Drug-Induced Liver Injury from Anti-Tuberculosis Treatment: A Retrospective Cohort Study

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Background: The aim of this study was to investigate the clinical characteristics and the risk factors associated with anti-tuberculosis (anti-TB) drug-induced liver injury (DILI).

Material/Methods: This retrospective study enrolled 140 hospitalized patients diagnosed with anti-TB DILI during January 2009 to December 2015. We assessed the baseline characteristics and performed regular follow-up up to the 24th week to assess the possible risk factors associated with the condition.

Results: The study population was 58.6% male and 41.4% female patients; 20.7% were diagnosed with grades 4–5 DILI and 79.3% with grades 1–3 DILI. Female patients were significantly more likely to be diagnosed with grades 4–5 DILI than with grades 1–3 DILI (58.6% *vs.* 36.9%, p=0.036). Patients treated with a multidrug anti-TB regimen were more commonly affected with grades 4–5 DILI (86.2% *vs.* 68.5%, p=0.045). A significant number of patients who reinitiated anti-TB therapy suffered severe liver injury in comparison to patients with grades 1–3 DILI (41.4% *vs.* 10.8%, P<.001). Laboratory examinations revealed significantly higher values for total bilirubin (TBL), International normalized ratio (INR), and Hy's law (P<.001) in the grades 4–5 group compare to the grades 1–3 group.

Conclusions: Female gender, combination therapy for antitubercular drugs (isoniazid, rifampicin and pyrazinamide), re-challenge were the risk factors associated with the severity of anti-TB DILI.

MeSH Keywords: Antitubercular Agents • Drug-Induced Liver Injury • Liver Failure

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Background

Tuberculosis (TB) is a chronic infection of global health concern due to the burden of high incidence, medical expenses, drug resistance, and coinfections [1]. China reports the second highest incidence of TB reported worldwide. with up to 1 300 000 new cases reported each year [2].

A combination of isoniazid (INH), rifampicin, pyrazinamide, and ethambutol is the commonly recommended treatment regimen for TB. However, drug-induced liver injury (DILI) is a major adverse event of anti-TB treatment, leading to nonadherence, treatment failure, or development of drug resistance. Globally, anti-TB DILI is reported in 2% to 28% [3] of patients according to various definitions, study populations, and treatment regimens, with China reporting an incidence rate of 2.55% [4].

The clinical features of anti-TB DILI can vary from mild asymptomatic elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to acute hepatitis or even liver failure. Although many studies have revealed the clinical features and outcomes of anti-TB DILI [3], the results have failed to explain the relationships between clinical and biochemical characteristics and outcomes of anti-TB DILI. The aim of the present retrospective study was to assess the clinical features, biochemical characteristics, and the outcomes of anti-TB DILI by following up these patients for 24 weeks.

Material and Methods

Study design and population

This was a single-center, retrospective cohort study conducted at the Liver Disease Center of Beijing Ditan Hospital. We enrolled 140 TB patients who were hospitalized with a diagnosis of drug-induced liver injury during anti-tubercular treatment between January 2009 and December 2015.

Patients ages 15–80 years were included in the study if they had: (1) normal liver function prior to the initiation of anti-tubercular treatment; (2) clinical symptoms of anti-tuberculosis drug-induced hepatotoxicity including fatigue, gastrointestinal disturbances, jaundice, or allergic manifestations; (3) abnormal liver function test; and (4) Roussel Uclaf Causality Assessment Method (RUCAM) simplified version [5] score of ≥6.

Exclusion criteria were: liver abnormalities prior to anti-tubercular treatment, including viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease, Wilson's disease, autoimmune liver disease, unexplained liver function abnormalities; malnourished patients; patients with chronic diseases such as HIV infection, severe cardiovascular and/or cerebrovascular

diseases, chronic renal insufficiency; and patients who could not participate in follow-up on time.

The study protocol was approved by the Institutional Review Board (IRB) of Beijing Ditan Hospital and conformed to the standards of the Declaration of Helsinki and its subsequent revisions.

Clinical classification of drug-induced liver injury

Based on the modified criteria for DILI [3] and the criteria established by the Chinese Medical Association, we categorized the patients into 3 categories [6]:

(1) hepatocellular injury, ALT ≥3×ULN and ALT/ALP ≥5; (2) cholestatic injury, ALP ≥2×ULN and ALT/ALP ≤2; (3) hepatocellular-cholestatic mixed injury, ALT ≥3×ULN, ALP ≥2×ULN and 2< ALT/ALP <5.

Classification criteria for the severity of drug-induced liver injury

Based on the different expert opinions put forward, we classified the severity of acute DILI into 5 grades [6]:

Grade 1 (mild liver injury): The patient's serum level of alanine transferase or alkaline phosphatase is elevated, but total bilirubin (TBIL) <2.5 ULN, and without coagulation dysfunction (International normalized ratio (INR) <1.5);

Grade 2 (moderate liver injury): Patients with elevated serum levels of alanine transferase or alkaline phosphatase, and TBIL ≥2.5 ULN or coagulation dysfunction (INR ≥1.5) despite lack of hyperbilirubinemia;

Grade 3 (severe liver injury): elevated serum aminotransferase and/or alkaline phosphatase, TBIL ≥5ULN, with or without INR ≥1.5 and requiring hospitalization for drug-induced liver injury (or prolonged hospitalization);

Grade 4 (acute liver failure): Evidence of coagulation abnormality indicated by INR ≥1.5 or PTA (prothrombin activity) <40%, signs of hepatic encephalopathy, and TBIL ≥10 ULN (10 mg/dL or 171 lmol/L) or daily increase ≥1.0 mg/dL (17.1 lmol/L) in 26 weeks after the DILI onset. Patients may have ascites and DILI-related dysfunction of other organs;

Grade 5 (fatal): Death due to DILI or necessitates a liver transplant for survival.

Table 1. Baseline characteristics including clinical features of grade 1–3 DILI and 4–5 DILI.

Clinical features	Grades 1–3 DILI N=111		Grades 4–5 DILI N=29		P value
Age (mean±SD)	40.71±15.94		42.38±19.67		0.676
Male N (%)	70	(63.1%)	12	(41.4%)	0.036
Symptoms and signs					
Fever N (%)	33	(29.7%)	16	(55.2%)	0.012
Rash N (%)	14	(12.6%)	8	(27.6%)	0.092
Fatigue N (%)	72	(64.9%)	22	(75.9%)	0.252
Brown urine N (%)	63	(56.8%)	27	(93.1%)	<0.001
Loss of appetite N (%)	76	(68.5%)	28	(96.6%)	<0.001
Comorbidity N (%)	31	(27.9%)	7	(24.1%)	0.6801
Primary liver disease N (%)	25	(22.5%)	7	(24.1%)	0.854
Concomitant medication N (%)	25	(22.5%)	7	(24.1%)	0.854
Tuberculosis *loci*					
Tuberculosis (lung) N (%)	84	(75.0%)	20	(58.8%)	
Tuberculous pleurisy N (%)	18	(16.0)	7	(20.6%)	
lymphoid tuberculosis N (%)	5	(4.5%)	4	(11.8%)	0.140
Bone tuberculosis N (%)	5	(4.5%)	2	(5.9%)	
Tuberculous meningitis N (%)	0	(0.0%)	1	(2.9%)	
Combination of isoniazid, rifampicin, pyrazinamide N (%)	76	(68.5%)	25	(86.2%)	0.045
Anti-tuberculosis treatment time (mean±SD)	64.71±51.0		48.76±52.81		0.152
Re-challenge N (%)	12	(10.8%)	12	(41.4%)	<0.001

Baseline examinations

Baseline evaluations included total physical examination and recording the vital signs, laboratory tests (complete blood cell count, urine examination, fecal occult blood, PTA, liver function tests, kidney function tests, blood lipids, blood sugar, autoantibodies and hepatitis virus panel), and abdominal Doppler examination (liver, gallbladder, Spleen, ascites, portal blood flow).

Treatment

The patients were advised to stop taking all anti-TB drugs immediately and were recommended to have a light diet along with ample bed rest. According to patients' individual conditions, they were treated with hepatoprotective agents; emergency liver transplantation was considered for patients with ALF/SALF.

Follow-up

Patients were followed up closely by a chest physician and a hepatologist weekly for the first 2 weeks and then were followed up at 4, 12, and 24 weeks. At each visit, the patients underwent a complete physical examination, including recording of the vital signs and laboratory tests (blood routine, PTA, liver and kidney function tests). At 24 weeks, the abdominal Doppler scan was repeated.

Statistical analysis

Statistical analysis was performed using SPSS 17.0. Quantitative data are expressed as mean±standard deviation. Comparison between groups was performed by *t* test or variance test. Nonnormally distributed quantitative data were analyzed by nonparametric rank sum test, Wilcoxon test, or Kruskal-Wallis test; qualitative data are represented using frequency or rate. The differences between groups were analyzed by chi-square

Table 2. Laboratory tests and clinical classification of 1–3 DILI and 4–5 DILI.

Laboratory tests and clinical classification	Grades 1–3 DILI N=111	Grades 4–5 DILI N=29	P value
Complete blood count			
WBC count (10⁹/L)	5.93±3.10	8.81±4.22	<0.001
EBC count(10⁹/L)	0.34±0.54	0.46±1.04	0.547
EBC >0.05×10⁹/L, N (%)	89 (80.2%)	17 (58.6%)	0.021
Liver function test			
ALT (U/L)	486.25±366.95	543.76±446.90	0.475
AST (U/L)	338.76±334.50	474.42±389.24	0.062
GGT (U/L)	155.57±128.58	147.25±94.71	0.745
ALP (U/L)	133.50±85.05	166.74±113.85	0.084
TBIL (umol/L)	87.31±103.27	359.03±161.35	<0.001
TBA (umol/L)	82.57±102.01	245.40±92.54	<0.001
ALB (g/L)	38.10±16.43	28.99±3.48	0.004
INR	1.17±0.20	2.60±0.84	<0.001
Serum creatinine Cr (umol/L)	67.51±43.76	71.66±41.35	0.647
Antinuclear antibodies			
Positive N (%)	16 (14.4%)	4 (13.8%)	
Negative (%)	80 (72.1%)	21 (72.4%)	0.996
Unknown N (%)	15 (15%)	4 (13.8%)	
Fits Hy's law	59 (53.2%)	29 (100.0%)	<0.001
MEID score	8.59±6.17	24.52±6.29	<0.001
Clinical classification			
Hepatocyte type	77 (69.4%)	19 (65.5%)	
Cholestasis type	21 (18.9%)	3 (10.3%)	0.172
Mixed type	13 (11.7%)	7 (24.1%)	

test or Fisher test. A value of P<.05 was considered statistically significant.

Results

Baseline characteristics

Among the 140 patients diagnosed with anti-TB DILI, 82 (58.6%) were males and 58 (41.4%) were females, with a mean age of 41 years. In our study, 104 patients had pulmonary TB, while extra-pulmonary TB involved the pleura in 25 patients, lymph nodes in 9 patients, and meninges in 1 patient. Concomitant medications included: 15 patients on long-term antihypertensive drugs, 12 patients on long-term hypoglycemic drugs, and 2 patients on allopurinol for hyperuricemia. The time interval from onset of anti-tuberculosis therapy and the detection of hepatotoxicity ranged from 7 to 90 days, and the average time was 24 days.

Based on the severity of liver injury, patients were categorized into 2 groups: Group A consisted of 111 patients with grades 1–3 DILI and Group B consisted of 29 patients with grades 4–5 DILI. The baseline characteristics of both groups are demonstrated in Table 1. The number of female patients in group B (grades 4–5 DILI) was significantly higher than that in

group A (58% *vs.* 36.9%; p=0.036). Anti-tuberculosis drugs included isoniazid, rifampicin, ethambutol, pyrazinamide, levofloxacin, moxifloxacin, and aminoglycosides. We calculated the proportion of patients treated with isoniazid, rifampicin, and pyrazinamide for anti-tuberculosis. From a total of 101 patients treated with anti-tuberculosis treatment regimens of isoniazid, rifampicin, and pyrazinamide, significantly more patients were diagnosed with grades 4–5 DILI in comparison to grades 1–3 (86.2% *vs.* 68.47%, p=0.045).

The proportion of patients who had re-challenge anti-TB therapy in group B was significantly higher than in group A (41.4% *vs.* 10.8, P<0.001).

Clinical features in study population

The clinical manifestations of anti-TB DILI reported in our study population included loss of appetite (n=104), fatigue (n=94), brown urine (n=90), fever (n=49), and rash (n=22). Clinical manifestations of fever, change in urine color, and loss of appetite was significantly more frequent in patients with grades 4–5 DILI in comparison to those with grades 1–3 DILI (Table 1). According to the clinical classification, 96 patients were diagnosed with hepatocellular type, while 24 patients had cholestasis type, and 20 patients reportedly had mixed-type injury.

Laboratory diagnosis

The detailed laboratory analysis is shown in Table 2. The complete blood count revealed significantly higher WBC counts in patients with grades 4–5 DILI in comparison to patients with grades 1–3 DILI (8.81±4.22 *vs.* 5.93±3.10, p<0.001). The liver function test revealed significantly higher total bilirubin (359.03±161.35 *vs.* 87.31±103.27; p<0.001) and total bile acids (245.40±92.54 *vs.* 82.57±102.01; p<0.001) and significantly lower albumin levels (28.99±3.48 *vs.* 38.10±16.43) in patients with grades 4–5 DILI in comparison to patients with grades 1–3 DILI. All the patients in group B met Hy's law and the difference between groups was statistically significant (p<0.001).

Outcome of treatment

All the patients in group A (grades 1–3) and 19 patients in group B (grades 4–5) recovered and were discharged from the hospital, while 10 patients in group B died because of liver disease.

Clinical features and laboratory tests in grades 4–5 DILI

Based on the treatment outcomes, we categorized group B patients into 2 sub-groups: a fatality group and an improvement group. The baseline characteristics, clinical features, and laboratory analysis of these groups are detailed in Tables 3 and 4. The patients in the fatality group had significantly higher total

bilirubin levels (429.91±96.86 *vs.* 321.72±177.61, P=0.043), INR (3.40±0.99 *vs.* 2.17±0.23; P=0.003) and MEID (28.73±5.91 *vs.* 22.31±5.38; P=0.006).

Discussion

In our study, we analyzed the incidence, clinical manifestations, biochemical characteristics, and outcomes based on the different grades of anti-DILI.

The average time elapsed from the initiation of anti-TB treatment to developing DILI was about 24 days, with longer onset time in patients with grade 1–3 in comparison to those with grade 4–5. The onset time reported in our study was shorter than that reported by et al. [7], who reported a median evolving time of 30 days, and was shorter than that found by Kumar et al. [8], who reported a median time of 28 days.

The clinical manifestations of anti-tuberculosis drug-induced liver injury are diverse and non-specific and can vary from an asymptomatic liver dysfunction to severe acute hepatitis, or even acute liver failure. The mechanism by which drug-induced hepatotoxicity occurs mainly involves hypersensitivity reactions clinically manifesting as fever, rash, or eosinophilia. In our study, the most common clinical manifestations were fever, rash, fatigue, loss of appetite, and dark brown urine. Although some patients present with clinical symptoms, about 20% of patients presents with asymptomatic transaminase elevation with standard anti-TB drug therapy [9,10]. In the course of treatment, the drug that likely caused the liver damage should be stopped and the use of prescribed liver-protecting drugs should be minimized to avoid exacerbations caused by recurrence of allergic reactions [11]. Liver injury can be fatal if diagnosis and management are not initiated immediately. Hence, it is advisable to routinely monitor liver function in patients receiving anti-TB drugs.

In the current cohort of anti-TB DILI patients, hepatocyte injury was more common compared to cholestasis and mixed-type liver injury. Liver injury is more severe in hepatocellular type, while patients with cholestatic/mixed type are more likely to develop chronic disease [12,13]. Studies have found that hepatocellular injury is more common in young females, while the cholestatic type of DILI is more common among the elderly, but it remains unclear why there is an association between age and DILI phenotypes [14].

According to the literature, there are many factors affecting the severity of DILI, including advanced age, female sex, alcohol consumption, and malnutrition [15–19]. In the present study we found no significant difference in age of patients diagnosed with grades 1–3 compared to those with grades 4–5 DILI.

Table 3. Baseline characteristics and clinical features in grade 4–5 DILI fatality group and the improvement group.

Clinical features	Grades 4–5 DILI fatality group N=10		Grades 4–5 DILI improvement group N=19		P value
Age (mean±SD)	35.00±18.39		46.26±19.66		0.146
Male N (%)	2	(20.0%)	10	(52.6%)	0.194
Symptoms and signs					
Fever N (%)	5	(50.0%)	11	(57.9%)	0.989
Rash N (%)	4	(40.0%)	4	(21.1%)	0.517
Fatigue N (%)	9	(90.0%)	13	(68.4%)	0.404
Brown urine N (%)	10	(100.0%)	17	(89.5%)	0.532
Loss of appetite N (%)	10	(100.0%)	18	(94.7%)	1.000
Comorbidity N (%)	1	(10.0%)	6	(31.6%)	0.404
Primary liver disease N (%)	1	(10.0%)	2	(10.5%)	1.000
Concomitant medication N (%)	3	(30.0%)	4	(21.1%)	0.937
Tuberculosis *loci*					
Tuberculosis (lung) N (%)	7	(58.3%)	13	(59.1%)	
Tuberculous pleurisy N (%)	3	(25.0%)	4	(18.2%)	
lymphoid tuberculosis N (%)	2	(16.7%)	2	(9.1%)	0.701
Bone tuberculosis N (%)	0	(0.0%)	2	(9.1%)	
Tuberculous meningitis N (%)	0	(0.0%)	1	(4.5%)	
Combination of isoniazid, rifampicin, pyrazinamide N (%)	8	(80.0%)	17	(89.5%)	0.891
Antituberculosis treatment time (mean±SD)	44.10±21.60		51.21±63.93		0.737
Rechallenge N (%)	5	(50.0%)	7	(36.8%)	0.774
Liver failure related complications N (%)	10	(100.0%)	11	(57.9%)	0.048
Ascites N (%)	8	(80.0%)	10	(52.6%)	0.298
Gastrointestinal hemorrhage N (%)	2	(20.0%)	0	(0.0%)	0.111
Hepatic encephalopathy N (%)	9	(90.0%)	2	(10.5%)	<0.001
Hepatorenal syndrome N (%)	3	(30.0%)	1	(5.3%)	0.249

We also observed that patients with grades 4–5 who died were younger in comparison to those who survived. However, Sharma et al., in India, reported deaths at an average age of 34.8±16.8 years whereas that of the survivors was 28.8±12.9 years [8]. There are few studies that have reported no associations between age and gender with DILI. It has been reported that women are at increased risk of developing hepatotoxicity when receiving anti-tuberculosis treatment. In the present study, the proportion of women with grades 4–5 liver injury was higher than that of men, suggesting that women receiving anti-tuberculosis drugs may be more prone to severe liver damage or even liver failure. Ichai et al. [20] and Kumar et al. [21] conducted studies in France and India, respectively, and both reported anti-TB drug-associated liver failure in about 70% of female patients.

Other risk factors associated with anti-TB DILI include alcoholism and viral hepatitis. Anand et al. reported that patients with hepatitis B virus infection had significantly higher incidence of anti-TB DILI than those without infection (37.5% *vs.* 10.2%, p<0.01) [21]. The patients enrolled in our study had normal liver function before anti-tuberculosis treatment, and

Table 4. Laboratory analysis and clinical classification of 4–5 grade DILI fatality group and improvement group.

Laboratory examination and clinical classification	Grades 4–5 DILI fatality group N=10	Grades 4–5 DILI improvement group N=19	P value
Complete blood count			
WBC count (10⁹/L)	9.36±6.11	8.52±2.96	0.688
EBC count (10⁹/L)	0.21±0.30	0.59±1.25	0.353
EBC >0.05×10⁹/L, N (%)	5 (50.0%)	12 (63.2%)	0.774
Liver function test			
ALT (U/L)	352.44±231.66	644.45±502.79	0.095
AST (U/L)	383.45±268.69	522.30±438.81	0.371
GGT (U/L)	152.35±94.59	144.57±97.25	0.838
ALP (U/L)	211.60±157.22	143.13±78.10	0.126
TBIL (umol/L)	429.91±96.86	321.72±177.61	0.043
TBA (umol/L)	220.95±80.60	258.27±97.80	0.310
ALB (g/L)	28.96±3.36	29.01±3.63	0.974
INR	3.40±0.99	2.17±0.23	0.003
Serum creatinine Cr (umol/L)	78.64±61.86	67.98±26.55	0.613
Antinuclear antibodies			
Positive N (%)	3 (30.0%)	1 (5.3%)	
Negative (%)	6 (60.0%)	15 (78.9%)	0.184
Unknown N (%)	1 (10.0%)	3 (15.8%)	
MEID score	28.73±5.91	22.31±5.38	0.006
Clinical classification			
Hepatocyte type	4 (40.0%)	15 (78.9%)	
Cholestasis type	2 (20.0%)	1 (5.3%)	0.106
Mixed type	4 (40.0%)	3 (15.8%)	

the results suggested that the severity of liver injury was not related to the presence of primary liver disease.

Most cases of anti-TB DILI are associated with multidrug combination therapy. In the present study, more patients who were treated by the combination of rifampicin+isoniazid+pyrazinamide were diagnosed with severe liver injury in comparison to those receiving other anti-tuberculosis treatment regimens. Earlier preclinical and clinical studies have demonstrated the synergistic effect of isoniazid and rifampicin on liver damage, and they concluded that the incidence of liver damage is significantly higher in combination doses [22]. A study that included 3007 patients with tuberculosis found that the incidence of DILI in patients treated with rifampicin+isoniazid was

0.8%, and this increased to 2.8% after the addition of pyrazinamide, suggesting that rifampicin+isoniazid+pyrazinple therapy can increase the risk of DILI and affect the severity of liver damage [23].

Although some drugs cause mild liver injury during the first exposure, drug re-challenge can cause severe damage leading to fatal reactions [24]. Re-challenge can help identify risk factors associated with drug-induced liver injury and aids in timely diagnosis. However, due to the high risk associated with re-challenge, it is generally not recommended unless the patient has no other available alternative regimen. In our study, the degree of liver injury was more severe in the re-challenge group. Among the 24 patients who reinitiated the previous

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anti-TB therapy, 12 patients suffered liver failure and 7 patients died. Among the other 116 patients, 17 patients suffered liver failure and 3 patients died. Due to patients' individual conditions, it is sometimes necessary to reinitiate the anti-tuberculosis drugs, and in those situations the patients should be informed about the associated risk and the treating physicians should try to avoid prescribing the same drugs that had been used before, and need to closely monitor changes in patient conditions.

As clinical symptoms and biochemical characteristics of anti-TB drug-induced DILI have been widely reported, clinicians have become aware of the condition and the incidence of the severe form of liver injury has thus decreased. In patients with liver failure, the mortality rate is high and the prognosis is extremely poor. Consistent with previous reports, we found that high total bilirubin levels, INR prolongation, elevated MELD scores, and hepatic encephalopathy were associated with poor prognosis.

Conclusions

This was a single-center retrospective study with a limited number of cases included. The study shows that anti-TB DILI is a common adverse event reported in patients with tuberculosis, which is more common in female patients. Female gender, combination therapy for antitubercular drugs (isoniazid, rifampicin and pyrazinamide), re-challenge were the risk factors associated with the severity of anti-TB DILI; high total bilirubin, INR, MELD score and appearance of hepatic encephalopathy indicated poor prognosis. Therefore it is advisable to prescribe selective anti-TB chemotherapy in high risk patients to reduce the incidence of DILI.

Conflicts of interest

None.

References:

1. Mao Q, Zhang K, Yan W, Cheng C: Forecasting the incidence of tuberculosis in China using the seasonal auto-regressive integrated moving average (SARIMA) model. J Infect Public Health, 2018; 11: 707–12

2. Chen Y, Ye P, Ren C et al: Pharmacoeconomics of three therapeutic schemes for anti-tuberculosis therapy induced liver injury in China. Open Med (Wars), 2018; 13: 53–63

3. Shang P, Xia Y, Liu F et al: Incidence, clinical features and impact on anti-tuberculosis treatment of anti-tuberculosis drug-induced liver injury (ATLI) in China. PLoS One, 2011; 6: e21836

4. Li F, Lu S: Interpretation of expert recommendation on diagnosis and treatment of anti-tuberculosis drug-induced liver injury. Community Acquir Infect, 2015; 2: 113

5. Danan G, Benichou C: Causality assessment of adverse reactions to drugs – I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol, 1993; 46: 1323–30

6. Yu YC, Mao YM, Chen CW et al: CSH guidelines for the diagnosis and treatment of drug-induced liver injury. Hepatol Int, 2017; 11: 221–41

7. Kumar R, Bhatia V, Khanal S et al: Antituberculosis therapy-induced acute liver failure: Magnitude, profile, prognosis, and predictors of outcome. Hepatology, 2010; 51: 1665–74

8. Tweed CD, Wills GH, Crook AM et al: Liver toxicity associated with tuberculosis chemotherapy in the REMoxTB study. BMC Med, 2018; 16: 46

9. Ormerod LP, Horsfield N: Frequency and type of reactions to antituberculosis drugs: Observations in routine treatment. Tuber Lung Dis, 1996; 77: 37–42

10. Blumberg HM, Burman WJ, Chaisson RE et al: American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med, 2003; 167: 603–62

11. Gu J, Tang SJ, Tan SY et al: An open-label, randomized and multi-center clinical trial to evaluate the efficacy of Silibinin in preventing drug-induced liver injury. Int J Clin Exp Med, 2015; 8: 4320–27

12. Norris W, Paredes AH, Lewis JH: Drug-induced liver injury in 2007. Curr Opin Gastroenterol, 2008; 24: 287–97

13. Meier Y, Cavallaro M, Roos M et al: Incidence of drug-induced liver injury in medical inpatients. Eur J Clin Pharmacol, 2005; 61: 135–43

14. Chalasani N, Bjornsson E: Risk factors for idiosyncratic drug-induced liver injury. Gastroenterology, 2010; 138: 2246–59

15. Zhang M, Wang S, Wilffert B et al: The association between the NAT2 genetic polymorphisms and risk of DILI during anti-TB treatment: A systematic review and meta-analysis. Br J Clin Pharmacol, 2018; 84: 2747–60

16. Chen L, Bao D, Gu L et al: Co-infection with hepatitis B virus among tuberculosis patients is associated with poor outcomes during anti-tuberculosis treatment. BMC Infect Dis, 2018; 18: 295

17. Chang TE, Huang YS, Chang CH et al: The susceptibility of anti-tuberculosis drug-induced liver injury and chronic hepatitis C infection: A systematic review and meta-analysis. J Chin Med Assoc, 2018; 81: 111–18

18. Abbara A, Chitty S, Roe JK et al: Drug-induced liver injury from antituberculous treatment: A retrospective study from a large TB centre in the UK. BMC Infect Dis, 2017; 17: 231

19. Wang S, Shangguan Y, Ding C et al: Risk factors for acute liver failure among inpatients with anti-tuberculosis drug-induced liver injury. J Int Med Res, 2018 [Epub ahead of print]

20. Ichai P, Saliba F, Antoun F et al: Acute liver failure due to antitubercular therapy: Strategy for antitubercular treatment before and after liver transplantation. Liver Transpl, 2010; 16: 1136–46

21. Anand AC, Seth AK, Paul M, Puri P: Risk factors of hepatotoxicity during anti-tuberculosis treatment. Med J Armed Forces India, 2006; 62: 45–49

22. Ramappa V, Aithal GP: Hepatotoxicity related to anti-tuberculosis drugs: Mechanisms and management. J Clin Exp Hepatol, 2013; 3: 37–49

23. Chang KC, Leung CC, Yew WW et al: Hepatotoxicity of pyrazinamide: Cohort and case-control analyses. Am J Respir Crit Care Med, 2008; 177: 1391–96

24. Chalasani NP, Hayashi PH, Bonkovsky HL et al: ACG Clinical Guideline: The diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol, 2014; 109: 950–66; quiz 967