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Original Article

Characteristics of Drug-induced Liver Injury in Chronic Liver Disease: Results from the Thai Association for the Study of the Liver (THASL) DILI Registry

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Abstract

Background and Aims: The impact of drug-induced liver injury (DILI) on patients with chronic liver disease (CLD) is unclear. There are few reports comparing DILI in CLD and non-CLD patients. In this study, we aimed to determine the incidence and outcomes of DILI in patients with and without CLD. ***Methods:*** We collected data on eligible individuals with suspected DILI between 2018 and 2020 who were evaluated systematically for other etiologies, causes, and the severity of DILI. We compared the causative agents, clinical features, and outcomes of DILI among subjects with and without CLD who were enrolled in the Thai Association for the Study of the Liver DILI registry. Subjects with definite, or highly likely DILI were included in the analysis. ***Results:*** A total of 200 subjects diagnosed with DILI were found in the registry. Of those, 41 had CLD and 159 had no evidence of CLD in their background. Complementary and alternative medicine (CAM) products were identified as the most common class of DILI agents. Approximately 59% of DILI in the CLD and 40% in non-CLD group were associated with CAM use. Individuals with pre-existing CLD had similar severity including mortality. Twelve patients (6%) developed adverse outcomes related to DILI including seven (3.5%) deaths and five (2.5%) with liver failure. Mortality was 4.88% in CLD and 3.14% in non-CLD subjects over median periods of 58 (8–106) days and 22 (1–65) days, respectively. ***Conclusions:*** In this liver disease registry, the causes, clinical presentation, and outcomes of DILI in subjects with CLD and without CLD patients were not different. Further study is required to confirm our findings.

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Keywords: Chronic liver disease; Cirrhosis; Drug-induced liver injury; Drug-induced liver injury network; Toxicity; Medication.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAM, complementary and alternative medicine; CI, confidence interval; CLD, chronic liver disease; DILI, drug-induced liver injury; IQR, interquartile range; RUCAM, Roussel Uclaf Causality Assessment Method; SD, standard deviation; THASL, Thai Association for the Study of the Liver; ULN, upper normal limit.

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Introduction

Drug-induced liver injury (DILI) is a common and frequently an under-recognized cause of liver problems. The incidence is difficult to determine because of under-reporting and because of differences in the diagnostic criteria that are used. A

population-based study that conducted over a 3-year period in a city in northern France reported an incidence of DILI of approximately 14 cases per 100,000 patient-years.[1] Of those with DILI, 6% died and 12% required hospitalization. The incidence of DILI seems to be higher in Asia than in Western countries. In a 3-year retrospective study in mainland China involving 308 medical centers, the incidence of hospitalization for DILI was 23.80 per 100,000 patient-years.[2] In that study, 1.08% of those with DILI progressed to hepatic failure and 0.39% died. However, the study included only hospitalized patients with DILI. The actual DILI incidence in Asia in the general population is thus unknown.

Some studies reported that DILI was linked with an increased risk of adverse outcomes in patients with chronic liver disease (CLD). Patients with viral hepatitis B or C coinfection with human immunodeficiency virus are at risk of DILI, especially from antituberculosis drugs or highly active antiretroviral therapy (HAART),[3] and immune reconstitution with HAART may lead to reactivation of an underlying viral hepatitis B and C reactivation. The effect of DILI on hepatic deterioration in patients with CLD is controversial because most relevant reports are retrospective studies.[4] The consequences of DILI in patients with CLD remain unknown. A better understanding would be useful in evaluating the risks of hepatotoxic drugs and informing stakeholders to create health awareness and prevention of DILI especially in patients with CLD. The goal of this study was to determine the incidence and seriousness of DILI, focusing on patients with CLD using prospective study data from a DILI registry.

Methods

The Thai Association for the Study of the Liver (THASL) DILI registry, is a cooperative data coordinating center that includes 12 academic medical centers across the country and the Center of Excellence for Biomedical and Public Health Informatics (BIOPHICS), Mahidol University. The THASL DILI registry prospective study is an ongoing observational study of adults with suspected DILI with the goal of creating a registry and biological sample repository for the clinical study of DILI. This prospective DILI registry is endorsed by and receives grant support from the THASL.

Data enrollment

Subjects considered for enrollment into the DILI registry signed a written informed consent form approved by the local institutional review board of each center. Subjects were at least 18 years of age at the time of enrollment, and were suspected of having DILI within the preceding 6 months. Subjects were excluded if a drug overdose such as acetaminophen or occurring after solid organ or bone marrow transplantation was suspected. The enrollment criteria included jaundice (total bilirubin >2.5 mg/dL or > 2 times the upper limit of normal (ULN) with elevations of alanine or aspartate aminotransferase (ALT or AST) or alkaline phosphatase (ALP) >2 times of ULN with elevation of gamma-glutamyl transpeptidase; or, in the absence of jaundice, elevation of ALT or AST >5 times the ULN or ALP >2 times ULN.[5–7] Study subjects were followed up at 1 month, 3 months, and then every 3 months or until normalization of liver enzymes.

Causality assessment

We evaluated the causal relationship between the clinical pattern of liver injury and the suspected drugs or complementary and alternative medicine (CAM) products with the Roussel Uclaf Causality Assessment Method (RUCAM) system. RUCAM is a validated and established tool to quantitatively assess causality in cases of suspected DILI and/or CAM product-induced liver injury.[8,9] We also use the Clinical Assessment of Causality Scale to assess the association as definite (>95% likelihood), highly likely (75–95%), probable (50–74%), possible (25–49%) or unlikely (<25%). In cases with several possible DILI-inducing agents, the overall situation was evaluated for the likelihood that it was DILI and each agent was given a separate score. If possible, one agent was be considered as being the most likely or definitely accountable. Some cases of CAM-induced DILI may have been complex because the CAM product contained several active ingredients. CAM products were adjudicated as a single agent at time of analysis. If a conflict of considered agents occurred, agreement among the investigators was achieved by email and teleconference. We considered only cases of DILI for study inclusion.

Assessment of clinical patterns and severity grading of liver injury

Clinical patterns of DILI were described by the R ratio, the ratio of serum ALT to ALP expressed as multiples of the ULN. Liver injury was defined as hepatocellular (R>5), cholestatic (R<2), or mixed (R=2–5).[8,9] The R ratio based on values at the onset of liver injury. Severity was defined as mild (elevated ALT/ALP reaching DILI criteria but with bilirubin concentration <2 times the ULN), moderate (elevated ALT/ALP reaching DILI criteria and bilirubin ≥2 times the ULN, or symptomatic severe hepatitis (moderate DILI with one of the following: international normalized ratio ≥1.5, ascites and/or encephalopathy, disease duration <26 weeks, and absence of underlying cirrhosis; other organ failure considered to result from DILI), death or transplantation because of DILI).[7]

Cohort selection and definition of CLD

We compared the impacts of DILI in subjects with CLD and those with normal background liver function. All enrolled subjects were reviewed by a panel of expert hepatologists to diagnose CLD, which was defined by the presence of chronic liver inflammation or injury that was revealed by a history of CLD, abnormal results of laboratory testing, and/or imaging studies. Cirrhosis was diagnosed from laboratory testing and/or imaging studies. Staging of cirrhosis followed the Child-Pugh classification. The causes of CLD included chronic hepatitis B and C viral infection, alcoholic liver disease, nonalcoholic steatohepatitis, and others. Subjects who did not drink alcohol regularly and had a history of normal liver health status with normal liver enzymes and negative for viral hepatitis that was serologically confirmed at time of enrollment were considered to have no evidence of CLD, i.e. a normal liver background.

Data management

BIOPHICS was in charge of all activities related to data collection, recording, and analysis. That included development and management of case record forms, database design, data generation, following queries, and clinical data management consultancy. Demographic and clinical data of subjects enrolled in the THASL DILI registry between December 1, 2018 and December 31, 2020 were extracted on January 14, 2021.

Statistical analysis

SAS 9.3 for windows (SAS Institute Inc., Cary, NC, USA) was used for the data analysis. The results were reported by descriptive statistics such as means and standard deviation (SD) or medians and interquartile range (IQR). Between-group differences were assessed with either Mann-Whitney *U* tests or Kruskal-Wallis tests. Categorical variables were compared with χ^2 tests, CMH-χ^2 tests or Fisher's exact test where appropriate. Two-sided 95% confidence intervals (CIs) were determined and *p*-values <0.05 were considered statistically significant.

Results

Demographic characteristics of study subjects and cohort selection

Between December 1, 2018 and December 31, 2020, a total of 200 DILI subjects were enrolled in the THASL DILI registry prospective study. We included only highly probable (26.5%) and probable subjects (73.5%) defined by the RUCAM score. Subjects in whom DILI was deemed as unlikely, such as experiencing a flare-up of underlying of liver disease were excluded from the analysis. Of those, 41 were reviewed by a panel of expert hepatologists and found to have underlying CLD from their medical history, laboratory testing, and/or imaging studies, and 159 had no evidence of CLD. Causes of pre-existing CLD were mainly hepatitis B viral infection (*n*=14), alcohol (*n*=9), and hepatitis C viral infection (*n*=5). Others causes were cryptogenic or nonalcoholic steatohepatitis (*n*=13).

Selected clinical and demographic information of the enrolled subjects compared by liver function background

We compared the clinical characteristics and laboratory parameters of the 200 study subjects divided into groups with CLD or normal liver function (control group). As shown in Table 1, subjects with CLD were predominantly male with clinical DILI presentation not different from the normal liver function group. Patterns of liver injury revealed hepatocellular in 41.5% in those with chronic liver disease group and 57.2% in the controls. Subjects with DILI trended to be in middle aged (mean age of 54 years in both groups). Immune-mediated characteristics, defined as at least two of three clinical features of fever, rash, or absolute eosinophilia >500 μL tended to be less frequent in the CLD group (26.8% vs. 44.7%, *p*=0.747). Liver biochemical features including ALT, ALP, and platelet count were significant lower in the CLD group. Differences in the presence of medical comorbidities in the two groups were not significant. Two patients (4.88%) in the CLD group and five patients (3.14%) in the normal liver group died over median periods of 58 (8–106) days and 22 (1–65) days, respectively (*p*=0.355).

Clinical outcomes after DILI

Among the 200 subjects with DILI, 12 (6%) developed adverse outcomes related to DILI including seven (3.5%) who died and five (2.5%) who developed liver failure (Table 2). Patients with CLD who had poor outcomes tended to have higher AST, ALT, and total bilirubin than those with complete recovery. Similarly, elevated total bilirubin was seen in patients in the normal liver function group. No subjects underwent liver transplantation or had severe cutaneous adverse reactions related to DILI.

Drugs associated with DILI occurrence

A total of 214 agents were identified as causing DILI in 200 study subjects, including 130 (60.8%) prescription drugs and 84 (39.2%) CAM products. In the CLD group, we identified 42 therapeutic agents that caused DILI in 40 subjects. CAM products were the most common class of DILI agents, accounting for 24 cases (58.5%, Table 3A) followed by antimicrobials in seven cases (17.1%). In the control group, CAM products were also identified as the most common class of DILI agents, accounting for 59 cases (37.1%, Table 3B), followed by antimicrobials in 37 cases (23.3%). Nearly all the antimicrobials causing DILI in both the CLD and control groups were antituberculosis drugs. Other therapeutic agents included antineoplastic drugs (15 cases, 9.4%), miscellaneous drugs (13 cases, 8.2%), and lipidemic drugs (10 cases, 6.3%). Most patients who had DILI with cholestatic liver injury had higher total bilirubin levels than the other groups.

Predictors of DILI severity grade

We classified predictors of severity grading using the subject variables. Twelve cases (34.3%) in the CLD group included eight (22.8%) with moderate and four (11.4%) with severe DILI. Fifty-nine cases (42.4%) in the normal group included 41 (29.5%) with moderate and 18 (12.9%) with severe DILI. Male subjects, acute presentation, and immune-mediated features predominated in the CLD group who developed moderate to severe DILI (Table 4). Immune-mediated features predominated in subjects in the normal liver group who had moderate to severe DILI. Overall liver enzymes were higher in patients who developed moderate to severe DILI. Univariate analysis of predictors of DILI severity is shown in Table 5. The presence of CLD was not associated with DILI severity grade. The variables that were significantly and inversely associated with the DILI severity grade included mixed pattern of liver injury, R-values of 2–5 and >5, hemoglobin ≥9 g/dL, and white blood cells $\geq 12\times10^3$/dL. Multivariate analysis did not find any subject variable that was significantly associated with DILI severity grade.

Discussion

DILI is an infrequent but important cause of liver injury. In the Thai THASL DILI registry conducted in Thailand, we identified 6% of subjects developed adverse outcomes related to DILI. In this study, moderate to severe DILI was seen in 34.3% and 42.4% of patients with and without CLD, especially among those with cholestatic liver injury who had high total bilirubin levels. We also found that 20% of subjects with DILI had known pre-existing CLD. Demographic and clinical features of pre-existing CLD were generally similar to those without pre-existing CLD, except that male subjects predominated in the first group. In our registry, the most commonly implicated agents were CAM products, followed by antimicrobials. The common causes of DILI were traditional herbal medicines used in China, India, Japan and Singapore, and antituberculosis drugs in India and China.[10–12] Antimicrobials, mostly amoxicillin-clavulanate, were reported as the most frequent cause of DILI in the USA[13] In our registry, individuals with pre-existing CLD had severity and mortality similar to those without CLD. How-

Table 1. Data at presentation of drug-induced liver injury between chronic liver disease and normal group

Characteristics	Outcome (% or SD)		p-value
	Chronic liver disease (N=41)	Normal liver (N=159)	
Gender, n (%)			0.001*
Male	28 (68.29%)	63 (39.62%)	
Symptoms, n (%)			0.737
Jaundice	7 (17.07%)	24 (15.09%)	
Jaundice + itching	1 (2.44%)	6 (3.77%)	
Jaundice + abdominal pain	1 (2.44%)	11 (6.92%)	
Jaundice + abdominal pain + itching	0 (0.00%)	4 (2.52%)	
Eosinophilia, n (%)			0.529
Yes	2 (4.88%)	18 (11.32%)	
Immune mediated, n (%)			0.747
Yes	11 (26.83%)	71 (44.65%)	
R value, n (%)			0.388
Less than 2	8 (19.51%)	23 (14.47%)	
From 2–5	7 (17.07%)	39 (24.53%)	
More than 5	17 (41.46%)	91 (57.23%)	
RUCAM score: Probable total			0.153
≤6	21 (51.22%)	52 (32.70%)	
7	12 (29.27%)	23 (14.47%)	
8	6 (14.63%)	33 (20.75%)	
RUCAM score: Highly probable total			1.000
9	2 (4.88%)	30 (18.87%)	
10	0 (0.00%)	8 (5.03%)	
≥11	0 (0.00%)	13 (8.18%)	
Age: (years)	54.56 (13.49)	54.09 (15.46)	0.924
AST (U/L)	316.04 (695.25)	425.67 (796.33)	0.051
ALT (U/L)	260.46 (322.51)	442.51 (651.98)	0.026*
ALP (U/L)	148.44 (110.12)	217.71 (168.14)	0.004*
PT (sec)	16.95 (6.48)	15.88 (9.84)	0.126
INR	1.56 (0.68)	1.43 (1.03)	0.096
Total bilirubin (mg/dL)	5.05 (9.14)	3.80 (5.79)	0.931
Direct bilirubin (mg/dL)	3.72 (7.19)	2.81 (4.46)	0.689
Hemoglobin (g/dL)	11.94 (2.53)	11.98 (1.86)	0.797
Platelet count ($\times 10^3$/dL)	165.44 (68.16)	250.05 (111.21)	<0.0001*
WBC ($\times 10^3$/dL)	6.53 (2.42)	8.09 (5.32)	0.231
Underlying condition, n (%)			
Hypertension	14 (34.15%)	44 (27.67%)	0.443
Diabetes mellitus	8 (19.51%)	23 (14.47%)	0.426
Dyslipidemia	12 (29.27%)	45 (28.30%)	0.715
Chronic kidney disease	4 (9.76%)	7 (4.40%)	0.247
Tuberculosis	3 (7.32%)	23 (14.47%)	0.492
Death, n (%)	2 (4.88%)	5 (3.14%)	0.355

*Significant difference with p-value ≤0.05. R value, the ratio of serum alanine transferase to alkaline phosphatase; RUCAM, the Roussel Uclaf Causality Assessment Method; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PT, prothrombin time; INR, international normalized ratio; WBC, white blood cell.

Table 2. Clinical Outcome after drug-induced liver injury between chronic liver disease and normal group

Characteristics Mean(SD)	Chronic liver disease		p-value	Characteristics Mean(SD)	Normal Liver		p-value
	Complete recovery (N=24)	Poor outcome (N=3)			Complete recovery (N=119)	Poor outcome (N=9)	
AST (U/L)	193.58 (280.57)	1,991.67 (2,035.64)	0.203	AST (U/L)	475.40 (882.78)	287.17 (352.23)	0.712
ALT (U/L)	203.45 (261.70)	858.33 (718.27)	0.217	ALT (U/L)	506.04 (731.10)	203.27 (231.77)	0.080
ALP (U/L)	131.95 (79.36)	209.00 (146.37)	0.296	ALP (U/L)	222.96 (175.82)	178.67 (104.91)	0.645
PT (sec)	16.50 (6.24)	22.50 (8.23)	0.178	PT (sec)	15.29 (9.03)	23.99 (17.36)	0.133
INR	1.53 (0.70)	2.07 (0.76)	0.261	INR	1.37 (0.95)	2.27 (1.86)	0.097
Total bilirubin (mg/dL)	5.89 (10.17)	12.34 (11.92)	0.110	Total bilirubin (mg/dL)	3.38 (4.75)	8.59 (11.30)	0.073
Direct bilirubin (mg/dL)	4.24 (7.79)	10.19 (10.52)	0.075	Direct bilirubin (mg/dL)	2.55 (3.98)	5.04 (5.78)	0.113
Hemoglobin (g/dL)	12.51 (2.51)	12.93 (0.93)	0.778	Hemoglobin (g/dL)	12.04 (1.84)	11.01 (1.91)	0.126
Platelet count ($\times 10^3$/dL)	160.12 (79.38)	143.67 (29.74)	0.732	Platelet count ($\times 10^3$/dL)	248.51 (109.78)	193.75 (71.81)	0.169
WBC ($\times 10^3$/dL)	6.16 (2.52)	7.98 (2.03)	0.254	WBC ($\times 10^3$/dL)	8.03 (5.63)	8.23 (1.21)	0.080

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PT, prothrombin time; INR, international normalized ratio; WBC, white blood cell.

ever, type II errors may have occurred when the events of DILI in our subjects with pre-existing CLD subjects were too few. Future studies should include large sample sizes to confirm the findings.

In our study, the negative impact of CLD on outcomes and clinical courses of DILI was not found. The risk of a fatal outcome after DILI development in patients with CLD and cirrhosis remains controversial. In the DILI Network Prospective Study, conducted in North America, subjects with CLD (n=89; 10%) had increased risks of adverse outcomes and mortality.[13] However, that population also had a high prevalence of diabetes that may have been a confounding factor. A retrospective study in China demonstrated an impact of antituberculosis therapy in cirrhotic patients with active tuberculosis.[14] In that Chinese study, the incidence of DILI, defined by abnormal liver enzyme levels, was more common among patients with cirrhosis compared with patients without pre-existing liver diseases, but the difference was not significant and there were no differences in the development of mild, moderate, and severe DILI.[14] Moreover, most cirrhotic patients with active tuberculosis were successfully rechallenged with standard non-hepatotoxic antituberculosis regimens.[14] A retrospective cohort study in Korea including 299 patients who started treatment of multidrug-resistant tuberculosis[15] reported that the frequency of DILI was significantly higher in patients with pre-existing CLD including alcoholic liver disease and viral hepatitis B or C infection, than in patients without pre-existing liver diseases. However, most patients had only mild to moderate hepatitis, no DILI-associated deaths or cases of liver failure were reported, and the treatment outcomes in those with and those without pre-existing CLD were similar.[15]

Limitations of our study include site selection bias and arbitrary laboratory eligibility criteria, as the DILI registration is not nationwide, and a central laboratory was not used. However, the study sites were selected based on the availability of expert hepatologists and were located across the country. Hence, our data represent the DILI cohort from referral centers in Thailand that have experienced hepatologists who cautiously made a diagnosis of DILI, especially when the suspected culprit agents were CAM products. The CAM analysis was limited by a small sample in the DILI registry, heterogeneity of CAM use, and the difficulty to identify the cause of DILI in patients with CAM-induced liver injury who sometimes used more than one type of CAM or used CAM and suspected drugs simultaneously.

This is the largest DILI registry in our country, and we have provided a characterization of DILI in Thailand. In conclusion, our study highlights that DILI in patients with CLD had outcomes similar to those in patients without CLD, but the result may need confirmation in a larger sample size. CAM products and antimicrobials were leading categories of agents causing DILI in both patients with and without pre-existing CLD.

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Table 3. Drugs incriminated in drug-induced liver injury occurrence

	Total n (%)	Time of first presentation to diagnosis (days) M±SD	Time of first presentation to enrollment (days) M±SD	Hospitalization due to DILI n (%)	cholestatic n (%)	Mixed n (%)	Hepatocellular n (%)	Acute n (%)	Chronic n (%)
Chronic liver disease N=41									
1. Antimicrobials	7 (17.07%)	2.56 (3.32)	36.44 (63.58)	4 (9.76%)	2 (4.88%)	0 (0.00%)	5 (12.20%)	1 (2.44%)	6 (14.63%)
2. Cardiovascular agents	1 (2.44%)	2.00 (-)	1.00 (-)	1 (2.44%)	1 (2.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)
4. Anti-neoplastic agents	2 (4.88%)	1.00 (0.00)	60.50 (82.73)	1 (2.44%)	0 (0.00%)	1 (2.44%)	1 (2.44%)	0 (0.00%)	2 (4.88%)
6. Immunomodulatory	3 (7.32%)	1.33 (0.58)	43.67 (46.97)	1 (2.44%)	1 (2.44%)	0 (0.00%)	2 (4.88%)	0 (0.00%)	3 (7.32%)
10. Rheumatologic	1 (2.44%)	1.00 (-)	78.00 (-)	0 (0.00%)	1 (2.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)
12. Musculoskeletal	1 (2.44%)	1.00 (-)	1.00 (-)	0 (0.00%)	0 (0.00%)	1 (2.44%)	0 (0.00%)	0 (0.00%)	1 (2.44%)
13. Herbal/Dietary supple	24 (58.54%)	20.80 (32.89)	25.20 (44.57)	3 (7.32%)	13 (31.71%)	5 (12.20%)	6 (14.63%)	10 (24.39%)	14 (34.15%)
14. Other	3 (7.32%)	1.00 (0.00)	7.00 (9.54)	2 (4.88%)	1 (2.44%)	2 (4.88%)	0 (0.00%)	0 (0.00%)	3 (7.32%)
Normal Liver N=159									
1. Antimicrobials	37 (23.27%)	5.30 (9.52)	49.14 (67.48)	17 (10.69%)	20 (12.58%)	9 (5.66%)	8 (5.03%)	9 (5.66%)	28 (17.61%)
2. Cardiovascular agents	3 (1.89%)	1.00 (0.00)	29.00 (46.78)	1 (0.63%)	0 (0.00%)	3 (1.89%)	0 (0.00%)	0 (0.00%)	3 (1.89%)
3. Central nervous system	7 (4.40%)	5.57 (8.32)	11.43 (18.46)	5 (3.14%)	3 (1.89%)	3 (1.89%)	1 (0.63%)	2 (1.26%)	5 (3.14%)
4. Anti-neoplastic agents	15 (9.43%)	12.13 (29.36)	56.07 (53.12)	3 (1.89%)	9 (5.66%)	3 (1.89%)	3 (1.89%)	3 (1.89%)	12 (7.55%)
5. Analgesics	3 (1.89%)	10.80 (10.62)	45.80 (97.94)	1 (0.63%)	1 (0.63%)	1 (0.63%)	1 (0.63%)	2 (1.26%)	1 (0.63%)
6. Immunomodulatory	8 (5.03%)	1.13 (0.35)	59.13 (50.67)	2 (1.26%)	5 (3.14%)	2 (1.26%)	1 (0.63%)	0 (0.00%)	8 (5.03%)
7. Endocrine	7 (4.40%)	4.86 (11.58)	65.71 (83.82)	3 (1.89%)	3 (1.89%)	0 (0.00%)	4 (2.52%)	1 (0.63%)	6 (3.77%)
8. Lipidemic	10 (6.29%)	6.50 (14.23)	67.10 (77.04)	0 (0.00%)	7 (4.40%)	3 (1.89%)	0 (0.00%)	2 (1.26%)	8 (5.03%)
9. Nutrition	2 (1.26%)	1.00 (0.00)	143.50 (31.82)	0 (0.00%)	1 (0.63%)	0 (0.00%)	1 (0.63%)	0 (0.00%)	2 (1.26%)
10. Rheumatologic	2 (1.26%)	6.00 (2.83)	11.00 (14.14)	1 (0.63%)	1 (0.63%)	1 (0.63%)	0 (0.00%)	1 (0.63%)	1 (0.63%)
12. Musculoskeletal	4 (2.52%)	5.50 (5.45)	77.00 (103.85)	0 (0.00%)	1 (0.63%)	3 (1.89%)	0 (0.00%)	2 (1.26%)	2 (1.26%)
13. Herbal/Dietary supple	59 (37.11%)	5.93 (12.60)	36.85 (62.46)	16 (10.06%)	43 (27.04%)	10 (6.29%)	6 (3.77%)	10 (6.29%)	48 (30.19%)
14. Other	13 (8.18%)	5.38 (9.31)	42.54 (72.27)	2 (1.26%)	6 (3.77%)	5 (3.14%)	2 (1.26%)	2 (1.26%)	11 (6.92%)

Table 4. Characteristics between chronic liver disease and normal group based on severity criteria of drug-induced liver injury

	Chronic liver disease		Normal Liver	
	Mild (N=23)	**Moderate to severe (N=12)**	**Mild (N=80)**	**Moderate to severe (N=59)**
Sex				
Male	11 (47.83%)	11 (91.67%)	27 (33.75%)	25 (42.37%)
Female	12 (52.17%)	1 (8.33%)	53 (66.25%)	34 (57.63%)
Age (years)				
<30	0 (0.00%)	2 (16.67%)	8 (10.00%)	10 (16.95%)
30–55	8 (34.78%)	4 (33.33%)	27 (33.75%)	16 (27.12%)
>55	15 (65.22%)	6 (50.00%)	45 (56.25%)	33 (55.93%)
Presentation (Time of first presentation to diagnosis of DILI)				
Acute (within 7 days)	17 (73.91%)	11 (91.67%)	65 (81.25%)	49 (83.05%)
Chronic (>7 days)	6 (26.09%)	1 (8.33%)	14 (17.50%)	10 (16.95%)
Type of liver injury				
Hepatocellular	11 (47.83%)	6 (50.00%)	51 (63.75%)	35 (59.32%)
Mixed	6 (26.09%)	1 (8.33%)	21 (26.25%)	10 (16.95%)
Cholestatic	6 (26.09%)	5 (41.67%)	8 (10.00%)	14 (23.73%)
Eosinophilia				
Yes	1 (4.35%)	1 (8.33%)	6 (7.50%)	10 (16.95%)
No	11 (47.83%)	11 (91.67%)	49 (61.25%)	45 (76.27%)
Immune Mediated				
Yes	3 (13.04%)	7 (58.33%)	25 (31.25%)	40 (67.80%)
No	1 (4.35%)	3 (25.00%)	9 (11.25%)	12 (20.34%)
R value				
Less than 2	3 (13.04%)	5 (41.67%)	6 (7.50%)	14 (23.73%)
From 2–5	3 (13.04%)	1 (8.33%)	22 (27.50%)	10 (16.95%)
More than 5	10 (43.48%)	6 (50.00%)	47 (58.75%)	35 (59.32%)
AST (U/L)				
<200	20 (86.96%)	5 (41.67%)	44 (55.00%)	22 (37.29%)
≥200	3 (13.04%)	7 (58.33%)	33 (41.25%)	37 (62.71%)
ALT (U/L)				
<200	15 (65.22%)	6 (50.00%)	28 (35.00%)	22 (37.29%)
≥200	8 (34.78%)	6 (50.00%)	50 (62.50%)	37 (62.71%)
ALP (U/L)				
<150	18 (78.26%)	5 (41.67%)	39 (48.75%)	18 (30.51%)
≥150	2 (8.70%)	7 (58.33%)	33 (41.25%)	40 (67.80%)
PT (sec)				
<13.5	7 (30.43%)	3 (25.00%)	26 (32.50%)	14 (23.73%)
≥13.5	0 (0.00%)	8 (66.67%)	3 (3.75%)	28 (47.46%)
INR				
<1.5	6 (26.09%)	4 (33.33%)	28 (35.00%)	29 (49.15%)
≥1.5	0 (0.00%)	7 (58.33%)	1 (1.25%)	13 (22.03%)
Total bilirubin (mg/dL)				
<5	16 (69.57%)	5 (41.67%)	68 (85.00%)	29 (49.15%)
≥5	1 (4.35%)	7 (58.33%)	3 (3.75%)	30 (50.85%)
Direct bilirubin (mg/dL)				
<3	16 (69.57%)	5 (41.67%)	67 (83.75%)	27 (45.76%)
≥3	1 (4.35%)	7 (58.33%)	3 (3.75%)	32 (54.24%)
Hemoglobin (g/dL)				
<9	2 (8.70%)	2 (16.67%)	1 (1.25%)	8 (13.56%)
≥9	10 (43.48%)	10 (83.33%)	53 (66.25%)	47 (79.66%)
Platelet count ($\times 10^3$/dL)				

(continued)

Table 4. *(continued)*

	Chronic liver disease		Normal Liver	
	Mild (N=23)	**Moderate to severe (N=12)**	**Mild (N=80)**	**Moderate to severe (N=59)**
<150	3 (13.04%)	6 (50.00%)	4 (5.00%)	9 (15.25%)
≥150	9 (39.13%)	6 (50.00%)	51 (63.75%)	46 (77.97%)
WBC ($\times 10^3$/dL)				
<12	12 (52.17%)	12 (100.00%)	52 (65.00%)	45 (76.27%)
≥12	0 (0.00%)	0 (0.00%)	3 (3.75%)	10 (16.95%)

R value, the ratio of serum alanine transferase to alkaline phosphatase; RUCAM, the Roussel Uclaf Causality Assessment Method; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PT, prothrombin time; INR, international normalized ratio; WBC, white blood cell.

Table 5. Predictors of severity grading of drug-induced liver injury

Predictor	**Severity**		**OR (95% CI)**	**P-value**
	Mild (N=103)	**Moderate to severe (N=73)**		
Liver Status				
Chronic liver disease	23 (65.71%)	12 (34.29%)	0.707 (0.326–1.535)	0.3813
Normal Liver	80 (57.55%)	59 (42.45%)	Ref.	
Sex				
Male	38 (51.35%)	36 (48.65%)	1.664 (0.905–3.060)	0.1011
Female	65 (63.73%)	37 (36.27%)	Ref.	
Age (years)				
<30	8 (38.10%)	13 (61.90%)	Ref.	
30–55	35 (62.50%)	21 (37.50%)	0.369 (0.131–1.038)	0.0589
>55	60 (60.61%)	39 (39.39%)	0.400 (0.152–1.054)	0.0637
Presentation: (Time of first presentation to diagnosis of DILI)				
Acute (within 7 days)	82 (56.94%)	62 (43.06%)	0.727 (0.325–1.629)	0.4392
Chronic (>7 days)	20 (64.52%)	11 (35.48%)	Ref.	
Type of liver injury:				
Hepatocellular	62 (59.05%)	43 (40.95%)	0.511 (0.231–1.129)	0.0968
Mixed	27 (71.05%)	11 (28.95%)	0.300 (0.112–0.803)	0.0166*
Cholestatic	14 (42.42%)	19 (57.58%)	Ref.	
Eosinophilia				
Yes	7 (38.89%)	11 (61.11%)	1.626 (0.590–4.481)	0.3477
No	60 (50.85%)	58 (49.15%)	Ref.	
Immune Mediated				
Yes	28 (36.84%)	48 (63.16%)	1.071 (0.428–2.681)	0.8828
No	10 (38.46%)	16 (61.54%)	Ref.	
R value[#]				
Less than 2 (Cholestatic pattern)	9 (32.14%)	19 (67.86%)	Ref.	
From 2–5 (Mixed pattern)	25 (69.44%)	11 (30.56%)	0.208 (0.072–0.604)	0.0039*
More than 5 (Hepatocellular pattern)	57 (57.00%)	43 (43.00%)	0.357 (0.147–0.867)	0.0229*
Hemoglobin (g/dL)				
<9	3 (21.43%)	11 (78.57%)	Ref.	
≥9	63 (52.07%)	58 (47.93%)	0.251 (0.067–0.945)	0.0410*
Platelet count ($\times 10^3$/dL)				
<150	7 (31.82%)	15 (68.18%)	Ref.	
≥150	60 (52.63%)	54 (47.37%)	0.420 (0.159–1.108)	0.0796
WBC ($\times 10^3$/dL)				
<12	64 (52.46%)	58 (47.54%)	Ref.	
≥12	3 (21.43%)	11 (78.57%)	4.046 (1.075–15.223)	0.0387*

P-value based on Likelihood Ratio (LR) Chi-Square test, *Significant difference (p-value ≤0.05), [#]Incomplete data, Ref.–Reference group, OR–Odds ratio, Row percentages were presented. R value, the ratio of serum alanine transferase to alkaline phosphatase; WBC, white blood cell.

Conflict of interest

ST has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2021. CB has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

Full access to all the data in the study and take responsibility for the integrity of said data and the accuracy of the data analysis (SC, AS).

Ethical statement

All subjects were properly instructed, and consented to participate in this trial by signing the informed consent regulation provided by each institutional review board. All the institutional review boards followed the World Medical Association DELCARATION OF HELSINKI, GUIDELINES FOR GOOD CLINICAL PRACTICE, International Council for Harmonization Tripartite Guidelines, Council for International Organizations of Medical Sciences, CODE of FEDERAL REGULATIONS Title 45 Public Welfare, Part 46 Protection of Human Subjects, and the Belmont Report to satisfy the ethics concerns in publications. Informed consent was obtained from all subjects, and all methods were conducted according to the relevant guidelines and regulations. Informed consent was obtained by signature of all participants and from all subjects to provide all the information regarding publication.

Data sharing statement

The datasets used during the current study are available from the corresponding author on reasonable request.

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