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Original Article

Time of Liver Function Abnormal Identification on Prediction of the Risk of Anti-tuberculosis-induced Liver Injury

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Abstract

Background and Aims: Anti-tuberculosis (anti-TB) drug-induced liver injury (AT-DILI) is the most common side effect in patients who received anti-TB therapy. AT-DILI management includes monitoring liver function until symptoms arise in patients without high-risk factors for liver damage. The present study aimed to investigate the effect of liver function test (LFT) abnormal identification on the risk of DILI, including liver failure and anti-TB drug resistance in patients without high-risk factors. ***Methods:*** A total of 399 patients without high-risk factors for liver damage at baseline and who experienced LFT abnormal during the 6 months of first-line anti-TB treatment were enrolled. The Roussel Uclaf Causal Relationship Assessment Method (RUCAM, 2016) was applied in suspected DILI. The correlations between the time of LFT abnormal identification and DILI, liver failure, and anti-TB drug resistance were analyzed by smooth curve fitting and multivariable logistic regression models. ***Results:*** Among all study patients, 131 met the criteria for DILI with a mean RUCAM causality score of 8.86±0.63. 26/131 and 105/131 were in the probable grading and highly probable grading, respectively. The time of abnormal LFT identification was an independent predictor of DILI, liver failure, and anti-TB drug resistance in the crude model and after adjusting for other risk patient factors. The time of abnormal LFT identification was positively correlated with DILI, liver failure, and anti-TB drug resistance. The late identification group (>8 weeks) had the highest risk of DILI, followed by liver failure compared with the other two groups. ***Conclusions:*** The time to identification of LFT was positively correlated with DILI, liver failure, and anti-TB drug resistance. The risk of DILI and liver failure was significantly increased in the late identification group with abnormal LFT identified after 8 weeks compared with 4 and 8 weeks. Early monitoring of LFT is recommended for patients without the high-risk factor of DILI after anti-TB treatment is initiated.

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Introduction

Tuberculosis (TB) is a major global public health concern affecting about 33% of the world's population.[1–5] Liver injury is the most common side effect during anti-TB therapy, occasionally fatal liver failure.[3,6,7] The incidence of anti-TB drug-induced liver injury (AT-DILI) varies across regions worldwide and may be related to race, socioeconomic status, geographical location, the diagnostic criteria for DILI, prevalence of viral hepatitis, and study design and subjects.[3,8] In countries with a high TB burden, such as India and China, AT-DILI accounts for a large proportion of all DILI cases.[6,7,9–14] In addition, the occurrence of DILI significantly affects drug selection and course of treatment. For AT-DILI management, the guidelines published by the American Thoracic Society (2006; updated 2016),[2,15] Asia Pacific Association of Study of Liver (APASL; 2021),[3] the National Institute for Health and Clinical Excellence (NICE) of the UK,[4] British Thoracic Society (BST),[16] and the World Health Organization (WHO; 2010),[5] recommend that liver function tests (LFTs) need not be performed routinely if the baseline was normal and unless symptoms, such as human immunodeficiency virus (HIV) infection, primary liver diseases, or current pregnancy, arise in patients who are not at high risk. However, some early clinical symptoms are easily ignored by patients and doctors[3] because patients do not visit the clinic until obvious clinical symptoms, such as jaundice, and serious gastrointestinal manifestations, are observed. Moreover, abnormal LFTs often occur before the symptoms arise. Hitherto, few studies have investigated the correlation between the time that abnormal LFTs are identified and DILI. In this study, we investigated the correlation

Keywords: Liver function abnormal identification time; Anti-tuberculosis induced liver injury; Liver failure; RUCAM causality scale.

Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CIs, confidence intervals; DILI, drug-induced liver injury; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; INR, international normalized ratio; LFT, liver function test; ORs, odds ratios; PTA, prothrombin time and activity; RUCAM, Roussel Uclaf Causal Relationship Assessment Method; TB, tuberculosis; TBIL, total bilirubin; ULN, upper limit of normal.

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between the time of abnormal LFT identification and DILI or liver failure in patients without high risk and with normal baseline LFTs, and whether early and frequent monitoring of abnormal LFTs is effective in preventing AT-DILI, liver failure, and drug resistance.

Methods

Study population and data collection

Patients with an abnormal LFT index during anti-TB treatment between January 2012 and December 2018 at the Third People's Hospital of Shenzhen were enrolled in this study. Adult active TB patients ≥18 years of age who were treatment-naïve and received first-line anti-TB therapy and follow-up at our hospital were included in this study. Patients with non-TB *Mycobacterium* infection and who received second-line anti-TB drugs were excluded. Patients at high risk of DILI by the following guidelines[2–5] were also excluded. (1) LFT was abnormal at anti-TB initiation; (2) There was a history of previous liver diseases: hepatitis A virus, hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus, hepatitis E virus, Epstein-Barr virus, cytomegalovirus (CMV), herpes virus infection, hepatocellular carcinoma, Wilson's disease, autoimmune hepatitis, alcoholic and nonalcoholic liver diseases, and HIV infection. This retrospective analysis of patient data was approved by the Third People's Hospital of Shenzhen Ethics Committee, and patients' informed consent was waived (no. 2021-007-02). Demographic and clinical data including sex, age, LFT indexes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), albumin (ALB), international normalized ratio (INR), and prothrombin time and activity (PTA) were recorded. The treatment regimen and drug resistance were reviewed.

Definitions

The time of identification of abnormal LFT was defined as the time from anti-TB treatment initiation to the first occurrence of an abnormal LFT. Abnormal LFT was diagnosed as an increase in ALT, AST, TBil, ALP, and GGT greater than the upper limit of normal (ULN). The case definitions for DILI, according to the 2019 EASL DILI Clinical Practice Guidelines[8] included one of the following thresholds: (1) ≥5 ULN elevation in ALT, (2) ≥2 ULN elevation in ALP (especially elevated GGT in the absence of known bone pathology raising the ALP level); (3) ≥3 times the ULN elevation in ALT and simultaneous elevation of TBIL concentration exceeding two times the ULN. DILI patterns were divided into three categories: a hepatocellular pattern (R-value ≥5 and ALT ≥3 times the ULN), a cholestatic pattern (R-value ≤2 and ALP ≥2 times the ULN), and a mixed pattern (R-value between 2 and 5 with ALT ≥3 times the ULN and ALP ≥2 times the ULN).[8] Patients with DILI met the criteria of the 2016 Roussel Uclaf Causal Relationship Assessment Method (RUCAM),[17] and with a RUCAM causality scale of >6 points.

Acute liver failure was defined according to the following APASL guidelines: a severe liver injury leading to coagulation abnormality, with an INR >1.5 or a PTA <40%, and TBIL levels >5 times the ULN, any degree of mental alteration (encephalopathy) in a patient without pre-existing liver disease, and an illness of up to 4 weeks.[18] The time of identifying an abnormal LFT was categorized into three groups: early identification (≤4 weeks), intermediate identification (>4 and ≤8 weeks), and late identification (>8 weeks). It was also divided into two groups: ≤2 weeks and >2 weeks based on the first instance of liver function monitoring for the patient as suggested by previous studies and consensus.[19–22]

Statistical analysis

Data were reported as frequency or percentage for categorical variables and as means±standard deviations for continuous variables. Smooth curve fitting was conducted to assess the nonlinear correlations between the time of LFT abnormal identification and DILI, liver failure, anti-TB treatment discontinuation, and anti-TB drug resistance in patients with adjustment for age and sex. The correlations were assessed by multivariable logistic regression models with and without adjustment for age and sex and reported as odds ratios (ORs) with 95% confidence intervals (CIs). The ORs of DILI, liver failure, treatment discontinuation, and drug resistance were estimated by the modeling time of LFT abnormal identification as a continuous and categorical variable. A two-tailed p <0.05 was considered statistically significant. Data were analyzed with SPSS 24.0 (IBM Corp., Armonk, NY, USA), Empower Stats 2.14.9 (X&Y Solutions Inc., Boston, MA, USA), and R software.

Results

Patient characteristics

A total of 525 patients who received regular anti-TB treatments and presented with abnormal LFT between 2012 and 2018 were identified in the electronic medical record database. Of those, 126 with potential high risk for liver injury were excluded (91 with HBV infection, 31 with HIV infection, and five with HCV infection). The remaining 399 patients were enrolled in the study (Fig. 1). The characteristics of patients in the early, intermediate, and late abnormal LFT groups are listed in Table 1. The median age was 34 (26–47) years of age, 68.67% were men, 131 (38.83%) were diagnosed as DILI, including 13 (3.26%) with liver failure. The RUCAM score for all suspected DILI patients was >6. The mean score was 8.86±0.63. Twenty-six with suspected DILI (19.85%) were classified as probable (6–8) and 105 (80.15%) were classified as highly probable (>8). The cumulative frequencies of patients with an abnormal LFT at 4 and 8 weeks were 58.02% and 86.26%, respectively (Fig. 2A). The mean times of LFT abnormal DILI and liver failure were 29.11 and 44.62 days, respectively. The times of abnormal LFT in the DILI and liver failure groups were significantly longer than those in the non-DILI and nonliver failure groups (p<0.001; Fig. 2B). The proportions of DILI and liver failure in the late identification group were significantly higher than those in the early identification and the intermediate identification groups (p<0.001). The most common pattern of liver injury was hepatocellular type in patients with DILI, and no significant differences were detected in the pattern of liver injury among the three groups. The median INR, ALT, AST, TBIL, and DILI levels at onset and peak LFT was significantly higher in the late identification and intermediate identification groups than in the early identification groups (Table 1).

Association between DILI and time of identification of abnormal LFT

Figure 3A shows a nonlinear dose-response correlation between the time of LFT abnormal and DILI. The risk of DILI

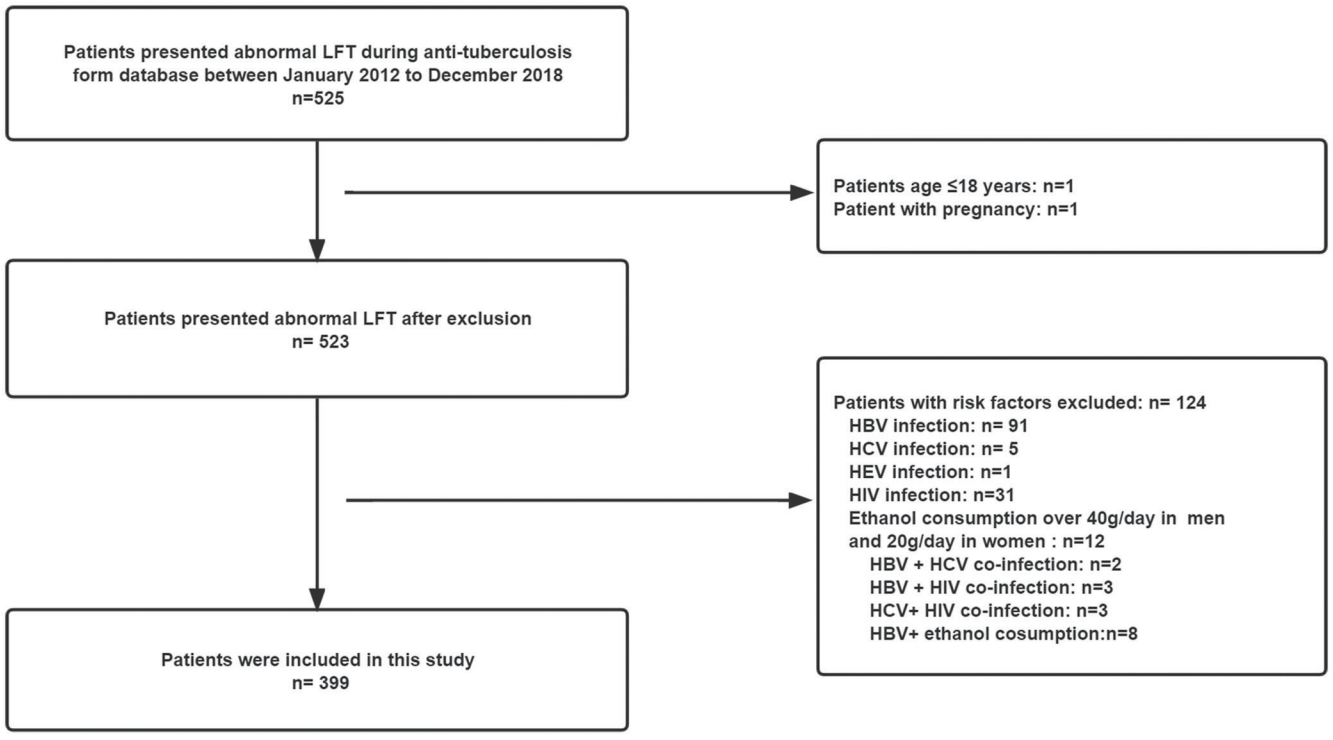

Fig. 1. Flowchart of patient inclusion.

tended to increase with the time of LFT abnormal identification, and the time of LFT abnormal identification was significantly related to the risk of DILI. Table 2 shows the OR for DILI according to the time of identification of an abnormal LFT in patients with DILI. A 36% (OR 1.36, 95% CI: 1.24–1.50, $p<0.0001$) increase was noted in the risk of DILI with every week delay in the time of LFT abnormal identification in both modes when the identification time was a continuous variable. Compared with the early identification group in all models, patients in the intermediate and late identification groups had a significantly higher risk of developing DILI, with full-adjusted OR of 4.60 (95% CI: 2.57–8.21) and 8.05 (95% CI: 3.22–20.12), respectively ($p<0.0001$). Compared with the ≤2 weeks group in all models, patients in the >2 weeks group had a significantly higher risk of developing DILI (model with full-adjusted: OR 4.62, 95% CI: 2.94–7.29, $p<0.0001$).

Association between liver failure and time of abnormal LFT identification

The association between time of abnormal LFT identification and liver failure showed a pattern similar to DILI. A nonlinear dose-response correlation between the time of LFT abnormal identification and the risk of developing liver failure increased rapidly after 4 weeks (Fig. 3B).

As shown in Table 2, a 29% (OR 1.29, 95% CI: 1.14–1.47, $p<0.0001$) increase was observed in the risk of liver failure with every week delay in the time of abnormal LFT identification. Patients in the late identification group had the highest risk of liver failure, and the adjusted ORs of liver failure for patients in the intermediate and late identification groups were 2.63 (95% CI: 0.60–11.60) and 14.11 (95% CI: 3.73–53.32), respectively, compared with those in the early identification group ($p=0.0002$). The risk of liver failure for patients in the >2 week group was higher than that in the ≤2 week group in both unadjusted and adjusted models, although not statistically significant ($p>0.05$).

Correlation between the time of LFT abnormal identification and treatment discontinuation and drug resistance

Compared with the early and intermediate identification groups, patients had significantly higher treatment discontinuation and drug resistance rates in the late identification group (Table 1). Similarly, a positive correlation was established between the time of abnormal LFT identification and treatment discontinuation and drug resistance (Fig. 3C, D). The ORs of treatment discontinuation and drug resistance for patients are shown in Table 3. The findings suggested that treatment discontinuation and drug resistance occur with increasing time of abnormal LFT identification.

Discussion

No effective low liver toxicity compound or alternative first-line drugs for treating TB are currently available. Monitoring of clinical symptoms and liver function effective for reducing liver injury. Although present guidelines do not recommend early monitoring of LFT before symptoms arise in patients who are not at high risk because of primary liver diseases or HIV coinfection, our study identified a positive correlation between time of LFT abnormal identification and DILI, liver failure, and TB drug resistance. The study also found that the risk of DLIL or liver failure for patients with abnormal LFT that occurred in >8 weeks were higher than those that occurred within 8 weeks during anti-TB treatment, even in patients not at high risk of liver injury.

Table 1. Characteristics among the study population

Characteristics	Total (N=399)	≤4 weeks (N=312)	>4, ≤8 weeks (N=62)	≥8 weeks (N=25)	P-value
Age, year	34.00 (26.00–47.00)	32.50 (25.00–45.25)	41.50 (30.00–56.75)	37.00 (33.00–51.00)	0.004
Sex, n (%)					0.735
Female	125 (31.33%)	95 (30.45%)	22 (35.48%)	8 (32.00%)	
Male	274 (68.67%)	217 (69.55%)	40 (64.52%)	17 (68.00%)	
Onset LFT abnormal					
INR	1.05 (0.97–1.13)	1.05 (0.97–1.11)	1.06 (0.98–1.19)	1.10 (0.99–1.41)	<0.001
ALT, U/L	96.00 (62.00–166.00)	87.50 (59.00–127.25)	256.00 (78.80–448.65)	236.00 (97.00–485.00)	<0.001
AST, U/L	97.00 (60.00–172.75)	86.00 (58.00–142.00)	195.00 (85.53–384.05)	168.00 (101.00–332.00)	<0.001
ALP, U/L	108.00 (81.50–145.50)	108.00 (81.00–146.00)	103.00 (86.00–145.00)	111.00 (75.00–143.75)	0.992
GGT, U/L	60.50 (35.00–114.25)	52.00 (34.00–108.50)	76.50 (42.00–156.50)	96.00 (45.10–172.00)	0.108
TBIL, umol/L	9.05 (5.80–14.97)	7.90 (5.50–12.90)	12.45 (7.95–20.32)	21.20 (9.90–42.30)	<0.001
DBIL, umol/L	3.40 (2.20–7.30)	2.94 (2.10–5.25)	5.65 (3.10–10.10)	8.70 (3.40–23.20)	<0.001
ALB, g/L	38.28 (5.81)	38.28 (5.71)	38.49 (5.79)	37.74 (7.14)	0.770
Peak LFT abnormal					
INR	1.04 (0.98–1.13)	1.04 (0.97–1.11)	1.05 (0.98–1.20)	1.10 (1.00–1.48)	0.002
ALT, U/L	128.00 (75.50–239.00)	111.20 (71.75–182.25)	309.00 (117.25–518.25)	287.00 (181.10–485.00)	<0.001
AST, U/L	108.00 (67.25–195.00)	96.00 (64.00–148.00)	208.00 (107.25–535.15)	228.00 (117.20–592.30)	<0.001
ALP, U/L	107.50 (77.00–146.00)	108.50 (78.25–141.25)	96.00 (74.00–148.00)	110.00 (73.00–165.00)	0.799
GGT, U/L	75.00 (41.65–136.00)	73.00 (40.00–132.00)	84.00 (44.00–158.00)	102.90 (54.50–188.00)	0.084
TBIL, umol/L	10.00 (6.30–16.65)	8.80 (5.90–14.20)	13.30 (8.80–22.20)	27.80 (13.30–53.40)	<0.001
DBIL,umol/L	3.60 (2.40–8.10)	3.40 (2.27–6.05)	6.10 (3.08–9.90)	12.60 (4.10–34.10)	<0.001
ALB, g/L	38.44 (5.99)	38.45 (6.06)	39.02 (5.24)	36.97 (6.77)	0.637
Patterns of DILI, n (%)					0.054
Hepatocellular	115 (85.82%)	62 (79.49%)	37 (97.37%)	16 (88.89%)	
Cholestatic	6 (4.48%)	5 (6.41%)	1 (2.63%)	0 (0.00%)	
Mixed	13 (9.70%)	11 (14.10%)	0 (0.00%)	2 (11.11%)	
Liver damage, n (%)					<0.001
Abnormal liver function	268 (67.17%)	236 (75.64%)	25 (40.32%)	7 (28.00%)	
DILI	131 (32.83%)	76 (24.36%)	37 (59.68%)	18 (72.00%)	
liver failure					<0.001
No	386 (96.74%)	307 (98.40%)	59 (95.16%)	20 (80.00%)	
Yes	13 (3.26%)	5 (1.60%)	3 (4.84%)	5 (20.00%)	
Anti-TB Drug resistance, n (%)					0.001
No	378 (94.74%)	301 (96.47%)	57 (91.94%)	20 (80.00%)	
Yes	21 (5.26%)	11 (3.53%)	5 (8.06%)	5 (20.00%)	
Anti-TB Discontinuation, n (%)					<0.001
No	109 (27.32%)	102 (32.69%)	6 (9.68%)	1 (4.00%)	
Yes	290 (72.68%)	210 (67.31%)	56 (90.32%)	24 (96.00%)	
Time to recovery, d	20.00 (11.00–35.00)	20.00 (10.00–33.50)	22.00 (16.00–45.00)	18.00 (14.00–35.00)	0.237
Death					<0.001
No	391 (97.99%)	309 (99.04%)	61 (98.39%)	21 (84.00%)	
Yes	8 (2.01%)	3 (0.96%)	1 (1.61%)	4 (16.00%)	

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; GGT, gamma-glutamyl transpeptidase; INR, international normalized ratio; LFT, liver function test; TB, tuberculosis; TBIL, total bilirubin.

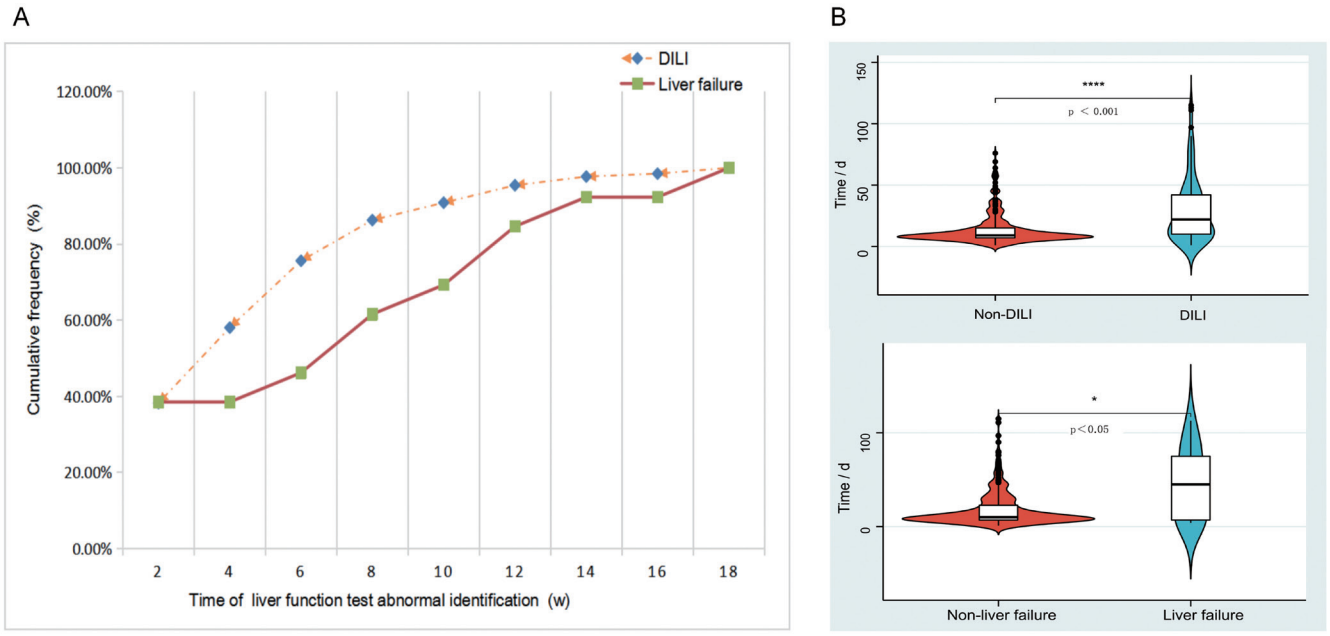

Fig. 2. Time of identification of abnormal liver function tests. (A) Cumulative frequency for DILI and liver failure groups; (B) Time of LFT abnormal identification between different liver injury groups. DILI, drug-induced liver injury; LFT, liver function test.

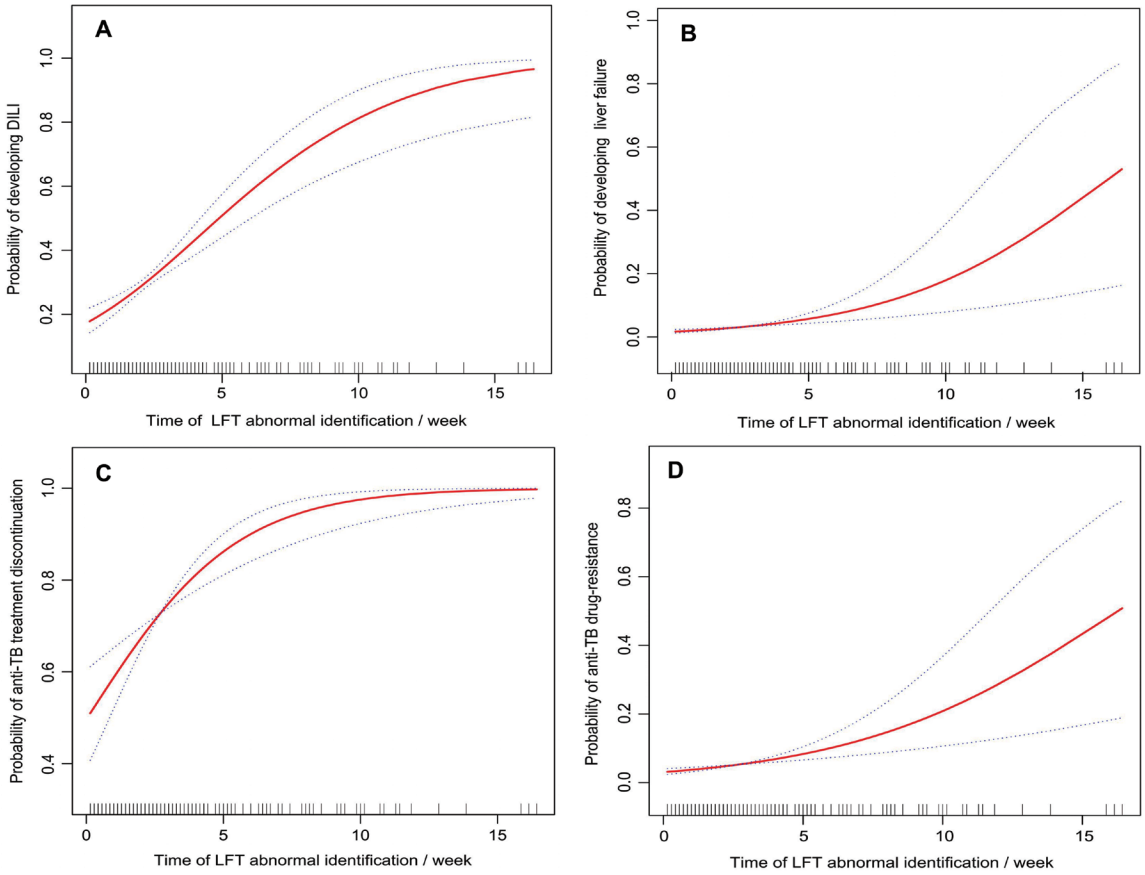

Fig. 3. Dose-response correlations between the time of identification of abnormal LFT and the probability of developing drug-induced liver injury (A), liver failure (B), anti-TB treatment discontinuation (C), and drug resistance (D). Adjustment factors included age and sex. Solid and dashed lines represent the estimated values and their corresponding 95% CIs. CIs, confidence intervals; LFT, liver function test; TB, tuberculosis.

Table 2. Multivariate regression analysis of the effect of time of identifying abnormal LFTs on drug-induced liver injury and liver failure

Exposure		Un-adjusted Model		Adjust Model	
DILI	N	OR (95%CI)	P-value	OR (95%CI)	P-value
LFT abnormal identification time, per week	131	1.36 (1.24, 1.50)	<0.0001	1.36 (1.24, 1.50)	<0.0001
Time/w; group 1					
Early identification group (≤4 w)	76	Ref.		Ref.	
Intermediate identification group (>4, ≤8 w)	37	4.60 (2.60, 8.12)	<0.0001	4.60 (2.57, 8.21)	<0.0001
Late identification group (>8 w)	7	7.98 (3.21, 19.85)	<0.0001	8.05 (3.22, 20.12)	<0.0001
P for trend			<0.0001		<0.0001
Time/w; group 2					
≤2 w	50	Ref.		Ref.	
>2 w	81	4.58 (2.93, 7.15)	<0.0001	4.62 (2.94, 7.29)	<0.0001
Liver failure	N	OR (95%CI)	P-value	OR (95%CI)	P-value
LFT abnormal identification time, per week	13	1.30 (1.14, 1.47)	<0.0001	1.29 (1.14, 1.47)	<0.0001
Time/w; group 1					
Early identification group (≤4 w)	5	Ref.		Ref.	
Intermediate identification group (>4, ≤8 w)	3	3.12 (0.73, 13.42)	0.1260	2.63 (0.60, 11.60)	0.2020
Late identification group (>8 w)	3	15.35 (4.10, 57.44)	<0.0001	14.11 (3.73, 53.32)	<0.0001
P for trend		<0.0001		0.0002	
Time/w; group 2					
≤2 w	5	Ref.		Ref.	
>2 w	8	2.72 (0.87, 8.47)	0.0845	2.39 (0.76, 7.57)	0.1371

Un-adjusted Model adjust for: None; Adjust Model adjust for: Sex; Age. DILI, drug-induced liver injury; LFT, liver function test; ORs, odds ratios.

Table 3. Multivariate regression analysis of the effect of time of identifying abnormal LFTs on anti-TB treatment discontinuation and drug resistance

Exposure		Un-adjusted Model		Adjust Model	
Anti-TB treatment discontinuation	N	OR (95%CI)	P-value	OR (95%CI)	P-value
LFT abnormal identification time, per week	290	1.46 (1.24, 1.72)	<0.0001	1.45 (1.23, 1.70)	<0.0001
Time/w; group 1		OR (95%CI)	P-value	OR (95%CI)	P-value
Early identification group (≤4 w)	210	Ref.		Ref.	
Intermediate identification group (>4, ≤8 w)	56	4.53 (1.89, 10.87)	0.0007	4.29 (1.77, 10.36)	0.0012
Late identification group (>8 w)	24	11.66 (1.56, 87.33)	0.0168	11.31 (1.50, 85.06)	0.0184
P for trend		4.07 (2.03, 8.16)	<0.0001	3.90 (1.94, 7.84)	0.0001
Time/w; group 2		OR (95%CI)	P-value	OR (95%CI)	P-value
≤2 w	161	Ref.		Ref.	
>2 w	129	3.17 (1.88, 5.34)	<0.0001	3.06 (1.80, 5.21)	<0.0001
Resistance-drug	N	OR (95%CI)	P-value	OR (95%CI)	P-value
LFT abnormal identification time, per week	21	1.24 (1.12, 1.38)	<0.0001	1.24 (1.11, 1.38)	0.0001
Time/w; group 1		OR (95%CI)	P-value	OR (95%CI)	P-value
Early identification group (≤4 w)	11	Ref.		Ref.	
Intermediate identification group (>4, ≤8 w)	5	2.40 (0.80, 7.17)	0.1168	2.33 (0.76, 7.12)	0.1382
Late identification group (>8 w)	5	6.84 (2.17, 21.60)	0.0010	6.67 (2.08, 21.32)	0.0014
P for trend		0.0009		0.0013	
Time/w; group 2		OR (95%CI)	P-value	OR (95%CI)	P-value
≤2 w	6	Ref.		Ref.	
>2 w	15	4.45 (1.69, 11.73)	0.0026	4.36 (1.63, 11.65)	0.0034

Un-adjusted Model adjust for: None; Adjust Model adjust for: Sex; Age. LFT, liver function test; ORs, odds ratios; TB, tuberculosis.

Previous studies have shown that the risk of liver injury persists throughout anti-TB treatment, but that approximately 75% of liver damage presents with abnormal LFTs within 2 months, and about 33% occur in the first 2 weeks after starting treatment.[14,23,24] The current results were similar to those described previously. DILI was identified in 58/1,928 (3.0%) patients involved in the REMoxTB study in the UK after a median of 28 days.[25] The mean time of abnormal LFT onset of 29 days in the present study was consistent with the median of 28 days in the REMoxTB study, and the mean latency of 33.8±34.6 days in study in Taiwan.[25,26] Together, the studies suggest that AT-DILI often occurred during the early period of anti-TB treatment.

The importance of the time of abnormal LFT has been previously reported.[27,28] Anti-TB drugs induce severe liver damage, such as acute liver failure that can be fatal if not recognized promptly. Some studies observed that the later the liver injury occurs, the more severe it is and the higher the incidence of DILI and liver failure.[29,30] Moreover, the time of LFT abnormal identification is also associated with frequent adjustment of anti-TB drug regimens and a high incidence of drug resistance.[31,32] This study found that the risk of DILI and liver failure increased with the time of LFT abnormal identification, and the risks of anti-TB discontinuation and drug resistance increased gradually. The risks in patients with abnormal LFTs identified after >8 weeks were higher than those associated with LFTs identified within 8 weeks. Regular monitoring, early detection of liver injury, and appropriate interventions reduce the risk of severe liver injury and improve prognosis.[33,34] Several recent studies reported that periodic liver function monitoring in the first 2 months reduced the risk of severe liver injury,[35–39] liver disease-related hospitalization, and poor outcomes[31] compared with passive detection. The studies included patients with and without increased risk, but few included only patients not at high risk or investigated the effect of onset-time on the risk of DILI. Typically, DILI differed between high- and low-risks patients. This current study analyzed the time of abnormal LFT identification as a continuous variable and identified the 4- and 8-week thresholds associated with increased risk of DILI and liver failure in patients not at high risk of liver injury. Moreover, to ensure the stability of results and minimize the bias, a smooth curve technique was utilized to explore the dose-response correlation. Multivariate logistic regression analysis and several models including unadjusted and adjusted mixed factors ruled out other influencing factors. Our study showed that in patients not at high risk, abnormal LFT presented in <4 weeks and those in the 4–8-week group had a lower risk of DILI, liver failure, anti-TB discontinuation, and drug resistance than those in the 8-weeks group. Eight week of monitoring is recommended for patients without high-risk.

A subgroup analysis found that the risk for DILI was lower in patients with abnormal LFTs within 2 weeks than in those with LFTs after 2 weeks. Several studies have assessed a 2-week LFT monitoring strategy and reported that it identified liver injury early because of a short treatment interruption period, improved anti-TB outcome, and the presence of any previous liver diseases.[27,40] A strategy of 2-week liver function monitoring could thus be beneficial to all patients. However, an observational study in London found that the value of 2-week monitoring had low sensitivity and specificity for the prediction of drug-induced liver injury.[27] This study found that some patients exhibited abnormal liver function indicators after 2 weeks. If LFTs were monitored for only 2 weeks, then liver injury might have been missed in those patients.

Nevertheless, the present study had some limitations. Firstly, this was a retrospective study that included multiple factors obtained from the medical record system, but risk factors, such as smoking habit, height, and weight, could not be collected. Secondly, this was a cross-sectional, single-center study in China. Hence, additional multicenter cohorts and well-designed prospective studies are required to confirm the current findings. Also, the long-term cost-efficiency of monitoring LFT should be explored further.

In conclusion, the risk of DILI, liver failure, anti-TB discontinuation, and drug resistance tended to increase with increasing time of identifying abnormal LFTs, and the risks for patients with abnormal LFT identified beyond 8 weeks were higher than those identified within 8 weeks. Therefore, periodic liver function monitoring is crucial for AT-DILI management during anti-TB treatment in all patients, regardless of the presence or absence of potential risk factors for liver injury.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceptualized and designed the study, received grant support, had full access to the data, guarantors for the integrity and accuracy of data analysis (JC, DH), and contributed to the writing of the report (HD, JP, YC). All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version.

Ethical statement

This retrospective analysis of patient data was approved by the Third People's Hospital of Shenzhen Ethics Committee, and patients' informed consent was waived (no. 2021-007-02).

Data sharing statement

The datasets analyzed during the current study are available from the corresponding authors on reasonable request.

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