Clinical characteristics and outcomes of drug-induced liver injury in Taiwan: With emphasis on the impact of chronic hepatitis B infection

Yi-Shin Huang[a,*], Shao-Yu Tseng[a], Wen-Wen Chen[b], Ting-Tsung Chang[c], Cheng-Yuan Peng[d], Gin-Ho Lo[e], Chao-Wei Hsu[f], Chi-Tan Hu[g], Yi-Hsiang Huang[a]

[a]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan, ROC; [b]Taiwan Drug Relief Foundation, Taipei, Taiwan, ROC; [c]Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, ROC; [d]Department of Internal Medicine, Center for Digestive Medicine, China Medical University Hospital, Taichung, Taiwan, ROC; [e]Department of Medical Research, Digestive Center, E-DA Hospital, Kaohsiung, Taiwan, ROC; [f]Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Lin-Kou, Chang Gung University College of Medicine, Taoyuan, Taiwan, ROC; [g]Division of Gastroenterology and Hepatology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan, ROC

Abstract

Background: Whether hepatitis B virus (HBV) infection can affect the outcomes of drug-induced liver injury (DILI) is controversial. This study aimed to evaluate the characteristics and outcomes of DILI in Taiwan, with an emphasis on the impact of HBV infection.

Methods: We prospectively recruited patients with DILI from multiple centers in Taiwan from 2010 to 2018.

Results: A total of 1,014 patients were enrolled. The leading culprit drug category was antimicrobials (481, 47.4%), followed by nonsteroidal anti-inflammatory drugs, anticonvulsants, and statins. Among the antimicrobials, antituberculosis agents were most likely to induce liver injury (257, 25.3%), followed by antibacterial, antifungal, and antiviral agents. The liver-related mortality rate was 8.2% (83/1,014). The patients who died had higher rates of hepatocellular-type liver injury, elevated liver biochemical tests, preexisting liver cirrhosis, jaundice, chronic HBV infection, and antituberculosis drug-induced liver injury (ATDILI) than the survivors. A total of 131 patients (12.9%) with DILI were HBV carriers, of whom 23 (17.6%) died of hepatic failure. The rate of HBV-DNA > 2000 IU/mL was higher in the patients who died (47.8% vs. 26.9%, $p = 0.047$) than in the survivors. After adjusting for possible risk factors, active HBV infection with HBV-DNA > 2000 IU/mL was the most significant risk factor for liver-related mortality (adjusted HR, 4.40, 95% CI, 2.31%-8.38%, $p < 0.001$). The other independent risk factors for mortality were ATDILI and albumin-bilirubin (ALBI) score (adjusted HR, 1.25 and 4.09, respectively, $p < 0.003$).

Conclusion: Antituberculosis agents were the leading cause of DILI in Taiwanese, and they were associated with poorer outcomes than other drug categories. Active HBV infection, ATDILI and ALBI score were independent risk factors for fatal DILI. Close monitoring of liver tests and timely antiviral therapy should be implemented in HBV carriers during the administration of high-risk drugs, such as antituberculosis agents.

Keywords: Adverse drug reaction; Antituberculosis drugs; Drug-induced liver injury; Hepatitis B; Hepatotoxicity

1.INTRODUCTION

Drug-induced liver injury (DILI) is an important and challenging adverse drug reaction (ADR), and the most common single reason to withdraw drugs from market.[1–3] It has also been a major reason to cease the development of many pre-clinical drugs. Severe DILI may induce hepatic failure and death. Many countries have launched national or international programs to detect and prevent DILI.[4–6] Understanding the clinical characteristics, risk factors and outcomes of DILI are crucial and can help to prevent or mitigate severe DILI. However, large-scale studies of DILI in Taiwan are lacking.

Taiwan is an endemic area for hepatitis B virus (HBV) infection, and both viral hepatitis B and C infection have been reported to increase the risk of antituberculosis drug-induced liver injury (ATDILI).[7–15] However, whether viral hepatitis infection can affect

Address correspondence: Dr. Yi-Shin Huang, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei, 112, Taiwan ROC. E-mail address: yshuang@vghtpe.gov.tw. (Y.-S. Huang).

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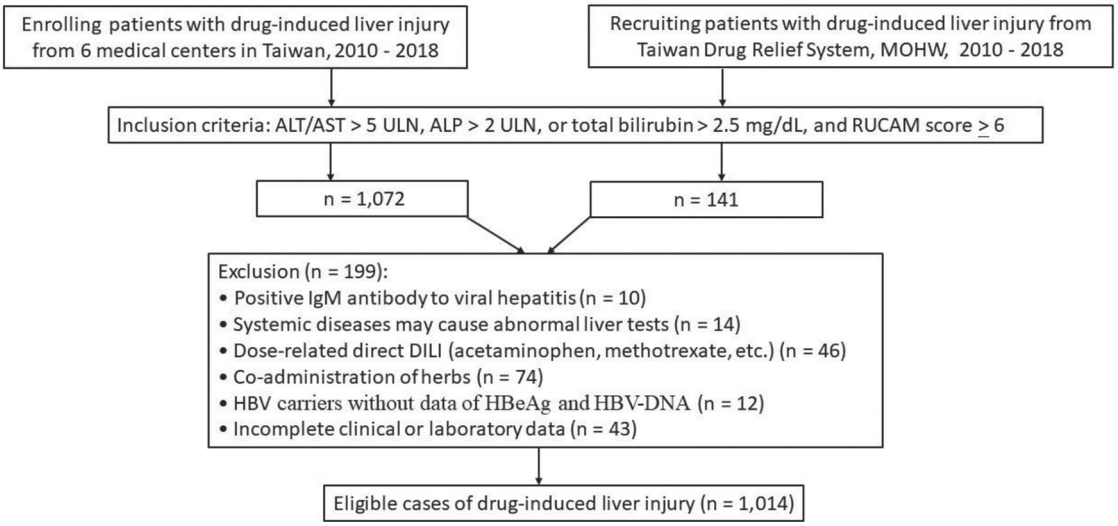

Fig. 1 The study flow chart for recruitment of patients with drug-induced liver injury. ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; MOHW = Ministry of Health and Welfare; RUCAM = Roussel Uclaf Causality Assessment Method; ULN = upper limit of normal value.

the outcomes of DILI is unknown. Therefore, the aim of this study was to evaluate the drugs, clinical characteristics, outcomes, and risk factors associated with mortality in Taiwanese patients with DILI through a nationwide multicenter cooperative program, with a special emphasis on the interaction with chronic HBV infection.

2. METHODS

2.1. Study population

We prospectively enrolled patients with DILI from six tertiary referral medical centers throughout Taiwan, and severe DILI cases recruited by the Taiwan Drug Relief Foundation (TDRF) from 2010 to 2018. The TDRF was founded by the Department of Health of the Executive Yuan (now the Ministry of Health and Welfare [MOHW]), and it is a nonprofit organization established to carry out drug-injury relief related activities, including receiving applications, carrying out investigations, and issuing relief payments.[16] The medical records and relevant data of all applicants to the TDRF were first inspected by experts in the field, and then reviewed by the board committee of the MOHW.

The inclusion criteria for patients with DILI were based on those proposed by the US Drug-Induced Liver Injury Network (DILIN) as follows: (1) intake of the incriminating drug(s) before onset of liver dysfunction; (2) an increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level greater than 5 times the upper limit of normal value (ULN), or an elevation in serum alkaline phosphatase (ALP) greater than twice the ULN[4]; (2) an ALT or AST level greater than 5 times the baseline value, or ALP greater than twice the baseline level if baseline ALT, AST or ALP is elevated; (3) any elevation in serum ALT, AST, or ALP level associated with an increase in total bilirubin (≥2.5 mg/dL), in the absence of Gilbert syndrome, hemolysis or hepatobiliary obstruction; and (4) a Roussel Uclaf Causality Assessment Method (RUCAM) score of 6 or higher.[17]

The exclusion criteria were as follows: (1) patients with positive serum immunoglobulin M antibodies to hepatitis A virus, hepatitis B core, Epstein Barr virus, cytomegalovirus, or herpes simplex virus; (2) other systemic diseases which may cause abnormal liver biochemical tests, such as Wilson disease, hemochromatosis, stones, or tumors of the hepatobiliary system, shock, hypoxia, heart failure, and respiratory failure; (3) dose-related direct DILI, such as acetaminophen and methotrexate; (4) coadministration of herbal drugs; (5) hepatitis B carriers without data of hepatitis B e antigen (HBeAg) and HBV-DNA; and (6) patients with incomplete clinical and laboratory data. The study protocol was approved by the Institutional Review Boards of the six medical centers, and it was conducted in accordance with the Helsinki Declaration of 1975.

2.2. Assessment of liver injury

The types of DILI on first recognition were classified according to the US DILIN.[4,18] The "hepatocellular" type was defined as a ratio of the times of ULN of ALT/times of ULN of ALP > 5. The "cholestatic" type was defined as a ratio < 2, and the "mixed" type as 2 ≤ ratio ≤ 5.

Chronic HBV and hepatitis C virus (HCV) carriers were defined as those positive for serum hepatitis B surface antigen or anti-hepatitis C antibody for >6 months. A serum total bilirubin level ≥ 2.5 mg/dL at any time during the clinical course was defined as indicating "jaundice" in accordance with the US DILIN.[4]

Habitual alcohol use was defined according to the American Association for the Study of Liver Disease as "alcohol consumption >21 standard drinks per week in men and >14 standard drinks per week in women for >2 years."[19]

The diagnosis of liver cirrhosis was based on the results of a liver biopsy, or on the clinical stigmata of cirrhosis including esophageal or gastric varices, hepatic encephalopathy, or hypoalbuminemia, in addition to the presence of ascites, an uneven surface on the liver, collateral circulation, and splenomegaly detected by ultrasonography or computed tomography.

Active HBV infection was defined as serum HBV DNA > 2,000 IU/mL in accordance with the American Association for the Study of Liver Diseases.[20] The HBV-DNA virus load was assessed using the COBAS TaqMan HBV Test (Roche Diagnostics, Basel, Switzerland), which has a sensitivity of 10 IU/mL.

2.3. Statistical analysis

The chi-square test, with or without Yates' correction, or Fisher's exact test was used to compare categorical variables. The Student's *t* test or analysis of variance (ANOVA) was used to compare continuous variables between groups, with Scheffe post hoc multiple comparisons. Survival analysis between groups was performed using the Kaplan-Meier method and log-rank test. A Cox proportional hazards regression model was used to calculate crude and multivariable-adjusted

Table 1

Culprit drugs in 1014 patients with drug-induced liver injury

1. Antimicrobials	**481 (47.4%)**
1.1 Antituberculosis agents	**257 (25.3%)**
Isoniazid/rifampicin/pyrazinamide	257
1.2 Antibacterial agents	**187 (18.4%)**
Sulfamethoxazole-trimethoprim	42
Amoxicillin-clavulanate	31
Minocycline	18
Cephalexin	15
Cefazolin	11
Azithromycin	10
Ciprofloxacin	9
Levofloxacin	8
Cefmetazole	7
Cefoperazone	6
Amoxicillin	6
Ceftriaxone	5
Erythromycin	5
Dicloxacillin	4
Piperacillin-tazobactam	3
Meropenem	2
Vancomycin	2
Clindamycin	2
Ertapenem	1
1.3 Antifungal agents	**33 (3.3%)**
Ketoconazole	15
Terbinafine	12
Itraconazole	6
1.4 Antiviral agents	**4 (0.4%)**
Ombitasvir/paritaprevir/ritonavir/dasabuvir	4
2. Nonsteroidal anti-inflammatory drugs	**118 (11.6%)**
Diclofenac	43
Mefenamic acid	20
Ibuprofen	18
Indomethacin	13
Etoricoxib	11
Celecoxib	9
Nimesulide	4
3.Anticonvulsants	**112 (11.1%)**
Phenytoin	32
Carbamazepine	27
Valproic acid	23
Gabapentin	18
Lamotrigine	12
4.Statins	**105 (10.4%)**
Rosuvastatin	20
Fluvastain	19
Atorvastatin	17
Simvastatin	17
Pravastatin	13
Lovastatin	10
Pitavastatin	9
5.Antigout agents	**50 (4.9%)**
Allopurinol	47
Febuxostat	3
6.Antiarrhythmia agents	**35 (3.5%)**
Amiodarone	29
Dronedarone	6
7.Antithyroid agents	**34 (3.4%)**
Propylthiouracil	21
Carbimazole	13
8.Androgens and antiandrogens	**23 (2.3%)**

(*Continued next page*)

Table 1 (Continued)

Culprit drugs in 1014 patients with drug-induced live

Flutamide	12
Cyproterone acetate	7
Testosterone	4
9.Proton pump inhibitors	**9 (0.9%)**
Esomeprazole	4
Omeprazole	3
Lansoprazole	2
10.Anesthetics	**5 (0.5%)**
Isoflurane	3
Sevoflurane	2
11.Miscellaneous	**42 (4.1%)**
Sulfasalazine	10
Ticlopidine	5
Azathioprine	4
Tamoxifen	4
Sorafenib	2
Others	17

hazard ratios (HRs) of DILI. Covariates in the multivariable analysis were chosen according to a forward stepwise regression model with a significance level of <0.05 for addition to the model. All of the statistical tests were based on a two-tailed probability, and a $p < 0.05$ was considered to be significant. All analyses were performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL).

3. RESULTS

3.1. Leading drugs inducing liver injury

A total of 1,014 patients were enrolled into this study (Fig. 1). The leading culprit drug category was antimicrobials (481/1014, 47.4%), followed by nonsteroidal anti-inflammatory drugs (NSAIDs) (118, 11.6%), anticonvulsants (112, 11.1%), statins (105, 10.4%), and antigout drugs (50, 4.9%) (Table 1). Among the antimicrobials, antituberculosis agents were most likely to induce liver injury (257, 25.3%), followed by antibacterial agents (187, 18.4%), antifungal drugs (33, 3.3%), and antiviral agents (4, 0.4%). Almost all of the patients with ATDILI received a three-drug regimen for active tuberculosis, which included isoniazid, rifampicin, and pyrazinamide. All three of these drugs had the potential to cause liver injury and could not completely be excluded from causing hepatotoxicity. Therefore, these three agents were classified into the antituberculosis drug category in this study, in accordance with the International DILI Expert Working Group.[18] Of the NSAIDs, diclofenac (43, 4.2%) was most likely to induce DILI, followed by mefenamic acid, ibuprofen, and indomethacin. The most popular anticonvulsants were phenytoin and carbamazepine. Rosuvastatin and allopurinol were the most common incriminating statin and antigout agent, respectively.

3.2. Clinical characteristics and liver-related mortality

The liver-related mortality rate was 8.2% (83/1,014, Table 2). The liver-related mortality group were older, had higher serum ALT, bilirubin, creatinine levels and albumin-bilirubin (ALBI) score,[21] and lower albumin level and platelet count than the survivor group. Although the hepatocellular type was the most common type of liver injury in both groups, the mortality group had a higher rate of the hepatocellular type than the survivor group (79.5% vs. 58.4%, $p = 0.001$, Table 2). The mortality group also had higher rates of elevated baseline liver biochemical tests, preexisting liver cirrhosis, jaundice, ATDILI, and hepatitis B carriers than the survivor group.

Table 2

Clinical characteristics and outcomes of patients with drug-induced liver injury in Taiwan

	Total (n = 1014)	Mortality cases[a] (n = 83)	Survivors (n = 931)	*p*
Sex, male	541 (53.4)	52 (62.7)	489 (52.5)	.076
Age (years old)	56.0 ± 19.6	62.2 ± 15.1	55.4 ± 19.9	<0.001*
Age > 65 years old	403 (39.7)	46 (55.4)	357 (38.3)	0.002*
Body mass index (kg/m^2)	24.8 ± 3.2	24.4 ± 2.3	24.9 ± 3.2	0.055
Diabetes mellitus	93 (9.2)	9 (10.8)	84 (9.0)	0.582
Habitual alcohol drinking	99 (9.8)	10 (12.0)	89 (9.6)	0.464
Elevated baseline liver tests	114 (11.2)	15 (18.1)	99 (10.6)	0.040
Preexisting cirrhosis	37 (3.6)	9 (10.8)	28 (3.0)	<0.001*
Latency (days)	27.8 ± 15.8	24.9 ± 16.3	28.0 ± 15.7	0.088
Liver tests-recognition				
ALT (U/L)	608.7 ± 639.3	1076.6 ± 939.7	567.0 ± 588.3	<0.001*
ALP (U/L)	203.3 ± 155.1	194.7 ± 121.7	204.0 ± 157.8	0.515
Bilirubin, total (mg/dL)	3.2 ± 3.7	8.4 ± 7.2	2.8 ± 2.7	<0.001*
Albumin (g/dL)	4.3 ± 0.6	3.8 ± 0.8	4.3 ± 0.6	<0.001*
Albumin-Bilirubin (ALBI) score	-2.62 ± 0.70	-1.85 ± 0.77	-2.69 ± 0.65	<0.001*
Creatinine (mg/dL)	1.2 ± 0.4	1.5 ± 0.4	1.2 ± 0.4	<0.001*
Platelet (1000/μL)	19.7 ± 3.7	18.3 ± 4.2	19.8 ± 3.7	<0.001*
Liver tests-peak				
ALT (U/L)	820.6 ± 844.3	1528.4 ± 1159.9	757.5 ± 780.4	<0.001*
ALP (U/L)	234.7 ± 203.2	242.5 ± 174.4	234.1 ± 205.6	0.717
Bilirubin, total (mg/dL)	6.2 ± 8.2	25.7 ± 8.0	4.5 ± 5.6	<0.001*
Jaundice (total bilirubin ≥ 2.5 mg/dL)	500 (49.3)	82 (98.9)	418 (44.9)	<0.001*
Type of liver injury—hepatocellular/mixed/cholestatic	610/222/182 (60.2/21.9/17.9)	66/7/10 (79.5/8.4/12.1)	544/215/172 (58.4/23.1/18.5)	0.001*
Antituberculosis drug-related	257 (25.3)	38 (45.8)	219 (23.5)	<0.001*
Antibacterial agent-related	187 (18.4)	14 (16.9)	173 (18.6)	0.699
Antifungal agent-related	33 (3.3)	3 (3.6)	30 (3.2)	0.896
Non-steroidal anti-inflammatory	118 (11.6%)	7 (8.4)	111 (11.9)	0.342
Drug-related				
Hepatitis B carriers	131 (12.9)	23 (27.7)	108 (11.6)	<0.001*
Hepatitis C carriers	36 (3.6)	6 (7.2)	30 (3.2)	0.114

Data are expressed as number (%) or mean ± SD.

[a]Liver-related mortality.

*p <0.05.

ALT = alanine aminotransferase; ALP = alkaline phosphatase.

A total of 37 (3.6%) patients had preexisting liver cirrhosis, of whom 25 were HBV-related, five were alcohol-induced, three were HCV-related, one was autoimmune hepatitis, one was primary biliary cholangitis, and the other two were cryptogenic cirrhosis. The median (interquartile range, IQR) time between the date of the diagnosis of DILI and the date of mortality was 61 days (54 days).

3.3. Risk factors for mortality and the interaction with HBV

Table 3 shows the clinical characteristics and outcomes of the patients stratified by HBV infection status. The active HBV carriers (HBV-DNA > 2000 IU/mL) had higher serum baseline creatinine and peak bilirubin levels, and lower serum albumin level and ALBI score than the inactive HBV carriers (HBV-DNA ≤ 2000 IU/mL) and non-HBV carriers. The active HBV carriers also had higher rates of elevated baseline liver biochemical tests, preexisting liver cirrhosis, jaundice, ATDILI, and mortality than the other two groups.

A total of 131 patients (12.9%) with DILI were HBV carriers, of whom 23 (17.6%) died of hepatic failure (Table 4). Among the HBV carriers, those who died had higher initial and peak serum ALT and bilirubin levels than the survivors. The mortality group also had higher rates of jaundice, hepatocellular type DILI, and ATDILI than the survivor group. Although there were no statistically significant differences in HBV-DNA viral load and HBeAg positivity between the mortality and survivor groups, the rate of HBV-DNA > 2000 IU/mL was higher in the mortality group compared to the survivor group (47.8% vs. 26.9%, p = 0.047). Most of the patients received entecavir or tenofovir treatment before or after the onset of DILI (Table 4). Fig. 2 shows that there were significant differences in survival rate between different subgroups. The HBV carriers had a lower survival rate than the non-HBV carriers (p < 0.001, Fig. 2A), and the active HBV carriers (HBV-DNA > 2000 IU/mL) had a lower survival rate than those with low HBV activity and the non-HBV carriers (p < 0.001, Fig. 2B). The patients with preexisting liver cirrhosis and those with ATDILI also had lower survival rates (p < 0.001 and p = 0.003, respectively, Fig. 2C, D). Furthermore, Fig. 3 shows that the patients with HBV-DNA > 2000 IU/mL and ATDILI had the highest mortality rate.

After adjusting for possible risk factors, active hepatitis B infection with HBV-DNA > 2000 IU/mL was the most significant risk factor for liver-related mortality (adjusted HR, 4.40, 95% CI, 2.31%-8.38%, p < 0.001, Table 5). The other independent risk factors for mortality were ATDILI and ALBI score (adjusted HR, 1.25 and 4.09, respectively, p < 0.003, Table 5).

Table 3

Clinical characteristics and outcomes of patients with drug-induced liver injury in different hepatitis B infection status

	HBV carriers			
	HBV-DNA >2000 IU/mL (n = 40)	HBV-DNA <2000 IU/mL (n = 91)	Non-HBV carriers (n = 883)	*p*
Sex, male	22 (55.0)	48 (52.7)	471 (53.3)	.972
Age (years old)	60.9 ± 18.7	62.5 ± 15.6	55.1 ± 19.9	0.001*
Body mass index (kg/m^2)	24.5 ± 3.1	24.7 ± 3.0	24.9 ± 3.2	0.620
Diabetes mellitus	6 (15.0)	12 (13.2)	75 (8.5)	0.144
Habitual alcohol drinking	2 (5.0)	5 (5.5)	92 (10.4)	0.188
Elevated baseline liver tests	13 (32.5)	18 (19.8)	83 (9.4)	<0.001*
Preexisting cirrhosis	8 (20.0)	17 (18.7)	12 (3.0)	<0.001*
Latency (days)	21.7 ± 12.0	19.8 ± 10.6	28.9 ± 16.1	<0.001*
Liver tests-recognition				
ALT (U/L)	673.1 ± 867.3	633.4 ± 566.8	603.3 ± 634.9	0.739
ALP (U/L)	212.4 ± 136.2	178.7 ± 119.0	205.4 ± 159.1	0.274
Bilirubin, total (mg/dL)	3.7 ± 3.7	4.0 ± 5.0	3.1 ± 3.5	0.073
Albumin (g/dL)	4.1 ± 0.8	4.1 ± 0.7	4.3 ± 0.6	0.001*
Albumin-Bilirubin (ALBI) score	-2.43 ± 0.78	-2.38 ± 0.74	-2.65 ± 0.68	<0.001*
Creatinine (mg/dL)	1.4 ± 0.5	1.3 ± 0.4	1.2 ± 0.4	0.083
Platelet (1000/μL)	19.0 ± 3.5	19.6 ± 4.2	19.7 ± 3.7	0.516
Liver tests-peak				
ALT (U/L)	883.3 ± 918.6	914.6 ± 791.7	757.5 ± 780.4	0.463
ALP (U/L)	233.4 ± 144.7	212.8 ± 188.7	237.1 ± 206.8	0.555
Bilirubin, total (mg/dL)	10.3 ± 11.4	9.1 ± 9.8	5.7 ± 7.8	<0.001*
Jaundice (total bilirubin ≥2.5mg/dL)	25 (62.5)	60 (65.9)	415 (47.0)	0.001*
Type of liver injury-hepatocellular/mixed/ cholestatic	24/7/9 (60.0/17.5/22.5)	58/20/13 (63.7/22.0/14.3)	528/195/160 (59.8/22.1/18.1)	0.784
Antituberculosis drug-related	17 (42.5)	27 (29.7)	213 (24.1)	0.020
Antibacterial agent-related	5 (12.5)	18 (19.8)	164 (18.6)	0.731
Antifungal agent-related	0 (0.0)	2 (2.2)	31 (3.5)	0.706
Non-steroidal anti-inflammatory Drug-related	3 (7.5)	10 (11.0)	105 (11.9)	0.836
Liver-related mortality	11 (27.5)	12 (13.2)	60 (6.8)	<0.001*

Data are expressed as number (%) or mean ± SD.

*p <0.05.

ALT = alanine aminotransferase; ALP = alkaline phosphatase.

Table 4

Outcome analysis of drug-induced liver injury in 131 hepatitis B carriers

	Total (N = 131)	Mortality cases[a] (N = 23)	Survivors (N = 108)	*p*
Sex, male	70 (53.4)	13 (56.5)	57 (52.8)	.744
Age (years old)	62.0 ± 16.6	66.5 ± 10.5	61.1 ± 17.5	0.054
Age > 65 years old	68 (51.9)	16 (69.6)	52 (48.1)	0.062
Habitual alcohol drinking	7 (5.3)	3 (13.0)	4 (3.7)	0.103
Elevated baseline liver tests	31 (23.7)	7 (30.4)	24 (22.2)	0.400
Preexisting cirrhosis	25 (19.1)	5 (21.7)	20 (18.5)	0.948
Latency (days)	20.4 ± 11.0	18.5 ± 12.0	20.8 ± 10.8	0.379
Liver tests-recognition				
ALT (U/L)	645.5 ± 669.6	1048.4 ± 977.2	559.8 ± 553.3	0.029*
ALP (U/L)	189.0 ± 125.0	160.0 ± 76.9	195.1 ± 132.4	0.092
Bilirubin, total (mg/dL)	3.9 ± 4.6	8.2 ± 7.8	3.0 ± 2.9	0.004*
Liver tests-peak				
ALT (U/L)	905.1 ± 829.0	1588.2 ± 980.8	759.6 ± 718.0	<0.001*
ALP (U/L)	219.1 ± 176.1	189.4 ± 91.7	225.4 ± 189.0	0.374
Bilirubin, total (mg/dL)	9.5 ± 10.3	25.1 ± 7.0	6.1 ± 7.4	<0.001*
Jaundice (total bilirubin ≥ 2.5 mg/dL)	85 (64.9)	23 (100.0)	62 (57.4)	<0.001*
Type of liver injury-hepatocellular/mixed/cholestatic	82/27/22 (62.6/20.6/16.8)	21/0/2 (91.3/0.0/8.7)	61/27/20 (56.5/25.0/18.5)	0.005*
Antituberculosis drug-related	44 (33.6)	16 (69.6)	28 (25.9)	<0.001
HBV-DNA titer (IU/mL)	2624.4 ± 5588.8	5473.2 ± 8983.1	2017.7 ± 4405.3	0.083

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Table 4 (Continued)

Outcome analysis of drug-induced liver injury in 131 hepatitis B carriers

	Total (N = 131)	Mortality cases[a] (N = 23)	Survivors (N = 108)	*p*
HBV-DNA > 2000 IU/mL	40 (30.5)	11 (47.8)	29 (26.9)	0.047*
HBeAg, positive	37 (28.2)	6 (26%)	31 (28.7%)	0.800
Nuc. therapy before and during onset of DILI[b]	23 (17.6)	3 (13.0)	20 (18.5)	0.764
Nuc. therapy after onset of DILI[c]	101 (77.1)	19 (82.6)	82 (75.9)	0.593
No nuc. therapy	7 (5.3)	1 (4.4)	6 (5.6)	1.000

Data are expressed as number (%) or mean ± SD.
*$p < 0.05$.
[a]Liver-related mortality.
[b]15 received entecavir, 8 received tenofovir treatment.
[c]81 received entecavir, 20 received tenofovir treatment.
ALP = alkaline phosphatase; ALT = alanine aminotransferase; nuc = nucleoside/nucleotide.

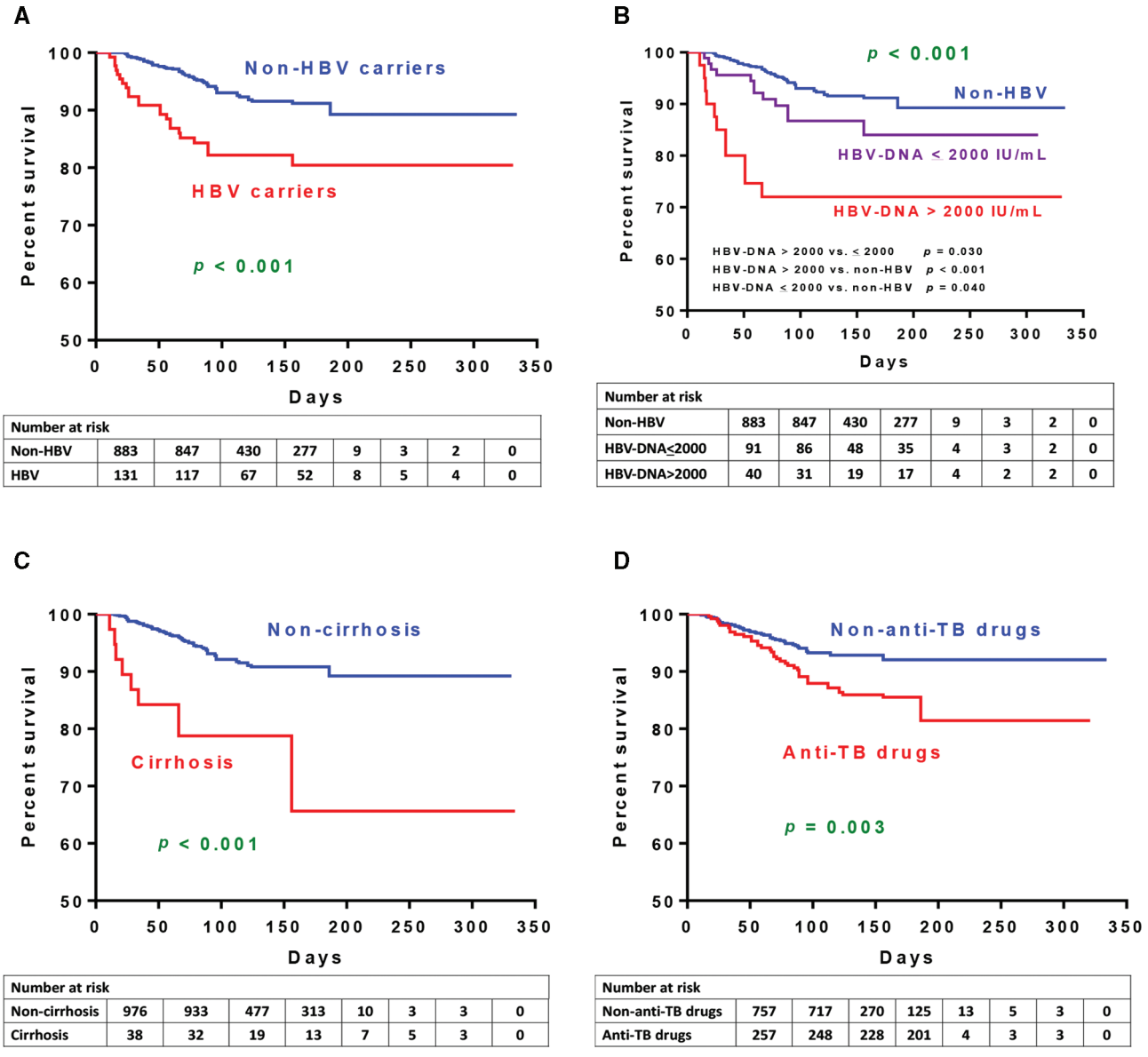
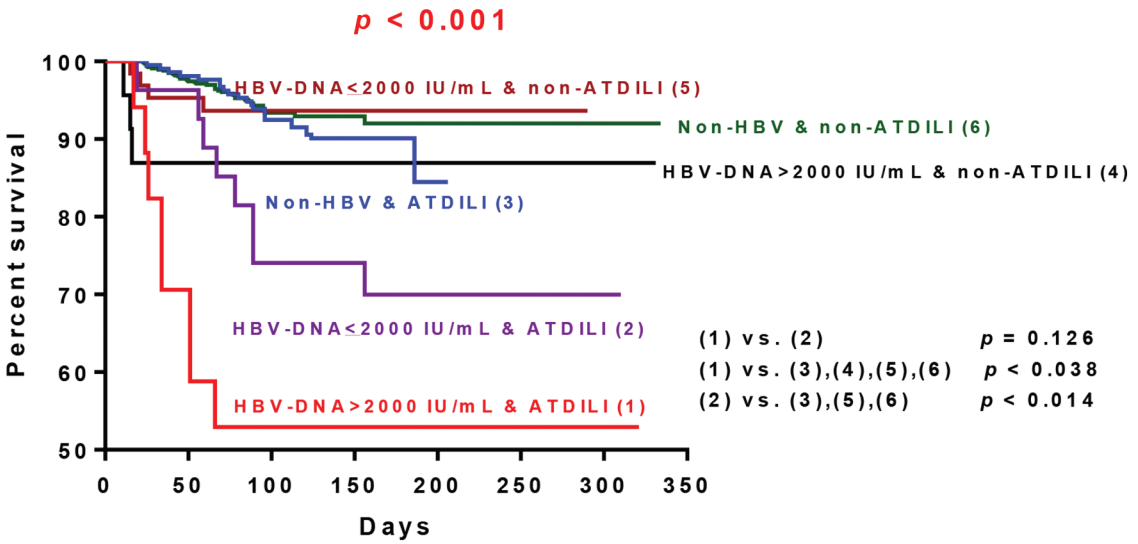


Fig. 2 Survival analysis of drug-induced liver injury between different risk factors by log-rank test. HBV = hepatitis B virus; TB = tuberculosis.



Number at risk								
(1)	17	14	10	10	4	4	4	0
(2)	27	27	22	19	2	2	2	0
(3)	213	210	199	174	2	1	1	0
(4)	23	19	10	8	5	2	2	0
(5)	64	60	28	16	3	2	1	0
(6)	670	638	234	104	8	3	2	0

Fig. 3 Survival analysis of drug-induced liver injury stratified by hepatitis B status and anti-tuberculosis drug-induced liver injury. The patients with HBV-DNA > 2000 IU/mL and antituberculosis drug-induced liver injury had the highest mortality rate. HBV = hepatitis B virus; ATDILI = antituberculosis drug-induced liver injury; non-ATDILI = drug-induced liver injury not induced by antituberculosis drugs.

4. DISCUSSION

DILI has become an important and challenging issue due to the increase in the development and marketing of new drugs. A better understanding of the risk factors and characteristics of DILI may help to prevent or alleviate this potentially fatal hepatotoxicity. In the present study, we identified the leading incriminating drugs and characteristics of DILI in Taiwan, and also found that chronic HBV infection was associated with severe liver injury and high mortality in the patients with DILI.

Chronic HBV infection is prevalent in Taiwan and many countries in Asia, and the interaction of HBV infection and DILI is a growing concern. Some studies have suggested that chronic HBV infection may increase the incidence and severity of ATDILI.[7–15] An early prospective study from Hong Kong reported that HBV carriers had both a higher risk of ATDILI and also more severe hepatotoxicity than controls.[8] Their findings are compatible with the results of the present study, in that the HBV carriers with ATDILI had a poor prognosis. However, two previous studies reported that only HBV carriers with

Table 5

Univariate and multivariable analysis of factors associated with liver-related mortality in drug-induced liver injury by Cox proportional hazards regression model

	Crude HR (95% CI)	*p*	Adjusted HR[a] (95% CI)	*p*
Hepatitis B status				
Non-hepatitis B carrier	1 (reference)		1 (reference)	
Hepatitis B carrier				
HBV-DNA ≤ 2000 IU/mL	1.91 (1.03-3.55)	0.041	1.48 (0.79-2.76)	0.221
HBV-DNA > 2000 IU/mL	4.59 (2.41-8.73)	<0.001	4.40 (2.31-8.38)	<0.001
Antituberculosis drug-related	1.92 (1.24-2.97)	0.004	1.25 (1.08-1.44)	0.003
Albumin-Bilirubin (ALBI) score	1.24 (1.07-1.44)	0.004	4.09 (3.09-5.41)	<0.001
Preexisting cirrhosis	3.33 (1.66-6.66)	0.001		NS
Age	1.02 (1.01-1.03)	0.018		NS
Elevated baseline liver tests	1.77 (1.01-3.10)	0.046		NS
Creatinine (recognition)	2.60 (1.78-3.80)	<0.001		NS
Platelet (recognition)	0.89 (0.84-0.95)	0.001		NS

[a]Covariates in multivariable analysis for adjusted HR were chosen according to forward stepwise regression model with a significance level < 0.05 for addition to the model.
CI = confidence interval; HR = hazard ratio; NS = not statistically significant.

positive HBeAg or high HBV-DNA load had a higher incidence and severity of DILI.[9,12] In the present study, we further found that the DILI patients with high HBV activity (HBV-DNA > 2000 IU/mL) had a higher mortality rate than those who were not HBV carriers and those with low HBV activity, which has not been reported before.

The reason why HBV carriers with ATDILI have a poor outcome remains to be clarified. The first possible explanation is reactivation of HBV in addition to DILI, which may then cause more severe liver damage. Another possibility is that the immune system may be improved due to control of tuberculosis infection, which may then lead to a rebound immunological response to the intrahepatocytic HBV.[13] Furthermore, HBV carriers who take anti-TB drugs may have liver dysfunction and impaired metabolism, resulting in the accumulation of more toxic metabolites. In addition, cytokines may be upregulated in HBV carriers leading to a mixed inflammatory response. This proinflammatory condition triggered by replicating HBV may increase susceptibility to the toxic metabolites from antituberculosis drugs.[9] However, further studies are needed to clarify the true mechanism of the interaction of HBV and ATDILI.

A simple and straightforward strategy to prevent serious DILI is to regularly monitor liver biochemical tests before and during treatment in patients taking high-risk drugs, such as antituberculosis agents. However, in our previous study, we found that liver biochemical tests were not closely followed up in more than half of the patients with antituberculosis treatment, which increased the risk of more severe ATDILI.[22] In the present study, we further confirmed that the HBV carriers with DILI had poor outcomes. To mitigate this serious ADR, regular monitoring of liver function for patients receiving antituberculosis treatment, and especially HBV carriers, should be re-emphasized. Furthermore, antiviral therapy for HBV should be evaluated in this cohort.

The main strength of this study is that it is an 8-year multicenter prospective study of 1,014 DILI patients, which can represent the real status of DILI in Taiwan. We also explored the risk factors for fatal DILI, including HBV infection. However, there are several limitations to this study. First, genetic polymorphisms of some drug-metabolizing enzymes and human leucocyte antigens have been proposed to be associated with the susceptibility and severity of ATDILI.[23–27] However, whether these genetic factors and HBV have synergic effects is open to debate. Further studies are needed to explore this association. Second, the impact of HCV infection in patients with DILI was unclear in this study, because too few patients had chronic hepatitis C infection limiting further analysis. Third, as a certified hepatitis E virus enzyme-linked immunosorbent assay is not available in Taiwan, we could not completely rule out the possibility of acute hepatitis E viral infection in some of the enrolled cases. Around 3% of the patients with suspected DILI had positive serum antihepatitis E immunoglobulin M in the US DILIN.[28] Acute hepatitis E may interfere with the diagnostic reliability of DILI. Fourth, although the high RUCAM score of the patients in this study increased the reliability of a diagnosis of DILI, we still cannot completely rule out the role of reactivation of HBV in the HBV carriers with DILI.

In conclusion, this study highlights the crucial role of DILI in drug safety. Antituberculosis agents were incriminated in 25% of our Taiwanese cohort with DILI, and the patients with ATDILI had poorer outcomes than those in the other drug categories. Active HBV infection, ATDILI, and ALBI score were independent risk factors for fatal DILI. Administering drugs to HBV carriers should be done prudently and cautiously due to the poor outcomes of the patients with DILI in this study. Close monitoring of liver biochemical tests and timely antiviral therapy should be considered in HBV carriers during the administration of high-risk drugs, such as antituberculosis agents.

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