

Risk factors for acute liver failure among inpatients with anti-tuberculosis drug-induced liver injury

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Abstract

Objective: To analyze the clinical and laboratory features and determine the predictors of acute liver failure (ALF) among inpatients with anti-tuberculosis (TB) drug-induced liver injury (DILI).

Method: Patients diagnosed with anti-TB DILI from 2010 to 2016 at The First Affiliated Hospital of Zhejiang University were retrospectively included in this study. Demographic and clinical data were collected by reviewing electronic medical records.

Results: Among 155 inpatients with anti-TB DILI, 55 (35.48%) developed ALF, with an overall mortality of 9.68%. The median time to DILI onset was significantly longer in the ALF compared with the non-ALF group (51 versus 24 days). Eighty-three patients (53.55%) developed DILI (53.55%) within the first month of anti-TB treatment, and 60% of ALF cases occurred within 2 months. Multivariable models for ALF incorporating aspartate aminotransferase, total bilirubin, platelets, white blood cell count, and pre-existing hepatitis yielded a concordance (C-statistic) of 98.93%.

Conclusions: The results of this study suggest that approximately half of all cases of DILI occur within the first month, while 60% of ALF cases occur within 2 months. Elevated total bilirubin, aspartate aminotransferase, white blood cell count, pre-existing hepatitis, and low platelet count are independent risk factors for the development of anti-TB drug-induced ALF.

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Keywords

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Introduction

The World Health Organization estimated that *Mycobacterium tuberculosis* was responsible for 6.3 million new active infections and 1.67 million deaths worldwide in 2016.¹ China has the third-highest burden of tuberculosis (TB) cases after India and Indonesia. Early diagnosis and appropriate treatment are important for preventing TB-related deaths, and short-course chemotherapy including isoniazid, rifampin, pyrazinamide, and ethambutol has effectively prevented the spread of TB. However, mild or fatal liver dysfunction is a major adverse effect of the three most widely used drugs, potentially resulting in treatment discontinuation.^{2,3} Anti-TB drugs are the second leading cause of drug-induced liver injury (DILI) in China, after traditional Chinese herbal medicine,^{4,5} with anti-TB DILI accounting for 15.3%–31.3% of all cases of DILI.^{4–6} There have been few population-based studies of anti-TB DILI in China; however, studies in a TB-endemic region in India found that anti-TB DILI patients who developed acute liver failure (ALF) accounted for approximately 5%–25.7% of all ALF cases.^{7–9} In contrast, approximately 39% of all ALF cases in the United States resulted from paracetamol-induced liver injury.¹⁰ In terms of morbidity, the severity of anti-TB DILI cannot be ignored, given that anti-TB drug-induced ALF tends to result in the need for liver transplantation, or in death.

Few studies have assessed the abilities of clinical characteristics and laboratory tests to predict the risk of ALF among patients with anti-TB DILI. Hy's Law suggests that DILI

results in alanine aminotransferase (ALT) levels >3 times the upper limit of normal (ULN) and total bilirubin levels (TBL) >2 times the ULN, after excluding other potential recent causes, conferring a 10% mortality rate.^{11–14} However, its application to DILI is restricted by its low specificity.

This study therefore aimed to analyze clinical and laboratory features, evaluate the importance of several consequential factors of ALF, and identify appropriate predictors of ALF among inpatients with anti-TB DILI. We also examined the relationship between the criteria for Hy's Law and a new model for predicting incident ALF.

Patients and methods

Patients

We conducted a retrospective survey from 2010 to 2016 to investigate the demographic, clinical, and laboratory features and outcomes of inpatients with anti-TB DILI who had received multidrug therapy for active TB at The First Affiliated Hospital of Zhejiang University. A total of 3376 inpatients were treated with anti-TB medication. The study complied with the relevant principles of the Declaration of Helsinki, and was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University. Written informed consent was obtained from each participant or his/her legal representatives.

Definitions

Patients were enrolled into the study if they met the following criteria: ALT or aspartate

aminotransferase (AST) level >5 times the ULN, or alkaline phosphatase (ALP) or TBL >2 times the ULN, or an international normalized ratio >1.5 times the ULN with any elevation in AST, ALT, or ALP.¹⁵ The pattern of liver injury was classified based on R values ($ALT \times ULN / ALP \times ULN$).¹⁶ Hy's Law cases were defined as ALT >3 times the ULN and bilirubin >2 times the ULN probably caused by drug, with no other potential causes.¹⁴ Risk factors such as sex, smoking, alcohol consumption, and pre-existing hepatitis were analyzed. Patients with hepatocellular carcinoma or who were pregnant were excluded. All eligible patients were estimated by the Roussel Uclaf Causality Assessment Method model (RUCAM)¹⁷ and Hy's Law according to liver biochemistries of DILI determined by three specialists in hepatology. Finally, 155 patients who met the inclusion criteria were enrolled in the study.

Drug-induced ALF was defined as follows: TBL level ≥ 10 times the ULN or international normalized ratio ≥ 2.0 in the presence of signs of hepatic decompensation (ascites or encephalopathy) and/or other organ failure; the need for liver transplantation; or death due to liver failure,^{17,18} based on peak parameters of laboratory inspection in electronic medical records. According to this definition, we separated patients with anti-TB DILI into an ALF group ($n = 55$) and a non-ALF group ($n = 100$).

Statistical analysis

All data were analyzed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). ALF events were considered as study endpoints. Normally distributed variables are summarized as the mean \pm standard deviation, data from skewed distributions are shown as the median (range), and categorical variables are summarized as frequency and percentages. A (two-tailed) P value < 0.05 was considered to be significant. Univariate logistic

regression analysis was performed to identify significant risk factors for ALF. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were computed from the model coefficients. Receiver operating characteristic curves were plotted to measure the performances of Hy's Law and the predictive model. All variables were evaluated using Student's t -test, Wilcoxon's rank-sum test, or Pearson's χ^2 test, as appropriate.

Results

Study population

A total of 155 inpatients with DILI received anti-TB chemotherapy from 2010 to 2016 (104 (67.10%) male; mean age 47.96 ± 15.75 years). The demographic data and laboratory findings are shown in Tables 1 and 2. The median duration of treatment was 50 days (range, 2 to 330 days). Of the included patients, 70 patients (45.16%) developed frequent jaundice and required hospitalization, and nine patients (5.81%) presented with encephalopathy before or after hospitalization. The RUCAM scores were highly probable for DILI in 35 patients (22.58%), probable in 88 patients (56.77%), and possible in 32 patients (20.65%). Forty-four (28.39%) patients had a history of liver disease, including chronic viral hepatitis ($n = 28$), fatty liver disease ($n = 12$), and liver schistosomiasis ($n = 4$), and six patients (3.87%) had human immunodeficiency virus infection.

A total of 119 (76.77%) patients who developed DILI were treated with standard anti-TB regimens, 25 (16.13%) received combined use of fluoroquinolone antibiotics, and the treatment was unknown in 11 patients (7.10%).

Outcomes

A total of 55 patients developed ALF. On the basis of the patterns of liver injury,

Table 1. Demographic data for patients with drug-induced liver injury (n = 155).

Variable	No ALF (n = 100)	ALF (n = 55)	P value
Age, year	46.64 ± 15.57	50.36 ± 15.95	0.16
Male, n (%)	70 (70)	34 (61.82)	0.3
Fluoroquinolone antibiotics used, n (%)	19 (19)	6 (10.91)	0.19
Pulmonary tuberculosis*, n (%)	74 (74)	43 (78.18)	0.56
Extrapulmonary tuberculosis*, n (%)	39 (44)	15 (27.27)	0.14
History of previous tuberculosis, n (%)	10 (10)	10 (18.18)	0.15
HIV, n (%)	6 (6)	0 (0)	0.16
Pre-existing hepatitis [†] , n (%)	19 (19)	25 (45.45)	4.74E-04
Fatty liver/alcohol liver, n (%)	7 (7)	5 (9.09)	
Chronic viral hepatitis, n (%)	12 (12)	16 (29.09)	
Liver schistosomiasis, n (%)	0 (0)	4 (7.27)	
Diabetes mellitus, n (%)	8 (8)	5 (9.09)	0.82
Pyrazinamide use, n (%)	80 (80)	39 (70.91)	0.20
Alcohol use, n (%)	20 (20)	14 (25.45)	0.43
Smoking, n (%)	28 (28)	14 (25.45)	0.73
Duration of treatment, days	24 (2-228)	51 (7-330)	3.51E-04
Hy's law positive, n (%)	15 (15)	29 (52.73)	6.21E-07
Highly probable/probable/possible, n (%)	26 (26)/56 (56)/ 18 (18)	9 (16.36)/32 (58.18)/ 14 (25.45)	0.30
Type of liver injury (R), n (%)			
Hepatocellular/cholestatic/mixed	49 (49)/14 (14)/ 37 (27)	30 (54.54)/16 (29.09)/ 9 (16.36)	0.01
Unknown treatment scheme, n (%)	8 (8)	3 (5.45)	0.75

*Separate registration of pulmonary tuberculosis and extrapulmonary tuberculosis.

[†]Pre-existing hepatitis including chronic viral hepatitis, fatty liver disease, liver schistosomiasis.

ALF, acute liver failure; HIV, human immunodeficiency virus; PZA, pyrazinamide.

hepatocellular, cholestatic, and mixed hepatitis accounted for 54.54%, 29.09%, and 16.36% of ALF, respectively. Of these 55 patients, 15 patients died (9.68% overall; 12 males, 3 females), including eight (53.33%) who presented with encephalopathy (any grade). Patients with digestive symptoms at admission were more likely to be in the ALF group than patients without these symptoms, including nausea (52.73% versus 20%, $P = 2.76E-05$) and abdominal distention (36.36% versus 15%, $P = 2.34E-03$) (Table 2). No patient underwent transplantation, but 19 received assistance from a non-bioartificial liver support system (NBALSS). There was no significant difference in age, sex, history of previous TB, alcohol use, smoking, diabetes

mellitus, or eosinophil percentage between the two groups.

Onset time of anti-TB ALF

Among the 155 patients with anti-TB DILI, DILI appeared within the first month of treatment in 83 (53.55%) patients. The occurrence of anti-TB ALF was highest at days 15-30 of chemotherapy, followed by days 1-14. Of the 155 patients with anti-TB DILI, 21.29% developed ALF within the first 2 months (Figure 1). The median time to DILI onset was significantly longer in the ALF compared with the non-ALF group (51 versus 24 days, $P = 3.51E-04$) (Table 1). ALF patients diagnosed with or suspected of having DILI were instructed to stop

Table 2. Symptoms and laboratory findings in 155 patients with drug-induced liver injury.

Variable	No ALF (n = 100)	ALF (n = 55)	P value
Jaundice, n (%)	20 (20)	50 (90.91)	2.11E-17
Nausea, n (%)	20 (20)	29 (52.73)	2.76E-05
Ascites, n (%)	14 (14)	23 (41.82)	1.01E-04
Vomiting, n (%)	17 (17)	19 (34.55)	0.13
Abdominal distention, n (%)	15 (15)	20 (36.36)	2.34E-03
Rash, n (%)	18 (18)	17 (30.91)	0.07
Itch, n (%)	10 (10)	13 (23.64)	0.02
Biochemical parameters of DILI recognition			
ALT, U/L	116 (8-924)	243 (17-2426)	0.03
AST, U/L	87.5 (17-599)	134 (35-1645)	0.01
ALP, U/L	85.5 (41-746)	141 (49.6-600)	2.75E-06
Total bilirubin, $\mu\text{mol/L}$	14.15 (4-158)	265 (17-668)	1.86E-21
Direct bilirubin, $\mu\text{mol/L}$	7 (1-112)	151 (7-404)	6.56E-21
PT, seconds	12.15 (9.8-16.3)	18.5 (3.1-56.7)	3.25E-16
Albumin, g/L	33.90 \pm 6.26	29.28 \pm 4.51	1.68E-06
Serum creatinine, $\mu\text{mol/L}$	55 (25-107)	56 (10-364)	0.04
Hemoglobin, g/L	126.42 \pm 18.59	115.24 \pm 21.93	9.86E-04
WBC, $10^9/\text{L}$	5.25 (1.9-29.6)	6.1 (2.1-58.6)	0.02
Platelets, $10^9/\text{L}$	198.83 \pm 89.48	150.13 \pm 88.68	1.41E-03
Alpha fetoprotein, ng/mL	2.35 (0.4-3428.1)	25.7 (1.4-1973)	2.73E-07
Eosinophil percent, %	3.5 (0-28.2)	2.7 (0-38.5)	0.14

ALF, acute liver failure; ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; PT, prothrombin time; WBC, white blood cell count.

taking potentially hepatotoxic medications (isoniazid, rifampin, and pyrazinamide).

Overall, among the 55 patients presenting with ALF, 22 (40%) and 33 (60%) patients were diagnosed at 1 and 2 months of initial chemotherapy, respectively, with a median time of onset of 51 days (range 7 to 330 days).

Predictors of anti-TB ALF

Univariate logistic regression analysis suggested that laboratory values at the time of DILI recognition, including transaminases, TBL, direct bilirubin, ALP, hemoglobin, platelets, albumin, and white blood cell count (WBC), as well as pre-existing hepatitis, symptoms (abdominal distension, nausea, vomiting, itching), ascites, and jaundice may be significant risk factors for the development of ALF during anti-TB

treatment (Table 3). Serum levels of alpha fetoprotein were higher in the ALF compared with the non-ALF group (OR 1.76; 95% CI 1.41 to 2.18; $P = 3.48\text{E}-07$). Long latency may also be a potential predictor of ALF (OR 2; 95% CI 1.38 to 2.89; $P = 2.25\text{E}-04$). Multiple logistic regression analysis identified AST (OR 8.24; 95% CI 2.37 to 28.58; $P = 8.95\text{E}-04$), TBL (OR 50.72; 95% CI 8.82 to 291.61; $P = 1.08\text{E}-05$), platelets (OR 0.04; 95% CI 4.05E-03 to 0.43; $P = 0.01$), WBC (OR 14.00; 95% CI 1.72 to 114.26; $P = 0.01$), and pre-existing hepatitis (OR 8.66; 95% CI 1.13 to 66.09; $P = 0.04$) as strong predictive factors of ALF. The ALF score was calculated using the following equation: $2.11 \times \log_e (\text{AST in U/L}) + 3.93 \times \log_e (\text{TBL in } \mu\text{mol/L}) + 2.64 \times \log_e (\text{WBC in } 10^9/\text{L}) - 3.18 \times \log_e (\text{platelets in } 10^9/\text{L}) + 2.16 \times (\text{pre-existing hepatitis}) - 17.14$.

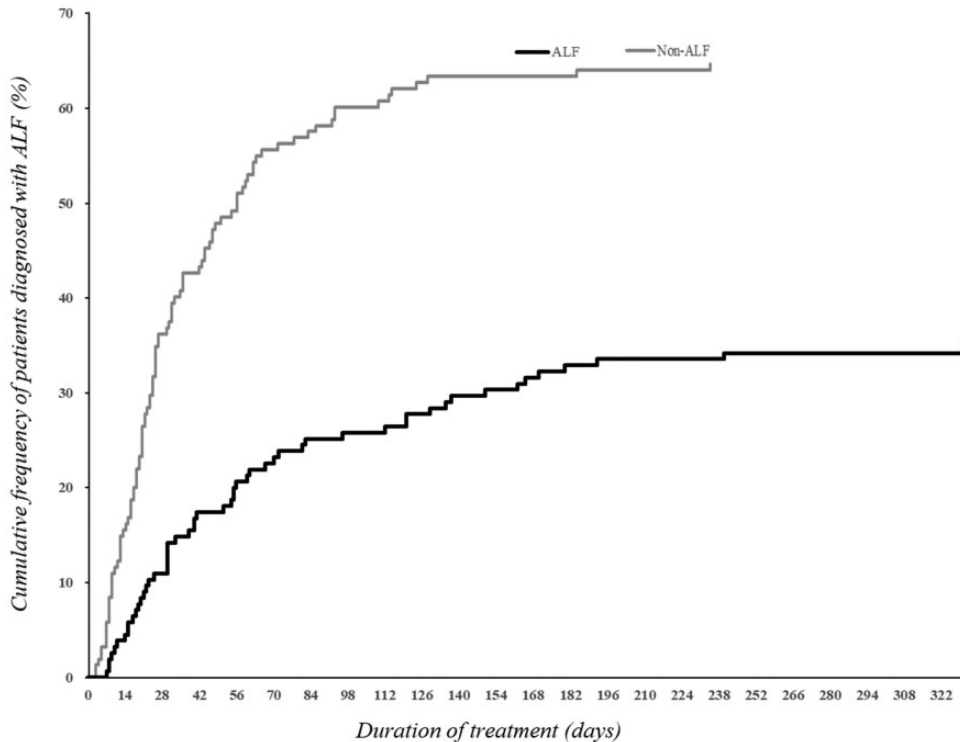


Figure 1. Time from beginning of treatment to onset of acute liver failure (ALF) in 155 patients with anti-tuberculosis drug-induced liver injury (DILI). Overall, 40% and 60% of the 55 patients who developed ALF were diagnosed at 1 and 2 months of initial chemotherapy, respectively. The median duration of treatment was 50 days (range 2 to 330 days). Among these patients, the cumulative frequencies of patients diagnosed with ALF at 1 and 2 months of initial chemotherapy were 14.19% (22/155) and 21.29% (33/155), respectively, and the cumulative frequencies of patients diagnosed with non-ALF were 39.35% (61/155) and 54.19% (84/155), respectively.

Multivariable analysis including all the study variables studied yielded a concordance (C-statistic) of 98.93%, which outperformed Hy's Law (C-statistic, 68.86%) (Figure 2).

Discussion

The current study showed a 35.48% incidence of ALF (55/155 patients) and an overall mortality of 9.68% among patients with anti-TB DILI. A long latency of jaundice appeared to have a marked effect on anti-TB ALF. A prognostic model including four main laboratory variables (AST,

TBL, platelets, and WBC) and pre-existing hepatitis predicted incident ALF with a C-statistic of 98.93%, which was superior to the predictive ability of Hy's Law (C-statistic 68.86%).

The primary cause of ALF in China is hepatitis virus, followed by traditional Chinese herbal medicines and anti-TB drugs.¹⁹ The incidence of anti-TB drug-induced ALF is similar across medical centers and regions, and was 35.48% in our study compared with 25.7% noted by Devarbhavi et al.⁸ and 28.8% by Shu et al.²⁰ Notably however, the current study showed lower anti-TB DILI-related

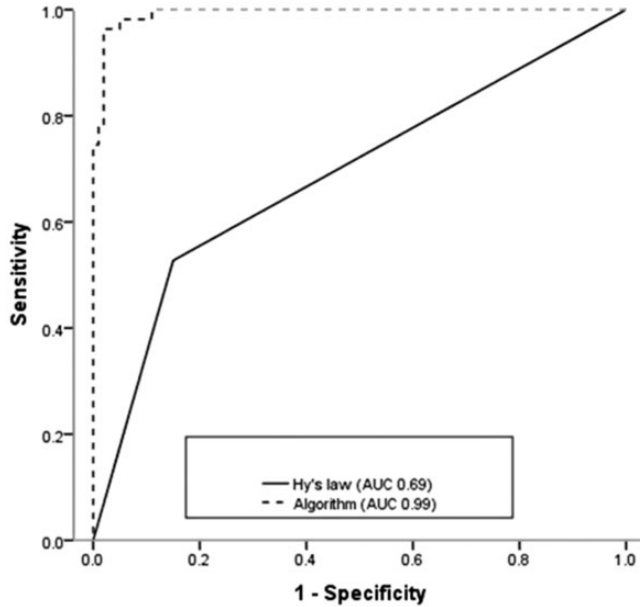


Figure 2. Comparison between the areas under the receiver operating characteristic curves for Hy's law criteria and the prognostic algorithm.

mortality (9.68%) than previous research, which reported 17.3% to 30% mortality in patients with drug-induced ALF,^{7,8,21,22} with especially high mortality in children (>50%)^{23,24} in India and the USA. The lower mortality in the current study may be attributable to the use of NBALSS to remove harmful substances and supply beneficial factors. We previously suggested that NBALSS reduced mortality (4-week survival rates of 42% for NBALSS versus 17% for non-NBALSS, $P < 0.05$) in patients with ALF mainly due to drug toxicity.²⁵ NBALSS may thus be a potentially valuable treatment for patients with anti-TB drug-induced liver failure.

Among the 55 patients presenting with ALF, 22 (40%) and 33 (60%) patients were diagnosed at 1 and 2 months of initial chemotherapy, respectively. The RUCAM score was >3 in all patients, indicating a credible diagnosis. Although anti-TB DILI frequently occurred during the first months of exposure to medication, late-occurring

DILI was significantly more likely to develop into ALF. We also aimed to identify the early predictors of ALF. Multivariate analysis identified high serum bilirubin, WBC, pre-existing hepatitis, AST, and low platelet count as independent predictors of early diagnosis. This also suggests that clinicians should consider universal testing every 2 weeks within the first 2 months in all patients receiving treatment,²⁶ and should be aware of any history of chronic liver disease.²⁷ Furthermore, in terms of symptom monitoring, our univariate analysis suggested that more attention should be paid to definitive diagnoses in clinical practice. Patients with DILI who presented with jaundice tended to have a poor outcome, in line with the results of earlier studies.⁷ Applying the current model at the patient's first visit could identify more cases of anti-TB DILI at increased risk of ALF progression, especially in overlapping epidemic cases of TB and hepatitis B virus infection. Alpha fetoprotein is produced

Table 3. Comparison of demographic, clinical, and laboratory variables in 155 patients with drug-induced liver injury with (n = 55) or without (n = 100) subsequent acute liver failure.

Variable	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value	C-statistic
Log _e (AST U/L)	1.90 (1.30–2.77)	9.16E–04	8.24 (2.37–28.58)	8.95E–04	0.99
Log _e (TBL μmol/L)	10.39 (4.95–21.80)	5.92E–10	50.72 (8.82–291.61)	1.08E–05	
Log _e (WBC 10 ⁹ /L)	2.35 (1.22–4.54)	0.04	14.00 (1.72–114.26)	0.01	
Log _e (PLA 10 ⁹ /L)	0.32 (0.17–0.62)	6.84E–04	0.04 (4.05E–03–0.43)	0.01	
Pre-existing hepatitis*	3.55 (1.71–7.36)	0.01	8.66 (1.13–66.09)	0.04	
PT (seconds)	1.82 (1.47–2.26)	3.77E–08			
Log _e (HGB g/L)	0.05 (0.01–0.33)	2.06E–03			
Log _e (DBIL μmol/L)	8.06 (4.16–15.41)	4.76E–10			
Log _e (AFP ng/mL)	1.76 (1.41–2.18)	3.48E–07			
Log _e (ALB g/L)	0.02 (3.33E–03–0.14)	6.77E–05			
Log _e (ALT U/L)	2.40 (1.13–5.04)	0.02			
Log _e (ALP U/L)	4.06 (2.02–8.14)	8.34E–05			
Log _e (duration of treatment, days)	2 (1.38–2.89)	2.25E–04			
Jaundice	40 (14.11–113.37)	0.01			
Abdominal distension	3.24 (1.49–7.04)	3.02E–03			
Nausea	4.46 (2.17–9.18)	4.83E–05			
Vomiting	2.58 (1.20–5.52)	0.02			
Itch	2.79 (1.13–6.87)	0.03			
Hy's law positive	6.32 (2.95–13.55)	2.15E–06			
Age	1.02 (0.99–1.04)	0.16			
Male	0.69 (0.35–1.39)	0.30			
Alcohol use	1.37 (0.63–2.98)	0.43			
Smoking	0.88 (0.42–1.85)	0.73			

*Pre-existing hepatitis including chronic viral hepatitis, fatty liver disease, liver schistosomiasis

AST, aspartate aminotransferase; TBL, total bilirubin; WBC, white blood cell count; PLA, platelets; PT, prothrombin time; HGB, hemoglobin; DBIL, direct bilirubin; AFP, alpha fetoprotein; ALB, albumin; ALT, alanine transaminase; ALP, alkaline phosphatase

by proliferating hepatocytes during liver injury, and confounding factors such as cancer, active viral hepatitis, and pregnancy thus should be removed when considering the connection between drug-induced liver failure and alpha-fetoprotein levels.

Our study had some limitations. First, this was a retrospective, single-center study from a grade IIIA hospital that followed a strict triage system. Some patients with mild liver dysfunction may thus have been missed, and our findings may not be representative of patients from other regions and of other ethnicities. Second, the floating population is a matter for

concern because these patients may stop anti-TB therapy or adjust their treatment once they have been released from hospital, and these changes would not be recorded. Further multicenter and prospective studies are needed to verify these results.

Conclusion

Among patients with DILI, 35.48% developed ALF and 9.68% died. The results of this study suggest that close monitoring of early signs, symptom, and laboratory test results during the first 2 months of anti-TB treatment is essential for identifying patients

at increased risk of ALF. Patients with signs of severe liver damage, such as elevated AST and TBL, and decreased platelet count, should stop taking the medication to reduce their risk of developing ALF.

Author contributions

WST, SGYW, and LPC participated in the design of the study, searched the literature, and drafted the manuscript. DC, YSG, and WJ participated in the data analysis. JZK, SJD, FH, YMF, SP, and RJJ contributed cases and collected follow-up information on the therapeutic effects and prognosis. YJ, SYZ, and LJN participated in the literature search. LLJ and XKJ wrote and revised the manuscript. All authors have read and approved the final manuscript.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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