Differences in clinical characteristics among 726 patients with Chinese herbal medicine- or Western medicine-induced liver injury

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Abstract
The differences between Chinese herbal medicine (CHM)- and Western medicine (WM)-induced liver injury have rarely been reported. Our aim was to investigate the clinical features of patients with drug-induced liver injury (DILI) caused by CHM or WM.

The number of inpatients with DILI in our hospital showed an increasing trend over time. The incidence of DILI caused by CHM exhibited a linear trend toward an increase with time (P = .0012). Of the 726 DILI patients, females accounted for 65.8%. There were 353 cases (48.6%) caused by CHM and 225 cases (40.0%) caused by WM. The 3 most common causative CHMs were Polygonum multiflorum (38 cases), Fructus Psoraleae (35 cases), and Epimedium (26 cases). The proportions of female patients, alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, total bilirubin (TBIL) levels and antinuclear antibody (ANA) positivity rates among cases caused by CHM were higher than those of cases caused by WM (P < .05). There were more patients with severe cases caused by CHM than with severe cases caused by WM (P < .05).

The clinical characteristics of DILI caused by CHM differ from those caused by WM. The incidence of DILI caused by CHM is increasing yearly. The medication time of DILI caused by CHM is longer than that of DILI caused by WM, and the severity is greater. Therefore, it is necessary to scientifically and rationally use traditional CHM and monitor liver function. For DILI caused by CHM, the CHM prescription should be recorded in detail to provide detailed clinical data for scientific research on the liver toxicity of CHM.

Abbreviations: AIH = autoimmune hepatitis, ALF = acute liver failure, ALT = alanine transaminase, AST = aspartate aminotransferase, ALP = alkaline phosphatase, ANA = antinuclear antibody, CHM = Chinese herbal medicine, CHM-DILI = DILI caused by CHM, DILI = drug-induced liver injury, HDS = herbal and dietary supplements, INR = international normalized ratio, IQR = interquartile range, TBIL = total bilirubin, ULN = upper limit of normal, WM = Western medicine, WM-DILI = patients with DILI caused by WM.

Keywords: clinical characteristics, Chinese herbal medicine, DILI, Western medicine

1. Introduction
Drug-induced liver injury (DILI) is an adverse reaction to drugs or other exogenous substances that can cause unintentional injury to the liver, damaging hepatocytes and other types of cells within the liver. Liver injury caused by DILI is usually self-limiting, but persistent liver injury, acute liver failure (ALF), death, and liver transplantation have been reported.[1] DILI is the main cause of ALF in Europe, the United States and Japan and is the most common reason for the withdrawal of drugs from the market.[2-3]

In addition to Western medicine (WM), various preparations, such as Chinese herbal medicine (CHM), biologics, health products, natural medicines and dietary supplements and their metabolites, can cause DILI. Different drugs can induce similar types of liver damage, and a particular drug may induce different liver damage phenotypes in different patients, making the diagnosis and treatment of DILI particularly difficult.[1]

CHM has been used for thousands of years. It not only plays an important role in China’s medical system but is also used in many countries and regions around the world. For example, in a national prospective study in South Korea, the leading cause of DILI was CHM, accounting for more than 72% of DILI cases.[4] In China, Japan and India, the incidence and proportion of DILI caused by traditional herbs are increasing.[5-9] Although liver injury caused by herbs and dietary supplements...
is relatively rare in the United States, the incidence is increasing, and it has become the second most common cause of DILI in that country. For example, according to the NIH-funded Drug Induced Liver Injury Network (DILIN), herbal and dietary supplements (HDS) accounted for 7% of DILI cases in 2004 to 2005, and it increased to 20% in 2013 to 2014. [10] A global ALF research group reported that approximately 20 to 40% of ALF caused by DILI is due to HDS. [11]

At present, there are few studies on the clinical characteristics of patients with DILI caused by CHM (CHM-DILI) and patients with DILI caused by WM (WM-DILI). In this study, we analyzed the clinical characteristics of 726 inpatients with DILI from our hospital and further analyzed differences between CHM- and WM-induced liver injury.

2. Materials and Methods

2.1. Patients

The patients enrolled were hospitalized with a principal diagnosis of DILI at the Peking University First Hospital from January 1995 through August 2019. The clinical and laboratory results of patients who were discharged with a principal diagnosis of DILI (ICD-10 code: K71.901, K71.601) were extracted from electronic medical records. The enrollment protocol is shown in Figure 1. The inclusion criteria were as follows: (1) a suspicious medication history before abnormal liver function and biochemical indicators meeting the Council for International Organizations of Medical Sciences (CIOMS) criteria regarding DILI, [12] including alanine aminotransferase (ALT) > 2 × the upper limit of normal (ULN) (if it is hepatocyte type, it must be > 3 × ULN) or direct bilirubin (DBIL) > 2 × ULN or concurrent increases in aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBIL), with 1 value > 2 × ULN; and (2) RUCAM score ≥ 3. Key exclusion criteria were as follows: (1) incomplete and unavailable hospital records; (2) a possibility of liver damage from other causes; (3) viral hepatitis, autoimmune hepatitis (AIH) or other underlying liver diseases; (4) excessive alcohol use; and (5) malignancy. The study protocol was approved by the ethics committee of the Peking University First Hospital.

Figure 1. The patient enrollment protocol.
2.2. Assessment of clinical patterns of liver injury
DILI is classified into 3 types according to CIOMS criteria,[12] hepatocellular, cholestatic, or mixed, based on its R-value. The R-value is defined as the serum ALT/ULN ratio divided by the serum ALP/ULN ratio. R-values > 5 are classified as hepatocellular type, < 2 as cholestatic type, and 2 to 5 as mixed type.

2.3. Severity assessment
A severity assessment was conducted according to the Chinese guidelines for the diagnosis and treatment of DILI in 2015,[19] as follows: ⊗ 1 (mild), serum enzyme elevations with TBIL < 2.5 × ULN and an international normalized ratio (INR) < 1.5; ⊗ 2 (moderate), serum enzyme elevations and TBIL ≥ 2.5 × ULN or an INR ≥ 1.5; ⊗ 3 (severe), serum enzyme elevations and TBIL ≥ 5 × ULN with or without an INR ≥ 1.5; and ⊗ 4 (acute liver failure), serum enzyme elevations and TBIL ≥ 10 × ULN or a daily elevation of TBIL ≥ 17.1 mol/L, an INR ≥ 2.0 or prothrombin time activity (PTA) < 40% and signs of hepatic or other organ failure related to DILI.

2.4. Statistical analysis
Statistical analysis was conducted with SPSS software (version 21.0) and R (version 4.1.0). Quantitative variables are expressed as the median and range. Categorical variables are presented as numbers and percentages. The Mann–Whitney U test was used for 2 nonnormal datasets. Chi-square tests or corrections for continuity were applied for categorical variables. The Mann–Whitney U test was employed to compare the time of drug use to onset for each group. The Cochran Armitage trend test was used for trend testing. P < .05 was considered statistically significant.

3. Results
3.1. Demographics
The number of inpatients with DILI in our hospital showed an increasing trend over time, with a minimum number of 23 cases from 1995 to 1999 and a maximum number of 248 cases.
from 2010 to 2014. The time distribution of DILI is shown in Figure 2A. Among the 726 DILI patients, 65.8% were female, and the median age was 53 years old. The age distribution of DILI patients is depicted in Figure 2B. Most cases clustered into 3 age groups, 41 to 50 years old, 51 to 60 years old, and 61 to 70 years old, with 138, 191, and 148 cases, respectively. These cases accounted for 65.7% of the total number of patients. The 726 cases of DILI included 575 hepatocellular DILI, 67 cholestasis DILI, and 84 mixed DILI cases, accounting for 79.2%, 9.2%, and 11.6% of the total cases, respectively. The demographic characteristics and biochemical characteristics of the 3 clinical subtypes of DILI are shown in Table 1.

### 3.2. Causative agents

The suspicious injury-causing drugs found for the 726 DILI cases in our hospital are shown in Table 2. Among the suspected drugs, there were 353 patients who had used CHM, accounting for 48.6%. WM included antimicrobial drugs, cardiovascular system drugs, antipyretics, analgesic and antiinflammatory drugs, antigout drugs, drugs for mental disorders, hormones, endocrine drugs, antitumor drugs, and combination drugs, with a total of 225 cases accounting for 40.0% of the total. In addition, 142 patients (19.6%) were treated with combination medicine and 103 (14.2%) with a combination of Chinese herbal medicine and western medicine. The suspected injury-causing drug in the 726 patients with DILI was statistically analyzed. Among the 353 cases caused by CHM, 147 could not be traced to concrete CHM components, accounting for 41.6% of the cases caused by CHM. Concrete CHM components were identified in 206 cases, accounting for 58.4% of the cases caused by CHM. Among these 206 cases caused by CHM in which the components could be identified, 7 cases were caused by a single prescription, accounting for 2.0% of CHM-DILI, 140 cases were caused by patent Chinese medicine, accounting for 39.7% of CHM-DILI, and 59 cases were caused by compound decoction, accounting for 16.7% of CHM-DILI. The common causative CHMs were Polygonum multiflorum (38 cases), Psoraleae (35 cases), Epimedium (26 cases), Bupleurum (22 cases), rhubarb (21 cases), Cortex Dictamni (13 cases), Rhizoma Corydalis (13 cases), and Rhizoma Smilacis Glabrae (12 cases).

### 3.3. Trends of the cases of DILI caused by CHM and WM

The trends of cases caused by CHM are illustrated in Figure 3. In 1995 to 1999, 2000 to 2004, 2005 to 2009, 2010 to 2014, and 2015 to 2019, cases caused by CHM accounted for 43.5%, 39.7%, 40.8%, 49.2%, and 57.0% of the total DILI cases, respectively. The lowest value was found in the 2000 to 2004 period and the highest in 2015 to 2019, showing an overall upward trend over time. According to the Cochran-Armitage trend test, there was a linear trend between the proportion of CHM-DILI and the year, and the incidence of CHM-DILI showed a linear increasing trend over time ($P < .0012$). However, WM-DILI cases reached a maximum in 2005 to 2009 and then began to decline sharply.
3.4. Clinical characteristics of cases caused by CHM and WM

The proportions of female patients, ALT levels, AST levels, and ANA positivity rates in the CHM-DILI group were higher than those in the WM-DILI group ($P < .05$). In terms of severity, there were fewer patients with mild cases caused by CHM than by WM, and there were more patients with severe cases in the CHM-DILI group than in the WM-DILI group ($P < .05$). The clinical characteristics of CHM-DILI and WM-DILI are shown in Table 3. In addition, we statistically analyzed the clinical characteristics of female and male patients with CHM-DILI. The rates of ANA and ALP positivity in female patients were higher than those in male patients, with statistically significant differences ($P < .05$) (Table 4).

The median time of drug use to onset of patients with CHM-DILI was 30 days and that of patients with WM-DILI was 29 days. “Time of drug use to onset” refers to the time from the start of the medication to the diagnosis of DILI. The Mann-Whitney U test was performed on these 2 datasets, and the difference between them was highly statistically significant ($P = .001$). The time of drug use to onset was stratified, and the results are shown in Figure 4. Overall, there was no statistical significance in the time of drug use to onset between the CHM-DILI and WM-DILI groups over 30 days ($P > .05$). When the time from drug use to onset was $<15$ days, there were fewer cases of WM-DILI than CHM-DILI. When the time of drug use to onset was 16 to 30 days, there were more cases of CHM-DILI than WM-DILI, and the difference was statistically significant ($P < .05$).

### Table 3

Clinical characteristics of DILI caused by CHM and WM.

| Variable                  | Chinese herbal medicine (n = 353) | Western medicine (n = 225) | $P$       |
|---------------------------|----------------------------------|---------------------------|-----------|
| Female, n (%)             | 256 (72.5)                       | 127 (56.4)                | <0.0001   |
| Age, yr (IQR)             | 53 (42–63)                       | 52 (38–63)                | 0.577     |
| Time of drug use to onset | 30 (18–60)                       | 29 (7–60)                 | 0.001     |
| Laboratory parameters (IQR) |                                 |                           |           |
| ALT ($\times$ULN)        | 715 (332–1137.6)                | 384 (190–810)             | <0.0001   |
| AST ($\times$ULN)        | 410 (197.8–692)                 | 198 (97.6–467)            | <0.0001   |
| ALP ($\times$ULN)        | 132 (94.5–176.2)                | 127.4 (81–201.3)          | 0.865     |
| TBLI ($\times$ULN)       | 66 (23.1–160)                   | 42.1 (16–137.75)          | 0.002     |
| ANA positive, n (%)      | 122 (34.6)                      | 31 (13.8)                 | <0.0001   |
| Liver injury patterns, n (%) |                                 |                           |           |
| Hepatocellular           | 304 (86.1)                      | 156 (69.3)                | <0.0001   |
| Cholestatic              | 24 (6.5)                        | 27 (12)                   | 0.032     |
| Mixed                    | 25 (7.1)                        | 42 (18.7)                 | <0.0001   |
| Severity, n (%)          |                                 |                           |           |
| 1 (mild)                 | 148 (41.9)                      | 116 (51.6)                | 0.0234    |
| 2 (moderate)             | 61 (17.3)                       | 40 (17.8)                 | 0.878     |
| 3 (severe)               | 137 (38.8)                      | 64 (28.4)                 | 0.011     |
| 4 (ALF)                  | 7 (2.0)                         | 5 (2.2)                   | 0.844     |

$ALF = $ acute liver failure, $ALT = $ alanine transaminase, $ALP = $ alkaline phosphatase, $ANA = $ antinuclear antibody, $AST = $ aspartate aminotransferase, $DILI = $ drug-induced liver injury, $IQR = $ interquartile range, $TBLI = $ total bilirubin, $ULN = $ upper limit of normal.

### 4. Discussion

Herbs, which grow in nature rather than being artificially synthesized, have been used in medical treatment for thousands of years and continue to play an important role.[13] In this study, we compared the clinical features of CHM-DILI and WM-DILI to help improve understanding of CHM-DILI. As our case collection spans 24 years, we provide a clearer understanding of the prevalence of DILI during this time. The total number of patients with DILI rose sharply in 2005, and CHM-DILI has increased rapidly since. With the improvement in living standards, Chinese people have begun to take a large number of CHM and CHM-related health products, many of which are used without the guidance of a doctor. This situation may be the reason for the sudden increase in the number of cases. Among the 726 DILI patients in this study, those aged 41 to 70 accounted for 66% of the total number. The proportion of DILI patients aged 65 years or older in this study (21.5%) was higher than that reported by the DILIN registry (18.5%)[14] This finding may be due to their age and the prevalence of illness, increasing the proportion of people who use CHM for treatment or health care.

Drugs causing DILI have always been a concern of the academic community. China is the country with the largest number of herboaceous plants in the world, with 5000 plant varieties. In this study, CHM-DILI accounted for 48.6% of cases, higher than the rate in Western countries.[10] Among CHM-DILI cases, self-health care is the top reason for CHM use. For WM-DILI, antimicrobial drugs are the primary injury-causing drugs, which is consistent with studies in other countries.[15]

The high prevalence of CHM-DILI in China is due to the following reasons. (1) The use of CHMs, especially Chinese patent medicines, has increased. Chinese patent medicines are convenient to take, and most of them are nonprescription drugs, which is consistent with a study in Northeast China. Most of the patients in this study also purchased these medicines by themselves for body care.[16] In fact, the curative effect of CHM lies not only in the medicine itself but also in the dialectic of the patient’s body according to the theory of traditional Chinese medicine, which is important for adjusting the type and dosage of the medicine or stopping the medicine in time to avoid injury. (2) There are fake medicines, which include crude drugs that are not processed in accordance with the prescribed methods and that contain heavy metals, pesticides, and substances not listed on the label, which will increase the toxicity of CHMs. For example, the hepatotoxicity of black cohosh[17,18] and *Pelargonium sidoides*[19] has been suspected, with controversial arguments regarding confounding variables, and these confounding factors may cause overreporting of CHM-DILI.[20] (3) Patients only value the curative effect of CHM but do not notice the side effects. According to *Zhou day official* (Zhouli Tiangong in Chinese), government doctors used poisons to treat diseases thousands of years ago. *Shennong’s Classic of Materia Medica* (shennongbencaojing in Chinese), written in the Eastern Han Dynasty in China, is the earliest known book on CHM. This book divides CHMs into nontoxic drugs, slightly toxic drugs, and toxic drugs. This classification shows that thousands of years ago, Chinese ancestors knew that the toxicity and efficacy of CHM coexisted. (4) Certain populations may have idiosyncratic constitutions or family genetic tendencies. For example, the HLA-B*35:01 allele is a potential marker for people who are susceptible to liver damage caused by *Polygonum multiflorum*. Even when the medication is used appropriately, there is a risk of liver damage.[21]

In a cohort study of 461 DILI patients from Spain, hepatocellular patterns of liver injury, female sex, and total serum
biliubin levels were identified as independent predictors of ALF.\textsuperscript{[22]} The high proportion of women in the CHM-DILI group may be related to the structure of the population taking CHM. Females may use CHM more for health care purposes, consistent with what has been reported by DILIN,\textsuperscript{[22]} Spanish DILI Registry,\textsuperscript{[23]} and Chinese studies.\textsuperscript{[24]} A study on herb-induced liver injury in China reported 88.5\% of cases to comprise hepatocellular-type injury.\textsuperscript{[25]} In this study, 86.1\% of cases were hepatocellular-type injuries, which was significantly higher than the percentage of WM-DILI. High transaminase and bilirubin levels can independently predict death in patients with hepatocellular injury or liver transplantation.\textsuperscript{[26]} In our research, patients with CHM-DILI had higher ALT, AST and TBIL levels than patients with WM-DILI, and levels were altered to a greater extent. It is necessary to use CHM scientifically and rationally and to monitor liver function. For CHM-DILI, it is also necessary to record the traditional CHM prescription in detail to provide detailed clinical data for scientific research on the liver toxicity of CHM.

In our study, the time from drug use to onset in the CHM-DILI group was longer than that in the WM-DILI group. Some studies believe that a long time of drug use to onset is more likely to lead to the development of chronic DILI and liver cirrhosis than is a short time.\textsuperscript{[27]} Therefore, when using CHM, regular monitoring of liver function is needed, especially for patients who take medication long-term.

There are 2 types of DILI. The intrinsic type is dose dependent; the idiosyncratic type is not dose dependent. Both innate and adaptive immunity have a clear and pivotal role in intrinsic and idiosyncratic DILI.\textsuperscript{[28]} There are some DILI patients with clinical features of autoimmune, such as autoantibody positivity and obvious liver immune cell infiltration. People use “autoimmune(-like)” DILI to describe these cases,\textsuperscript{[29]} and these cases have clinical features similar to those of AIH. In this study, the proportion of ANA-positive patients in the CHM-DILI group was significantly higher than that in the WM-DILI group. Therefore, CHM-DILI patients have a greater tendency to show clinical characteristics similar to those of AIH patients. In the CHM-DILI group, the proportion of ANA-positive patients and ALP levels were significantly higher in females than males, indicating that females in the CHM-DILI group were more likely to

| Variable                  | Female (n = 256) | Male (n = 97) | P     |
|--------------------------|-----------------|--------------|-------|
| Age,years (IQR)          | 54 (43–63)      | 51 (41–64)   | 0.769 |
| Time of drug use to onset: days (IQR)| 30 (17–60) | 30 (20–60) | 0.799 |
| Laboratory parameters (IQR) |                 |              |       |
| ALT (×ULN)               | 699.5 (322.5–1067) | 866.3 (375.9–1487.5) | 0.027 |
| AST (×ULN)               | 410 (197.8–692)  | 198 (97.6–467) | 0.609 |
| ALP (×ULN)               | 132 (94.5–176.2) | 127.4 (81–201.3) | <0.0001 |
| TBIL (×ULN)              | 66 (23.1–160)    | 42.1 (16–137.75) | 0.174 |
| ANA positive, n (%)      | 101 (39.5)       | 21 (21.6)    | 0.002 |
| Liver injury patterns, n (%) |            |              |       |
| Hepatocellular           | 221 (86.3)       | 83 (85.6)    | 0.854 |
| Cholestatic              | 16 (6.3)         | 8 (8.2)      | 0.506 |
| Mixed                    | 19 (7.4)         | 6 (6.2)      | 0.686 |
| Severity, n (%)          |                 |              |       |
| 1 (mild)                 | 108 (42.2)       | 40 (41.2)    | 0.872 |
| 2 (moderate)             | 46 (17.9)        | 15 (15.5)    | 0.578 |
| 3 (severe)               | 98 (38.3)        | 39 (40.2)    | 0.740 |
| 4 (ALF)                  | 4 (1.6)          | 3 (3.1)      | 0.357 |

\textsuperscript{ALF = acute liver failure, ALT = alanine transaminase, ALP = alkaline phosphatase, ANA = antinuclear antibody, AST = aspartate aminotransferase, DILI = drug-induced liver injury, IQR = interquartile range, TBIL = total bilirubin, ULN = upper limit of normal.}

**Figure 4.** Time of drug use to onset of DILI caused by CHM and WM (**P < .01; ****P < .0001).
present “autoimmune(-like)” DILI. In terms of treatment, AIH requires long-term immunosuppression, whereas DILI does not. In addition to “autoimmune(-like)” DILI, there are many other clinical scenarios involving both DILI and AIH, for example, DILI combined with AIH, drug-induced AIH,[30] a second episode of DILI mimicking a relapsing course of AIH,[31] and chronic DILI mimicking AIH.[32] These cases are difficult to define because there is no consensus on the nomenclature and etiologies as such, differential diagnosis is particularly important.

The HLA genotype and that of drug-metabolism genes affect susceptibility to DILI due to a range of drugs and correlate with the underlying mechanisms.[33,34] The metabolic etiology; as such, differential diagnosis is particularly important. to define because there is no consensus on the nomenclature and etiologies as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important. The metabolic etiology; as such, differential diagnosis is particularly important.

There are some limitations in our study. Among the 353 cases caused by CHM, the CHM composition in 147 cases (41.6%) could not be identified, which may be due to the following reasons: ① the clinician failed to record the medication status of the patient in detail; ② some patients took folk or secret prescriptions and could not provide medication prescriptions; and ③ some patients failed to provide CHM prescriptions due to lost prescriptions or complicated prescriptions and could not recall the CHM composition. Not knowing the CHM composition will affect a clinician’s diagnosis of DILI, which is not conducive to the clinical study of CHM-DILI. In addition, the 726 DILI cases were from a single clinical center, which may have caused selection bias, and the proportion of Chinese medicine-induced DILI may have been overestimated. Patient outcomes were not analyzed in this study because the patients were not followed up.

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