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Research Article

Association between exceeding recommended weight-based doses of first-line antituberculosis drugs and hepatotoxicity during the intensive treatment phase among patients with tuberculosis: A hospital-based case-control study

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ABSTRACT

Tuberculosis remains a global health burden. Although first-line antituberculosis drugs are essential for effective treatment, their use may be associated with hepatotoxicity. This study examined the association between the prescribed weight-based doses of isoniazid, rifampicin, pyrazinamide, and ethambutol, and hepatotoxicity during the intensive phase of tuberculosis treatment in routine clinical practice. A hospital-based retrospective case-control study was conducted between January and February 2021 using medical records of patients diagnosed with tuberculosis from 2013 to 2020. A total of 192 subjects were included, comprising 64 cases who developed hepatotoxicity during the intensive phase and 128 matched controls without hepatotoxicity. The exposure variables were the prescribed dose of the first-line antituberculosis drugs isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (ETB), expressed in mg/kg/day and categorized according to whether they were within or exceeded the recommended weight-based dosing ranges. Multivariable logistic regression was performed to evaluate the association between drug dosage and hepatotoxicity after adjustment for age, sex, baseline body weight, HIV infection, baseline serum total bilirubin, baseline serum albumin, and concomitant hepatotoxic medication use. An INH dose exceeding the recommended weight-based range was significantly associated with higher odds of hepatotoxicity (Adjusted Odds Ratios [AOR] = 2.60, 95% Confidence Interval [CI]: 1.03-6.59). In contrast, doses exceeding the recommended range for RIF (AOR = 1.61, 95%CI: 0.21-12.22), PZA (AOR = 0.61, 95% CI: 0.05-7.58), and ETB (AOR = 1.10, 95% CI: 0.34-3.59) were not significantly associated with hepatotoxicity. These findings indicated that an increased odds of hepatotoxicity during the intensive phase of tuberculosis treatment. Careful verification of weight-based INH dosing and appropriate clinical monitoring should therefore be emphasized in routine tuberculosis care.

Keywords:
Tuberculosis; First-line antituberculosis drugs; Isoniazid; Hepatotoxicity

1. INTRODUCTION

Tuberculosis (TB) continues to be a major global public health concern. Caused by *Mycobacterium tuberculosis*, TB primarily affected the lungs[1], with approximately 88% of patients presenting with pulmonary TB, while approximately 20% develop extrapulmonary disease[2]. Despite substantial advances in TB prevention

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and treatment, the disease remains one of the leading causes of morbidity and mortality worldwide, particularly in low- and middle-income countries[3,4]. In 2021, an estimated 10.6 million people developed TB and 1.6 million died for the disease globally[3]. The Southeast Asia Region bears a substantial proportion of this burden, accounting for nearly half of all reported TB cases worldwide[5]. In Thailand, the incidence of TB has gradually declined from 214 cases per 100,000 population in 2000 to 150 cases per 100,000 population in 2020[6]. Nevertheless, Thailand remains one of the 30 high TB burden countries and continues to face a considerable burden of TB/HIV coinfection[7].

The cornerstone of tuberculosis treatment is the use of first-line antituberculosis drugs, including isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (ETB). The standard treatment regimen consists of a 2-month intensive phase with INH, RIF, PZA and ETB (2HRZE), followed by a 4-month continuation phase with INH and RIF (4HR) or INH and ethambutol (4HE), resulting in a total treatment duration of six months[8]. Although these drugs are highly effective, their use is associated with adverse drug reactions, the most clinically important of which is antituberculosis drug-induced hepatotoxicity (DIH). DIH may lead to treatment interruption, regimen modification, reduced adherence, and unfavorable treatment outcomes[9].

Previous studies have reported a wide range in the incidence of hepatotoxicity among patients receiving first-line antituberculosis drugs, with estimates of up to 24.6%[10]. However, the association between individual first-line antituberculosis drugs and hepatotoxicity remains inconclusive. Previous studies have reported inconsistent findings, often with wide confidence intervals and limited statistical precision because of relatively small sample sizes[11-14]. A recent hospital-based case-control study conducted in southern Thailand identified female sex and HIV coinfection as a significant factors associated with hepatotoxicity during the intensive phase of tuberculosis treatment[15]. Nevertheless, the association between exceeding the recommended weight-based doses of individual first-line antituberculosis drugs and hepatotoxicity has not been adequately investigated, particularly in routine clinical practice in Thailand. Therefore, this study aimed to examine the association between exceeding the recommended weight-based doses of first-line antituberculosis drugs and hepatotoxicity during the intensive phase of tuberculosis treatment. By focusing on actual prescribed weight-based doses in routine clinical practice, this study complements previous evidence and provides clinically relevant information to support individualized dosing strategies and improve medical safety among patients receiving tuberculosis treatment.

2. METHODS

2.1. Study design and setting

This hospital-based retrospective case control study used secondary data obtained from the electronic medical records of patients diagnosed with tuberculosis (TB) in Phatthalung Province, southern Thailand. The study conducted across one secondary-care hospital and ten community hospitals within the provincial healthcare network. The present study used the same hospital network and retrospective database as the previously published study by Hemmarak et al.[15] but focused specifically on the association between prescribed weight-based doses of first-line antituberculosis drugs and hepatotoxicity.

2.2. Study participants

Patients diagnosed with tuberculosis (TB) between January 2013 and September 2020 were retrospectively identified using the International Classification of Diseases, 10th Revision (ICD-10) diagnostic codes A15-A19. Eligible participants included patients with the either pulmonary or extrapulmonary TB who were received a standard first-line antituberculosis treatment regimen.

Cases were defined as patients who developed hepatotoxicity during the intensive phase of TB treatment. Hepatotoxicity was identified either from ICD-10 diagnostic codes (K71-K76) or through abnormal liver function tests (LFTs) results that fulfilled the predefined hepatotoxicity criteria. A total of 64 cases were identified, including 14 physicians-diagnosed cases and 50 additional cases identified based on LFT criteria. Controls were randomly selected using a 1:2 case-to-control ratio and matched by treatment facility, resulting in 128 controls. Therefore, a total of 192 participants were included in the final analysis. Only hepatotoxicity occurring during the intensive phase of treatment was considered eligible for case classification.

2.3. Data collection and variables

Data were obtained from the HosXp electronic medical records system. Demographic, clinical and pharmacological characteristics were retrieved, including baseline age, sex, baseline body weight, HIV coinfection status, baseline serum albumin and total bilirubin levels, and the use of concomitant medications with potential hepatoxic effects. The data collection procedures and variables definitions were consistent with those described in the previous study by Hemmarak et al.[15]. The exposure variables of interest were the prescribed doses of the first-line

antituberculosis drugs INH, RIF, PZA, and ETB. For each drug, the prescribed daily dose was divided by patient's baseline body weight and expressed as milligrams per kilogram per day (mg/kg/day). Each dose was categorized as either within or above the recommended weight-based dosing range according to the World Health Organization (WHO) tuberculosis treatment guidelines and other internationally accepted references. The recommended daily dosing ranges were 4-6 mg/kg/day for INH, 8-12 mg/kg/day for RIF, 20-30 mg/kg/day for PZA, and 15–25 mg/kg/day ETB, without exceeding the recommended maximum daily dose[16,17]. Patients whose prescribed doses exceeded the upper limit of the corresponding weight-based range were classified as having received a dose exceeding the recommended range. The pattern of liver injury was classified using the R-ratio, calculated as follows: R ratio = (ALT/ULN of ALT)/(ALP/ULN of ALP), where ALT denotes alanine aminotransferase, ALP denotes alkaline phosphatase, and ULN denotes the upper limit of normal. Liver injury was classified as hepatocellular, cholestatic, or mixed according to the predefined R-ratio thresholds. Hepatocellular injury was defined as an R ratio greater than 5, cholestatic injury as an R ratio less than 2, and mixed liver injury as an R ratio between 2 and 5[18,19].

2.4. Statistical analysis

Descriptive statistics were used to summarized baseline clinical and pharmacological characteristics of the study participants. Continuous variables were summarized as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data distribution, whereas categorical variables were presented as frequencies and percentage.

Univariate associations between hepatotoxicity and individual variables were evaluated using simple logistic regression. Multivariate logistic regression analyses were performed to estimate the adjusted odds ratios (AORs) and 95% confidence intervals (CIs) for the relationship between exceeding the recommended weight-based dose of each first-line antituberculosis drug and hepatotoxicity. All adjusted models included the following prespecified covariates: age, sex, baseline body weight, HIV coinfection status, baseline serum albumin level, baseline total serum bilirubin level[15], and concomitant use of medications with potential hepatotoxic effects, which was included as a clinically relevant potential confounder. The partial likelihood ratio test was used to evaluate the statistical significance of each exposure variable in the multivariable models. A two-side p-value <0.05 was considered statistically significant. ORs and AORs greater than 1 indicated higher odds of hepatotoxicity among patients receiving doses above the recommended weight-based range compared with those receiving doses within the recommended range, whereas values less than 1 indicated lower odds relative to the reference group. Statistical significance was determined using the corresponding 95% confidence intervals and two-sided p-values.

3. RESULTS

3.1. Clinical and pharmacological characteristics of the study participants

The clinical and pharmacological characteristics of the study population are summarized in Table 1. The study included 64 patients with hepatotoxicity (cases) and 128 patients without hepatotoxicity (controls). The proportion of participants with one comorbidity was similar between the two groups (31.25% vs. 32.81%). However, multiple comorbidities were more frequent among cases than controls (29.69% vs. 17.97%). Polypharmacy, defined as the concurrent use of five or more medications, was observed in 17.19% of cases and 9.38% of controls. A history of drug allergy or adverse drug reaction was recorded in 7.81% of cases and 3.91% of controls.

Exposure to medications with potential hepatotoxic effects before initiation of antituberculosis treatment was more common among cases than controls (40.63% vs. 15.63%). Among cases, the most frequently used hepatotoxic medications were sulfamethoxazole/trimethoprim (20.31%), fluconazole (18.75%), and simvastatin (15.63%). Among controls, simvastatin (7.03%) and omeprazole (4.69%) were most commonly reported medications, whereas sulfamethoxazole/trimethoprim (2.34%) and antiretroviral drug combinations were less frequently prescribed.

Regarding antituberculosis treatment, fixed-dose combination (FDC) formulations were prescribed for 12.50% of cases and 19.53% of controls. The proportion of patients receiving doses exceeding the recommended weight-based range was highest for INH, occurring in 50.00% of cases compared with 35.16% of controls. Smaller differences between cases and controls were observed for RIF, PZA, and ETB. The actual prescribed weight-based doses of INH, RIF, PZA and ETB are also presented in Table 1. Patients with hepatotoxicity had higher prescribed INH doses than without hepatotoxicity, whereas the distributions of prescribed RIF, PZA and ETB doses were generally similar between the two groups. Because concomitant use of medications with potential hepatotoxic effects differed between the two groups, this variable was included as a prespecified covariate in all multivariable logistic regression analyses.

Table 1. Clinical characteristics of TB patients with and without hepatotoxicity (n = 192).

Clinical characteristics	Cases (n = 64 patients)		Controls (n = 128 patients)	
	n	%	n	%
Comorbidity				
No	25	39.06	63	49.22
Single disease	20	31.25	42	32.81
Multiple disease	19	29.69	23	17.97
Total number of concomitant drugs used				
None	27	42.19	68	53.13
1-4 drugs	26	40.63	48	37.50
≥5 drugs	11	17.19	12	9.38
History of using drugs related to allergy or side effects				
No	59	92.19	123	96.09
Yes	5	7.81	5	3.91
History of using drugs related to hepatotoxicity				
No	38	59.38	108	84.38
Yes	26	40.63	20	15.63
Sulfamethoxazole / trimethoprim	13	20.31	3	2.34
Fluconazole	12	18.75	1	0.78
Simvastatin	10	15.63	9	7.03
Omeprazole	7	10.94	6	4.69
Emtricitabine / tenofovir / efavirenz	5	7.81	3	2.34
Losartan	4	6.25	3	2.34
Efavirenz	1	1.56	1	0.78
Pioglitazone	1	1.56	2	1.56
Using a fixed-dose antituberculosis combination				
No	56	87.50	103	80.47
Yes	8	12.50	25	19.53
An average dosage of using antituberculosis drugs (mg/kg/day)				
Isoniazid (INH)				
Within recommended dose (≤6)	32	50.00	83	64.84
Exceeded recommended dose (>6)	32	50.00	45	35.16
INH dose (mg/kg/day), mean ± SD	6.38 ± 1.22		5.71 ± 1.05	
Rifampicin (RIF)				
Within recommended dose (≤12)	60	93.75	123	96.09
Exceeded recommended dose (>12)	4	6.25	5	3.91
RIF dose (mg/kg/day), mean ± SD	10.12 ± 1.34		9.88 ± 1.21	
Pyrazinamide (PZA)				
Within recommended dose (≤30)	62	96.88	122	95.13
Exceeded recommended dose (>30)	2	3.13	6	4.96
PZA dose (mg/kg/day), median (IQR)	26.8 (24.5–29.3)		26.4 (24.1–28.9)	
Ethambutol (ETB)				
Within recommended dose (≤20)	55	85.94	109	85.16
Exceeded recommended dose (>20)	9	14.06	19	14.84
ETB dose (mg/kg/day), mean ± SD	18.41 ± 2.14		18.41 ± 2.29	

Comorbidity was classified into three groups: no comorbidity, single comorbidity, and multiple comorbidities. Total drug uses refers to the number of concurrently prescribed medications at baseline and was categorized into no medications, 1–4 items, and ≥5 items. History of using drugs related to allergy or side effects was based on medical record documentation. History of using drugs related to hepatotoxicity included medications previously associated with liver injury, identified from the patient's medication history. For the fixed-dose antituberculosis combination, this refers to the use of combined formulations of isoniazid, rifampicin, pyrazinamide, and ethambutol. Dosage classification of first-line antituberculosis drugs—isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (ETB)—was based on World Health Organization (WHO) recommended maximum dose thresholds. Overdose was defined as exceeding these recommended values: INH >6 mg/kg/day, RIF >12 mg/kg/day, PZA >30 mg/kg/day, and ETB >20 mg/kg/day.

Table 2. Bivariate and multivariate analysis of antituberculosis drugs dosage associated with hepatotoxicity (n = 192).

Antituberculosis drugs (mg/kg/day)	n	%	Crude OR (95% CI)	Adjusted OR (95% CI)*	p-value**
Isoniazid (INH)					0.040
Within recommended dose (≤6)	32	27.83	Ref.	Ref.	
Exceeded recommended dose (>6)	32	41.56	1.84 (1.00-3.39)	2.60 (1.03-6.56)	
Rifampicin (RIF)					0.643
Within recommended dose (≤12)	60	32.79	Ref.	Ref.	
Exceeded recommended dose (>12)	4	44.44	1.64 (0.42-6.33)	1.61 (0.21-12.22)	
Pyrazinamide (PZA)					0.695
Within recommended dose (≤30)	62	33.70	Ref.	Ref.	
Exceeded recommended dose (>30)	2	25.00	0.66 (0.13-3.34)	0.61 (0.05-7.58)	
Ethambutol (ETB)					0.871
Within recommended dose (≤20)	55	33.54	Ref.	Ref.	
Exceeded recommended dose (>20)	9	32.14	0.94 (0.40-2.21)	1.10 (0.34-3.59)	

*Adjusted odds ratios were derived from multivariable logistic regression models accounting for age, sex, baseline body weight, HIV coinfection, baseline serum total bilirubin, and baseline serum albumin, and concomitant hepatotoxic medication use.
**P-values were calculated using the partial likelihood ratio test for comparing models with and without the corresponding antituberculosis drug dose variables.

3.2. Association between hepatotoxicity and the dosing of first-line antituberculosis drugs

Table 2 presents the results of the univariate and multivariable logistic regression analyses elevating the association between exceeding the recommended weight-based doses of individual first-line antituberculosis drugs and hepatotoxicity. After adjustment for the prespecified covariates, patients receiving INH at doses exceeding the recommended weight-based range (>6 mg/kg/day) had significantly higher odds of hepatotoxicity than those receiving doses within the recommended range (AOR = 2.60; 95% CI: 1.03–6.56). in contrast, exceeding the recommended weight-based doses of RIF, PZA, or ETB was not significantly associated with hepatotoxicity after adjustment for potential confounders. Concomitant use of medication with potential hepatotoxic effects was included as a prespecified adjustment variable in the multivariate model but was not independently associated with hepatotoxicity (AOR = 0.64, 95% CI: 0.28–1.46; p-value = 0.287).

3.3. Combined association of isoniazid and rifampicin weight-based dosing with hepatotoxicity

An additional multivariable analysis was performed to evaluate the combined association of INH and RIF weight-based dosing with hepatotoxicity. Compared with patients who received both drugs within the recommended weight-based ranges, those who received INH above the recommended range while receiving RIF within the recommended range had significantly higher odds of hepatotoxicity after adjustment for the prespecified covariates (AOR = 2.59, 95% CI: 1.03–6.51). Patients who received doses above the recommended ranges for both INH and RIF also had higher odds of hepatotoxicity (AOR = 4.43, 95% CI: 0.75–25.99). The results of the combined-dose analysis are presented in Table 3.

4. DISCUSSION

This study found that exceeding the recommended weight-based hose of INH during the intensive phase of tuberculosis treatment was significantly associated with hepatotoxicity. After adjustment for demographic characteristics, clinical factors, and concomitant use of medications with potential hepatotoxic effects, patients receiving INH at dose above the recommended weight-based range (>6 mg/kg/day) had approximately 2.6-fold higher odds of hepatotoxicity than those receiving doses within the recommended range. In contrast, exceeding the recommended weight-based doses of RIF, PZA, and ETB were not significantly associated with hepatotoxicity. Furthermore, the combined-dose analysis showed that patients receiving INH above the recommended weight-based range while receiving RIF within the recommended range also had significantly higher odds of hepatotoxicity, whereas the association was not statistically significant among patients receiving doses above the recommended ranges for both INH and RIF.

The present study found that exceeding the recommended weight-based dose of INH was independently associated with hepatotoxicity during the intensive phase of tuberculosis treatment. This finding is consistent with the well-established hepatotoxic potential of INH. In the present study, 50.00% of patients with hepatotoxicity received INH do ses above the recommended weight-based range, compared with

Table 3. Combined weight-based dosing of isoniazid and rifampicin associated with hepatotoxicity (n = 192).

Combined INH-RIF dose category	n	%	Crude OR (95% CI)	Adjusted OR (95% CI)*	p-value
Both INH and RIF within recommended doses	115	27.83	Ref.	Ref.	
INH exceeded recommended dose; RIF within recommended dose	68	41.18	1.82 (0.96-3.42)	2.59 (1.03-6.51)	0.043
Both INH and RIF exceeded recommended doses	9	44.44	2.08 (0.52-8.22)	4.43 (0.75-25.99)	0.099

*Adjusted for age, sex, baseline body weight, HIV coinfection, baseline total serum bilirubin, baseline serum albumin, and concomitant hepatotoxic medications. The overall likelihood-ratio test for the combined INH–RIF dose variable was performed (p-value = 0.081).

35.16% of those without hepatotoxicity. This difference remained significant after adjustment for demographic characteristics, clinical factors, and concomitant use of medications with potential hepatotoxic effects. In contrast, no significant association were observed for RIF, PZA, or ETB, which may partly reflect the relatively small proportion of patients receiving doses above the recommended weight-based ranges for these drugs.

The biological plausibility of the observed association is supported by the hepatic metabolism of INH. Isoniazid is metabolized primarily through acetylation to acetylisoniazid and subsequently to metabolites including acetylhydrazine and hydrazine. These reactive metabolites have been shown to induce oxidative stress, deplete intercellular glutathione, and cause hepatocellular injury through mitochondrial dysfunction and lipid peroxidation[20-22]. The susceptibility to INH-induced hepatotoxicity may be further influenced by host factors such as N-acetyltransferase 2 (NAT2) acetylator status, with slow acetylators exhibiting prolonged exposure to hepatotoxic metabolites and a greater risk of liver injury[23-24]. Although, NAT2 genotype was not available in the present study, the observed association between higher prescribed weight-based INH doses and hepatotoxicity is biologically plausible and is consistent with the known dose-dependent hepatic toxicity of INH. These findings emphasize the importance of careful verification of weight-based INH dosing in routine clinical practice to minimize unnecessary exposure above the recommended dosing while maintaining effective tuberculosis treatment.

To address the potential confounding by concomitant medications with hepatotoxic potential, this variable was included in the multivariable logistic regression model. Concomitant hepatotoxic medication use was not independently associated with hepatotoxicity, and its inclusion did not materially alter the association between an INH dose exceeding the recommended weight-based range and hepatotoxicity. This suggests that the observed association was not fully explained by concomitant exposure to other potentially hepatotoxic medications. However, residual confounding cannot be excluded because information on the duration, dose, and timing of these medications was limited. Because all participants received RIF as part of the standard intensive-phase regimen, the present study evaluated INH dosing in the context of concomitant RIF therapy rather than INH monotherapy. In the combined-dose analysis, patients who received INH above the recommended weight-based range while receiving RIF within the recommended range had significantly higher odds of hepatotoxicity than those who received both drugs within the recommended range. Patients who received doses above the recommended ranges for both INH and RIF also had higher estimated odds of hepatotoxicity; however, the association was not statistically significant and had a wide confidence interval, reflecting the small number of patients in this category. Overall, these findings reinforce the clinical importance of verifying weight-based INH dosing during combination antituberculosis therapy.

Previous studies have reported findings broadly consistent with the observed association between higher INH doses and hepatotoxicity. A retrospective cohort study in Brazil reported that high INH doses were associated with an increases risk of hepatotoxicity (RR = 1.30, 95% CI: 1.10–1.70)[10]. Similarly, a case-control study in Thailand found approximately twofold higher odds of hepatotoxicity among patients receiving higher INH doses (OR = 2.00, 95% CI: 1.04–3.95)[11]. While a study conducted in Morocco reported a more modest association (OR = 1.45, 95% CI: 1.18–3.11)[9]. The present findings therefore add to the evidence that weight-based INH dosing may be clinically relevant to the occurrence of hepatotoxicity during tuberculosis treatment. In contrast, the present study did not identify statistically significant association between doses exceeding the recommended weight-based ranges for RIF, PZA, or ETB and hepatotoxicity. This differs from some previous studies conducted in Thailand and India, which reported higher odds of hepatotoxicity among patients receiving RIF or PZA doses above the recommended ranges, with ORs ranging from 2.00 to 5.03[12,14,25]. The absence of significant association in the present study may partly reflect the relatively small number of participants exposed to doses above the recommended ranges for these drugs, resulting in limited statistical precision. In addition, one Moroccan study reported no significant association between higher PZA doses and

hepatotoxicity (OR = 0.95, 95% CI: 0.87–1.03)[10]. Differences across studies may be attributable to variations in patient characteristics, dose distributions, definitions of hepatotoxicity, concomitant medication use, treatment regimens, and analytical methods.

Although the present study did not identify statistically significant associations between doses exceeding the recommended weight-based ranges for RIF, PZA or ETB and hepatotoxicity, these findings may reflect differences in the hepatotoxic potential of individual drugs, the proportion of patients receiving higher doses, or interindividual variability in drug metabolism and susceptibility. RIF has been reported to induce hepatic cytochrome p450 enzymes and may contribute to cholestatic or mixed-pattern liver injury through alterations in bile acid transport, reactive metabolites formation, and endoplasmic reticulum stress[23,24,26]. PZA has also been associated with hepatotoxicity, with proposed mechanisms including mitochondrial dysfunction, oxidative stress, and dose-dependent hepatocellular injury[27]. In contrast, ETB undergoes minimal hepatic metabolism and is generally considered to have a more favorable hepatic safety profile than the other first-line antituberculosis drugs[24,28]. Previous epidemiological studies have reported inconsistent findings regarding the hepatotoxicity of these drugs. Meta-analysis evaluating RIF- and PZA-containing regimens among patients with HIV did not demonstrate a significantly increased risk of severe hepatotoxicity compared with INH-containing regimens[29,30]. Conversely, several pediatric studies have suggested the PZA may contribute substantially to hepatotoxicity during first-line tuberculosis treatment[31]. The lack of statistically significant associations observed in the present study may therefore be attributable to the relatively small number of participants receiving doses above the recommended weight-based ranges for RIF, PZA, and ETB, resulting in limited statistical precision. In addition, difference in patient characteristics, treatment regimens, genetic susceptibility, and monitoring practices across studies may have contributed to the heterogeneous findings reported in the literature. Future large-scale prospectively studies incorporating pharmacogenetic information and detailed dose-response analyses are warranted to clarify the independent contributions of RIF, PZA, and ETB to antituberculosis drug-induced hepatotoxicity.

A strength of this study was the use of routinely collected electronic medical-record data from hospitals providing tuberculosis care across Phatthalung Province. The records were maintained by healthcare professionals directly involved in patient management and included relevant clinical, pharmacological, and laboratory information, particularly liver function test results. In addition, prescribed antituberculosis doses and hepatotoxicity classifications were independently reviewed by a researcher with training in pharmacology using predefined criteria. These standardized procedures may have reduced variability in exposure and outcome assessment and strengthened the consistency of the data used in the analysis. Nevertheless, as with all retrospective studies based on medical records, incomplete documentation and residual misclassification cannot be entirely excluded.

Another important consideration is the use of fixed-dose combination (FDC) formulations. Slight deviations above the recommended weight-based dose may not necessarily indicated prescribing errors but may result from the standardized weight-band dosing approach used for FDC regimens. Because these formulations are prescribed according to predefined body-weight categories rather than fully individualized mg/kg calculations, patients whose weight is near the lower boundary of a dosing band may receive a calculation dose slightly above the recommended mg/kg range. Accordingly, minor deviations should be interpreted cautiously and may reflect the practical characteristics of routine tuberculosis treatment rather than inappropriate prescribing. In the present study, FDC formulations were used in 12.50% of cases and 19.53% of controls; therefore, formulation type should be considered when interpreting small deviations above the recommended weight-based dose.

Several limitations should be acknowledged. First, only 14 patients were clinically diagnosed with hepatotoxicity during the study period, presenting 0.32% of the 4,340 patients registered for the tuberculosis treatment. This low recorded proportion may reflect incomplete clinical recognition or documentation of hepatotoxic events and may therefore underestimate the occurrence of hepatotoxicity in routine practice. To improve case ascertainment, an additional 50 patients (1.15%) were identified through retrospective review of abnormal LFT results recorded during the intensive treatment phase. Nevertheless, the use of both physician diagnoses and laboratory-based criteria may have introduced outcome misclassification, and asymptomatic events may have remained undetected among patients who did not undergo complete or timely liver function testing. Second, the retrospective case-control design limits the availability and completeness of several potentially important variables. Residual confounding may have persisted because information on alcohol consumption, viral hepatitis, diabetes mellitus, nutritional status, and genetic susceptibility was not consistently available, although these factors have been associated with antituberculosis drug-induced hepatotoxicity[25,32]. In addition, the temporal relationship between dose exposure and hepatotoxicity could not always be established with the same precision as in a prospective study. Accordingly, the observed associations cannot be interpreted as causal effects. Third, detailed information

regarding the severity of hepatotoxicity, time to onset, treatment interruption, regimen modification, rechallenge, recovery, and subsequent treatment outcomes was not consistently documented in the medical records. These clinically important outcomes could therefore not be evaluated. Future prospective studies should incorporate standardized liver function monitoring, detailed assessment of clinical, behavioral, and genetic risk factors, and longitudinal documentation of hepatotoxicity severity, management, and recovery to better characterize the independent and combined factors associated with antituberculosis drug-induced hepatotoxicity.

The present findings emphasize the importance of careful verification of weight-based dosing of first-line antituberculosis drugs, particularly INH, during the intensive phase of tuberculosis treatment. In routine clinical practice, prescribed doses exceeding the recommended weight-based range may by associated with higher odds of hepatotoxicity and therefore warrant careful attention. Clinicians should verify drug dosages according to patients' body weight and perform appropriate liver function monitoring, particularly among patients with established risk factors for hepatotoxicity, such as HIV coinfection, hypoalbuminemia, or abnormal baseline liver function. Pharmacist can contribute to medication safety by independently verifying weight-based dosing, reviewing potential drug interactions and concomitant hepatotoxic medications, supporting therapeutic monitoring, and facilitating early recognition and management of suspected hepatotoxicity. Where feasible, the incorporation of electronic prescribing systems or weight-based dosing calculators into routine tuberculosis care may help improve dosing accuracy. Collectively, these findings support the implementation of institutional strategies to strengthen medication safety and reinforce education on appropriate weight-based prescribing and monitoring of antituberculosis therapy among healthcare professionals.

The present findings also highlight the important role of pharmacists as members of the multidisciplinary tuberculosis care team. Pharmacists can contribute to medication safety by conducting comprehensive medication reviews, verifying individualized weight-based dosing before treatment initiation, and identifying patients who receive doses exceeding the recommended therapeutic ranges. During treatment, pharmacists can support therapeutic monitoring through regular review of liver function test results, identification of potential drug–drug interactions and concomitant medications with hepatotoxic potential, and patient counseling on the early recognition and prompt reporting of symptoms suggestive of hepatotoxicity. Pharmacists also play an important role in pharmacovigilance by documenting and reporting suspected adverse drug reactions, thereby facilitating timely clinical intervention and continuous monitoring of medication safety. Because exceeding the recommended weight-based dose of isoniazid was associated with hepatotoxicity in the present study, pharmacist-led verification of individualized dosing before treatment initiation and throughout therapy may represent a practical strategy to enhance medication safety and optimize tuberculosis treatment outcomes.

5. CONCLUSION

In conclusion, this study found that exceeding the recommended weight-based dose of INH during the intensive phase of tuberculosis treatment was independently associated with higher odds of hepatotoxicity. In contrast, no statistically significant association were observed between doses exceeding the recommended weight-based ranges for RIF, PZA, or ETB and hepatotoxicity. These findings highlight the importance of careful verification of weight-based INH dosing in routine clinical practice. Appropriate dose adjustment according to body weight, regular liver function monitoring, and close clinical surveillance of patients at increased risk of hepatotoxicity may contribute to improving the safety of antituberculosis treatment. Further prospectively studies with large sample sizes and comprehensive assessment of clinical, pharmacogenetic, and treatment-related factors are warranted to confirm these findings.

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Authors contribution

KK, BC, and SW conceptualized and designed the study. KK and SW were responsible for data collection and literature review. Data analysis and interpretation were performed by KK and BC The initial draft of the manuscript was prepared by BC and SW, with critical revisions and intellectual input from all authors. Project supervision was jointly conducted by SW and BC. SW also served as the guarantor of the study, ensuring the accuracy, integrity, and completeness of the entire work. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Conflicts of interest

The authors declare that they hold no competing interests.

Ethics approval

Access to patient data was authorized by the hospital directors. The study protocol was approved by the Ethics Committee for Research Involving Human Subjects at Thaksin University, Thailand (COA No. TSU 2021_001, REC No. 0246), on January 4, 2021.

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