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Risks of hepatotoxicities during the intensive phase of tuberculosis treatment: A hospital-based case control study

Khanaphan Kemmarak[1], Bhunyabhadh Chaimay[2]✉, Somkiattiyos Woradet[2]

[1]*Department of Pharmacy, Sri Naggarindra Hospital, Srinagarindra District, Phatthalung Province, 93000, Thailand*

[2]*Faculty of Health and Sport Science, Thaksin University, Phatthalung Campus, Phatthalung, 93210, Thailand*

ABSTRACT

Objective: To identify factors associated with hepatotoxicity during the intensive phase of treatment in tuberculosis (TB) patients.

Methods: A case-control study was conducted of TB patients treated with first-line anti-TB drugs from 2013 to 2020. Cases were defined as patients who developed hepatotoxicity, while controls were those without hepatotoxicity, at a 1:2 ratio. Controls were randomly selected from the same hospitals as the cases. The primary outcome was the occurrence of hepatotoxicity during the intensive treatment phase, with data retrospectively collected from medical records. Descriptive statistics and multiple logistic regression with backward elimination were used for analysis.

Results: Among 3 021 tuberculosis patients who received first-line anti-tuberculosis regimen, 50 had abnormal liver function and 14 developed hepatotoxictiy. In addition, 2 957 patients had normal liver function and 128 served as controls for this analysis. Multiple logistic regression analysis revealed that female patients had about twice the risk of hepatotoxicity compared to males (adjusted *OR* 2.25, 95% *CI* 1.11-4.59), and patients with HIV coinfection were nearly 10 times more likely to develop hepatotoxicity than those without HIV (adjusted *OR* 9.74, 95% *CI* 3.12-30.41).

Conclusions: Female sex and HIV coinfection were found to be significant risk factors for hepatotoxicity during the intensive phase of TB treatment. Enhanced monitoring and preventive strategies are recommended for these high-risk groups to reduce the risk of hepatotoxicity.

KEYWORDS: Hepatotoxicity; Anti-tuberculosis drugs; First-line drugs; Tuberculosis

1. Introduction

Tuberculosis (TB) remains a significant global health issue, being one of the leading causes of infection and mortality worldwide. TB is caused by the *Mycobacterium* (*M.*) *tuberculosis* complex, a group of *Mycobacteria* that can infect virtually any organ in the human body[1]. Pulmonary TB, which affects the lungs, accounts for the majority of cases (88%)[2]. Extrapulmonary TB, on the other hand, can affect various other organs, including the pleura, lymph nodes,

Summary

Question: What factors are associated with hepatotoxicity during intensive phase treatment in tuberculosis patients?

Findings: This hospital-based case control study found that female sex and HIV coinfection were significantly associated with hepatotoxicity. Female patients had about twice the risk of developing hepatotoxicity (adjusted *OR* 2.25, 95% *CI* 1.11-4.59), and HIV coinfection increased the risk nearly tenfold (adjusted *OR* 9.74, 95% *CI* 3.12-30.41).

Meaning: This study emphasizes the need for enhanced monitoring and preventive measures for high-risk groups, particularly female patients and those with HIV coinfection, to reduce the risk of hepatotoxicity during TB treatment.

✉To whom correspondence may be addressed. E-mail: bchaimay@tsu.ac.th

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abdomen, genitourinary tract, skin, joints, bones, and meninges. The economic burden of TB has been considerable, with global health expenditures related to TB between 2000 and 2015 placing a heavy strain on economies. In African and Southeast Asian countries, TB costs accounted for more than 1% of their gross domestic product during this period[3].

Globally, approximately a quarter of the world's population is infected with TB, with many cases progressing to symptomatic illness[4]. The global burden of TB remains a major public health challenge, particularly in low- and middle-income countries. It is estimated that 23% of the global population (95% *CI* 20-26, approximately 1.7 billion people) are infected with TB[5]. While the overall trend in TB cases has seen a slight decline, new and relapse cases increased steadily between 2000 and 2016[6]. The Southeast Asia region accounts for 39% of global TB cases, with an estimated 3.4 million new cases reported in countries such as India, Bangladesh, Indonesia, Myanmar, and Thailand[7]. In Thailand, the average annual percent change in TB incidence and mortality decreased between 1990 and 2019. Projections also suggest a slight decline in TB incidence and mortality rates in Thailand by 2025, 2030, and 2035[8].

During treatment, the first-line anti-TB drug regimen is preferred for patients susceptible to TB. This regimen includes a combination of isoniazid, rifampicin, pyrazinamide, and ethambutol, which are administered intensively during the first two months. While most of these drugs are hepatotoxic, ethambutol is not. Hepatotoxicity refers to liver damage caused by chemical substances, in this case, medications[9]. The incidence of drug-induced hepatotoxicity ranged from 1.7% to 6.3% in previous decades[10], but more recent studies have reported rates as high as 24.6%[11].

Several risk factors for hepatotoxicity have been reported, but the relationship between these factors and hepatotoxicity remains unclear and controversial[12]. Some studies have identified a minimal to high risk of factors associated with hepatotoxicity, but their findings were often not statistically significant, likely due to small sample sizes. To the best of our knowledge, this study is the first to investigate multiple healthcare settings in central and southern Thailand, covering both community and secondary care hospitals. Therefore, the aim of this study was to determine the factors associated with hepatotoxicity during the intensive phase of treatment in TB patients.

2. Methods

2.1. Ethical considerations

Access to the HosXp database for TB care was granted by the hospital directors. This study received approval from the Ethics Committee on Human Rights Related to Human Experimentation at Thaksin University, Thailand, under COA No. TSU 2021_001 and REC No. 0246, dated January 4, 2021.

2.2. Study design

This hospital-based case control study was conducted between January and February 2021. We utilized secondary data from medical records and the HosXp database, focusing on TB patients in Phatthalung Province.

2.3. Study subjects

Initially, we retrospectively reviewed all TB patients registered in the HosXp database across hospitals in Phatthalung Province, southern Thailand. The study was conducted in 11 public hospitals, including one secondary hospital and ten community hospitals. Inclusion criteria were as follows: (1) patients diagnosed with TB between January 2013 and September 2020 using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes A15-A19 referring to tuberculosis of respiratory and other organ[13]; (2) patients who received a first-line anti-TB drug regimen (isoniazid, rifampicin, pyrazinamide, and ethambutol) during the intensive phase of treatment; and (3) patients with complete medical recodes available in the HosXp database, including demographic and clinical information at baseline.

The study subjects included patients diagnosed with both pulmonary and extrapulmonary TB. A total of 4 340 patients were diagnosed with TB during this period. Of these, 3 021 met the eligibility criteria of receiving the first-line anti-TB drug regimen. The cases were defined as patients who developed hepatotoxicity during the intensive phase of treatment, while controls were those who did not. Fourteen cases of hepatotoxicity were diagnosed by physicians (ICD-10 codes: K71-K76 refer to toxic liver diseases and other liver disorders), and an additional 50 cases were identified based on abnormal liver function test (LFT) results indicative of hepatotoxicity during treatment, even if not formally diagnosed. The LFT results meeting the following criteria were considered indicative of hepatotoxicity: (1) elevation of ALT and/or AST >3 times the upper limit of normal (ULN) with symptoms such as nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice; (2) elevation of ALT and/or AST >5 times the ULN without symptoms; or (3) total serum bilirubin >1.5 mg/dL. Additionally, the pattern of hepatotoxicity was assessed using the R-ratio, calculated as follows: R-ratio=(ALT/ALT_{ULN}) / (ALP/ALP_{ULN}). An R-ratio >5 indicated hepatocellular injury, 2-5 indicated mixed pattern injury, and <2 indicated cholestatic injury, based on standard definitions of drug-

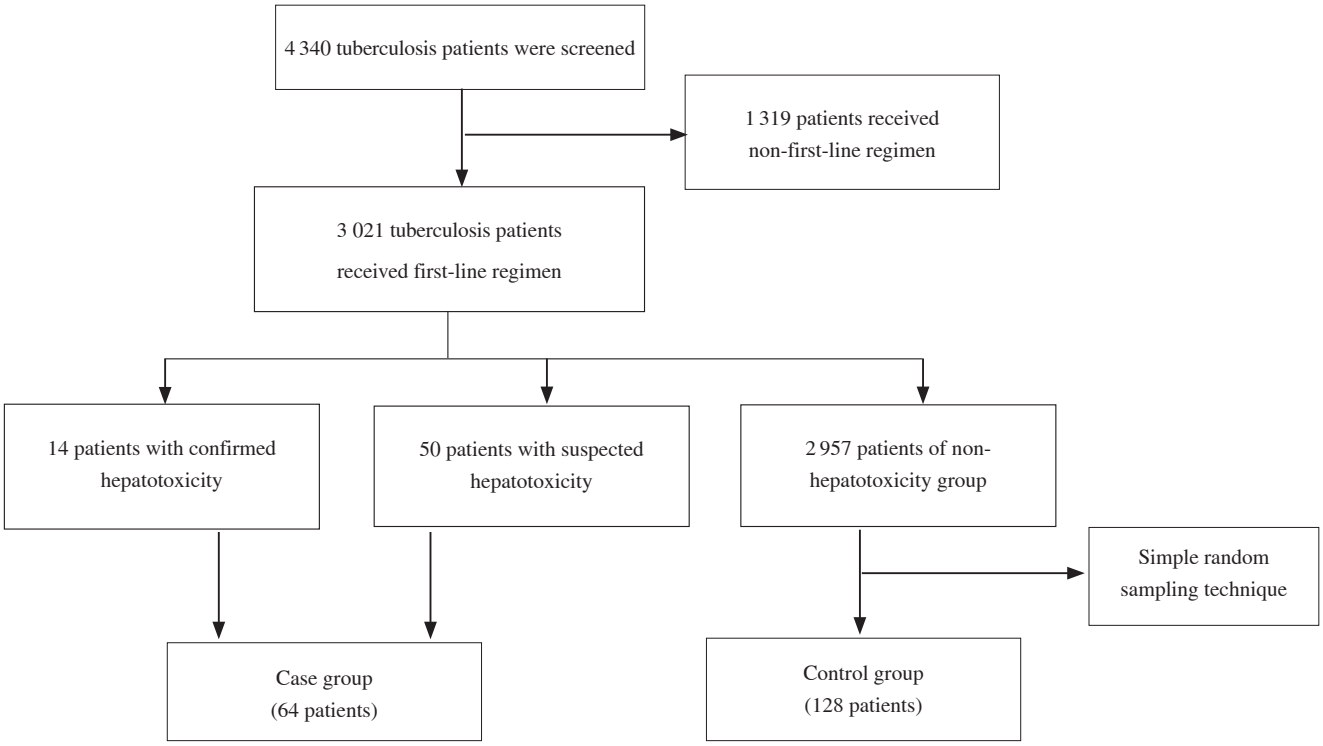

Figure 1. Flowchart depicting the selecting process of the study samples.

induced liver injury (DILI)[14–16]. LFT results were retrospectively reviewed from medical records and the HosXp database. In total, 64 cases were defined and included in the study. Controls were TB patients who met all inclusion criteria but did not develop hepatotoxicity during in the intensive phase of treatment. In total, 128 patients were randomly selected using computerized randomization from the same hospitals where the cases were treated, maintaining a case-to-control ratio of 1: 2 as shown in Figure 1.

Additionally, the statistical power of the study was calculated using a continuity correction for case-control studies[17–19]. The number of cases was 64, and the number of controls was 128. We set the alpha level (α) at 0.05, Z (0.975) at 1.959, and the power (1- β) at 1.00. The proportions of human immunodeficiency virus (HIV) coinfection among cases and controls were 0.27 and 0.04, respectively. This yielded a power of 97% for the study, indicating a strong likelihood of detecting a significant association if one exists.

2.4. Data collection

All data were retrospectively reviewed and obtained from the hospital information system, specifically the HosXp database, which records information through the Standard Structured Database of Medical and Public Health in 43 folders. The data were monitored and supervised by health professionals responsible for TB care management from the Department of Disease Control, Provincial Public Health Office, Phatthalung Province. All information used in this study was recorded by well-trained nurses and physicians who specialize in TB care at each health service setting.

The demographic characteristics assessed included sex, age, smoking status, alcohol consumption, and body weight at baseline treatment. Clinical characteristics comprised TB classification, results of acid-fast bacilli (AFB) smear at baseline, comorbidities, HIV coinfection, a history of previous TB illness, and liver enzyme levels from LFT at baseline. The liver enzyme measurements included Aspartate aminotransferase (AST, IU/L), Alanine aminotransferase (ALT, IU/L), Alkaline phosphatase (ALP, IU/L), and total serum bilirubin (Tbil, mg/dL). The selection of these variables was based on a systematic review of the literature, which has been published elsewhere[12].

Additionally, hepatotoxicity was categorized into three groups using the R-ratio method[20]. The R-ratio was calculated by dividing ALT by ALP and then multiplying by the upper limit of normal for both values. The interpretation of R-ratios was defined as follows: hepatocellular injury (R-ratio >5), cholestatic injury (R-ratio <2), and mixed injury (R-ratio 2-5).

2.5. Data analysis

Descriptive statistics were employed to summarize the demographic and clinical characteristics of the study subjects. The prevalence of hepatotoxicity during intensive phase treatment was calculated as the

proportion of identified cases among the total cohort. Comparisons of demographic and clinical characteristics between cases and controls were performed using the *Chi*-square test or Fisher's exact test for categorical variables, either the independent *t*-test or Mann-Whitney *U* test for continuous variables, as appropriate. Bivariate analysis using simple logistic regression was conducted to examine the factors associated with hepatotoxicity among the subjects. Subsequently, multivariate logistic regression analysis was performed to identify the factors associated with hepatotoxicity while accounting for potential confounding variables.

Initially, logistic regression modeling was conducted to investigate potential factors associated with hepatotoxicity. A separate model was constructed for each variable of interest. Continuous variables, such as patient age, were tested in both categorical and continuous forms. Polytomous variables, including smoking status and alcohol consumption, were categorized into dichotomous variables. All potential factors with a Wald's test *P*-value 0.25 were considered for inclusion in the final model. Consequently, this study incorporated all relevant factors into the final model, accounting for confounding variables such as TB classification (*P*-value=0.232), comorbidity (*P*-value=0.898), and total bilirubin (Tbil) (*P*-value=0.110). The *P*-value for the final model was determined using the partial likelihood ratio method.

The results were presented as crude odds ratios (*OR*) and adjusted odds ratios (adjusted *OR*), along with a 95% confidence interval (95% *CI*). An *OR* of 1 indicated no association, while an *OR* greater than 1 indicated as an increased likelihood of hepatotoxicity. Conversely, an *OR* less than 1 represented a statistically significant protective association.

3. Results

3.1. Demographic characteristics among subjects

Please briefly summarize the general characters of all the paricipants first (age, ratio of male and female, *etc*.)

As shown in Table 1, the demographic and clinical characteristics of the study subjects were compared between cases and controls. two-thirds of both cases and controls were male [62.5% (40/64) and 75.0% (96/128), respectively]. Approximately one-third of cases and controls were aged ⩾60 years [29.7% (19/64) and 35.2% (45/128), respectively]. The average age of cases was (52.6±16.6) years, while for controls it was (53.4±16.8) years. Smokers or ex-smokers comprised one-third of both groups [34.4% (22/64) of cases and 32.8% (42/128) of controls]. Additionally, one-fourth of cases and controls were alcohol drinkers or ex-drinkers [23.4% (15/64) and 24.2% (31/128), respectively]. Around half of the cases and controls had a body weight of ⩾50 kg at baseline treatment [46.9% (30/64) and 52.3% (67/128), respectively]. The average body weight for cases was (50.3±10.0) kg, while for controls it was (49.6±9.1) kg.

Most cases and controls had pulmonary TB [80.0% (51/64) and 91.4% (117/128), respectively]. More than half of both groups tested positive for AFB smear at baseline treatment [54.7% (35/64) of cases and 61.7% (79/128) of controls]. Comorbidity was present in two-thirds of cases and half of the controls [60.9% (39/64) and 50.8% (65/128), respectively]. One-third of cases had HIV coinfection [26.6% (17/64), compared to only 3.9% (5/128) of controls. A small proportion of both cases and controls had a history of TB (7.8% (5/64) and 5.5% (7/128), respectively].

3.2. Laboratory test and prevalence of hepatotoxicity among subjects

Regarding LFT at baseline treatment, a small number of cases in both cases and controls exhibited mild LFT elevations in AST [7.8% (5/64) and 4.7% (6/128)], ALT [3.1% (2/64) and 5.5% (7/128)], ALP [7.8% (5/64) and 7.0% (9/128)], and total bilirubin [42.2% (27/64) and 29.7% (38/128)], which did not meet the diagnostic criteria for hepatotoxicity. However, only the cases fulfilled the specific criteria used for defining hepatotoxicity. These cases were further classified based on the type of hepatotoxicity as follows: hepatocellular injury [21.9% (14/64)], cholestatic injury [45.3% (29/64)], and mixed injury [32.8% (21/64)].

3.3. Bivariate analysis of the factors associated with hepatotoxicity among subjects

A bivariate analysis of logistic regression is presented in Table 2. The results indicated that several factors were associated with hepatotoxicity among the subjects. Specifically, individuals with HIV coinfection were found to be almost nine times more likely to experience hepatotoxicity (*OR* 8.90, 95% *CI* 3.11-25.48) compared to those without HIV coinfection. Furthermore, subjects diagnosed with extrapulmonary TB were about three times more likely to experience hepatotoxicity (*OR* 2.71, 95% *CI* 1.14-6.45) compared to those with pulmonary TB.

3.4. Multivariate analysis of the factors associated with hepatotoxicity among subjects

A multivariate logistic regression model with backward elimination identified significant factors associated with hepatotoxicity among TB patients. Females were found to be two times more likely to experience hepatotoxicity (adjusted *OR* 2.25, 95% *CI* 1.11-4.59) compared to males. Additionally, individuals with HIV coinfection

Table 1. Demographic and clinical characteristics among tuberculosis patients during intensive phase treatment.

Demographic and clinical characteristics	Cases (*n*=64)	Controls (*n*=128)	*P*-value
Sex			0.094
Male	40 (62.5)	96 (75.0)	
Female	24 (37.5)	32 (25.0)	
Age, years, mean ± SD	52.6±16.6	53.4±16.8	0.629
<60	45 (70.3)	83 (64.8)	0.448
⩾60	19 (29.7)	45 (35.2)	
Smoking status			0.847^
No	39 (60.9)	81 (63.3)	
Yes and ex-smokers	22 (34.4)	42 (32.8)	
Unknown	3 (4.7)	5 (3.9)	
Alcohol drinking			0.891^
No	45 (70.3)	87 (68.0)	
Yes and ex-drinker	15 (23.4)	31 (24.2)	
Unknown	4 (6.3)	10 (7.8)	
Bodyweight at baseline treatment, kg, mean ± SD	50.26±9.93	49.62±9.12	0.625
<50	34 (53.1)	61 (47.7)	0.476
⩾50	30 (46.8)	67 (52.3)	
Classification of tuberculosis			0.037
Pulmonary tuberculosis	51 (79.7)	117 (91.4)	
Extrapulmonary tuberculosis	13 (20.3)	11 (8.6)	
Result of sputum AFB smear at baseline treatment			0.370
Negative	29 (45.3)	49 (38.3)	
Positive	35 (54.7)	79 (61.7)	
Comorbidity			0.186
No	25 (39.1)	63 (49.2)	
Yes	39 (60.9)	65 (50.8)	
HIV coinfection			<0.001
No	47 (73.4)	123 (96.1)	
Yes	17 (26.6)	5 (3.9)	
History of a previous illness with tuberculosis			>0.05
No	59 (92.2)	121 (94.5)	
Yes	5 (7.8)	7 (5.5)	
AST, IU/L, median (Q1-Q3)	27 (18.25-35.75)	24 (16.00-32.00)	<0.001#
Normal (<2X of ULN)	59 (92.2)	122 (95.3)	0.532
High (⩾2X of ULN)	5 (7.8)	6 (4.7)	
ALT, IU/L, median (Q1-Q3)	20 (12.35-27.65)	21 (12.23-29.78)	0.119#
Normal (<2X of ULN)	62 (96.9)	121 (94.5)	0.715^
High (⩾2X of ULN)	2 (3.1)	7 (5.5)	
ALP, IU/L, median (Q1-Q3)	97 (77.50-116.50)	100 (71.00-129.00)	0.255#
Normal (<2X of ULN)	59 (92.2)	119 (93.0)	>0.05
High (⩾2X of ULN)	5 (7.8)	9 (7.0)	
Tbil, mg/dL, median (Q1-Q3)	0.52 (0.35-0.69)	0.50 (0.38-0.63)	0.314#
Normal (<0.6 mg/dL)	37 (57.8)	90 (70.3)	0.087
High (⩾0.6 mg/dL)	27 (42.2)	38 (29.7)	

Data were expressed as *n* (%) unless otherwise specified. *P*-values were calculated using Fisher's exact test (^), *t*-test and Mann-Whitney *U* test (#), otherwise, *Chi*-square test. AFB: acid fast bacilli, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ULN: upper limit of normal, ALP: alkaline phosphatase, Tbil: total serum bilirubin, IU/L: international units per litre, mg/dL: milligrams per decilitre; Smoker was defined as a person currently smoking at the time of tuberculosis diagnosis. Ex-smoker referred to a person who had quit smoking for at least 6 months before diagnosis. Alcohol drinker was defined as someone who consumed alcoholic beverages at least once per week in the past year. Ex-alcohol drinker referred to a person who had stopped drinking alcohol for at least 6 months prior to tuberculosis diagnosis.

Table 2. Multivariate analysis of factors associated with hepatotoxicity during intensive phase treatment in tuberculosis patients.

Factors	*n* (%)	Univariate analysis		Multivariate analysis	
		OR (95% *CI*)	*P*-value	Adjusted *OR* (95% *CI*)	*P*-value*
Sex			0.076		0.024
Male	40 (29.4)	Ref.		Ref.	
Female	24 (42.9)	1.80 (0.94-3.43)		2.25 (1.11-4.59)	
Age, years			0.446		
<60	45 (35.2)	Ref.		-	-
⩾60	19 (29.7)	0.78 (0.41-1.49)		-	-
Smoking			0.937		
No	39 (32.5)	Ref.		-	-
Yes or ex-smokers	22 (34.4)	1.09 (0.57-2.07)		-	-
Unknown	3 (37.5)	1.25 (0.28-5.48)		-	-
Alcohol drinking			0.909		
No	45 (34.1)	Ref.		-	-
Yes or ex-drinkers	15 (32.6)	0.94 (0.46 - 1.91)		-	-
Unknown	4 (28.6)	0.77 (0.23 - 2.60)		-	-
Bodyweight at baseline treatment, kg			0.475		
<50	34 (35.8)	Ref.		-	-
⩾50	30 (30.9)	0.80 (0.44 - 1.46)		-	-
Classification of tuberculosis			0.024		0.232
Pulmonary tuberculosis	51 (30.4)	Ref.		Ref.	
Extrapulmonary tuberculosis	13 (54.2)	2.71 (1.14 - 6.45)		1.78 (0.69-4.59)	
Result of sputum AFB smear at baseline treatment			0.351		
Negative	29 (37.2)	Ref.		-	-
Positive	35 (30.7)	0.75 (0.41-8.20)		-	-
Comorbidity			0.182		0.898
No	25 (28.4)	Ref.		Ref.	
Yes	39 (37.5)	1.51 (0.82-2.78)		0.96 (0.47-1.92)	
HIV infection			<0.001		<0.001
No	47 (27.7)	Ref.		Ref.	
Yes	17 (77.3)	8.90 (3.11-25.48)		9.74 (3.12-30.41)	
History of illness with tuberculosis			0.534		
No	59 (32.8)	Ref.		-	-
Yes	5 (41.7)	1.46 (0.45-4.81)		-	-
AST, IU/L			0.390		
Normal (<2X of ULN)	59 (32.6)	Ref.		-	-
High (⩾2X of ULN)	5 (45.5)	1.72 (0.50-5.88)		-	-
ALT, IU/L			0.454		
Normal (<2X of ULN)	62 (33.9)	Ref.		-	-
High (⩾2X of ULN)	2 (22.2)	0.56 (0.11-2.76)		-	-
ALP, IU/L			0.845		
Normal (<2X of ULN)	59 (33.2)	Ref.		-	-
High (⩾2X of ULN)	5 (35.7)	1.12 (0.36-3.49)		-	-
Tbil, mg/dL			0.087		0.110
<0.6	37 (29.2)	Ref.		Ref.	
⩾0.6	27 (41.5)	1.73 (0.92-3.23)		1.75 (0.88-3.47)	

OR: odds ratios, 95% *CI*: 95 percent confidence interval, Ref: reference group, AFB: acid fast bacilli, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ULN: upper limit of normal, ALP: alkaline phosphatase, Tbil: total serum bilirubin, IU/L: international units per liter, mg/dL: milligrams per decilitre; The cut-off point for body weight (⩾50 kg) was based on national and international TB treatment guidelines, which commonly stratify first-line anti-TB drug dosages at 50 kg body weight to ensure therapeutic effectiveness and safety. The age cut-off (⩾60 years) was used to differentiate between elderly and non-elderly groups, as individuals aged 60 and above are at higher risk for drug-induced hepatotoxicity due to age-related physiological changes in liver metabolism and reduced hepatic clearance. *The *P*-value was calculated using a partial likelihood ratio test. -: not conducted.

were ten times more likely to develop hepatotoxicity (adjusted *OR* 9.74, 95% *CI* 3.12-30.41) compared to those without HIV coinfection, as detailed in Table 2.

4. Discussion

In our study population of TB patients who experienced hepatotoxicity during the intensive treatment phase, we observed that female sex and HIV coinfection were significantly associated with the condition.

Our study revealed that patients' sex was significantly associated with hepatotoxicity during the intensive phase of treatment, with female subjects being twice as likely to experience hepatotoxicity compared to males. The liver plays a crucial role in metabolism, energy and lipid storage, and the detoxification of xenobiotics. Notably, around 72% of liver-related genes exhibit differences based on sex. These differences may manifest as increased susceptibility to liver diseases in females, leading to a higher incidence of drug-induced hepatotoxicity and both acute and chronic liver conditions compared to males[21,22]. This increased vulnerability may contribute to drug-induced liver injury among female TB patients receiving first-line anti-TB drug regimens during the intensive treatment phase.

Previous studies have indicated a significant association between patients' sex and hepatotoxicity in individuals with TB. For instance, a retrospective study conducted in a teaching chest hospital in Germany found that female patients with TB were 1.60 times more likely to experience hepatotoxicity (*OR* 1.60, 95% *CI* 1.00-2.50)[10]. Similarly, a case cohort study at a medical center in Taiwan reported that female patients with pulmonary TB had a 1.54-fold increased likelihood of hepatotoxicity compared to males (*OR* 1.54, 95% *CI* 1.04-2.28)[23]. Additionally, a prospective study in India demonstrated that females were 2.78 times more likely to experience hepatotoxicity than males (*OR* 2.78, 95% *CI* 1.00-7.69)[24]. However, these studies presented a lower probability of association between female sex and hepatotoxicity, as evidenced by the 95% confidence intervals that approached one.

Recent studies have indicated a moderate to high risk associated with female sex and hepatotoxicity among patients with TB. For example, a prospective study in Turkey reported an *OR* of 1.21 (95% *CI* 0.81-1.82)[25], a study in Canada reported an *OR* of 2.20 (95% *CI* 0.70-6.90)[26], a study conducted in Nepal reported a relative risk of 3.82 (95% *CI* 0.43-34.23)[27]. Conversely, some studies have demonstrated a protective effect of female sex on hepatotoxicity in TB patients. For instance, a cross-sectional study in Iran reported an *OR* of 0.60 (95% *CI* 0.24-1.54)[28]. Similarly, a prospective cohort study in the USA reported an *OR* of 0.53 (95% *CI* 0.20-1.25)[29]. Other studies conducted in Morocco reported an *OR* of 0.64 (95% *CI* 0.26-1.57)[11], China reported an *OR* of 0.71 (95% *CI* 0.33-1.43)[30], and Malaysia reported an *OR* of 0.75 (95% *CI* 0.36-1.53)[31] also reported similar findings. However, these studies did not establish a statistically significant association between female sex and hepatotoxicity. This variation in findings highlights the complexity of the relationship between sex and hepatotoxicity, suggesting that further research is needed to clarify the underlying mechanisms and factors influencing this association. These variations across studies may be attributed to multiple factors. Genetic polymorphisms related to drug metabolism, such as variations in NAT2 and CYP enzymes, may influence susceptibility to hepatotoxicity differently in males and females. Additionally, environmental factors (*e.g.*, nutrition, alcohol intake), differences in body fat distribution, and varying study methodologies (*e.g.*, diagnostic criteria, data collection methods) may contribute to the inconsistencies observed. Future research should further explore these sex-specific biological and contextual factors to better understand the underlying mechanisms of hepatotoxicity.

The findings of this study highlight a significant association between HIV coinfection and hepatotoxicity among patients with TB. Patients with TB who are also coinfected with HIV face a markedly elevated risk of hepatotoxicity. This heightened risk can be attributed to the severely compromised immune systems of individuals with HIV, which predisposes them to various severe illnesses and opportunistic infections[32]. Among these opportunistic infections, TB stands out as one of the most prevalent and impactful conditions in patients with advanced HIV infection[33]. Furthermore, liver-related diseases have emerged as leading causes of morbidity and mortality among individuals infected with HIV. The presence of viral infections, such as HIV, can adversely affect liver function and exacerbate liver injury mechanisms[34]. Consequently, TB patients with HIV are at a significantly greater risk of experiencing hepatotoxicity during the intensive phase of treatment. This interaction emphasizes the importance of closely monitoring liver function in this HIV-TB coinfected patient population and implementing strategies to mitigate the risk of hepatotoxicity in individuals undergoing treatment for both TB and HIV.

Previous studies have highlighted a significant moderate risk of hepatotoxicity associated with HIV coinfection in patients with TB. For instance, case-control studies conducted in Taiwan (*OR* 3.08, 95% *CI* 1.40-6.78)[23] and Malaysia (*OR* 3.54, 95% *CI* 1.25-10.05)[31] found strong associations. Additionally, a cross-sectional study in Iran reported an *OR* of 3.50 (95% *CI* 1.31-9.35)[28], while retrospective studies in Brazil reported an *OR* of 2.30 (95% *CI* 1.20-4.10)[35] and Ethiopia reported an *OR* of 3.60 (95% *CI* 1.50-8.50)[36] also supported these findings. Conversely, some studies suggested

a protective effect of HIV coinfection on hepatotoxicity among TB patients. For example, a prospective cohort study in the USA reported an *OR* of 0.70 (95% *CI* 0.10-5.60)[29], and a retrospective study in Morocco reported an *OR* of 0.93 (95% *CI* 0.18-4.68)[11]. However, these studies did not show a statistically significant association.

The present study benefits from utilizing secondary data recorded in the HosXp database. This health information management system is designed to routinely monitor clinical outcomes among patients. Additionally, all data related to TB care were documented by well-trained healthcare professionals responsible for managing TB treatment. Consequently, the data are consistent and reliable, which helps minimize information bias.

The study had some limitations. Notably, we found that alcohol consumption was not associated with hepatotoxicity among patients with TB, despite previous research indicating that high alcohol intake and a history of alcohol consumption are common causes of hepatotoxicity[37,38]. In our study, alcohol consumption was treated as a categorical variable, with approximately a quarter of both cases and controls reporting current or previous alcohol use (23.44% and 24.22%, respectively). However, we did not account for the dose-response relationship of alcohol, as the volume of alcohol consumed can significantly impact liver function and has direct toxic effects on the liver. This oversight was due to the absence of recorded data on the quantity of alcohol consumed in the database. Consequently, the results of this study were not adjusted for confounding variables, which may have led to dose-response bias. This limitation may have attenuated the true effect of alcohol on hepatotoxicity, potentially underestimating its role as a risk factor. Future studies should incorporate quantitative alcohol intake data to better elucidate this relationship. Furthermore, this study did not include information on hepatitis B or C virus infection status, as these data were not routinely recorded in the HosXp database. The inability to control for viral hepatitis, which is a well-established risk factor for liver injury, may have confounded the observed associations between anti-TB drugs and hepatotoxicity. Future studies should incorporate hepatitis virus screening to better isolate the effects of anti-TB drugs from other hepatotoxic causes.

It is important to note that the findings of this study are specific to a subgroup of TB patients who developed hepatotoxicity during the intensive phase of treatment. Therefore, the results may not be generalizable to all TB patients. The associations observed, such as those related to sex and HIV coinfection, should be interpreted within the context of this specific population. Further research is warranted to examine whether similar patterns are observed in the broader TB population.

In conclusion, factors such as female sex and HIV coinfection significantly increase the risk of hepatotoxicity among patients with TB during the intensive phase of treatment. This study emphasizes the need for heightened awareness regarding these vulnerabilities. Female patients and those with HIV require more rigorous screening and monitoring protocols to identify hepatotoxicity early. Healthcare providers should implement regular liver function tests to facilitate timely intervention. Moreover, personalized treatment plans are crucial for high-risk groups, including women and HIV-positive patients; clinicians should consider alternative treatment regimens or supportive measures to mitigate the risk of hepatotoxicity. Education for both healthcare professionals and patients about the potential risks of hepatotoxicity associated with TB treatment is essential. This education should encompass recognizing the signs and symptoms of liver injury and adhering to established monitoring protocols. The study also highlights gaps in understanding the impact of alcohol consumption on hepatotoxicity, indicating the need for future research to explore the dose-response relationship of alcohol intake. These findings can inform public health initiatives aimed at improving TB care, especially for at-risk populations. Finally, the study emphasizes the importance of considering confounding variables in future research to gain a comprehensive understanding of all risk factors associated with hepatotoxicity in TB patients.

Conflicting interest statement

The authors declare that they hold no competing interests.

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Authors' contributions

KK, BC, and SW contributed to the conceptualization and design of the study. Data collection and literature review were conducted by KK and SW, while data analysis and interpretation were performed by KK and BC. BC prepared the initial draft of the manuscript, with critical revisions and input from KK and SW during the review and editing process. SW and BC provided overall supervision of the project. BC served as the guarantor, ensuring the accuracy, integrity, and completeness of the work from inception to final manuscript preparation. All authors reviewed and approved the final version of the manuscript and confirmed their agreement with its content and integrity.

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