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ORIGINAL RESEARCH

Clinical Features of Anti-Tuberculosis Drug-Induced Liver Injury and Risk Factors for Severe Cases: A Retrospective Study in China

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Background: Anti-tuberculosis drug-induced liver injury (ATB-DILI) is a common adverse reaction associated with tuberculosis (TB) treatment, significantly impacting treatment adherence and therapeutic outcomes. However, large-scale studies on hospitalized patients in China remain limited.

Purpose: To characterize the clinical features and liver injury patterns in hospitalized TB patients with ATB-DILI and to identify risk factors associated with severe ATB-DILI.

Methods: We retrospectively reviewed 28,753 hospitalized TB patients at Beijing Chest Hospital from 2014 to 2023. ATB-DILI was diagnosed in 567 patients (2.0%) based on serum biochemical criteria and causality assessment. Demographic, clinical, and laboratory data were analyzed to characterize liver injury types and identify risk factors for severe cases. Subgroup analyses based on liver injury patterns were performed to further evaluate the association between age and severe ATB-DILI.

Results: Overall, 567 cases with ATB-DILI (2.0%) were analyzed. Hepatocellular injury was the most common type (71.4%), followed by cholestatic (13.8%) and mixed (14.8%) injury patterns. Most patients (68.4%) were asymptomatic and diagnosed via routine biochemical monitoring; jaundice occurred in 18.2%. Patients with hepatocellular damage were significantly younger, while those with cholestatic injury were older ($p < 0.001$). Severe ATB-DILI occurred in 46 patients (8.1%), with advanced age (≥60 years) identified as an independent risk factor (OR = 2.45, 95% CI: 1.33–4.52, $p = 0.004$). Subgroup analysis showed that this association between age and severe ATB-DILI was significant in the hepatocellular injury type (unadjusted OR = 3.59, 95% CI: 1.61–8.02, $p = 0.002$), while no statistically significant association was observed in cholestatic or mixed types, which may reflect limited statistical power in these subgroups.

Conclusion: Routine liver function monitoring and age-specific risk assessment are essential for early identification and management of ATB-DILI in hospitalized TB patients.

Keywords: anti-tuberculosis drugs, drug-induced liver injury, hepatotoxicity, severe liver injury, risk factors

Introduction

Tuberculosis (TB) is a major global public health issue and ranks as the first deadliest infectious disease. According to the World Health Organization (WHO) Global Tuberculosis Report 2024,[1] approximately 10.8 million people are expected to develop TB worldwide, with 1.25 million deaths attributed to the disease. As one of the countries with the highest TB burden, China accounts for approximately 6.8% of the new global TB cases and faces significant challenges, including high drug resistance rates, poor treatment adherence, and the presence of co-infections.

Anti-tuberculosis drug-induced liver injury (ATB-DILI) is one of the most common adverse events associated with TB treatment. The reported prevalence of ATB-DILI varies considerably, ranging from 2% to 28%, depending on diagnostic criteria and geographic region.[2–4] One study demonstrated that ATB-DILI occurring during active TB

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treatment increases the risk of treatment failure and relapse by threefold.[5] Among first-line anti-TB drugs, isoniazid, rifampicin, and pyrazinamide are the principal contributors to hepatotoxicity, while second-line drugs also play a role in hepatic adverse events.[6,7] In Western countries, drug-induced liver injury (DILI) is commonly associated with antibiotics, cardiovascular agents, and non-steroidal anti-inflammatory drugs (NSAIDs). In contrast, anti-TB drugs are the predominant cause of DILI in many Eastern countries, likely reflecting differences in pharmacogenetic and immunological profiles.[8] Furthermore, developing countries, which often lack robust pharmacovigilance systems and have patient populations with poorer baseline health status, report even higher rates of ATB-DILI. Despite its clinical significance, comprehensive and large-scale epidemiological data on ATB-DILI remain limited.

Recent studies have reported an increasing global trend in ATB-DILI incidence, rising from 5.1% in 1999 to 29.4% in 2020.[9] In China, the number of reported DILI cases increased by 62% between 2012 and 2016, with anti-TB drugs being the most frequently identified cause.[10] A single-center study in China reported that the incidence of drug-related liver injury increased from 2.21% in 2002 to 6.70% in 2022.[11] These findings highlight the urgent need for enhanced drug safety surveillance and standardized diagnostic criteria for ATB-DILI. However, existing studies in China often suffer from limitations such as small sample sizes, inconsistent diagnostic approaches, and a lack of detailed investigations into liver injury types and their severity. To address these gaps, we conducted a retrospective analysis of hospitalized TB patients at Beijing Chest Hospital, Capital Medical University, from 2014 to 2023. This study aimed to evaluate the clinical characteristics of different ATB-DILI types and identified risk factors associated with severe ATB-DILI. To increase the likelihood that severe liver injury events were anti-TB drugs related, we excluded patients with preexisting liver and biliary tract diseases, as well as other potential causes of acute liver injury. The findings from this study provide novel insights into the prevention, monitoring, and management of ATB-DILI, particularly in high-burden TB settings like China.

Methods

Study Design and Sample Size

This study retrospectively analyzed the clinical data of patients with active TB who were hospitalized at Beijing Chest Hospital of Capital Medical University between January 2014 and December 2023. Beijing Chest Hospital is a tertiary institution specializing in tuberculosis care in China. Among a total of 28,753 hospitalized TB patients, 567 cases (2.0%) were confirmed as ATB-DILI and were included in the final analysis. We extracted data from electronic health records, which included demographic characteristics, inpatient diagnoses, medical histories, laboratory results, and medical treatment information. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[12] Ethical approval was granted by the Institutional Review Board of Beijing Chest Hospital, and the requirement for informed consent was waived by the same committee.

Study Population

Inclusion criteria for patients with active TB: (1) no restrictions on age or gender; (2) no restrictions on lesion sites, including pulmonary and extrapulmonary sites; (3) diagnosis of TB by clinical or laboratory criteria. Exclusion criteria: (1) patients with malignant tumors who are receiving concurrent radiotherapy, chemotherapy, or immunotherapy; (2) co-infection with non-TB mycobacteria; (3) co-infection with HIV; (4) pregnancy; (5) ICU patients were also excluded due to their complex clinical conditions and polypharmacy, which may confound the attribution of liver injury to anti-TB drugs. Patients with repeat hospitalizations were only included in the hospitalization where peak liver function was observed.

Diagnostic Criteria for ATB-DILI

The diagnostic criteria were based on the Chinese guidelines for ATB-DILI and implemented through a two-step process:[13] First, liver injury was identified according to biochemical criteria, meeting either of the following: (1) alanine aminotransferase (ALT) $\geq 3 \times$ upper limit of normal (ULN) and/or total bilirubin (TBIL) $\geq 2 \times$ ULN; or (2) concurrent elevation of aspartate aminotransferase (AST), alkaline phosphatase (ALP), and TBIL, with at least one value $\geq 2 \times$

ULN. Abnormal liver function is defined as an elevation of liver enzymes that does not meet the above criteria. The ULN values used in our laboratory are 40 IU/L for ALT, 40 IU/L for AST, 150 IU/L for ALP, and 20.5 μmol/L for TBIL. Second, to confirm anti-tuberculosis drugs as the causative agent, we applied the updated Roussel Uclaf Causality Assessment Method (RUCAM), a validated tool for DILI attribution.[14,15] Patients with a RUCAM score of ≥6 were included in the study. To enhance diagnostic specificity, we rigorously excluded cases with: (1) cirrhosis, such as alcoholic cirrhosis, hepatitis B cirrhosis, and hepatitis C cirrhosis; (2) liver transplantation status or liver abscess; (3) intra- and extra-hepatic bile duct obstruction, such as biliary stones, bile duct stenosis, and bile duct obstruction or compression; (4) recent history of hypotension, right heart failure, septicemia, and total parenteral nutrition; (5) liver injury from non-anti-TB drugs, such as herbal medicines, cold remedies, NSAIDs; and (6) poorly documented medication history.

Types of Drug-Induced Liver Injury

According to the R value [R value = (serum ALT/ALT ULN)/ (serum ALP/ALP ULN)].[16,17] Cases were classified as "hepatocellular" if the R value was ≥5, "cholestatic" if the R value was ≤2, and "mixed" if the R value was 2–5.

Definition and Criteria for Severe ATB-DILI

Severe liver injury is defined based on the peak liver function index meeting any of the following criteria:[18] (1) elevated serum ALT or AST >3 × ULN, serum TBIL >2 × ULN, and serum ALP <2 × ULN; and (2) international normalized ratio (INR) ≥1.5, with TBIL levels >2 × ULN. Both definitions represent severe acute liver injury and are used by the US Food and Drug Administration's Sentinel System to assess drug-induced acute liver injury in post-marketing clinical settings.[19] Criterion (1) follows Hay's Law biochemical standards,[20,21] indicating hepatocellular injury severe enough to affect bilirubin excretion and increase the risk of mortality.[22,23] Criterion (2) highlights liver function abnormalities that may occur in the late stages of acute liver failure, where hepatic transaminases may not yet be elevated enough to meet the first criterion. The potential preemptive use of anticoagulants should be excluded when assessing criterion (2).

Definition for Anaphylactic Reactions Due to Anti-Tuberculosis Drugs

Eosinophilia is defined as a serum eosinophil count exceeding 4% to 6% of the total white blood cell count, depending on the normal reference range for each hospital. In our laboratory, the upper normal limit is 5%. Lymphopenia is defined as serum lymphocyte levels <10%, both based on blood tests conducted when diagnosing ATB-DILI. The rash is an acute skin condition involving skin texture or color changes, which may present as inflammation or hypersensitivity. Allergy at the time of ATB-DILI diagnosis is identified if any of the following symptoms are present: drug fever, rash, eosinophilia, lymphopenia, or arthralgia.[24]

Risk Factors for Severe ATB-DILI

Risk factors investigated for severe ATB-DILI included age, gender, history of alcohol consumption, smoking history, comorbidities (such as diabetes and hypertension), allergic reactions, time from drug exposure to DILI recognition, type of liver injury, use of prophylactic hepatoprotective agents, and prior history of ATB-DILI. The interval between drug exposure and DILI onset was defined as the number of days from the initiation of anti-TB therapy (day 0) to the appearance of the first clinical symptom, physical sign, or abnormal laboratory finding indicative of liver injury.[15]

Statistical Analyses

Data analysis was performed using SPSS version 29.0 software. Quantitative data are presented as either the mean ± standard deviation (Mean ± SD) or median with interquartile range (Median [IQR]), based on the data distribution. The independent samples *t*-test or Mann–Whitney *U*-test was applied appropriately for comparisons between the two groups. For comparisons involving multiple groups, one-way analysis of variance (ANOVA) or the Kruskal–Wallis test was used. Categorical variables are presented as frequencies and percentages, with group differences assessed using the chi-square test (χ^2) or Fisher's exact test. Variables with $p < 0.1$ in univariate analysis were included in a multivariate logistic regression model, with stepwise selection for variable inclusion. A two-tailed p-value of less than 0.05 was considered

statistically significant. Post hoc power analysis was conducted using PASS 2021 based on the observed odds ratios and actual sample sizes. Furthermore, subgroup analyses were performed to evaluate the association between age and severe ATB-DILI within each liver injury subtype (hepatocellular, cholestatic, and mixed) using univariate logistic regression models. To address multiple comparisons in subgroup analyses, Bonferroni correction was applied (adjusted α=0.0167).

Results

Study Population and Case Selection

A total of 28,753 hospitalized patients with active TB who received anti-TB treatment were initially assessed for eligibility. Among them, 3233 patients (11.2%) exhibited abnormal liver function based on blood biochemical tests, and 930 (3.2%) were clinically diagnosed with liver injury. After excluding 363 cases with alternative causes of liver injury, as determined by the RUCAM criteria, 567 patients (2.0% of the total population) were confirmed or highly suspected to have ATB-DILI. These 567 cases constituted the final sample included in the present study. The detailed inclusion and exclusion process is illustrated in Figure 1.

Demographic and Clinical Characteristics of Patients with ATB-DILI

The distribution of anti-TB regimens among the 567 ATB-DILI patients, categorized by liver injury pattern, severity, and allergic manifestations, is presented in Table 1. The median age was 44 years (IQR: 28.0–62.0), with a predominance of male patients (356, 62.8%). Most patients (67.0%) received prophylactic hepatoprotective agents. Comorbid conditions included diabetes mellitus (15.0%) and hypertension (14.1%). A prior history of ATB-DILI was documented in 7.2% of

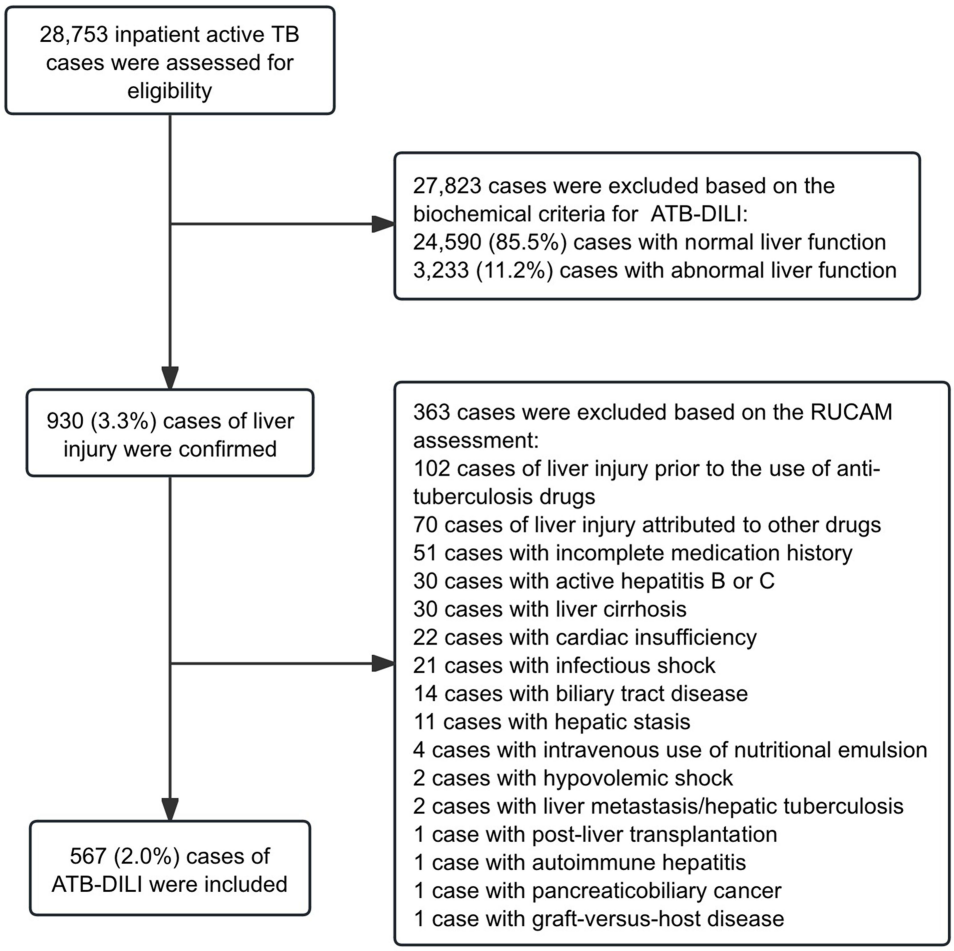

Figure 1 Patient inclusion and exclusion flowchart for ATB-DILI.

Table 1 Distribution of the Anti-TB Regimens in 567 Cases of ATB-DILI According to the Type of Liver Damage, Severity of Hepatic Injury, and Presence of Allergy

Drug Regimens	Total Cases (N)	Type of Liver Injury (N)			Allergy (N)	Severe Liver Injury (N)
		Hepatocellular	Cholestatic	Mixed		
HRZE	245	203	14	28	96	14
HRZE+ Lfx	55	43	5	7	19	4
HRZE + Mfx	31	18	7	6	10	3
HR ± FQs	57	26	17	14	23	9
HRftZE ± FQs	39	25	7	7	9	3
HRftE ± FQs	25	8	14	3	13	4
HZ ± FQs	14	11	2	1	4	0
RZ ± FQs	10	10	0	0	7	1
H ± FQs	4	3	1	0	3	0
Includes Z, not HR	5	3	1	1	2	1
Other regimens include second-line drugs	82	56	9	17	35	7

Notes: The HRZE group includes 11 patients who received the HRZE fixed-dose combination (FDC), a single-tablet formulation containing isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E).

Abbreviations: H, isoniazid; R, rifampicin Z, pyrazinamide; E, ethambutol; Lfx, levofloxacin; Mfx, moxifloxacin; FQs, fluoroquinolones, including levofloxacin and moxifloxacin; Rft, rifapentine.

patients, and 6.9% reported previous allergic reactions to anti-TB drugs. Most patients (85.5%) were undergoing initial treatment, while 14.5% were receiving retreatment. Regarding TB classification, pulmonary TB was diagnosed in 49.4%, extrapulmonary TB in 21.0%, and both forms in 29.6% of patients. The median latency from drug exposure to liver injury onset was 20 days (IQR: 11.0–36.0). Clinical manifestations included gastrointestinal symptoms (35.1%), jaundice (18.2%), drug rash (9.5%), drug fever (9.5%), and other discomforts (3.9%). Notably, 68.4% (388 patients) were asymptomatic and were identified solely through abnormal liver biochemical markers during routine monitoring (Tables 2 and 3).

Table 2 Characteristics of Subjects With Different Patterns of ATB-DILI

	Entire Cohort (N=567)	Hepatocellular (N= 406, 71.6%)	Cholestatic (N= 77, 13.6%)	Mixed (N=84, 14.8%)	p-value
Age, y, IQR	44.0 (28.0–62.0)	37.0 (26.0–57.0)	66.0 (46.0–75.5)	47.5 (29.0–66.8)	<0.001
Age group, y (%)					<0.001
<30	162 (28.6)	134 (33.0)	6 (7.8)	22 (26.2)	
30–59	251 (44.3)	191 (47.0)	28 (36.4)	32 (38.1)	
≥60	154 (27.2)	81 (20.0)	43 (55.8)	30 (35.7)	
Male sex (%)	356 (62.8)	250 (61.6)	49 (63.6)	57 (67.9)	0.548
Location (%)					0.715
Urban	347 (61.2)	252 (62.1)	44 (57.1)	51 (60.7)	
Rural	220 (38.8)	154 (37.9)	33 (42.9)	33 (39.3)	

(*Continued*)

Table 2 (Continued).

	Entire Cohort (N=567)	Hepatocellular (N= 406, 71.6%)	Cholestatic (N= 77, 13.6%)	Mixed (N=84, 14.8%)	p-value
Body mass index, kg/m², IQR	20.7 (18.6–23.3)	20.8 (18.6–23.2)	20.1 (18.4–23.2)	20 (18.7–23.7)	0.455
Prophylactic use of hepatoprotectants (%)	380 (67.0)	265 (65.3)	57 (74.0)	58 (69.0)	0.305
Previous history of ATB-DILI (%)	41 (7.2)	30 (7.4)	6 (7.8)	5 (6.0)	0.880
A history of allergy to anti-TB drugs (%)	39 (6.9)	34 (8.4)	2 (2.6)	3 (3.6)	0.101
Current smoking (%)	148 (26.1)	100 (24.6)	25 (32.5)	23 (27.4)	0.342
Alcohol use (%)	73 (12.9)	50 (12.3)	12 (15.6)	11 (13.1)	0.733
Type of treatment (%)					0.069
Initial treatment	485 (85.5)	356 (87.7)	62 (80.5)	67 (79.8)	
Re-treatment	82 (14.5)	50 (12.3)	15 (19.5)	17 (20.2)	
Comorbidities (%)					
Diabetes mellitus	85 (15.0)	53 (13.1)	17 (22.1)	15 (17.9)	0.092
Renal Insufficiency	14 (2.5)	5 (1.2)	4 (5.2)	5 (6.0)	0.006
Hypertension	80 (14.1)	39 (9.6)	23 (29.9)	18 (21.4)	<0.001
Cardiovascular disease	45 (7.9)	21 (5.2)	10 (13.0)	14 (16.7)	<0.001
Fatty Liver Disease[a]	63 (11.1)	47 (11.6)	8 (10.4)	8 (9.5)	0.842
Biliary tract disease[b]	25 (4.4)	15 (3.7)	6 (7.8)	4 (4.8)	0.229
Current TB (%)					0.331
Pulmonary TB	280 (49.4)	209 (51.5)	35 (45.5)	36 (42.9)	
Extrapulmonary TB	119 (21.0)	79 (19.5)	16 (20.8)	24 (28.6)	
Both pulmonary and extrapulmonary TB	168 (29.6)	118 (29.1)	26 (33.8)	24 (28.6)	

Notes: a and b are both patients with abnormal findings by imaging (ultrasound or abdominal CT) during hospitalization for patients with fatty liver and biliary tract disease with normal baseline liver function.

Table 3 Clinical Pictures and Laboratory Tests With Different Patterns of ATB-DILI

	Entire Cohort (N=567)	Hepatocellular (N=406, 71.6%)	Cholestatic (N=77, 13.6%)	Mixed (N=84, 14.8%)	p-value
Days between exposure and DILI recognition, d, IQR	20.0 (11.0–36.0)	20.0 (11.0–36.0)	20.0 (9.5–41.5)	17.0 (9.3–36.8)	0.679
Clinical manifestations (%)					
Digestive Tract Symptoms	199 (35.1)	135 (33.3)	37 (48.1)	27 (32.1)	0.037
Drug Rash	54 (9.5)	39 (9.6)	7 (9.0)	8 (9.5)	0.990
Drug Fever	54 (9.5)	41 (10.1)	3 (3.9)	10 (11.9)	0.154
Jaundice	103 (18.2)	29 (7.1)	54 (70.1)	20 (23.8)	<0.001
Other discomforts	22 (3.9)	13 (3.2)	7 (9.1)	2 (2.4)	0.056
No complaints	388 (68.4)	316 (77.8)	19 (24.7)	53 (63.1)	<0.001

(*Continued*)

Table 3 (Continued).

	Entire Cohort (N=567)	Hepatocellular (N=406, 71.6%)	Cholestatic (N=77, 13.6%)	Mixed (N=84, 14.8%)	p-value
Blood routine examination					
WBC, $\times10^9$/L, IQR	5.8 (4.7–7.7)	5.6 (4.6–7.0)	7.3 (5.3–1.2)	6.5 (4.9–8.7)	<0.001
HB, g/L, IQR	125.0 (112.0–139.0)	129.0 (117.0–141.3)	109.0 (96.0–125.0)	123.0 (105.0–133.8)	<0.001
PLT, $\times10^9$/L, IQR	226.0 (180.0–296.0)	223.5 (181.8–286.5)	216.0 (158.5–306.5)	242.5 (181.5–368.8)	0.089
Absolute eosinophils, $\times10^9$/L, IQR	0.13 (0.06–0.26)	0.14 (0.07–0.28)	0.06 (0.01–0.12)	0.14 (0.06–0.25)	<0.001
Biochemical indicators, peak values, IQR					
ALT, U/L, IQR	186.0 (135.0–306.0)	229.5 (157.0–391.0)	37.0 (17.0–78.5)	144 (122.3–176.5)	<0.001
AST, U/L, IQR	174.0 (103.0–314.0)	200 (119.5–348.5)	88.5 (35.5–162.8)	145.5 (77.8–250.3)	<0.001
ALP, U/L, IQR	96.0 (75.0–137.0)	88.0 (71.0–107.0)	162.0 (94.5–288.0)	136.0 (112.0–184.0)	<0.001
GGT, U/L, IQR	74.4 (45.8–129.4)	66.0 (43.1–102.8)	126.6 (53.4–310.0)	117.9 (68.3–208.0)	<0.001
TBIL, μmol/L, IQR	14.6 (9.5–29.0)	12.8 (8.9–18.5)	48.1 (36.0–58.6)	16.1 (9.1–40.2)	<0.001
TBA, μmol/L, IQR	9.3 (4.7–21.7)	8.3 (4.4–17.3)	20 (7.2–77.9)	11.2 (5.6–30.2)	<0.001
Albumin, g/L, IQR	36 (31.5–39.5)	37.4 (33.2–40.6)	29.0 (26.0–33.2)	34.1 (29.2–38.0)	<0.001
Serum Iron, μmol/L, IQR	11.2 (6.8–16.5)	11.9(7.8–16.6)	8.7 (5.3–14.2)	9.8 (5.4–16.9)	0.015
INR, IQR	1.1 (1.0–1.2)	1.1(1.0–1.2)	1.1 (1.0–1.3)	1.0 (1.0–1.1)	0.037
PTA, %, IQR	78.3 (64.6–88.6)	78.8 (65.0–89.6)	75.3 (59.0–85.5)	80.2 (65.9–89.6)	0.375
Fits Hy's law (%)	46 (8.1)	27 (6.7)	11 (14.3)	8 (9.5)	0.070
Acute liver failure (%)	8 (1.4)	7 (1.7)	0 (0)	1 (1.2)	0.849
Severe liver injury (%)	46 (8.1)	27 (6.7)	11 (14.3)	8 (9.5)	0.070

Notes: Gastrointestinal symptoms include abdominal discomfort, nausea, vomiting, poor appetite, and diarrhea; Other discomforts include malaise, fatigue, joint pain, and bleeding spots on the skin.
Abbreviations: WBC, white blood cell; HB, hemoglobin; PLT, platelet; GGT, γ-glutamyl transferase; TBA, total bile acids; PTA, prothrombin time activity.

Demographic and Clinical Characteristics Stratified by Liver Injury Patterns

As presented in Tables 2 and 3, the hepatocellular type of liver injury was the most prevalent, accounting for 71.4% of cases, while cholestatic and mixed types comprised 13.8% and 14.8%, respectively. Patients with hepatocellular injury were significantly younger ($p < 0.001$) and less likely to exhibit clinical jaundice, with the majority (77.8%) being asymptomatic. In contrast, patients with cholestatic liver injury were older and more likely to present with pronounced jaundice (69.2%) and prominent gastrointestinal symptoms. The mixed liver injury type demonstrated intermediate characteristics between hepatocellular and cholestatic injuries in terms of patient age. No statistically significant differences were observed among the liver injury types in terms of gender, body mass index, prophylactic hepatoprotective use, incubation period, smoking, alcohol consumption, types of TB or severity of liver injury (all $p > 0.05$). Laboratory analysis revealed that patients with hepatocellular injury had significantly higher levels of ALT, albumin, and serum iron (all $p < 0.05$), whereas patients with cholestatic or mixed injury exhibited higher levels of ALP, GGT, TBIL, and TBA (all $p < 0.001$).

Comparisons Between Severe and Non-Severe ATB-DILI

Severe liver injury in this study was evaluated based on Hy's law and diagnostic criteria for acute liver failure. The findings revealed that Hy's law was effective in identifying patients with acute liver failure. Among the 567 patients

diagnosed with ATB-DILI, 46 (8.1%) were identified as having severe liver injury. The median age of patients with severe liver injury was 58 years (IQR: 39.0–70.3), which was significantly older than the median age of 43 years (IQR: 28.0–60.0) for patients with non-severe liver injury ($p < 0.001$). The severe liver injury group exhibited higher proportions of cholestatic and mixed liver injury types compared to the hepatocellular type ($p = 0.043$). No significant differences ($p > 0.05$) were observed between severe and non-severe ATB-DILI groups in terms of gender, urban versus rural residency, use of prophylactic hepatoprotective drugs, prior history of ATB-DILI, smoking history, alcohol consumption, or types of TB (Table 4).

Multivariable logistic regression analysis was performed on variables with $P < 0.1$ in the univariate analysis (including age ≥60 years and liver injury type). The analysis identified age ≥60 years as an independent risk factor for severe ATB-DILI (OR = 2.45, 95% CI: 1.33–4.52, $p = 0.004$). Post hoc power analysis for the logistic regression model

Table 4 Demographic Characteristics, Clinical and Laboratory Findings With Non-Severe ATB-DILI Versus Patients With Severe ATB-DILI

	Entire Cohort (N=567)	Non-Severe ATB-DILI (N= 521, 91.9%)	Severe ATB-DILI (N=46, 8.1%)	p-value
Age, y, IQR	44.0 (28.0–62.0)	43.0 (28.0–60.0)	58.0(39.0–70.3)	<0.001
Male sex (%)	356 (62.8)	329 (63.1)	27 (58.7)	0.549
Location (%)				0.320
Urban	347 (61.2)	322 (61.8)	25 (54.3)	
Rural	220 (38.8)	199 (38.2)	21 (45.7)	
Body mass index, kg/m², IQR	20.7 (18.6–23.3)	20.6 (18.6–23.2)	21.6 (18.4–24.1)	0.196
Prophylactic use of hepatoprotectants (%)	380 (67.0)	350 (67.2)	30 (65.2)	0.786
Previous history of ATB-DILI (%)	41 (7.2)	37 (7.1)	4 (8.7)	0.565
Current smoking (%)	148 (26.1)	132 (25.3)	16 (34.8)	0.162
Alcohol use (%)	73 (12.9)	66 (12.7)	7 (15.2)	0.621
Comorbidities (%)				
Diabetes mellitus	85 (15)	77 (14.8)	8 (17.4)	0.634
Hypertension	80 (14.1)	70 (13.4)	10 (21.7)	0.121
Fatty Liver Disease	63 (11.1)	55 (10.6)	8 (17.4)	0.157
Days between exposure and DILI recognition, IQR	20.0 (11.0–36.0)	20.0 (10.0–36.0)	28.0 (13.8–39.3)	0.187
Treatment type, (%)				0.143
Initial treatment	485 (85.5)	449 (86.2)	36 (78.3)	
Re-treatment	82 (14.5)	72 (13.8)	10 (21.7)	
Jaundice (%)	103 (18.2)	57 (10.9)	46 (100.0)	<0.001
Allergy (%)	221 (39.0)	200 (38.4)	21 (45.7)	0.333
Pattern of liver injury (%)				0.043
Hepatocellular damage	406 (71.6)	379 (72.7)	27 (58.7)	
Cholestatic & Mixed damage	161 (28.4)	142 (27.3)	19 (41.3)	

(*Continued*)

Table 4 (Continued).

	Entire Cohort (N=567)	Non-Severe ATB-DILI (N= 521, 91.9%)	Severe ATB-DILI (N=46, 8.1%)	p-value
Current TB (%)				0.422
Pulmonary TB	280 (49.4)	258 (49.5)	22 (47.8)	
Extrapulmonary TB	119 (21.0)	112 (21.5)	7 (15.2)	
Both pulmonary and extrapulmonary TB	168 (29.6)	151 (29.0)	17 (37.0)	
Blood routine examination, IQR				
WBC, $\times 10^9$/L, IQR	5.8 (4.7–7.7)	5.8 (4.7–7.5)	6.2 (4.5–8.9)	0.603
HB, g/L, IQR	125.0 (112.0–139.0)	125.0 (112.0–139.0)	123.0 (115.8–258.0)	0.922
PLT, $\times 10^9$/L, IQR	226.0 (180.0–296.0)	229.0 (183.5–299.5)	186.5 (131.8–258.0)	0.003
Biochemical indicators, peak values, IQR				
ALT, U/L, IQR	187.0 (136.0–306.0)	184.0 (137.5–297.0)	272.0 (87.8–511.0)	0.175
AST, U/L, IQR	174.0 (103.0–314.0)	168.0 (100.0–292.5)	324.5 (168.0–675.5)	<0.001
AST/ALT, IQR	0.9 (0.6–1.4)	0.9 (0.6–1.4)	1.4 (0.8–2.7)	<0.001
ALP, U/L, IQR	96.0 (75.0–137.0)	94.0 (74.0–129.5)	131.5 (103.8–164.5)	<0.001
TBIL, μmol/L, IQR	14.6 (9.5–29.0)	13.7 (9.2–23.0)	55.4 (49.1–89.8)	<0.001
TBA, μmol/L, IQR	9.3 (4.7–21.7)	8.5 (4.4–17.9)	124.9 (32.2–234.8)	<0.001
INR, IQR	1.1 (1.0–1.2)	1.0 (1.0–1.1)	1.3 (1.2–1.5)	<0.001
Albumin, g/L, IQR	36 (31.5–39.5)	36.5 (31.9–39.9)	30.8 (28.2–35.9)	<0.001
Serum Iron, μmol/L, IQR	11.2 (6.8–16.5)	10.7 (6.7–15.8)	13.7 (9.2–24.4)	0.008

indicated sufficient statistical power (81.8%) to detect the observed effect size (Table 5). We further assessed the relationship between age and severe ATB-DILI in different subgroups of liver injury types. Among patients with hepatocellular injury, those age ≥60 years had a significantly higher risk of severe ATB-DILI compared to those age <60 years (unadjusted OR = 3.59, 95% CI: 1.61–8.02, p = 0.002). In contrast, no statistically significant association was observed in patients with cholestatic or mixed liver injury patterns (Figure 2).

Table 5 Non-Biochemical Variables Independently Associated With Severe ATB-DILI

Independent Variables	Coefficient	SE	Wald $\chi 2$	OR (95% CI)	p-value
Age ≥ 60	0.90	0.31	8.22	2.45 (1.33–4.52)	0.004

Note: Post hoc power was 81.8%.
Abbreviations: CI, confidence interval; OR, odds ratio.

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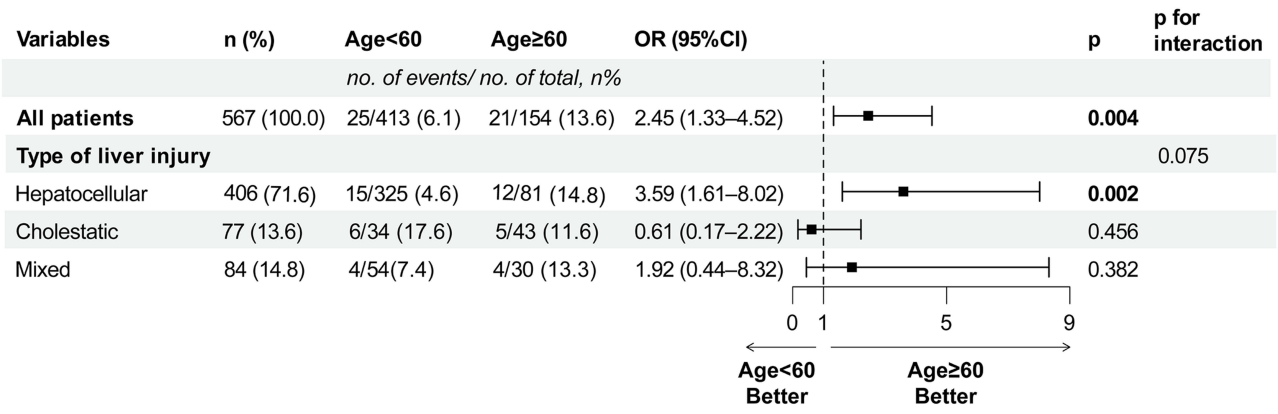

Figure 2 Effect of age on severe ATB-Dili according to different types of liver injury. Shown are subgroup-specific odds ratios for all the patients and for those who were hepatocellular, cholestatic, or mixed liver injury. Odds ratios are plotted as squares, the horizontal lines represent 95% confidence intervals. Bold p-values indicate statistical significance ($p < 0.05$). Post hoc power analysis indicated that the statistical power for detecting associations in the hepatocellular group was 89.7% (or 76.2% after Bonferroni correction), whereas the cholestatic and mixed groups had limited power (23.1% and 34.5%, respectively).

Discussion

In this Chinese hospitalized cohort of 28,753 patients with active TB, 2.0% had ATB-DILI. However, this finding may not be directly generalizable to other populations due to differences in region, genetics, lifestyle, and medical practices. The observed result is lower than the cumulative incidence of ATB-DILI reported in a previous Chinese cohort study, which was 2.55% (95% CI: 2.04%-3.06%),[25] and the 5.4% incidence found in another cohort study of 3155 patients.[26] These differences may be attributed to variations in study design and methodology. In this study, a retrospective analysis combined with a rigorous review of electronic medical records and causality assessments ensured the inclusion of only liver injury cases occurring during hospitalization. Consequently, the overall incidence of ATB-DILI may have been underestimated. Furthermore, the study encompassed patients receiving both first-line and second-line anti-TB regimens, reflecting real-world medication practices and potentially mitigating drug-related biases. In comparison, international studies report varying ATB-DILI incidences: a single-center study in the UK found a prevalence of 6.9%,[27] a study in Thailand reported 6.4%,[28] and a tertiary hospital in South Korea documented an incidence of 11.9%.[29] These discrepancies are likely due to differences in study populations, diagnostic criteria, and treatment protocols, highlighting the challenges of cross-study comparisons.

The diagnosis of DILI remains challenging, primarily relying on exclusionary criteria, which can result in misdiagnosis.[30] This study addressed the limitations of traditional DILI reporting systems by systematically excluding non-drug-related causes of liver injury. A UK study previously demonstrated that nearly 50% of adverse liver reactions initially attributed to drugs were ultimately found to have non-drug-related causes upon thorough evaluation.[31] Additionally, prescribing habits in China, including the widespread use of traditional Chinese medicine and herbal therapies, as well as high rates of self-medication, add complexity to DILI diagnosis. In this study, 70 patients were found to have liver injury caused by non-anti-TB drugs, while liver injury in another 102 patients occurred before anti-TB treatment, emphasizing the importance of careful evaluation.

Early recognition and management of DILI are critical for improving patient outcomes.[32] Most ATB-DILI events (87%) occur within the first two months of anti-TB treatment when four first-line drugs are typically used in combination.[27] Routine liver function monitoring every two weeks has been shown to detect ATB-DILI early and may also help predict late-onset DILI in patients undergoing anti-tuberculosis treatment.[33] Observational studies have also demonstrated that regular liver function monitoring every 2–4 weeks during the initial weeks of treatment can facilitate early detection of DILI, prevent progression to severe liver injury, and ultimately improve patient outcomes.[34] In our study, the median time between the initiation of treatment and the onset of liver injury was 20 days (IQR: 11–36). Notably, 68.4% of patients exhibited no apparent clinical symptoms, and liver injury in these cases was identified solely through routine biochemical surveillance. This supports previous evidence and underscores the importance of early liver function tests in diagnosing ATB-DILI.

In our cohort, hepatocellular injury was the predominant form of ATB-DILI, accounting for 71.4% of cases. This is consistent with previous DILI studies in China, which reported hepatocellular injury in 51.4% of cases, though our proportion is notably higher.[35] We further found that the hepatocellular pattern was more common in younger patients, while cholestatic injury tended to occur in older individuals. This age-related pattern of liver injury aligns with findings from other DILI studies,[24,36] but contrasts with a study conducted in Pakistan.[37] However, the exact underlying mechanisms require further investigation. Previous studies have shown that cholestatic DILI is strongly associated with chronic DILI progression and adverse outcomes, including acute liver failure and increased mortality.[11] Malnutrition and low hemoglobin levels have also been linked to a higher risk of severe ATB-DILI.[38] In our study, severe ATB-DILI occurred in 46 patients (8.1%), with advanced age (≥60 years) identified as an independent risk factor.

To further explore the interaction between age and severe ATB-DILI, we performed subgroup analyses. A significant association between advanced age and severe ATB-DILI was observed in the hepatocellular subgroup (OR = 3.59, p = 0.002), while the association did not reach statistical significance in the cholestatic or mixed types. However, post hoc power analysis revealed that these subgroups were underpowered (cholestatic: 23.1%, mixed: 34.5%), and the absence of significance should be interpreted with caution. The borderline interaction p-value (p = 0.075) indicates a potential modification effect by injury type. This emphasizes the importance of age-based risk stratification, particularly in patients with hepatocellular-type ATB-DILI. These findings contribute nuanced evidence to an area with limited prior data. While hepatocellular injury appears more common and strongly associated with age-related severity, we cannot exclude similar risks in other subtypes due to statistical limitations. Future studies with larger subgroup sizes are warranted to validate these trends.

Several studies have highlighted hyperbilirubinemia as an independent predictor of mortality in patients with DILI.[39] In the present study, jaundice was observed in 18.2% of patients, which is like the 15.9% reported in another study,[26] but lower than in other centers that reported higher mortality rates.[39] This difference may be attributable to an earlier diagnosis of liver injury in the current study. Our study found no statistically significant difference in the use of prophylactic hepatoprotective drugs between patients with severe and non-severe ATB-DILI. This phenomenon may be attributed to inter-individual variability and differential responses to hepatoprotective agents among patients with different patterns of liver injury. The efficacy of prophylactic hepatoprotective drugs has been a topic of considerable debate. Some retrospective studies have failed to demonstrate a significant reduction in the risk of ATB-DILI associated with their use,[40] while others have reported potential benefits in preventing liver injury during anti-tuberculosis treatment.[41,42] These conflicting findings highlight the need for further research to clarify the role of hepatoprotective drugs in managing ATB-DILI. Moreover, while ATB-DILI generally has a favorable prognosis, approximately 5% of cases may progress to acute liver failure.[26] In our study, 46 patients (8.1%) fulfilled Hy's law criteria, and 8 patients (1.4%) were diagnosed with acute liver failure. A multicenter prospective study in the United States over a decade ago identified standard anti-TB treatment as the leading cause of drug-induced acute liver failure, with 40% of cases requiring liver transplantation and 32% resulting in death.[43] However, with improved medical care and increased awareness of ATB-DILI, a lower incidence of severe liver injury was observed in our study, consistent with previous reports.[25,26]

This study has several limitations. First, as a single-center retrospective analysis lacking long-term follow-up data, it is subject to selection bias and limited generalizability. We were unable to assess clinical outcomes such as mortality or liver function recovery, which restricts the comprehensive evaluation of disease severity. Second, the cohort consisted of patients from a tertiary care hospital, whose characteristics may not reflect those in primary or community settings. Third, reliance on inpatient data may have excluded milder or outpatient ATB-DILI cases, potentially underestimating the true prevalence. Additionally, the small number of severe cases in the cholestatic and mixed subgroups limited statistical power, raising the possibility of type II error. Future multicenter studies with larger and more diverse populations are needed to validate the age-related risk across all liver injury types.

Conclusion

In conclusion, this retrospective study of hospitalized TB patients in China revealed that ATB-DILI occurs in approximately 2.0% of cases, with hepatocellular injury being the predominant pattern. Most patients were asymptomatic and diagnosed through routine biochemical monitoring. Advanced age (≥ 60 years) was identified

as an independent risk factor for severe ATB-DILI. Subgroup analysis showed that this association was significant in the hepatocellular injury type, while the associations in the cholestatic and mixed types did not reach statistical significance, this may reflect limited statistical power in these subgroups. These findings suggest that in clinical practice, enhanced liver function monitoring and early identification of liver injury should be prioritized in elderly patients receiving anti-tuberculosis therapy. Future research should prioritize prospective, multicenter designs to validate these associations and improve risk stratification tools.

Data Sharing Statement

The data supporting the findings of this study are included in the article. Further inquiries can be directed to the corresponding authors.

Ethics Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee of Beijing Chest Hospital approved the study. Given the retrospective study design and the use of anonymized patient data, the requirement for informed consent was waived.

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Disclosure

The authors declare that there are no commercial or financial relationships that could be perceived as a potential conflict of interest in relation to this research.

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