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

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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 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 (heporenal 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 (ATP III) 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].
**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), ALP, and gamma-glutamyltranspeptidase (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 (25th and 75th 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 ($\chi^2$) 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.
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, osteoarthritis 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
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) | 294 (93.5)  |         |              |            |
| Yes, N (%)                      | 24 (13.1)  | 23 (6.5)    |         |              |            |
| 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                             | 0.033      |                |         |              |            |
| 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.
Table 3. Therapeutic classes of drugs that caused liver injury in 168 Chinese patients.

| Drug Class                | 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            |
| 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  | Level ≥3   | p* | AOR (95% CI)* | p** |
|----------------------------|------------|------------|----|---------------|-----|
| Gender                     |            |            |    |               |     |
| Female, N (%)              | 102 (78.5) | 25 (65.8)  | 0.110 | –              | –   |
| Male, N (%)                | 28 (21.5)  | 13 (34.2)  | –   | –              | –   |
| Age (years)                |            |            |    |               |     |
| <60                        | 112 (86.2) | 32 (84.2)  | 0.763 | –              | –   |
| ≥60                        | 18 (13.8)  | 6 (15.8)   | –   | –              | –   |
| Smoking history            |            |            |    |               |     |
| No, N (%)                  | 112 (86.2) | 29 (76.3)  | 0.146 | –              | –   |
| Yes, N (%)                 | 18 (13.8)  | 9 (23.7)   | –   | –              | –   |
| Alcohol history            |            |            |    |               |     |
| No, N (%)                  | 119 (91.5) | 27 (71.1)  | 0.001 | 6.506 (2.184–19.384) | 0.001 |
| Yes, N (%)                 | 11 (8.5)   | 11 (28.9)  | –   | –              | –   |
| History of hypersensitivity|            |            |    |               |     |
| No, N (%)                  | 103 (79.2) | 33 (86.8)  | 0.293 | –              | –   |
| Yes, N (%)                 | 27 (20.8)  | 5 (13.2)   | –   | –              | –   |
| CVD                        |            |            |    |               |     |
| No, N (%)                  | 117 (90.0) | 35 (92.1)  | 0.697 | –              | –   |
| Yes, N (%)                 | 13 (10.0)  | 3 (7.9)    | –   | –              | –   |
| Variables                  | Level 0–2 N=130 | Level ≥3 N=38 | p* | AOR (95% CI)* | p** |
|----------------------------|-----------------|---------------|----|---------------|-----|
| Diabetes                   |                 |               |    |               |     |
| No, N (%)                  | 117 (90.0)      | 36 (94.7)     | 0.368 | –             | –   |
| Yes, N (%)                 | 13 (10.0)       | 2 (5.3)       |     |               |     |
| History of liver disease   |                 |               |    |               |     |
| No, N (%)                  | 104 (80.0)      | 27 (71.1)     | 0.242 | –             | –   |
| Yes, N (%)                 | 26 (20.0)       | 11 (28.9)     |     |               |     |
| History of malignancy      |                 |               |    |               |     |
| No, N (%)                  | 125 (96.2)      | 37 (97.4)     | 0.723 | –             | –   |
| Yes, N (%)                 | 5 (3.8)         | 1 (2.6)       |     |               |     |
| Fatty Liver                |                 |               |    |               |     |
| No, N (%)                  | 104 (80.0)      | 30 (78.9)     | 0.887 | –             | –   |
| Yes, N (%)                 | 26 (20.0)       | 8 (21.1)      |     |               |     |
| Dyslipidemia               |                 |               |    | 3.095 (1.345–7.123) | 0.008 |
| No, N (%)                  | 90 (69.2)       | 18 (47.4)     | 0.013 |               |     |
| Yes, N (%)                 | 40 (30.8)       | 20 (52.6)     |     |               |     |
| Hypertension               |                 |               |    |               |     |
| No, N (%)                  | 106 (81.5)      | 34 (89.5)     | 0.248 | –             | –   |
| Yes, N (%)                 | 24 (18.5)       | 4 (10.5)      |     |               |     |
| Type of medication         |                 |               |    |               |     |
| 1                          | 69 (53.1)       | 23 (60.5)     | 0.376 | –             | –   |
| 2-4                        | 49 (37.7)       | 14 (36.8)     |     |               |     |
| ≥5                         | 12 (9.2)        | 1 (2.6)       |     |               |     |
| Daily medication dose      |                 |               |    |               |     |
| ≤10 mg                     | 11 (8.5)        | 5 (13.2)      | 0.075 | –             | –   |
| 11–49 mg                   | 41 (31.5)       | 5 (13.2)      |     |               |     |
| ≥50 mg                     | 78 (60.0)       | 28 (73.7)     |     |               |     |
| Duration of medication     |                 |               |    |               |     |
| ≤31 days                   | 38 (29.2)       | 11 (28.9)     | 0.003 | 1              | 0.004 |
| 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 (25th, 75th 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.
The findings of the present study 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.

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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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