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Original Research

Incidence, outcomes, and risk factors of antituberculosis drugs induced liver injury in Thailand: A retrospective cohort study

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Abstract

Background: Tuberculosis (TB) is a persistent health concern in numerous regions, including Thailand. The adverse effects of tuberculosis (TB) treatments, particularly liver injuries, can complicate treatment protocols, thereby increasing the likelihood of treatment discontinuation and the risk of subsequent drug resistance. **Objective:** This study was conducted to investigate the incidence, predisposing factors, and treatment outcomes associated with antituberculosis drugs induced liver injury (ATDILI) in Northeastern Thailand. **Methods:** A retrospective analysis was conducted at Mahasarakham Hospital in 2019. Patient data were retrieved from hospital records and databases. Inclusion criteria included receiving a first-time TB diagnosis, starting a standard TB regimen, and having normal liver function. To compare baseline characteristics between ATDILI patients and controls, Chi-square tests and T-tests were used. Bivariate and multivariable regression analyses were conducted to identify factors associated with drug-induced hepatitis. **Results:** 346 of 602 TB patients (57.5%) were enrolled. The study found an incidence of ATDILI at 14.45% (50 cases), which is notably higher than the Thai average of 4.8%. Risk factors were identified as malnutrition (adjusted OR=6.71, 95%CI 3.11:14.45), concurrent diseases (adjusted OR=2.42, 95%CI 1.20:4.89), and alcohol consumption (adjusted OR=4.24, 95%CI 1.45:12.38). In terms of therapeutic outcomes, only 18 patients were cured (36.0%). The probability of hepatotoxic events was addressed during the initial treatment phase, emphasizing the critical need for rigorous liver function monitoring during the first month of TB therapy. The ATDILI group had a mortality rate of 16%, which was higher than the national TB-related average of 8.2%. **Conclusion:** The marked presence of ATDILI in the cohort under study accentuates the immediate need for enhanced clinical monitoring, especially among susceptible groups. It is imperative to implement strategies aimed at early detection, prompt intervention, and holistic management of ATDILI, complemented by endeavors to boost cure rates for the affected population.

Keywords: tuberculosis; drug-induced liver injury; hepatotoxicity; risk factors

INTRODUCTION

Tuberculosis (TB), despite being preventable and curable, continues to pose a significant global health challenge. According to the World Health Organization (WHO), in 2021, TB was responsible for approximately 1.4 million deaths, including 187,000 among HIV-positive individuals. This placed it as the second leading infectious cause of death, following closely behind COVID-19.[1]

The standard treatment for tuberculosis involves the concurrent administration of four medications: isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). Typically administered during the first two months, these medications play a crucial role in preventing drug resistance and assuring treatment efficacy.[2,3] However, coadministration raises difficulties. Hepatitis, dermatological manifestations, gastrointestinal issues, and neurological disturbances are documented adverse reactions. Antituberculosis drugs induced liver injury (ATDILI) comes out as the primary reason for discontinuing treatment.[4] Notably, three of the four compounds (H, R, and Z) have hepatotoxic potential, with ethambutol being the exception.[3,4] Their concurrent use may increase the incidence and severity of ATDILI. Although these adverse effects are not always severe.[5-7], they can complicate treatment protocols, increasing the likelihood of treatment cessation, non-compliance, and subsequent risk of drug resistance.[8]

There are several different factors that contribute to the development of ATDILI. Alcohol consumption, nutritional deficiencies, a body mass index (BMI) below 18.5 kg/m^2, co-existing HIV infection, pre-existing hepatitis viral infections, age above 35 years, concurrently intake of hepatotoxic drugs, and daily consumption of anti-tuberculosis medications are risk factors.[2,4,9-14] Moreover, genetic predispositions, such as the SLCO1B1*15 haplotype gene[15], GSTP1[16], NAT2 slow acetylator genotype[17], and CYP2E1 Rsal/PstI c1/c1 genotype[18] have been identified as increasing susceptibility.

When diagnosing ATDILI, the standard treatment protocol results in discontinuing antituberculosis drugs and reintroducing them carefully after hepatotoxicity has resolved.[2-4] According to numerous studies, the consequences of discontinuing

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these medications can vary from successful medication reintroduction to treatment failures and even the emergence of drug resistance.[5,7,13,19-23]

Although numerous studies have examined ATDILI, the incidence and predisposing factors reported in these studies varies.[24] Furthermore, there is limited of research on ATDILI in Thailand, particularly in the northeastern region.[10,19,25] Notably, many of these studies overlook the results of drug reintroduction after ATDILI.[10,25] This research gap will be filled by examining the incidence, predisposing factors, treatment strategies, and outcomes of ATDILI. Acquiring this information is essential to improving preventative strategies, refining treatment guidelines, and minimizing the negative outcomes of ATDILI.

METHODS

Study design and data source

A retrospective study was conducted between January and December 2019 at Mahasarakham Hospital, the largest hospital in Mahasarakham province, Thailand. With 580 beds, the hospital serves nearly 1,500 outpatients daily. Because multiple departments deliver TB care (TB clinic, Outpatients clinic, medical ward), data was collected from a variety of sources, including medical charts, outpatient cards, and the hospital's medication and clinical labs databases. Study protocol was approved from both Mahasarakham University (MSU EC 208/63 Date 01/07/2023) and Mahasarakham Hospital's Ethics Committees (MSKH_REC 64-01-010 Date 29/03/2021) before data collection.

Inclusion and exclusion criteria

Inclusion criteria of this study were patients diagnosed with TB for the first time between January and December 2019. These patients began a standard short-course TB regimen (2HRZE/4HR) and had normal liver function indicators, with AST/ALT levels not exceeding three times the upper normal limit (UNL) before treatment. Exclusion criteria were individuals under 18 years of age, those with a history of allergies to typical TB medicines, those with liver enzyme values three times above the UNL, those who showed significant diagnostic changes during treatment, and those who discontinued their TB medication early without experiencing ATDILI.

Sample size determination

The sample size for this study was determined based on previous research in Thailand.[10,19,25] The hepatotoxicity rates related to TB drugs ranging from 0.63% to 9.19%, with an average rate of 4.8%. To achieve 80% power at a significant level of 0.05, 109 participants were required. Nonetheless, the study decided to include all 602 TB patients who were treated during that year and 346 of these met the criteria.

Data collection

A review of the hospital's medication database was conducted to identify patients prescribed TB treatment. Patient records and laboratory tests were searched for demographic and medical data. Patients who met the inclusion criteria were enrolled, and the ICD-10 or pharmacist ADR monitoring systems were used to identify those with ATDILI. The management of these cases was recorded.

Liver function assessment, clinical presentation, severity, and ATDILI management

Liver function was recorded both before and after starting the TB treatment, using the World Health Organization's guidelines.[2,3] For ATDILI, the definitions were: (a) ALT levels rising to or above five times the normal limit. (b) ALP levels increasing to or above twice the ULN, especially if there were also rises in specific enzyme levels without any known bone-related cause. (c) ALT levels increasing three times alongside a bilirubin level rise of twice the ULN. The clinical DILI type was determined through the R-value from initial liver tests. Cases were labeled as 'hepatocellular' if $R \geq 5.0$, 'cholestatic' if $R \leq 2.0$, and 'mixed' if R was between 2.1 and 4.9.

For the first two months of chemotherapy, patients underwent regular blood checks. Liver tests were planned at 2, 4, and 8-week intervals. Treatment adjustments, whether pausing or restarting, were based on individual needs as assessed by physicians.[3]

Statistical analysis

Data were entered into Microsoft Excel and subsequently analyzed in STATA (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX). Descriptive statistics, such as means, ranges, and medians, were employed as appropriate. Chi-square and T-tests were used for baseline comparisons. The correlation between independent variables and ATDILI was assessed using simple logistic regression. Significant factors (p-value < 0.2) were incorporated into multivariate logistic regression via a stepwise method. Multicollinearity occurs when two or more independent variables in a regression model are highly correlated. To test for this, the variance inflation factor (VIF) and tolerance were used. The cut-off points were set at VIF > 2.5 and tolerance > 0.10.[26] A p-value of less than 0.05 and a 95% CI were used as criteria for determining statistical significance.[21]

RESULTS

Socio-demographic and clinical characteristics

In this cohort, 346 patients were evaluated, showing a significant male predominance (n=260, 75.1%). The ages of the participants ranged from 19 to 90 years, with an average age of 54.3 years (SD 15.7). The majority of the patients had pulmonary TB (n=260, 75.1%). When assessing Body Mass Index (BMI), the average value was found to be within the normal range at 20.50 kg/m^2(SD 3.70). The average albumin level, a primary indicator of nutritional status, was 3.6 mg/L (SD 0.7), which is within the standard range for most individuals. HIV infections were found in 11.8% of the participants. Renal assessments revealed that 3.2% of the subjects were in the advanced stages of chronic kidney disease (CKD stages 4 and 5), with a creatinine clearance (CrCl) below 30 ml/min. In terms of socio-behavioral data,

forty-three (12.4%) currently smoked, 13.2% reported alcohol consumption, and 2% used herbal treatments or supplements. Following treatment with TB drugs, 50 patients exhibited signs of ATDILI, as detailed in Table 1. Patients with ATDILI exhibited distinct differences when compared to non-ATDILI patients. The age of ATDILI patients was significantly higher (p-value = 0.009), and they more frequently had comorbid conditions (p-value < 0.01). The ATDILI group had a significantly higher incidence of HIV infections (18% vs 10.8%, p-value = 0.019) and CKD (8.0% vs 2.3%, p-value < 0.01). Malnutrition, current alcohol consumption, and current smoking were also significantly more prevalent among ATDILI patients (p-value < 0.01). However, ATDILI was not associated with serum albumin levels (p-value > 0.05). Furthermore, there were no significant differences in BMI, viral hepatitis infections, and herbal use between the two groups (p-value > 0.05), as shown in Table 1.

Characteristics of cases with anti-tuberculosis drug-induced hepatotoxicity

Of the 346 newly diagnosed tuberculosis patients included in this study, 50 (14.45%) exhibited elevated liver function test results post-initiation of antituberculosis therapy, subsequently being diagnosed with hepatotoxicity. Table 2 shows elevated serum concentrations of ALT, AST, and total bilirubin. Among these patients, 13 (36%) were outpatients, while 37 (74%) were admitted, as shown in Figure.1.

The onset of hepatotoxicity post-initiation of antituberculosis therapy in this study ranged from 2 to 84 days, with an average of 17.16 days (SD 13.34). The majority of hepatotoxicity cases were observed in the first and second months of treatment (98%). Only one patient (2%) developed hepatotoxicity post the intensive phase of the initial two months. Using the R-ratio for liver injury pattern assessment, the most common injury was the cholestatic pattern (R<2), identified in 23 out of 50 patients (46%). This was followed by the hepatocellular pattern (R>5) in 14 patients (28%), and the mixed pattern (R=2.1–4.9) in 13 patients (26%), as described in Table 2. The most frequent drug responsible for hepatotoxicity was Pyrazinamide, affecting 20 patients (40%), closely followed by Rifampicin in 17 patients (34%).

Table 1. Socio-demographic of study patients

Characteristics	Total patients n=346	ATDILI n=50	Non-ATDILI n=296	p-value*
Age (years), mean (SD)	54.3 (15.7)	59.12 (15.5)	53.47 (15.6)	**0.009**
Male, n (%)	260 (75.1)	37 (74.0)	223 (75.3)	0.834
Type of TB, n (%) - Pulmonary TB - Bones and Joints TB - Pleural TH - Adrenal Gland TB - Meninges TB - Urinary Tract TB - Abdominal TB	 249 (72.0) 33 (9.5.0) 29 (8.4) 18 (5.2) 10 (2.9) 4 (1.2) 3 (0.9)	 32 (64.0) 5 (10.0) 5 (10.0) 2 (4.0) 6 (12.0) 0 (0.0) 0 (0.0)	 217 (73.3) 28 (9.5) 24 (8.1) 16 (5.1) 4 (1.4) 4 (1.4) 3 (1.0)	**0.004**
Weight (kg), Mean (SD)	54.2 (11.3)	52 (9.9)	54.6 (11.5)	0.934
BMI, Mean (SD)	20.5 (3.7)	20.1 (3.7)	20.5 (3.7)	0.748
Serum albumin (g/dL), Mean (SD)	3.6 (0.7)	3.0 (0.5)	3.7 (0.7)	1.000
Comorbid conditions, n (%)	240 (69.3)	24 (48.0)	216 (73.0)	**0.000**
Viral hepatitis infections - Yes - Unknown	7 (2.1) 269 (77.7)	4 (8) 23 (46)	3 (1) 246 (83.2)	0.199
HIV infection - Yes - Unknown	 41 (11.8) 85 (24.7)	 9 (18) 22 (44)	 32 (10.8) 63 (21.3)	**0.011**
Chronic kidney diseases (CrCl<30 ml/min), n (%) - Yes - Unknow	 11 (3.2) 6 (1.7)	 4 (8.0) 6 (12.0)	 7 (2.3) 0 (0.0)	**0.019**
Malnutrition, n (%)	133 (38.4)	39 (78.0)	94 (31.7)	**0.000**
Current alcohol consumption, n (%)	46 (13.2)	16 (32.0)	30 (10.1)	**0.000**
Current smoking, n (%)	43 (12.4)	14 (28.0)	29 (9.8)	**0.000**
Herbal use, n (%) - Yes - Unknown	 7 (2.0) 295 (94.0)	 2 (4.0) 45 (90.0)	 5 (1.7) 250 (94.6)	0.214
High doses of TB drugs, n (%)	13 (3.8)	5 (10.0)	8 (2.7)	**0.012**

*Analysis conducted using the independent t-test for continuous variable and chi-square test for categorical variable, ATDILI=Antituberculosis drug induced liver injury, BMI=Body mass index, CrCl=Creatinine clearance, HIV=Human immunodeficiency virus, TB=Tuberculosis, SD=Standard deviation

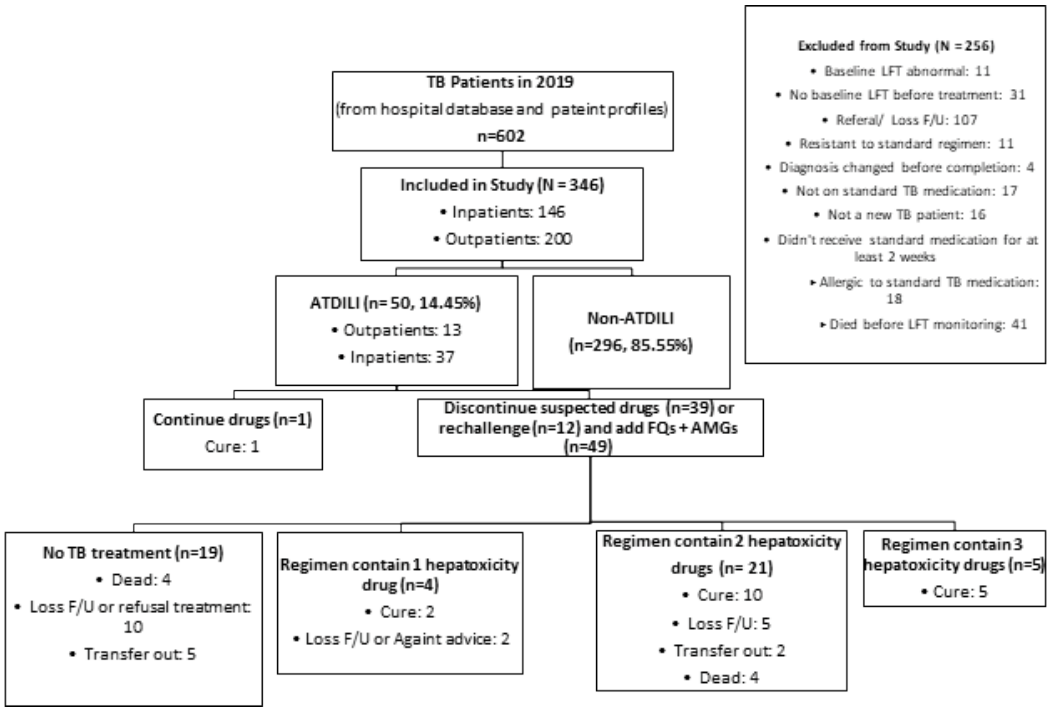

Figure 1. Incidence and outcome of ATDILI patients (AMGs=Aminoglycosides, ATDILI=Antituberculosis drug induced liver injury, Qs= Fluoroquinolones, F/U= Follow up, LFT=Liver function test)

Table 2. Liver function test of after TB treatments

Variables	ATDILI n=50	Non-ATDILI n=296	p-value*
AST (IU/L), Mean (SD)	38 (23.0)	29.6 (14.7)	**0.000**
ALT (IU/L), Mean (SD)	28.6 (25.2)	23.1 (16.1)	**0.021**
ALP (IU/L), Mean (SD)	128.8 (120.6)	103.1 (59.7)	**0.01**
Total protein (g/dL), Mean (SD)ss	6.8 (1.4)	7.6 (0.9)	0.137
Direct bilirubin (mg/dL), Mean (SD)	0.3 (0.2)	0.3 (0.3)	0.329
Total bilirubin (mg/dL), Mean (SD)	0.6 (0.4)	0.5 (0.4)	0.179

* Analysis conducted using the independent t-test, ALP= Alkaline phosphatase, ALT= Alanine transaminase, AST= Aspartate aminotransferase, ATDILI=Antituberculosis drug induced liver injury, SD=standard deviation

Management of ATDILI

Of the patients who experienced ATDILI, 49 (98%) were advised by physicians to discontinue the standard drug regimen. All these patients were transitioned to an alternative regimen while awaiting normalization of their liver function tests (AST/ALT < 2 times the normal value and Total bilirubin <1.5 mg/dL). Every patient continued with Ethambutol and had Aminoglycosides and Fluoroquinolones added to their treatment. A significant 74% (37 patients) did not undergo a rechallenge with drugs individually, but rather stopped the suspected causative drug. Meanwhile, 24% (12 patients) underwent a drug rechallenge, starting predominantly with Isoniazid followed by either Rifampicin or Pyrazinamide, depending on the hepatotoxicity risk profile. The rechallenge process was conducted at an average interval of 9.58 days, with the range being 7-15 days. All patients underwent liver function tests before and after each subsequent antituberculosis drug trial. The follow-up duration after each rechallenge averaged 9.7 days, ranging from 7-15 days.

Final regimen and therapeutic outcome

Depending on the type of hepatotoxicity experienced, the drug regimen varied among the patients in this study. Of the 49 cases that changed the TB drug regimen, 19 patients (38.8%) were unable to undergo rechallenge due to reasons such as death (4 patients, 8.2%), loss of follow-up or refusal of treatment (10 patients, 20.4%), or transfer to a different hospital for continued care (5 patients, 10.2%). Of the remaining 30 patients (61.2%) who opted for a final antituberculosis regimen after experiencing hepatotoxicity, 26 (53.1%) successfully completed treatment with regimens containing two hepatotoxic drugs, while 4 cases (8.2%) used regimens containing only one

Table 3. Onset and type of ATDILI in TB patients

Variable	n (total=50, %)
Onset (days), - Range - Mean (SD)	 2-84 17.16 (13.34)
Type of ATDILI - Hepatocellular (R>5) - Cholestatic (R<2) - Mixed (R=2.1-4.9)	 14 (28.0) 23 (46.0) 13 (26.0)

ATDILI=Antituberculosis drug induced liver injury, SD=standard deviation

hepatotoxic drug. All of these patients underwent a longer course of treatment than the standard 6-month regimen, as depicted in Figure 1.

Among the group of 50 patients diagnosed with ATDILI, diverse treatment outcomes were observed. Seventeen patients (34.0%) were lost to follow-up, while 18 (36.0%) were determined to be cured. Only five patients (10.0%) successfully completed the standard short-course TB regimen. Unfortunately, 8 patients (16.0%) death. Moreover, seven patients (14.0%) were transferred to other hospitals, as illustrated in Figure 1.

ATDILI risk factors

Upon testing for multicollinearity using VIF and the tolerance value, we discerned no interrelation among the factors (VIF > 2.5, Tolerance > 0.10). On bivariate logistic regression analyses, patients with new pulmonary TB who were geriatric (aged ≥60 years), malnourished, had comorbidities, consumed alcohol, smoked, or experienced an overdose of TB drugs exhibited an increased risk for ATDILI. Nevertheless, multivariable logistic regression analyses found no significant differences in baseline characteristics such as sex, age, and liver function tests between ATDILI cases and controls. However, three factors were found to be statistically associated with an increased risk of ATDILI. Malnutrition (BMI < 18.5 mg/m^2 or albumin < 3.5 g/dL) correlated with nearly a seven-fold rise in ATDILI risk (Adjusted OR=6.71, 95%CI 3.11:14.45). In addition, individuals with comorbid conditions were more than twice as likely to develop ATDILI (Adjusted OR = 2.43, 95%CI 1.20:4.89). Lastly, regardless of the amount consumed, alcohol consumption was associated with a fourfold increase in ATDILI risk (Adjusted OR=4.24, 95% CI 1.45:12.38) (Table 4).

DISCUSSION

In our study, an incidence of ADIH of 14.45% was observed. This Figure exceeds the previously documented average of 4.8 % from other studies in Thailand.[10,19,25] When viewed from a global perspective, the reported incidences of hepatotoxicity range between 1.10% and 36.70%, pooled incidence of ATLI was 11.50% (95%CI 10.10:12.97) and showed an upward trend.[24]

Several factors can explain the observed variances. The retrospective nature of our research might have allowed for the inclusion of a broader patient population compared to prospective studies. A significant portion of our data was derived from hospital records, encompassing all patients undergoing anti-TB treatment. Nonetheless, it has been noted that some Thai medical institutions lack comprehensive registration systems for TB patients. Consequently, treatments are sometimes provided in departments separate from specialized TB clinics. The criteria for participant selection also vary considerably across studies. The notably high incidence rate of 36.70% in Brazil[27] can be attributed to their study's emphasis on HIV-positive patients. This group of patients has shown an increased risk of hepatotoxicity when administered anti-tuberculosis medications. In studies from India and Turkey, medications were reintroduced to individuals who had previously experienced hepatotoxicity. This reintroduction led to an elevated incidence rate of 24% when the full dosage was resumed.[6,28] Conversely, some studies reported lower rates of drug-induced liver injury (DILI) when participants with risk factors, such as viral hepatitis or HIV, were excluded.[6,10,13]

In our study, the latency between the initiation of TB treatment and the onset of ATDILI ranged from 2 to 84 days, with a mean of 17.16 days (SD 13.34). Both Thai and international studies have indicated that ATDILI is most frequently reported during the first month of treatment.[6,7,11,13,19,27] From our findings, it can be inferred that there is a higher risk of ATDILI during the first two months of the intensive phase of TB treatment, highlighting the necessity of intensive liver function monitoring. The average time for liver function to return to normal following drug discontinuation was found to be 16.59 days (SD 11.54), which is consistent with the findings of other studies. It was determined that early detection of ATDILI, along with immediate discontinuation of TB medications, accelerates the return of liver functions to normal levels.

The typical approach to TB drug reintroduction began with isoniazid, followed by either rifampicin or pyrazinamide, depending on the type of liver toxicity risk. This was in accordance with Thai guidelines that recommend beginning with Isoniazid.[3] The average interval between introducing each drug was 9.58 days. While there is no universal method for reintroducing drugs after ATDILI, our research suggests that the drug being chosen should be based on the specific manifestation of liver toxicity. Drugs known to be toxic to the liver, such as Pyrazinamide and Rifampicin, are typically avoided.[29,30]

Table 4. Risk Factors for Hepatotoxicity Development in TB Patients

Variables	Bivariate Analysis			Multivariate Analysis		
	Crude OR	p-value	95% CI	Adjusted OR	p-value	95% CI
Malnutrition	7.62	0.000*	3.74-15.54	6.71	**0.000***	3.11-14.45
Age ≥ 60	1.78	0.061	0.97-3.25	1.93	0.063	0.96-3.86
Comorbid condition	2.93	0.001*	1.59-5.39	2.43	**0.013***	1.20 –4.89
Alcohol consumption	4.17	0.000*	2.06- 8.44	4.24	**0.008***	1.45-12.38
Tobacco consumption	3.58	0.001*	1.73-7.40	1.68	0.353	0.56-5.02
High doses of Anti-TB drugs	4.00	0.019*	1.25-12.77	3.37	0.081	0.86-13.18

*Statistical significance (p-value < 0.05), CI=confidence interval

In this research, a strong correlation was identified between drug-induced liver injury (DILI) and factors such as malnutrition, excessive alcohol consumption, and other health conditions. These findings are consistent with studies conducted in Nepal, India, and Thailand.[6,7,10,11,13,19,22,31,32]

The impact of DILI on TB treatments is significant. A correlation has been established between liver toxicity and increased mortality rates or less successful treatment outcomes. Notably, our mortality rate of 16% in ATDILI patients is higher than that reported in Thailand at year 2021.[1] The findings presented here are consistent with worldwide trends, highlighting the significance of maintaining an efficient surveillance system.

The strengths of our study include an intensive data collection strategy, utilizing hospital records and specialized programs. This methodology incorporated data from both inpatient and outpatient settings, thus broadening our patient sample. Additionally, our comprehensive examination of the rechallenge process provides clinicians with valuable insights that may influence subsequent therapeutic strategies. However, there were some limitation in this research. The data was derived from medical records, which may contain inherent inaccuracies. It is possible that comprehensive details, particularly those associated with key risk factors, were not fully captured, thereby affecting the accuracy of the results. Given that the data came from a single hospital, it may be difficult to generalize the findings to broader contexts. A more detailed exploration of patient experiences during hepatotoxicity episodes was not conducted, potentially omitting important perspectives. Certain essential aspects, such as previous herbal consumption, past incidences of liver infections, and HIV status, were not thoroughly investigated, creating potential gaps in the research results.

CONCLUSION

In this study, the incidence of ATDILI was 14.45%. A statistically significant was observed between ATDILI and malnutrition, concurrent comorbidities, and alcohol consumption. Notably, the pattern of ATDILI, particularly the early onset of hepatotoxic episodes during the initial phases of treatment, highlighted the critical importance of close monitoring during the first month of tuberculosis treatment. While hepatotoxicity from TB medications is not the primary cause of mortality, its effect on prolonged hospital stays and intensive treatment is evident. These results highlight the need for increased clinical awareness, especially among at-risk populations. Future research could develop effective strategies for the early detection, intervention, and management of ATDILI.

DECLARATIONS

Ethical approval: The study received ethic approval from both Mahasarakham University (MSU EC 208/63 Date 01/07/2023) and Mahasarakham Hospital's Ethics Committees. (MSKH_REC 64-01-010 Date 29/03/2021). We confirm that the study was carried out according to internationally approved guidelines for human research in the declaration of Helsinki.

Conflicts of interest: The authors declare that they have no competing interests.

Author contribution: The authors confirm contribution to the paper as follows: study conception and design: PP, RS; data collection: PA, PP, SJ; analysis and interpretation of results: PA, PP, RS; draft manuscript preparation: PA, PP. All authors have critically reviewed and approved the final draft of the study and agreed to be accountable for all aspects of the work.

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