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Dyslipidemia is a Risk Factor for the Incidence and Severity of Drug-Induced Liver Injury (DILI): A Retrospective Population-Based Study in China

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

DE 1 Xu Li
CF 2 Le Wang
B 1 Dezhao Li
A 1 Junqi Niu
AG 1 Pujun Gao

1 Department of Hepatology, The First Hospital of Jilin University, Jilin University, Changchun, Jilin, P.R. China
2 Department of Ultrasound, The First Hospital of Jilin University, Jilin University, Changchun, Jilin, P.R. China

Corresponding Authors: Junqi Niu, e-mail: 874030867@qq.com, Pujun Gao, e-mail: gpj0411@163.com
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Background: A Chinese population-based study aimed to investigate the risk factors for the incidence and severity of drug-induced liver injury (DILI) from Chinese herbal medicines and conventional Western medicines.

Material/Methods: Liver biopsy and routine laboratory testing, including serum lipid measurements, was performed on 465 patients, including 168 patients with DILI and 297 patients without DILI. Histological grading of DILI used the METAVIR scoring system and the severity of DILI was graded as levels 0–5. Multivariate and univariate regression analysis were used to compare the two study groups, using a risk-adjusted odds ratio (AOR).

Results: There was no significant association between age, alcohol status, cardiovascular disease (CVD), hypertension, or type 2 diabetes mellitus and development of DILI. However, when compared with controls, patients with dyslipidemia (AOR, 2.173; 95% CI, 1.388–3.401; P=0.001) had an increased incidence of DILI, and men had a reduced incidence of DILI when compared with women (AOR, 0.276; 95% CI, 0.169–0.450; P<0.001). Risk factors for severe DILI (≥level 3) included drinking alcohol (AOR, 6.506; 95% CI, 2.184–19.384; *P*=0.001), and dyslipidemia (AOR, 3.095; 95% CI, 1.345–7.123; P=0.008). Patients with an increased duration of drug treatment of >1 year had a reduced risk of developing severe DILI compared with patients with a medication duration of ≤1 month (AOR, 0.259; 95% CI, 0.084–0.802).

Conclusions: Increased risk of the incidence of DILI was significantly associated with female gender and dyslipidemia, and the risk of developing severe DILI was associated with drinking alcohol and dyslipidemia.

MeSH Keywords: Drug-Induced Liver Injury • Dyslipidemias • Risk Factors

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Background

Drug-induced liver injury (DILI), also known as drug-induced hepatotoxicity, is due to an adverse reaction to a medication or a combination of medications and represents a major health concern. Although DILI is relatively uncommon, its incidence has risen steadily over the last decade in adults across all regions of the world [1–4]. The reported incidence of DILI is likely to be lower than the actual incidence due to under-reporting and difficulty in the diagnosis. The diagnosis is complicated by the varied clinical presentation of DILI, which arises from individual or idiosyncratic responses to medications and specific host interactions with the causative drug or combination of drugs [5,6]. Fortunately, when the offending drug is withdrawn, liver damage is largely resolved, but DILI can persist and even progresses in a small percentage of cases.

There are several complex risk factors for the occurrence and severity of DILI [7]. Many of these risk factors are related to genetic, immunological, and metabolic factors of the individual, and each plays an important role [8]. Specifically, individuals who are elderly [9], female [3], or who suffer from chronic liver disease [10] are more susceptible to DILI. Recently, additional risk factors, such as excess weight, metabolic syndrome, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD), have been suggested to contribute to the presentation and outcome in patients with DILI, but evidence supporting these risk factors is limited [11,12]. The characteristics of the causative drug may also contribute to DILI, including the medication dose, lipophilicity, and the extent of hepatic metabolism, but there have been few studies to identify these drug characteristics with the incidence of DILI.

Therefore, a retrospective population-based study aimed to investigate the risk factors for the incidence and severity of drug-induced liver injury (DILI) from Chinese herbal medicines and conventional Western medicines in China.

Material and Methods

Patients

A retrospective population-based case-control study was conducted at The First Hospital of Jilin University in China between January 2010 and June 2018. A total of 1,887 patients who underwent liver biopsy and routine laboratory tests were retrospectively screened for inclusion in the study. We excluded 1,422 patients with incomplete medical information, and the remaining 465 patients with complete laboratory information, medical history, and drug history were included in the study. Of these, 168 patients with a diagnosis of drug-induced liver injury (DILI) were included in the study group, and 297 patients without DILI were included in the control group.

The Independent Institutional Review Board of The First Hospital of Jilin University approved the recruitment of study participants and the study protocol. Each study participant provided written informed consent prior to enrollment in the study.

Liver biopsy and histological levels of drug-induced liver injury (DILI)

DILI was diagnosed based by histology of the percutaneous liver biopsies, which were collected using ultrasound localization and the Menghini technique [13]. Liver samples were fixed in formalin and paraffin-embedded for histological analysis. Liver biopsies were excluded from analysis if they contained less than three portal tracts. Histopathology was performed by two liver pathologists who were blinded to all clinical information. If required, diagnostic differences between the two pathologists were settled by a third experienced hepatopathologist who was blinded to clinical information and the diagnosis of the other pathologists. The METAVIR scoring system was used to quantify the degree of inflammation and fibrosis histologically in the liver biopsies that showed DILI [14].

Evaluation of the severity of DILI

The severity of DILI was defined in levels according to the 2015 Chinese Guideline for Diagnosis and Treatment of DILI [15]. The levels ranged from exposure to a causative drug but no liver injury (level 0) to death of the patient or severe liver damage requiring a transplant (level 5). Level 1 DILI was defined by a mild increase in serum enzyme activity, including total bilirubin (TBil) <2.5 ULN, and International Normalized Ratio (INR) <1.5. More extensive liver injury with early impairment of liver function, indicated by increased serum alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP), TBil ≥2.5 ULN, or INR ≥1.5, was defined as level 2 DILI. Severe clinical illness with significant jaundice and disabling symptoms and TBil ≥5 ULN and/or INR ≥1.5 indicated level 3 DILI. Level 4 DILI was defined by an increase in ALT and/or ALP, TBil ≥10 ULN, or a TBil that increased by ≥17.1 μmol/L per day, INR ≥2.0, prothrombin activity (PTA) >40%, or secondary loss of other organ functions, such as the brain (encephalopathy) or kidney (hepatorenal syndrome).

Diagnosis of fatty liver and dyslipidemia

The diagnosis of fatty liver was based on liver biopsy examination or ultrasound scan [16]. Dyslipidemia was defined based on the National Cholesterol Education Program Adult Treatment Panel III (ATPIII) criteria. Patients were considered to have dyslipidemia if they had total cholesterol >240 mg/dL, high-density lipoprotein cholesterol (HDL-C) <40 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥160 mg/dL, or triglyceride ≥200 mg/dL [17].

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Table 1. Demographic and clinical characteristics of cases of drug-induced liver injury (DILI) and controls.

Variable	DILI N=168	Non-DILI N=297	P-value
Male, N (%)	41 (24.4)	146 (49.2)	<0.001
Age (years)	50.00 (44.00–55.00)	43.00 (32.00–54.00)	<0.001
Smoking, N (%)	27 (16.1)	41 (13.8)	0.506
Drinking, N (%)	22 (13.1)	49 (16.2)	0.327
History of malignancy, N (%)	6 (3.6)	2 (0.7)	0.021
History of hypersensitivity, N (%)	32 (19.0)	26 (8.8)	0.001
CVD, N (%)	16 (9.5)	9 (3.0)	0.003
Hypertension, N(%)	28 (16.7)	25 (8.4)	0.007
Dyslipidemia, N(%)	60 (35.7)	64 (21.5)	0.001
Diabetes, N (%)	15 (8.9)	26 (8.8)	0.949
Fatty Liver, N (%)	34 (20.2)	63 (21.2)	0.804
AST (IU/L)	109.00 (48.83–230.60)	43.50 (28.85–103.65)	<0.001
ALT (IU/L)	159.00 (55.58–319.55)	66.10 (33.05–167.35)	<0.001
TBIL (μmol/L)	27.95 (12.48–122.13)	17.40 (11.60–29.95)	<0.001
ALP (IU/L)	124.70 (95.85–196.73)	91.00 (68.10–140.10)	<0.001
GGT (IU/L)	147.65 (77.33–275.53)	72.30 (28.85–183.00)	<0.001

DILI – drug-induced liver injury; AST – aspartate aminotransferase; ALT – alanine aminotransferase; TBIL – total bilirubin; ALP – alkaline phosphatase; GGT – gamma-glutamyltransferase; CVD – cardiovascular disease. Continuous variables are expressed as median (25^{th}, 75^{th} percentiles). Categorical variables are shown as numbers and percentages.

Demographic and clinical variables

The demographic and clinical characteristics evaluated in this study included gender, age, smoking history, history of drinking alcohol, a cause for liver disease, a history of hypersensitivity, the presence of cardiovascular disease (CVD), the presence of hypertension, malignancy, type 2 diabetes, fatty liver disease, and dyslipidemia. Data on the history of liver disease, duration of exposure to the medication, the daily dose of the medication, type of medication, and drugs that caused DILI in patients in the study group were analyzed.

Biochemical parameters of the patients were also evaluated at the time of liver biopsy by the collection of fasting blood samples and subsequent routine laboratory testing. The biochemical parameters measured included ALT, aspartate aminotransferase (AST), TBil, ALP, and gamma-glutamyl transpeptidase (GGT). Also, the INR and PTA were analyzed in patients with DILI for the classification of the severity of liver injury.

Statistical analysis

Continuous variables were represented by the mean (25^{th} and 75^{th} percentiles), and categorical variables were described by counts and percentages. Continuous variables were compared using two-tailed independent sample t-tests, and categorical variables were compared using the chi-squared (χ^2) test. Multivariate logistic regression analysis was adjusted for potential confounding variables, and the adjusted odds ratios (AOR) and 95% confidence intervals (CI) were calculated. All data analysis was performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA), and $P<0.05$ indicated statistical significance.

Results

Patient and control characteristics

Baseline demographic and clinical characteristics of 168 patients with drug-induced liver injury (DILI) and 297 patients without DILI who were included in the study (total, n=465) are shown in Table 1. Of the 168 patients with DILI, 41 were male and 127 were female. The median age of the patients was 50.0 years, and 27 patients (16.1%) had a smoking history, 22 patients (13.1%) had a history of drinking alcohol, 28 patients (16.7%) had hypertension, 60 patients (35.7%) had dyslipidemia, 32 patients (19.0%) had hypersensitivity, 34 patients (20.2%) had fatty liver, 6 patients (3.6%) had a history of malignancy, 16 patients (9.5%) had a history of cardiovascular disease (CVD), and 15 patients (8.9%) had type 2 diabetes.

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In the 297 patients without DILI, approximately half (49.2%) were male. The median age of the control patients was 43.00 years, and 41 patients (13.8%) had a smoking history, 49 patients (16.2%) had a history of drinking alcohol, 25 patients (8.4%) had hypertension, 64 patients (21.5%) had dyslipidemia, 26 patients (8.8%) had hypersensitivity, 63 patients (21.2%) had fatty liver, 2 patients (0.7%) had a history of malignancy, 9 patients (3.0%) had a history of CVD, and 26 patients (8.8%) had type 2 diabetes. Also, the serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBil), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) levels in the study group were significantly greater than in the control group.

Clinical and demographic characteristics associated with the incidence of DILI

Univariate analysis showed that gender, age, history of malignancy, history of hypersensitivity, and the presence of CVD, hypertension, and dyslipidemia were significantly different between the study and control patients. Therefore, gender, age, smoking status, alcohol drinking status, history of hypersensitivity, presence of CVD, hypertension, type 2 diabetes, fatty liver, dyslipidemia, and history of malignancy underwent multivariate analysis.

Patients with dyslipidemia had an adjusted odds ratio (AOR) of 2.173 (95% CI, 1.388–3.401; P=0.001) when compared with patients without dyslipidemia (Table 2). Study participants who smoked had an AOR of 2.273 (95% CI, 1.211–4.265; P=0.011) compared with non-smoking participants. Additionally, male participants had an AOR of 0.276 (95% CI, 0.169–0.450; P=0.001) compared with female participants. Study participants with a history of hypersensitivity had an AOR of 1.833 (95% CI, 1.008–3.331; P=0.047) compared with those without hypersensitivity. Study participants with a history of malignancy had an AOR of 7.800 (95% CI, 1.479–41.123; P=0.015) compared with those without malignancy. There was no significant association between age, alcohol drinking status, CVD, hypertension, fatty liver or type 2 diabetes and the development of DILI.

Therapeutic classes and uses of drugs associated with DILI

The therapeutic classes of drugs used by patients in the DILI group are listed in Table 3. There were 80 patients with DILI (47.6%) who used Chinese herbal medicines, 60 (35.7%) used Western medicines, and 28 (16.7%) used a combination of the two. To further evaluate the indications for the herbal drugs, the 80 patients who used Chinese herbal medications were subdivided into causal categories (Table 4). Dietary supplements, anti-inflammatory drugs, cardiovascular drugs, osteoarthropathy drugs, and digestive system drugs were the top five types of herbal drugs.

Clinical and demographic characteristics associated with the severity of DILI

Risk factors for severity of DILI were evaluated in 168 patients with DILI (Table 5). Univariate analysis showed that drinking alcohol, dyslipidemia, and duration of medication were significantly different between patients with severe (≥level 3) and mild (level 0–2) DILI. Gender, age, smoking status, alcohol drinking status, history of hypersensitivity, the presence of CVD, type 2 diabetes, fatty liver, a history of liver disease, malignancy, dyslipidemia, hypertension, medication type, and the daily dose of medication, and medication duration were included in the multivariate analysis.

Study participants with dyslipidemia had an AOR of 3.095 (95% CI, 1.345–7.123; P=0.008) when compared with those with normal plasma lipid. Study participants who drank alcohol had an AOR of 6.506 (95% CI, 2.184–19.384; P=0.001) compared with non-drinking study participants. When compared with participants with a medication duration of ≤31 days, participants with a longer medication duration (>1 year) had a lower risk for the development of severe DILI (AOR, 0.259; 95% CI, 0.084–0.802; P=0.019). However, there was no significant association between the daily dose of medication and the severity of DILI.

Discussion

In response to drug exposure at a threshold level, drug-induced liver injury (DILI) is now believed to be mediated by the adaptive immune response, which is triggered by damage-associated molecular pattern (DAMP) molecules [18]. Other contributing factors include reactive metabolite formation, oxidative stress, endoplasmic reticulum stress, mitochondrial injury, DNA damage, epigenetic modifications, or inhibition of bile acid excretion [19]. Host factors of individuals are also likely to influence toxicological responses, leading to the wide variation in the risk of developing DILI.

Consistent with previous findings, the findings of the present study showed associations between dyslipidemia and both the incidence and severity of DILI. The increased risk of DILI in dyslipidemia may be explained by several mechanisms. First, malnutrition could slow drug clearance and subsequently lead to delayed drug elimination and higher drug plasma levels [7]. Second, host factors, such as overnutrition and alcohol, may increase the pre-existing cellular oxidants of the host, modifying the drug-induced oxidative liver damage, resulting in steatosis, lipid peroxidation, and mitochondrial degeneration [11,20]. Third, patients with hyperlipidemia are frequently treated with statins, which have been shown to result in hepatotoxicity, as reported in several major prospective and retrospective studies on DILI [1,21–24], with more than 150 cases having been

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Table 2. Univariate and multivariate analyses of variables associated with drug-induced liver injury (DILI).

Variable	DILI N=168		Non-DILI N=297		P#	AOR (95% CI)*	P**
Gender					<0.001	0.276 (0.169–0.450)	<0.001
Female, N (%)	127	(75.6)	151	(50.8)			
Male, N (%)	41	(24.4)	146	(49.2)			
Age					0.436		
<60 years, N (%)	144	(85.7)	262	(88.2)			
≥60 years, N (%)	24	(14.3)	35	(11.8)			
Smoking					0.506	2.273 (1.211–4.265)	0.011
No, N (%)	141	(83.9)	256	(86.2)			
Yes, N (%)	27	(16.1)	41	(13.8)			
Drinking alcohol					0.327		
No, N (%)	146	(86.9)	248	(83.5)			
Yes, N (%)	22	(13.1)	49	(16.5)			
History of hypersensitivity					0.001	1.833 (1.008–3.331)	0.047
No, N (%)	136	(81.0)	271	(91.2)			
Yes, N (%)	32	(19.0)	26	(8.8)			
CVD					0.003		
No, N (%)	152	(90.5)	288	(97.0)			
Yes, N (%)	16	(9.5)	9	(3.0)			
Hypertension					0.007		
No, N (%)	140	(83.3)	272	(91.6)			
Yes, N (%)	28	(16.7)	25	(8.4)			
Diabetes					0.949	-	-
No, N (%)	153	(91.1)	271	(91.2)			
Yes, N (%)	15	(8.9)	26	(8.8)			
Fatty liver					0.804		
No, N (%)	134	(79.8)	234	(78.8)			
Yes, N (%)	34	(20.2)	63	(21.2)			
Dyslipidemia					0.001	2.173 (1.388–3.401)	0.001
No, N (%)	108	(64.3)	233	(78.5)			
Yes, N (%)	60	(35.7)	64	(21.5)			
History of malignancy					0.021	7.800 (1.479–41.123)	0.015
No, N (%)	162	(96.4)	295	(99.3)			
Yes, N (%)	6	(3.6)	2	(0.7)			

DILI – drug-induced liver injury; AOR – adjusted odds ration; CI – confidence interval; CVD – cardiovascular disease. # P value for univariate analysis. ** P value for multivariate analysis. *Adjusted for gender, age, smoking, drinking, allergic history, CVD, hypertension, diabetes, hyperlipemia, and history of malignancy.

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Table 3. Therapeutic classes of drugs that caused liver injury in 168 Chinese patients.

	No. of cases	Percentage
Chinese herbal medicines	80	47.6%
Western medicines	60	35.7%
Both	28	16.7%

Table 4. Indications of drugs that caused liver injury in 80 Chinese patients with drug-induced liver injury (DILI) from Chinese herbal medicines.

Drug indications	No. of cases
Dietary supplements	32
Anti-inflammatory drugs	10
Cardiovascular drugs	9
Osteoarthropathy drugs	7
Digestive system drugs	6

Drug indications	No. of cases
Obstetric/gynecological drugs	4
Rheumatism drugs	3
Endocrine drugs	4
Others	5

DILI – drug-induced liver injury.

Table 5. Univariate and multivariate analysis of variables associated with the severity of drug-induced liver injury (DILI).

Variables	Level 0–2 N=130	Level ≥3 N=38	P#	AOR (95% CI)*	P**
Gender			0.110	–	–
Female, N (%)	102 (78.5)	25 (65.8)			
Male, N (%)	28 (21.5)	13 (34.2)			
Age (years)			0.763	–	–
<60	112 (86.2)	32 (84.2)			
≥60	18 (13.8)	6 (15.8)			
Smoking history			0.146	–	–
No, N (%)	112 (86.2)	29 (76.3)			
Yes, N (%)	18 (13.8)	9 (23.7)			
Alcohol history			0.001	6.506 (2.184–19.384)	0.001
No, N (%)	119 (91.5)	27 (71.1)			
Yes, N (%)	11 (8.5)	11 (28.9)			
History of hypersensitivity			0.293	–	–
No, N (%)	103 (79.2)	33 (86.8)			
Yes, N (%)	27 (20.8)	5 (13.2)			
CVD			0.697	–	–
No, N (%)	117 (90.0)	35 (92.1)			
Yes, N (%)	13 (10.0)	3 (7.9)			

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Table 5 continued. Univariate and multivariate analysis of variables associated with the severity of drug-induced liver injury (DILI).

Variables	Level 0–2 N=130	Level ≥3 N=38	P#	AOR (95% CI)*	P**
Diabetes			0.368	–	–
No, N (%)	117 (90.0)	36 (94.7)			
Yes, N (%)	13 (10.0)	2 (5.3)			
History of liver disease			0.242	–	–
No, N (%)	104 (80.0)	27 (71.1)			
Yes, N (%)	26 (20.0)	11 (28.9)			
History of malignancy			0.723	–	–
No, N (%)	125 (96.2)	37 (97.4)			
Yes, N (%)	5 (3.8)	1 (2.6)			
Fatty Liver			0.887		
No, N (%)	104 (80.0)	30 (78.9)			
Yes, N (%)	26 (20.0)	8 (21.1)			
Dyslipidemia			0.013	3.095 (1.345–7.123)	0.008
No, N (%)	90 (69.2)	18 (47.4)			
Yes, N (%)	40 (30.8)	20 (52.6)			
Hypertension			0.248		
No, N (%)	106 (81.5)	34 (89.5)			
Yes, N (%)	24 (18.5)	4 (10.5)			
Type of medication			0.376	–	–
1	69 (53.1)	23 (60.5)			
2-4	49 (37.7)	14 (36.8)			
≥5	12 (9.2)	1 (2.6)			
Daily medication dose			0.075	–	–
≤10 mg	11 (8.5)	5 (13.2)			
11–49 mg	41 (31.5)	5 (13.2)			
≥5 0mg	78 (60.0)	28 (73.7)			
Duration of medication			0.003		0.004
≤31 days	38 (29.2)	11 (28.9)		1	
32–365 days	34 (26.2)	20 (52.6)		1.518 (0.591–3.899)	0.386
>1 year	58 (44.6)	7 (18.4)		0.259 (0.084–0.802)	0.019

DILI – drug-induced liver injury; AOR – adjusted odds ratio; CVD – cardiovascular disease. Continuous variables are expressed as median (25^{th}, 75^{th} percentiles). # P value for univariate analysis. ** P value for multivariate analysis. *Adjusted for sex, age, smoking, drinking, allergic history, CVD, DM, hypertension, hyperlipemia, history of liver disease, history of malignancy, medications, daily medication dose, and duration of medication.

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described [25–28]. This association is not surprising, given that all available statins are primarily cleared by the liver [29].

Previous studies have shown that patients with non-alcoholic fatty liver disease (NAFLD) are at higher risk of DILI compared with patients without NAFLD [30,31]. Therefore, host factors could influence key mechanistic components of DILI, such as drug handling, toxicological responses, inflammation and immune responses, and imbalance between tissue damage and the induction of repair processes [7]. However, in the present study, we did not find an association between fatty liver and DILI, possibly because steatosis and steatohepatitis are rare but well-documented types of DILI [32]. It can be difficult to distinguish between fatty liver and DILI on histology of liver biopsies, and the retrospective design of the present study prevented us from obtaining detailed information about the cause of fatty liver which might have also been due to alcohol, obesity, or metabolic factors.

The findings of the present study showed that patients with a history of hypersensitivity had a one-fold to two-fold higher risk of DILI than patients without hypersensitivity. Disease progression in DILI can be classified as immune or non-immune [33]. Therefore, it could be anticipated that immune-mediated DILI occurs due to host hypersensitivity to a portion of the drug or its metabolite, and some cases of DILI could be considered to be an allergic or hypersensitivity reaction [33]. Patients who have a history of hypersensitivity might be hypersensitive to the metabolite or a portion of the drug and develop DILI on contact with the drug.

The findings of this study also showed that patients who drank alcohol had a 6-fold to 7-fold increase in the incidence of DILI when compared with patients who did not drink. Although the relationship between alcohol consumption and DILI is not well established, chronic alcohol use has been shown to increase the risk of both non-idiosyncratic DILI from acetaminophen and fibrosis and cirrhosis from methotrexate [34–37]. Also, the risk of fibrosis and cirrhosis in long-term users of methotrexate is also increased in patients who consume large amounts of alcohol [38,39]. Alcohol use increases hepatotoxicity of anti-tuberculosis drugs [39,40], potentially through alcohol-mediated induction of hepatic CYP2E1. Although these previous findings and the findings of the present study support a connection between alcohol use and the incidence of DILI, prospective registries have not identified significant associations between alcohol consumption and the severity or duration of DILI [22,41]. Therefore, additional studies are necessary to determine the relationship between alcohol consumption and idiosyncratic DILI.

The findings of the present study showed that patients with shorter medication duration (≤31 days) had more severe DILI than patients with longer duration (>1 year), which is inconsistent with some previous studies [42]. One explanation these findings is that DILI arising from long-term medication is usually not immune-mediated and lacks the systemic features of immune DILI, and non-immune-mediated DILI is not associated with rapid reinjury upon drug re-challenge [33]. Therefore, immune-mediated DILI following short-term medication use may result in increased severity of liver injury severity, but it is also possible that the variety of drugs responsible for inducing liver injury in this study may have influenced the findings.

Recently, the general characteristics of medications that pose a higher risk of DILI have been progressively identified [43]. However, we did not find a relationship between the type of medication and the severity of DILI in this study. Previous reports have attempted to identify correlations between medication combinations and DILI, but with mixed results. For example, a retrospective study from the General Practice Research Database (GPRD) [42] found that combinations of two or more hepatotoxic drugs increased the risk of DILI. In contrast, a prospective study from Switzerland found that the risk of DILI was not associated with either increased comorbidity or medication combination [44]. A further study also failed to find any clinically important interactions between statin hepatotoxicity and concomitant medications [25].

Because DILI is known to occur at a drug exposure threshold that is dependent on the degree of hepatic metabolism and dose of the drug, it has been suggested that idiosyncratic DILI has a dose-dependent component. This view is supported by the observation that discontinued drugs and drugs with a black box warning for hepatotoxicity are usually prescribed in doses of 50 mg or more per day [5,43,45,46]. However, we did not find an association between high drug doses (≥50 mg) and the severity of DILI in this study, suggesting that idiosyncratic factors, such as reactive hepatic metabolites, are still important [47]. The importance of hepatic metabolism has been emphasized by findings from a study of DILI in the US, which found that drugs with ≥50% hepatic metabolism had a significantly higher risk of hepatotoxicity [48]. Substantial hepatic metabolism of drugs is also associated with significantly increased levels of serum alanine transaminase (ALT), liver failure, and fatal DILI [47]. Thus, it is logical that drugs with both high metabolism and a high daily dose may pose an even higher risk for the development of DILI. A further consideration is the route of hepatic disposal, as medications excreted through the biliary system are more closely associated with jaundice resulting from DILI when compared with those without biliary excretion [47].

Worldwide, herbal medications are also emerging as a major cause of DILI, and cases of DILI due to herbal medicines represent approximately 9% of cases of DILI in the United

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States, and between 19–63% of cases of DILI in Asian countries [23,49,50]. In the present study, the ratio of herbal to Western medicine associated with DILI was 1.3: 1, excluding patients taking a combination of both drugs. Importantly, 42% of patients with DILI associated with the use of Chinese herbal medicine also used dietary supplements, highlighting the potential adverse effects of combination drug use.

This study had several limitations. This was a retrospective study that relied on the accuracy of medical records. There was limited available patient data on the body mass index (BMI) and levels of glycated hemoglobin (HbA1c) in the patient population. Additional studies are required to further investigate the associations between glucose levels, alcohol consumption, and idiosyncratic DILI. Also, the limited number of cases in this study resulted in small numbers of subjects in the subgroup analysis, due to the inclusion criteria that required patients with available details of their medical history and blood lipid data. The limited study size may have affected the study findings regarding the lack of association between the risk and severity of DILI and medication dose and medication type.

Conclusions

A retrospective population-based study conducted in China aimed to investigate the risk factors for the incidence and severity of drug-induced liver injury (DILI) from Chinese herbal medicines and conventional Western medicines. Increased risk of the incidence of DILI was significantly associated with female gender and dyslipidemia, and the risk of developing severe DILI was associated with drinking alcohol and dyslipidemia. Dyslipidemia was associated with both an increased risk of DILI and with more severe forms of DILI.

Conflict of interest

None.

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