patient with chronic liver disease such as cirrhosis. The decrease in serum albumin concentration usually reflects the severe liver damage with reduced albumin synthesis[28]. Furthermore, the hypoalbuminemia may be found in the condition of the others, including systemic inflammation or malnutrition state. Many previous studies supported that advanced age was a risk factor associated with anti-TB DIH[9-13].

Although HIV seropositive status[17], or chronic viral hepatitis[29-31], were reported as the risk factors associated with anti-TB DIH, the authors found only a small number of patient with viral hepatitis and HIV co-infection in the present study cohort to detected these association. However, there were three more factors associated with anti-TB DIH on the univariable analysis but not final multivariable analysis, which might be due to small sample size. They were alcohol consumption, current smoking status and history of liver disease. Some of the previous studies supported the higher risk of developing anti-TB DIH in alcohol consumption[9,12,13,32,33], and chronic liver disease patients[16].

All those eighteen patients with DIH in the present study stopped anti-TB drugs and rechallenged after AST and ALT levels <2 times of ULN and total bilirubin <2 mg/dL following the National Tuberculosis Control Program Guidelines, Thailand 2018[34]. DIH is the cause of drug discontinuation in 11% of patients received INH, RMP, and PZA combination regimen[4]. A meta-analysis of anti-TB treatment associated hepatotoxicity reported the frequency of overt clinical hepatitis caused by INH, RMP, or both were 0.6%, 1.1%, and 2.6%, respectively[7]. The mean dosage of FLDs in the present study was comparable to the dosage in guideline recommendation[13] and there was no significant difference between hepatitis and non-hepatitis group. This finding supported by Jeong et al reported that basal serum drug concentration was not associated with the risk anti-TB DIH in patients being treated with the currently recommended doses of FLDs[35]. Although idiosyncratic DIH is typically not dose-related, the daily dose of 50 to 100 mg is the threshold that usually required for the individual patient[6]. The median duration of onset for DIH in the present study was approximately two weeks which compatible with the idiosyncratic type that had a longer latency period (days to weeks) than intrinsic DIH[6].

There were a few limitations in the present study. First, not all patients had the liver function test result before or during received anti-TB medications. Although there was a study reported an increased risk of hepatotoxicity during TB treatment among patients with abnormal baseline transaminases[36], TB guideline did not recommend the routine performed liver function before treatment among low-risk patients[37]. Furthermore, monitoring liver function test routinely during the first two months of FLDs therapy would have detected approximately 75% of patients with a peak enzyme elevation of ≥3 times of ULN[38]. Second, the small sample size leading to low statistical power to conclude some interesting parameters. Third, the retrospective nature of the study limited the completeness of the data collection. Thus, the missing data were unavoidable and lack of information about herbal dietary supplements and the other medications that were potential causative agents associated with liver injury.

Conclusion

The prevalence of first-line anti-TB DIH in Suratthani Hospital was comparable to many developing countries. Advanced age of more than 60 years and pre-treatment serum albumin of less than 3.5 g/dL were found to be significant risk factors for developing first-line anti-TB induced hepatotoxicity.

What is already known on this topic?

First-line anti-TB DIH is one of the most common and severe adverse effects during treatment. The knowledge regarding factors associated with DIH might aid the clinicians in monitoring and prevention the occurrence of DIH in high-risk patients.

What this study adds?

Prevalence of DIH was 9.1%, similar to many developing countries. Age of more than 60 years and low serum albumin of less than 3.5 g/dL were significant risk factors associated with first-line anti-TB DIH.

Authors' contributions

All the authors had contributed to this paper in the following ways: conception and design of the work: Morasert T and Ruengchaisiwawaith T, data collection: Ruengchaisiwawaith T, data analysis and interpretation: Morasert T, drafting the article: Ruengchaisiwawaith T, critical revision of the article: Morasert T. Final approval of the version to be published: Morasert T and Ruengchaisiwawaith T.

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Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

Data are available upon reasonable request. All data relevant to the study are included in the article.

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