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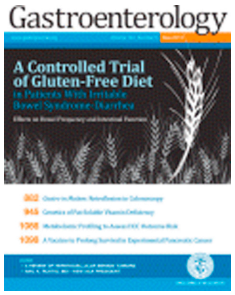

Incidence and Etiology of Drug-Induced Liver Injury in Mainland China

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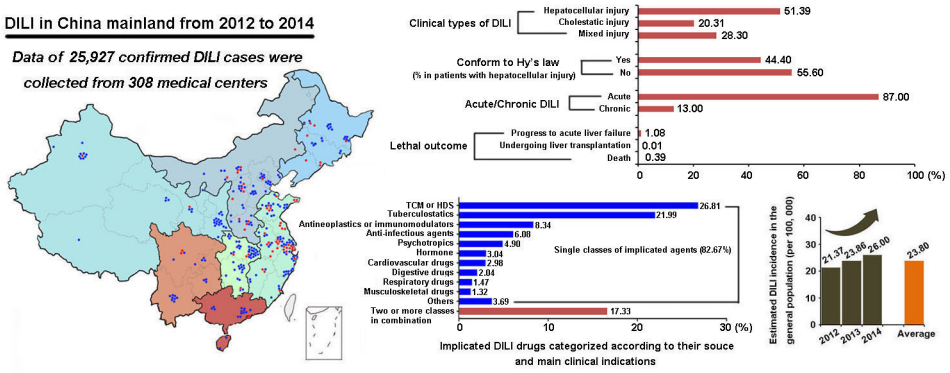

Incidence and Etiology of Drug-Induced Liver Injury in Mainland China

Short title: DILI in Mainland China

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Abbreviations： DILI, drug-induced liver injury; ALF, acute liver failure; CSH, Chinese Society of Hepatology; TCM, traditional Chinese medicines; HDS, herbal and dietary supplements; ADR, adverse drug reaction; CAMs, complementary and alternative medicines; ALT, alanine aminotransferase; AST, aspertate aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; TBil, total bilirubin; DBil, direct bilirubin; TBA, total bile acid; TP, total protein; ALB, Albumin; GLO, globulin; PT, prothrombin time; INR, international normalized ratio; Cr, creatinine; ULN, upper limit of normal; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; EBV, epstein-barr

virus; CMV, cytomegalovirus; CI, confidence level; SD, standard deviation; HCC, hepatocellular carcinoma; RUCAM, Roussel Uclaf Causality Assessment Method; TB, tuberculosis; MDR-TB, multidrug-resistant tuberculosis; XCHT, Xiao-Chai-Hu-Tang

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Incidence and Etiology of Drug-Induced Liver Injury in Mainland China

Abstract

Background & Aims: We performed a nationwide, retrospective study to determine the incidence and causes of drug-induced liver injury (DILI) in mainland China.

Methods: We collected data on a total of 25,927 confirmed DILI cases, hospitalized from 2012 through 2014 at 308 medical centers in mainland China. We collected demographic, medical history, treatment, laboratory, disease severity, and mortality data from all patients. Investigators at each site were asked to complete causality assessments for each case whose diagnosis at discharge was DILI (n=29,478) according to the Roussel Uclaf Causality Assessment Method.

Results: Most cases of DILI presented with hepatocellular injury (51.39%; 95% CI, 50.76–52.03), followed by mixed injury (28.30%; 95% CI, 27.73–28.87) and cholestatic injury (20.31%; 95% CI, 19.80–20.82). The leading single classes of implicated drugs were traditional Chinese medicines or herbal and dietary supplements (26.81%) and anti-tuberculosis medications (21.99%). Chronic DILI occurred in 13.00% of the cases and, although 44.40% of the hepatocellular DILI cases fulfilled Hy's Law criteria, only 280 cases (1.08%) progressed to hepatic failure, 2 cases underwent liver transplantation (0.01%), and 102 patients died (0.39%). Among deaths, DILI was judged to have a primary role in 72 (70.59%), a contributory role in 21 (20.59%), and no role in 9 (8.82%). Assuming the proportion of DILI in the entire hospitalized population of China was represented by that observed in the 66 centers where DILI capture was complete, we estimated the annual

incidence in the general population to be 23.80 per 100,000 persons (95% CI, 20.86–26.74). Only hospitalized patients were included in this analysis, so the true incidence is likely to be higher.

Conclusions: In a retrospective study to determine the incidence and causes of drug-induced liver injury (DILI) in mainland China, the annual incidence in the general population was estimated to be 23.80 per 100,000 persons—higher than that reported from western countries. Traditional Chinese medicines, herbal and dietary supplements, and anti-tuberculosis drugs were the leading causes of DILI in mainland China.

Keywords: jaundice; RUCAM, Asia, epidemiology

Drug-induced liver injury (DILI) is a common adverse drug reaction (ADR), and it can lead to liver failure and even death.[1-3] DILI is increasingly appreciated to be one of the most challenging diseases for physicians and gastroenterologists. However, the burden of DILI in China, which has the world's largest population, has not been estimated.

In the west, the incidence of DILI has been estimated to be 1/100,000- 20/100,000 in the general population.[2, 4-7] Two population-based studies conducted in France and Iceland estimated the annual incidences of DILI to be approximately 13.9/100,000 and 19.1/100,000 respectively.[8, 9] In the United States, the annual incidence of DILI in the general population has been recently estimated as 2.7 per 100,000 adults, through surveillance in the state of Delaware.[10] Also, the most common causative drugs were anti-infectious agents, anti-TB drugs and natural herbal medicines across various registries.[11] In the past, epidemiologic surveys of DILI in mainland China have been focused on patients from a small number of medical institutions. In 2013, Yuan et al. performed a comprehensive database search of Chinese literature (279 studies from 1994 to 2011) to obtain some relevant data on DILI.[12] However, their study lacked consistent application of standardized causality assessment methods and some critical information (such as outcome) was incomplete, which limited the conclusions of the study. To date, epidemiological data on DILI from medical centers across mainland China have not been available.

The multiple clinical presentations of DILI and the lack of specific diagnostic tests for DILI

create challenges in studying the epidemiology of DILI. In order to help Chinese clinicians to better identify and manage DILI, the first edition of guideline for diagnosis and treatment of DILI was issued in 2015 by Chinese Society of Hepatology (CSH), and finally published in 2017 in English.[13] Simultaneously, under the CSH guideline, we carried out a retrospective study covering 308 medical centers in major cities across mainland China to characterize DILI in hospitalized patients including the implicated drugs, its clinical features, and to estimate the incidence of DILI.

Materials and Methods

A three-year retrospective multicentric study ("DILI-R")

Case finding and data collection: This was a retrospective study involving 308 medical centers in major cities of mainland China. The protocol for the present study was reviewed and approved by the institutional review board at Renji Hospital of Shanghai JiaoTong University, Shanghai, China (ClinicalTrials.gov Identifier: NCT02407964). Owing to the retrospective analysis of existing administrative and clinical data, the requirement to obtain informed patient consent was waived by the institutional review board.

In each center, the records for the in-patients during a period between January 1, 2012 and December 31, 2014 were searched for the following diagnoses at discharge, "drug-induced liver injury," "drug-induced hepatitis," "drug-induced cirrhosis," and "drug-induced liver failure," or using other diagnostic terms for various types of liver injury that were likely caused by drugs. Patients who were admitted to the hospitals for other conditions but developed DILI while hospitalized were eligible if the discharge diagnoses indicated a DILI event. Inclusion criteria did not include specific cut-off levels for liver chemistries.

Standardized case report forms (CRFs) were filled out for all cases with help from local senior gastroenterologists; demographic details and clinical information were recorded. The Hepatox website (www.hepatox.org/), a Chinese nationwide DILI research network resource, was utilized

as the data collection platform for participants to submit their DILI cases. Each patient was given a unique number allowing identification of multiple visits to different centers or readmissions during the 3-year period and thereby avoiding duplication. Patients with hepatocellular carcinoma or biliary obstructive processes were excluded. Patients with pre-existing chronic liver injury were not excluded if they were considered to have developed superimposed DILI.

Of the initial 29,478 cases whose diagnosis at discharge was DILI, 80 cases with admission date out of range and 2,153 cases with missing data were excluded resulting in 27,245 cases with eligible data (Figure 1A).

The following parameters were collected for all the enrolled patients: (1) Demographics; (2) disease history and alcohol consumption history; (3) information about the implicated drug that might have caused the liver injury, including the time of onset after starting the drug and the time of recovery after stopping the drug; (4) symptoms and signs, including time of occurrence, time of disappearance and symptoms at discharge were recorded in detail; (5) serum biochemical parameters before and during the DILI event, including values of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), serum total bilirubin (TBil), direct bilirubin (DBil), albumin (ALB), globulin (GLO), prothrombin time (PT), international normalized ratio (INR), and creatinine (Cr); (6) examinations for excluding other causes of liver injury (including hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes virus, Wilson's disease, and autoimmune hepatitis); and (7) severity and mortality of all enrolled patients during and after hospitalization.

Causality assessment: Investigators at each site were asked to complete causality assessment scoring for each case whose diagnosis at discharge was DILI (n=29,478) according to the Roussel Uclaf Causality Assessment Method (RUCAM).[14, 15] Cases with scores greater than or equal to 6 ("probable", n = 13,555) were entered into the study directly. Cases with RUCAM scores less than 6 (n=13,690) were further reviewed by a panel of 3 hepatologists with DILI

expertise (consistent with the expert opinion method of causality assessment[16]). Cases judged by at least two of the three hepatologists as probable DILI (n=12,372) were enrolled in the study. Thus, a total of 25,927 eligible DILI cases were enrolled in "DILI-R" (Figure 1A). The distribution of RUCAM scores (52.28% for ≥6; 31.14% for 5; 10.83% for 4 and 5.75% for 3) of the enrolled 25,927 DILI cases are presented in Supplementary Figure 1. The panel did not evaluate why the RUCAM scores were calculated as below 6 for the enrolled cases.

The enrolled cases with RUCAM scores < 6 were similar to those with RUCAM scores ≥ 6 in terms of demographic and clinical features (Supplementary Figure 2), liver chemistries (Supplementary Figure 3) and etiology (Supplementary Figure 4) supporting the causality assessment processes.

Clinical presentation: The clinical type of DILI was classified by the R value calculated from the liver tests obtained at presentation (R-value = serum [ALT/ALT upper limits of normal (ULN)]/[ALP/ALP ULN]). Cases were classified as hepatocellular if R value ≥5.0, cholestatic if R value ≤2.0, and mixed if R-value was 2.0–5.0.[11]

Severity of DILI and outcomes: Hy's Law cases were defined as a patient who experienced elevations in serum ALT or AST > 3×ULN and a concomitant rise in serum TBil to > 2× ULN and: (1) the implicated drug is known to cause elevated serum ALT or AST >3×ULN, (2) there was no evidence of cholestasis (serum ALP activity must be ≤2×ULN). (3) there is no more likely cause of liver injury such as viral hepatitis, alcohol abuse, ischemia, or preexisting liver disease.[3]

The definition of acute liver failure (ALF) includes evidence of coagulation abnormality indicated by INR≥ 2.0, signs of hepatic encephalopathy, and TBil≥10× ULN (10 mg/dL or 171 μmol/L) or successive daily elevations ≥1.0 mg/dL (17.1μmol/L) with an illness of <26 weeks duration. Patients may also have ascites and DILI-related dysfunction of other organs.[13] Chronic DILI was defined as: 6 months after the onset of DILI, serum ALT, AST, ALP, or TBil continued to remain abnormal, or radiographical evidence of portal hypertension or histological evidence of ongoing liver injury.[13] For the death cases, we categorized DILI as having a primary, a contributory,

or no role with the help of local senior gastroenterologists.

The entire 25,927 DILI cases were used for analysis of demographic and clinical features and causes of DILI. Of the 308 involved centers, 66 centers provided all recorded hospitalized DILI cases during the 3-year period of observation, and the other 242 centers just provided DILI cases from some but not all clinical departments. Therefore, to estimate the incidence of DILI in mainland China, only DILI cases from the 66 centers with complete event capture were used. There were a total of 13,691 DILI cases collected from these 66 centers between Jan 1, 2012 and Dec 31, 2014. A flow diagram summarizing the process of DILI case identification is presented in Figure 1A. Geographic distribution of all 308 medical centers that participated in this study (including 66 centers that contributed to the incidence dataset) is shown in Figure 1B and Supplementary Table 1.

Statistical analysis

The incidence of DILI in the general population was evaluated as (number of DILI inpatients in 66 centers annually ÷ total number of inpatients in 66 centers annually) × (number of inpatients nationwide annually ÷ the general population in mainland China annually).

SAS 9.3 for windows (SAS Institute Inc., Cary, NC, USA) was used for data analysis. Values were given as median and interquartile range (IQR) or as percentages where appropriate. Between-group differences were assessed using either the Mann-Whitney U test or Kruskal-Wallis test. Categorical variables were analyzed with χ^2 test, CMH-χ^2 test or Fisher's exact test where appropriate. The two-sided 95% confidence levels (CIs) were determined. Statistical tests were interpreted at a two-sided significance level of 5%.

Results

Demographic features

In this study, a total of 25,927 DILI cases among hospitalized patients were collected from 308 medical centers between January 1, 2012 and December 31, 2014 (Figure 1A). As shown in Table 1, men with DILI were found slightly more frequently than females. The highest proportion of DILI cases were in patients with ages between 40 and 59 years followed by ages 18-39, ages ≥ 60 and ages < 18 years old. Thus, DILI in children and teenagers represented the lowest proportion of the subjects enrolled. We found that the vast majority (25,113 cases, 96.93%) of DILI patients was Han Chinese and only 3.07% (795 cases) were minorities and this is consistent with the overall population composition. In addition, our study showed that DILI patients appeared most frequently in departments of internal medicine (41.74%; 95% CI 41.14-42.34) and infectious diseases (32.59%; 95% CI 32.02-33.16), while only 14.42% (95% CI 13.99-14.85) and 3.35% (95% CI 3.13 - 3.57) were diagnosed in departments of hepatology and oncology respectively (Table 1).

Clinical presentations

In 25,927 DILI cases, 49.47% (95% CI 48.86- 50.08) had serum ALT≥5×ULN when abnormal hepatic biochemical indexes were measured for the first time. Cases with serum ALT≥ 3×ULN and <5× ULN and cases with serum ALT<3×ULN formed 16.73% (95% CI 16.27- 17.17) and 33.81% (95% CI 33.23 - 34.39) of the cases respectively (Table 1). Most DILI cases were hepatocellular injuries (51.39%; 95% CI 50.76 -52.03), following by mixed injury (28.30%; 95% CI 27.73 - 28.87) and cholestatic injury (20.31%; 95% CI 19.80-20.82) (Table 1).

Eighty-seven % (95% CI 86.55 - 87.38) of the 25,927 DILI cases presented as acute DILI (Table 1). In addition, 13.00% of the DILI cases (95% CI 12.44-13.25) progressed to chronic DILI with persistent evidence of liver injury at least 6 months after DILI onset. Follow-up data based on a small subset of cases indicated that some patients who were defined as chronic DILI at month 6

normalized their liver chemistries after 1- or 2-year's observation, suggesting delayed recovery (Supplementary Figure 5). Of note is that 44.40% (95% CI 43.52 -45.28, n = 5,460) of hepatocellular injuries resulted in laboratory values consistent with Hy's Law (serum ALT > 3 × ULN and total serum bilirubin>2 ×ULN) (Table 1).

Of note, few cases progressed to life-threatening outcomes, which included 280 progressing to hepatic failure (1.08%), two undergoing liver transplantation (.01%) and 102 dying (.39%). Of 102 death cases, DILI was judged to have had a primary role in 72 (70.59%), a contributory role in 21 (20.59%), and no role in 9 (8.82%) (Table 1). Causes of death, the drugs implicated as causing DILI, and the last hepatic biochemistry values obtained prior to death are shown in Supplementary Table 2.

Except for those life-threatening ("fatal") DILI cases (1.48%), most DILI cases did not experience jaundice (80.76%) and only 17.76% cases presented with jaundice (Supplementary Figure 6). It was noteworthy that the higher proportions of hepatocellular DILI were found in fatal cases (65.67%, *P*<.0001) and in cases with jaundice (65.09%, *P*<.0001) than in non-fatal cases or in the absence of jaundice (48.53%) (Supplementary Figure 6).

Latency period was considered as the time span between the start of treatment with the implicated drugs and the time that abnormal serum liver chemistries (ALT, AST, ALP or TBil) were first detected. In this study, latency period in DILI cases without jaundice was shorter than in cases with jaundice (*P* < .0001) and in fatal cases (*P* < .0001) (Supplementary Figure 6). Additionally, cases with hepatocellular injury displayed longer latency than cholestatic and mixed types (*P*< .0001) (Supplementary Table 3); DILI cases induced by traditional Chinese medicines presented with longer latency than cases caused by western medications (*P* < .0001) and cases induced by implicated drugs within three or more classes in combination displayed shorter latency than those caused by drugs with single or two classes in combination (*P* < .0001) (Supplementary Table 3).

Interestingly, we observed that a significant proportion of our cohort, 23.38% (95% CI 22.86 -

23.90), had pre-existing liver disease (Table 1). The highest proportion of pre-existing liver disease was among the in fatal cases (64.32%), followed by cases with jaundice (29.21%) and cases without jaundice (21.34%) ($P < .0001$) (Supplementary Figure 6). The distribution of pre-existing liver disease is presented in Supplementary Figure 7. These results indicated that pre-existing liver disease was associated with more severe outcome from DILI.

Effect of age, gender and ethnicity

Latency, duration of usage of the implicated agents and clinical indicators of DILI patients, were compared according to gender, age and ethnicity. As shown in Figure 2, females experienced longer latency ($P<.0001$) than males. Also, female patients had higher serum TBil ($P <.01$), DBil ($P < .01$), TBA ($P < .0001$), ALT ($P < .0001$), AST ($P < .0001$) and ALP ($P < .0001$) than males. Of note, compared to the DILI cases without jaundice, female gender occupied higher frequencies than that of men, either in cases with jaundice ($P < .0001$) or in life-threatening DILI ($P < .01$) (Supplementary Figure 6).

As expected, higher values of TBil, DBil, TBA, ALT, AST and GGT (all $P <.0001$) were found in hepatocellular DILI than in cholestatic and mixed DILI and conversely, higher ALP values were higher in cholestatic DILI than in other two types of liver injuries (Figure 2). In addition, compared with adult patients, liver disorders were relatively milder in children (<18 years old). Also, children had a shorter mean latency period ($P <.0001$) and duration of usage of implicated agents ($P<.0001$), and lower peak levels of TBil, DBil, TBA, ALT, AST and GGT than in adults ($P<.0001$). As expected from continuing bone growth, children generally had higher ALP levels than adults (Figure 2). In summary, female and older DILI patients tended to have more severe DILI than male and younger individuals.

Interestingly, we found that the latency period ($P <.05$) and duration of usage of implicated agents ($P < .01$) was significantly longer in ethnic minorities than in Han Chinese. However, the Han Chinese had generally more severe liver injury (TBA, $P < .01$; ALT, $P < .0001$; AST, $P < .0001$

and GGT, $P < .01$) than in ethnic minorities (Figure 2).

Causes of DILI

As shown in Figure 3A, the implicated drugs were categorized according to their class and main clinical indication. Most DILI events were reported to be caused by drugs within single classes (82.67%). TCM or HDS (26.81%) and anti-TB drugs (21.99%) were the two leading classes of implicated agents. As is well known, TCM and HDS included traditional Chinese medicines, natural medicines, Tibetan medicines, Mongolian medicines, health care products, and herbal and dietary supplements. TCM and HDS are being used increasingly worldwide, especially in China. A high proportion of Chinese prefers to use traditional Chinese medicines based on the mistaken belief that these drugs have little or no side effects.

The anti-TB drugs included isoniazid, rifampicin, pyrazinamide and ethambutol. Besides TCM, HDS and anti-TB drugs, other single classes of implicated agents with occurrence >1% included antineoplastics or immunomodulators (8.34%), anti-infectious agents (6.08%), psychotropics (4.90%), non-sex hormones (3.04%), cardiovascular drugs (2.98%), digestive drugs (2.04%), respiratory drugs (1.47%) and musculoskeletal drugs (1.32%). In addition to single agents, implicated agents were from two or three classes in 14.06% and 3.27% of DILI patients, respectively (Figure 3A).

Besides analyzing implicated drugs according to their class and main clinical indication, we also ranked the incidence of DILI due to specific implicated drugs. Most of the specific implicated drugs also belonged to classes of anti-TB drugs or TCM or HDS (Figure 3B).

Interestingly, our data showed that DILI due to TCM or HDS was more common in females than in males, and DILI due to anti-TB drugs was more common in males than in females (Supplementary Figure 8).

Estimation of incidence of DILI

Of the 308 medical centers that participated in this study, only 66 centers provided all recorded hospitalized DILI cases during the three-year observation period and could therefore be used to estimate the proportion of DILI patients among all inpatients. Specifically, a total of 8,102,732 individuals from 2012 to 2014 were hospitalized in these 66 centers and 13,691 were diagnosed with DILI (Table 2). The location of these participating medical centers is listed in Supplementary Table 1. No hospitals from Hong Kong, Macau or Taiwan were included in this study. As shown in Table 2, the average percentage of total inpatients with a diagnosis of DILI in 2012, 2013 and 2014 were calculated to be 1.62‰ (95% CI 1.57-1.67), 1.69‰ (95% CI 1.64-1.74) and 1.74‰ (95% CI 1.70-1.79), respectively. The mean percentage was therefore estimated as 1.69‰ (95% CI 1.66-1.72) of hospitalized patients during the three year interval. Interestingly, higher proportions were found in South China (6.53‰) and Southwest China (5.02‰) than in other regions (Supplementary Table 4).

As reported in 2016 by China health and family planning statistical digest (issued by National Health and Family Planning Commission),[17] there were 178.57 million, 192.15 million and 204.41 million inpatients in 2012, 2013 and 2014 in mainland China, respectively. There were approximately 1.354, 1.361 and 1.368 billion inhabitants in 2012, 2013 and 2014 in mainland China, respectively, according to the Population Sample Survey conducted by the National Bureau of Statistics. Thus, the percentages of inpatients in the general population were calculated as 13.19%, 14.12% and 14.94% in 2012, 2013 and 2014, respectively (Table 3).

As described in “materials and methods”, the incidence of DILI was assessed as the proportion of DILI cases among inpatients in 66 centers annually × number of inpatients nationwide annually ÷ the general population in mainland China. In this case, the annual incidence of DILI was calculated as 21.37 per 100,000 (95% CI 18.59 - 24.15), 23.86 per 100,000 (95% CI, 20.92 - 26.80) and 26.00 per 100,000 (95% CI 22.93 - 29.07) in 2012, 2013 and 2014, respectively (Table 3). Accordingly, the annual incidence of DILI increased gradually from 2012 to

2014 and the average incidence was estimated as 23.80 per 100,000 (95% CI 20.86 - 26.74).

Discussion

This nation-wide study for the first time provides an estimate of the burden of DILI in mainland China. In our multicenter study involving case records of over 8 million patients from 66 centers throughout mainland China, 1.69‰ of the patients had a diagnosis of DILI during the period between 2012 and 2014. Extrapolating this information to the data from the National Health and Family Planning Commission, we estimated the incidence of DILI to be 23.80 per 100,000 populations. In mainland China, health care of Chinese inhabitants has been covered by the public medical service system, medical insurance system and the rural cooperative medical system since 2003. This means that most DILI patients recognized to have DILI are referred to the hospitals for management. In addition, in mainland China, hepatoprotective agents are generally administered to hospitalized patients with DILI. Because of this, we believe that most patients discovered to have DILI in mainland China were hospitalized during the time interval we examined. However, there was likely a proportion of DILI patients with a mild or moderate liver injury who were either not recognized to have DILI or were managed as outpatients and were therefore not considered in our study. In addition, in underdeveloped parts of the country not well covered by our survey, there is a higher than average incidence of diseases requiring hepatotoxic drug treatment, such as tuberculosis, viral hepatitis and even HIV/AIDS.[18-20] Therefore, the actual DILI incidence in mainland China is very likely higher than our estimate of 23.80 per 100,000 in general population, which was still higher than that estimated in Iceland (19.1/100,000) [7], France (13.9/100,000),[9] the United states (2.7/100,000),[10] Spain (3.42/100,000)[21] and Sweden (2.4/100,000)[22] (Table 4).

In this study, 44.40% of those with hepatocellular pattern met the threshold of 'Hy's law'. Overall, 17.76% of cases developed jaundice, 1.08% progressed to hepatic failure and 0.4% died or had transplantation as a consequence (Table 1 and Supplementary Figure 6). Of those who

died, DILI was assessed as a primary cause of death in 70.59% and as contributing to death in another 20.59% (Table 1). Our study did not have inclusion criteria based on liver chemistry values, and therefore, our cohort of DILI patients included cases of mild liver injury not included in other registries. However, our incidence of chronic DILI was comparable to that has been reported in other registries (Table 4). Moreover, almost half of our cases with hepatocellular DILI fulfilled biochemical criteria for Hy's Law indicating potentially life-threatening liver injury. It is therefore interesting that the DILI fatality rate in our study was much lower than has been observed in other registries[21, 23-26]. The reasons for this discrepancy are not clear, but the dilution with a large number of milder cases, less availability of liver transplantation (considered a fatality equivalent in other studies) and possibly the frequent administration of hepatoprotective agents, may have contributed to the lower DILI fatality rate in China. Our observations may need to be considered when interpreting the significance of Hy's Law cases observed in clinical trials involving Chinese participants.

Whether gender is a risk factor for susceptibility to DILI is still controversial. In this study, male patients accounted for just over half the cases of DILI. Though females are suggested to have a higher risk of idiosyncratic DILI than males in many retrospective studies,[8, 27-30] females have been reported to have increased,[8, 26, 27, 31] unchanged,[9, 30] or even decreased[12, 21] incidence of DILI (Table 4). In China, it was estimated that 918,000 individuals suffered from tuberculosis (TB) (including TB co-infected with HIV) with overall incidence of 67/100,000 population, which accounted for 8.65% of the world's reported cases of TB in 2015 (WHO Global tuberculosis report 2016).[32] Among TB patients, male to female ratio was 2.1:1.[32] A very similar gender distribution ratio was found in our study among patients with DILI due to TB treatments (65.6% for men vs. 34.4% for women) (Supplementary Figure 9) suggesting susceptibility was not affected by gender. Although men made up a slightly larger proportion of the overall DILI population, more severe clinical manifestations were observed in females, as shown by higher serum levels of TBil, DBil, TBA, ALT, AST and ALP (Figure 2), and higher frequency of DILI with jaundice (Supplementary Figure 6), which is in line with reports by others.[21, 31] We also observed that 4.29% (95% CI

4.04-4.54) of DILI patients in our study were children and teenagers (<18-year-old) and that DILI severity as indicated by peak liver chemistries was lower in children than that in adults (Table 1 and Figure 2). Differences of implicated drugs, dosing, pharmacokinetic factors, or inherent differences in DILI susceptibility may contribute to the observed differences between children and adults in DILI phenotypic characteristics.

As reported by the western studies, acute liver failure was most associated with use of non-steroidal anti-inflammatory drugs (NSAIDs), anti-infective drugs, and herbs and dietary supplements (HDS).[13, 33, 34] In mainland China, as indicated in our data (Figure 3), TCM or HDS and anti-tuberculosis drugs were the major offending agents of DILI.

TCM or HDS were the single drug class implicated in this study (Figure 3). In fact, despite the recent recognition of the potential hepatotoxicity of HDS, usage of HDS has increased tremendously worldwide, not only in Asian countries (such as China, Korea, Japanese and South Asian countries), but also in the western countries. Individuals who consume these HDS usually choose to ignore or be unaware of the potential side effects. Additionally, compared to conventional prescription medications, the absence of regulatory guidelines for the production and sale of herbal compounds further contribute to their overuse. For instance, it is not generally known among the Chinese population that natural medicines, such as the single herbs Heshouwu or Leigongteng, or the composite agents Xiao-Chai-Hu-Tang (XCHT) have been associated with DILI, although laboratory studies have also shown that these treatments cause immune activation, metabolic disorders, apoptosis and damage to liver cells.[35-39] We believe that such analyses of Chinese herbal medicines are essential and urgent in order to find out whether these and other toxic ingredients are present.

In addition to TCM or HDS, over 20% of DILI cases were attributed to anti-TB drugs (Figure 3), which is consistent with China having the second highest TB burden worldwide. The cornerstone of tuberculosis management is a 6-month course of isoniazid, rifampicin, pyrazinamide and ethambutol. All these anti-TB drugs have hepatotoxicity potential and could lead to DILI during

anti-tuberculosis treatment, which commonly leads to interruption of anti-TB treatment and may promote antibiotic resistance.[40] It is estimated that in China, 5.7% new TB cases and up to 26% among previously treated TB cases carry multidrug-resistance (MDR-TB).[41]

Liver injury caused by antineoplastic or immunomodulators includes hepatocyte necrosis, hepatic steatosis, hepatic mitochondrial injury, cholestasis and vascular injury.[42-45] Consistent with the previous reports, we found the rate of DILI caused by antineoplastic or immunomodulators was the third leading cause of DILI, just behind TCM or HDS and anti-TB drugs.

In this study, 6.08% of DILI cases were attributed to anti-infectious agents including antibiotics, antifungals, anthelmintics, antimalarials, antiprotozoals, and antivirals (in the present study, anti-TB drugs were given a separate classification). In the West, anti-infectives are the leading drugs associated with DILI. Interestingly, the percent of DILI cases due to anti-infection agents in our study seems low since antibiotics are used more frequently in China than in any other country. For example, according to one survey approximately two-thirds of inpatients in China were administered antibiotics, which is twice that reported in many other countries.[46] Antibiotic overuse has become a severe issue in China. A joint effort from authorities, physicians, patients and media should be taken to improve public knowledge of both risks and benefits of anti-infective therapy.

In our study, we had no entrance criteria based on liver chemistries so may have included more relatively mild cases than in other registries. Additionally, our relatively low enrollment of children and teenagers (<18 years old) may be related to the relatively limited number of pediatric hospitals participating in the study.

In summary, in the largest registry of its kind, we have provided a complete characterization of DILI in mainland China. We conclude that DILI has a higher incidence in mainland China than in western countries and that TCM, HDS and anti-tuberculosis drugs are the leading categories of agents causing DILI.

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Author names in bold designate shared co-first authorship.

Figure legends

Figure 1. The centers participating in DILI patient recruitment. (A) A flow diagram for DILI patient recruitment in this study. (B) Geographical distribution of all 308 participating medical centers. *Of the 308 involved centers, only 66 centers provided all recorded hospitalized DILI cases during 3-year observation (red dots). Thus, DILI cases from these 66 centers were used to assess the diagnostic rate of DILI in this study, since all inpatients were screened for the occurrence of DILI.

Figure 2. Comparison of latency, duration of usage of implicated agents, and maximal values of

clinical chemistries during the course of the injury among patients according to gender, age and ethnicity. Clinical indicators included serum total bilirubin (TBil), direct bilirubin (DBil), total bile acid (TBA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and γ glutamyl transpeptidase (GGT). All data were shown as median and IQR and asterisks indicated significant levels by either the Mann-Whitney U test or the Kruskal-Wallis test where appropriate (2-tailed; *, *P*< .05; **, *P*< .01; ***, *P*< .0001).

Figure 3. Causes of DILI in this study. (A) Implicated DILI drugs were categorized according to their therapeutic class source and main clinical indications. Percentages of patients with one or more implicated classes of agent(s) are also shown. (B) Implicated specific DILI drugs were ranked according to single agent, combination of two agents and combination of three or more agents. TCM, traditional Chinese medicine; HDS, herbal and dietary supplements; *Anti-infectious agents included antibiotics, antiviral and antifungal drugs, but not anti-tubercular agents. [#]sex hormones were not included. [ξ]The detailed information is unknown.

Table 1. Demographic and Clinical features of 25,927 DILI cases from 308 centers nationwide

	Number	%	95% CI
Gender[a]			
Male	12,930	50.83	[50.22, 51.45]
Female	12,507	49.17	[48.55, 49.78]
Age[b]			
≥60	5,694	22.09	[21.58, 22.60]
40-59	11,015	42.73	[42.13, 43.34]
18-39	7,962	30.89	[30.33, 31.45]
<18	1,105	4.29	[4.04, 4.54]
Ethnicity[c]			
Han	25,113	96.93	[96.72, 97.14]
Non-han	795	3.07	[2.86, 3.29]
Department of diagnosis			
Internal medicine	10,822	41.74	[41.14, 42.34]
Infectious diseases	8,450	32.59	[32.02, 33.16]
Hepatology	3,738	14.42	[13.99, 14.85]
Oncology	869	3.35	[3.13, 3.57]
Others	2,048	7.90	[7.57, 8.23]
Pre-existing liver diseases			
Yes	6061	23.38	[22.86, 23.90]
No	19866	76.62	[76.10, 77.14]
Initial serum ALT values[d]			
≥ 5× ULN	12826	49.47	[48.86, 50.08]
≥3× ULN and < 5 × ULN	4335	16.72	[16.27, 17.17]
< 3× ULN	8766	33.81	[33.23, 34.39]
Clinical types of DILI[e]			
Hepatocellular injury (R≥5)	12,298	51.39	[50.76, 52.03]
Conform to Hy's law	5,460	44.40	[43.52,45.28]
Others	6,838	55.60	[54.72,56.48]
Cholestatic injury(R≤2)	4,860	20.31	[19.80, 20.82]
Mixed injury (2<R<5)	6,771	28.30	[27.73, 28.87]
Acute/chronic DILI			
Acute DILI	22,556	87.00	[86.55, 87.38]
Chronic DILI	3,371	13.00	[12.44, 13.25]
Life-threatening outcomes			
Progress to acute liver failure[f]	280	1.08	[0.95, 1.21]
Undergoing liver transplantation	2	0.01	[0.00, 0.02]
Death	102	0.39	[0.32, 0.47]

DILI had primary role	72	70.59	[61.75, 79.43]
DILI had contributory role	21	20.59	[12.74, 28.44]
DILI had no role	9	8.82	[3.32,14.33]

[a]Gender information of 490 cases was missing or unknown. [b]Age information of 151 cases was missing or unknown. [c]Ethnicity information of 19 cases was missing or unknown.[d] ALT values when abnormal hepatic biochemical indexes occurred for the first time. [e]In 1,998 cases "R" value could not be calculated as ALP value was missing when abnormal ALT or AST occurred for the first time. [f]ALF cases who received liver transplantation or died during hospitalization were not included.

Table 2. Evaluation of the proportion of DILI cases among inpatients in mainland China based on "DILI-R" study

Years	Number of inpatients	Number of DILI inpatients	Proportion of DILI (‰)[a]	95% CI
2012	2,373,358	3,845	1.62	[1.57, 1.67]
2013	2,746,378	4,643	1.69	[1.64, 1.74]
2014	2,982,996	5,203	1.74	[1.70, 1.79]
Total	8,102,732	13,691	1.69	[1.66, 1.72]

[a]The proportion of DILI = number of DILI inpatients in 66 centers annually ÷ number of inpatients in 66 centers annually.

Table 3. Estimation of the annual incidence of DILI in the general population of mainland China between 2012-2014

Years	Inpatients nationwide[a] (million)	the general population in mainlandChina[b] (billion)	Percentage of inpatients In the general population annually (%)	Estimated DILI incidence[c] in the general population (per 100,000)	95% CI
2012	178.57	1.354	13.19%	21.37	[18.59, 24.15]
2013	192.15	1.361	14.12%	23.86	[20.92, 26.80]
2014	204.41	1.368	14.94%	26.00	[22.93, 29.07]
Average	191.71	1.361	14.08%	23.80	[20.86, 26.74]

[a]The data were cited from China health and family planning statistical digest 2016, which was issued by the National Health and Family Planning Commission. [b]The data were estimated by the Population Sample Survey annually and cited from National Bureau of Statistics of the People's Republic of China (http://data.stats.gov.cn/index.htm). [c]The incidence of DILI in the general population = the proportion of DILI cases in inpatients in 66 centers annually×(number of inpatients nationwide annually ÷ the general population in China mainland).

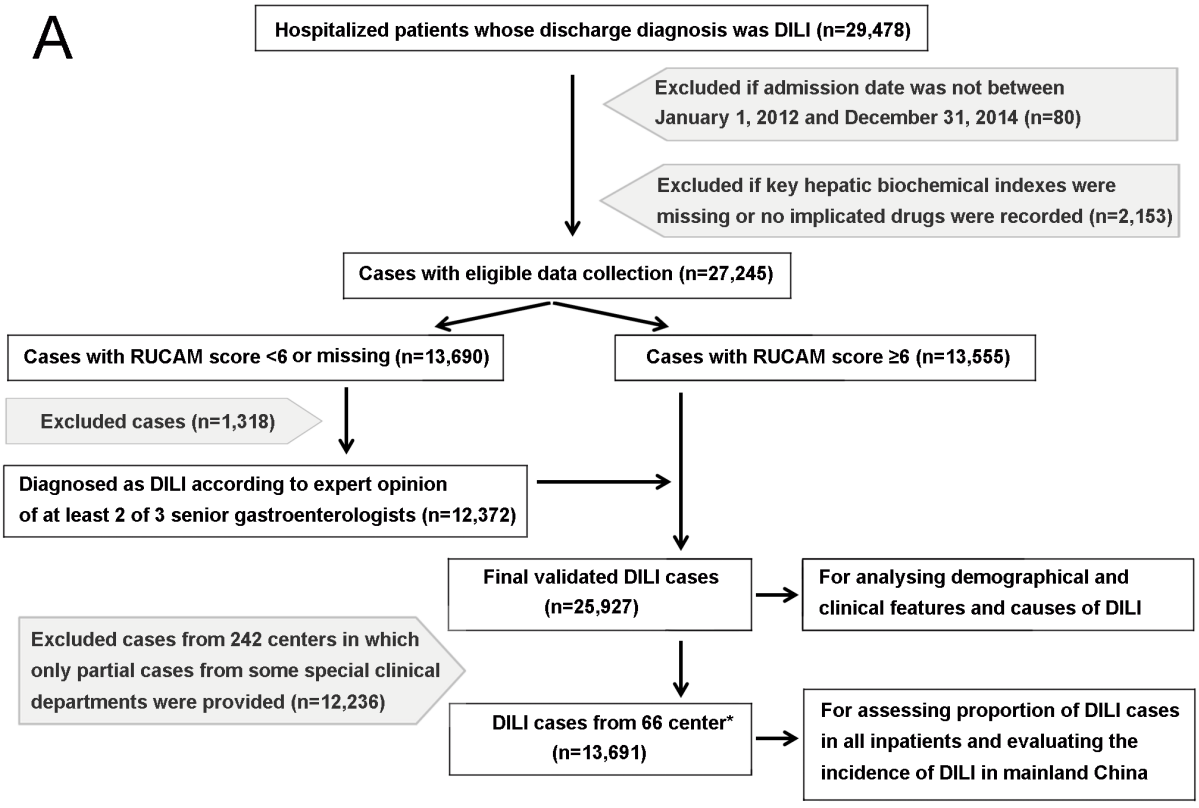
Table 4. Clinical features of DILI in our study *vs.* reported from 7 other countries.

Study	Iceland[8]	France[9]	United States[23]	Spain[21]	Sweden[24]	India[25]	Japan[26]	China (current study)

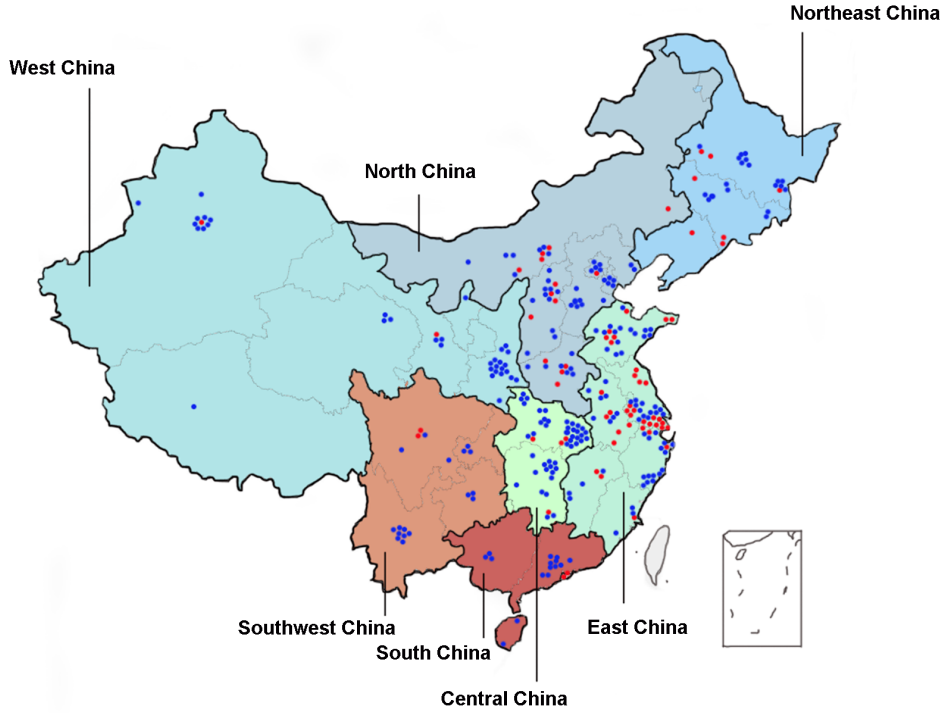
Study design	Prospective	Prospective	Prospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective
Duration (years)	2010-2011	1997-2000	2004-2013	1994-2004	1970-2004	1997-2008	1997-2006	2012-2014
Incidence per year	19.1 per 100,000 inhabitants	13.9 per 100,000 inhabitants	2.7 per 100,000 adults in Delaware[10]	3.42 per 100,000 inhabitants[22]	2.4 per 100,000 person[29]	N/A[a]	N/A	23.80 per 100,000 inhabitants (estimated)
Number of cases	96	34	899	461	784	313	1676	25,927
% Female	56.25%	64.70%	59%	48.65%	57.7%	42%	57%	49.17%
Dominated age range	40-59 Y/O[b]	≥50 Y/O	N/A	≥60 Y/O	N/A	N/A	50-69 Y/O	40-59 Y/O
% Chronic	7%	N/A	18%	10.31%	N/A	0.32%	N/A	13.00%
HC/Chol/Mix[c]	42%, 32%, 26%	47.1%, 20.6%, 26.5%	54%, 23%, 23%	57.8%, 20.0%, 22.2%	52.2%, 26,3%, 21.5%	N/A	59%, 20%, 21%	51.39%, 20.31%, 28.30%
Fatality (%)	1.04%	5.88%	6%	5.38%	9.18%	17.3%	0.4%	0.39%
Top implicated drugs (%)	Antimicrobials (37.0%), HDS[d] (16.0%), NSAIDs (6%)	anti-infectious (25.0%), psychotropic (22.5%), hypolipidemic (12.5%), and NSAIDs[e] drugs (10.0%)	antimicrobials (45.4%), HDS (16.1%), CVS[f] drugs (9.8%), CNS[g] drugs (9.1%)	amoxicillin/clavulanate (13.23%), TB[h] drugs (6.95%), ebrotidine (4.93%)	antibiotics (27.04%), NSAIDs (4.85%), anesthetics (1.91%)	TB drugs (57.8 %), phenytoin (6.7 %), olanzapine (5.4%), dapsone (5.4%)	Antibiotics (14.3%), psychotropics and neurological drugs (10.1%), dietary supplements (10.0%)	TCM[i] or HDS (26.81%), tuberculostatics (21.99%), antineoplastic or immunomodulators (8.34%) and anti-infectious (6.08%)

[a]N/A, not available; [b]Y/O, years old; [c]HC/Chol/Mix, hepatocellular injury/cholestatic injury/mixed injury; [d]HDS, herbal and dietary supplements; [e]NSAIDs, non-steroidal anti-inflammatory drugs; [f]CVS, cardiovascular system; [g]CNS, central nervous system; [h]TB, tuberculosis; [i]TCM, traditional Chinese medicine.

A


Hospitalized patients whose discharge diagnosis was DILI (n=29,478)
Excluded if admission date was not between January 1, 2012 and December 31, 2014 (n=80)
Excluded if key hepatic biochemical indexes were missing or no implicated drugs were recorded (n=2,153)
Cases with eligible data collection (n=27,245)
Cases with RUCAM score <6 or missing (n=13,690)
Cases with RUCAM score ≥6 (n=13,555)
Excluded cases (n=1,318)
Diagnosed as DILI according to expert opinion of at least 2 of 3 senior gastroenterologists (n=12,372)
Final validated DILI cases (n=25,927)
For analysing demographical and clinical features and causes of DILI
Excluded cases from 242 centers in which only partial cases from some special clinical departments were provided (n=12,236)
DILI cases from 66 center* (n=13,691)
For assessing proportion of DILI cases in all inpatients and evaluating the incidence of DILI in mainland China

B


Northeast China
West China
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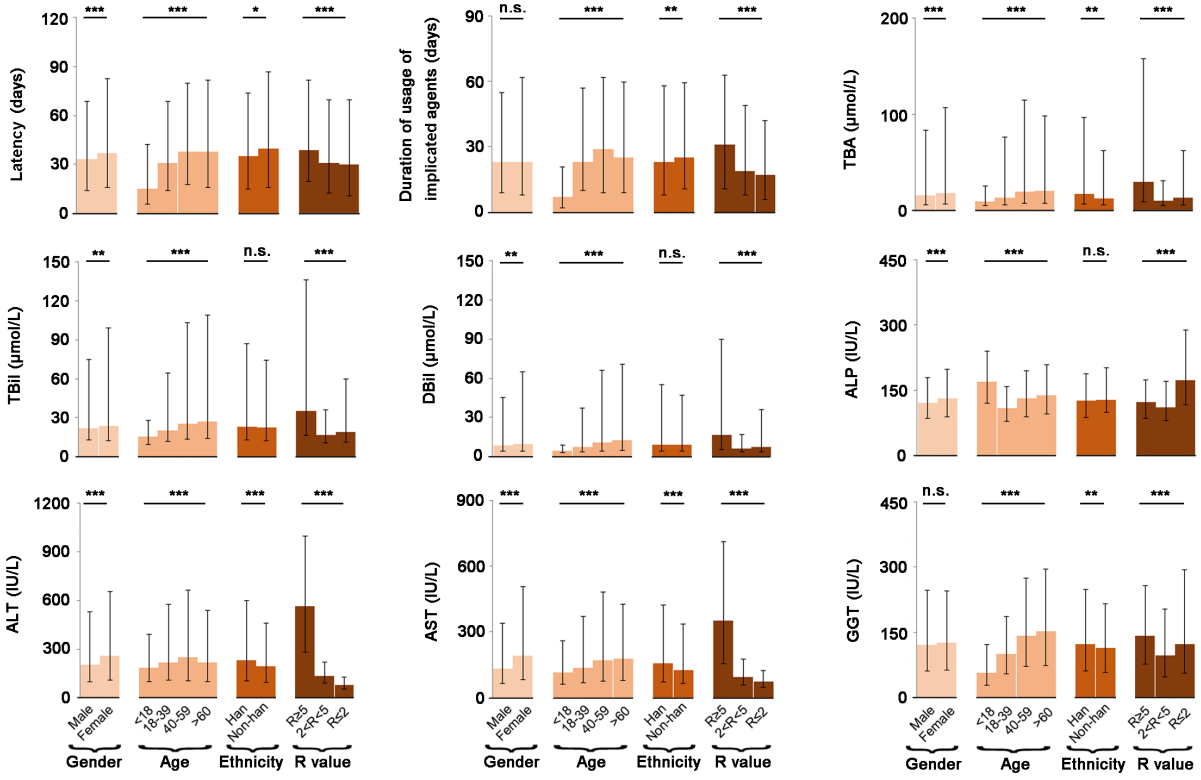
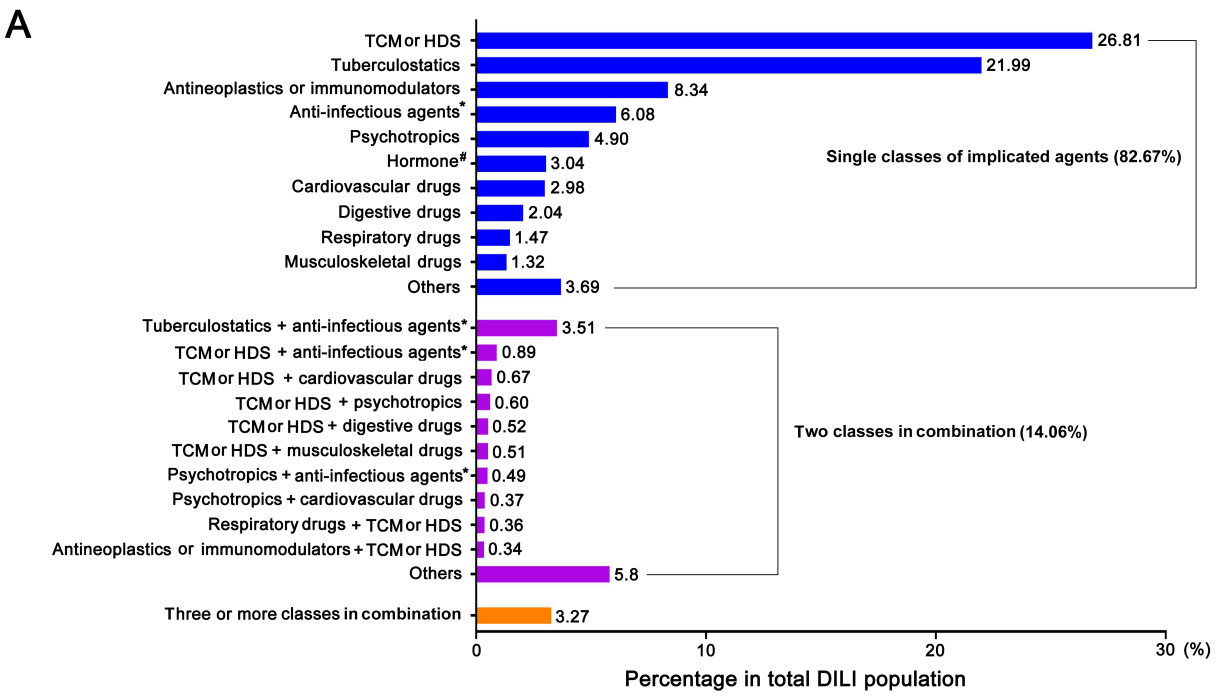
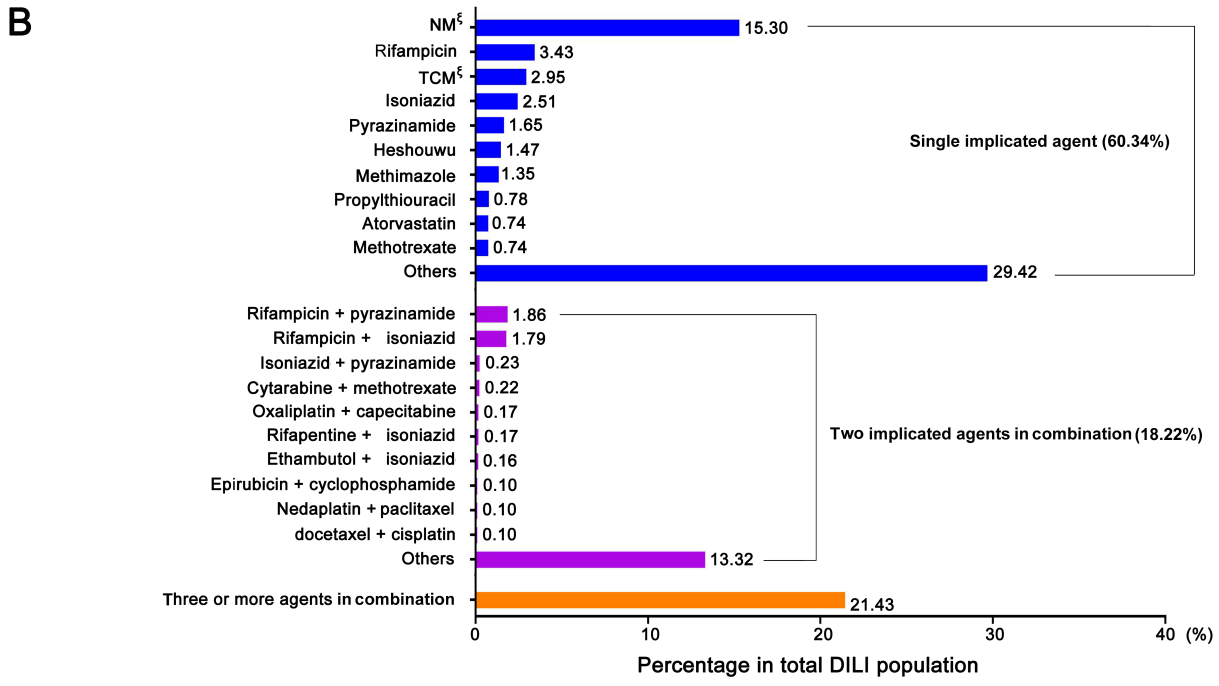
Southwest China
South China
East China
Central China







Supplementary data for manuscript entitled "Incidence and Etiology of Drug-Induced Liver Injury in Mainland China"

Supplementary Table 1. The Recruitment at the 308 centers (including 66 centers specific for assessing of diagnostic rate of DILI) participating in the study

Regions/Provinces	308 centers recruited in the study	66 centers with complete enrollment of all DILI cases
North China	**59**	**14**
Beijing	6	1
Tianjin	5	0
Inner Mongolia	13	4
Hebei	9	0
Shanxi	16	4
Henan	10	5
Northeast China	**25**	**7**
Heilongjiang	15	3
Jilin	9	3
Liaoning	1	1
East China	**97**	**35**
Shanghai	16	8
Shandong	23	6
Zhejiang	19	2
Jiangsu	13	9
Anhui	16	5
Fujian	4	3
Jiangxi	6	2
Central China	**50**	**4**
Hubei	34	3
Hunan	16	1
South China	**17**	**2**
Guangdong	12	2
Guangxi	3	0
Hainan	2	0
Southwest China	**19**	**2**
Sichuan	5	2
Chongqing	3	0
Guizhou	3	0
Yunnan	8	0
Northwest China	**41**	**2**
Shanxi	21	0

Ningxia	1	0
Gansu	4	1
Qinghai	3	0
Xinjiang	11	1
Xizang	1	0
Total	**308**	**66**

Supplementary Table 2. Causes of death, implicated drugs of causing DILI, and the last hepatic biochemistry values obtained prior to death in these death cases with DILI

Case NO.	Causes of death	Implicated drugs in causing DILI	ALT (IU/L)	AST (IU/L)	GGT (IU/L)	ALP (IU/L)	TBA (μM)	TBIL (μM)	DBIL (μM)	TP (g/L)	ALB (g/L)
DILI-induced liver failure played a primary role in these death cases (n=72)											
368082	DILI	Oxcarbazepine/Carbamazepine	268	90	97	99	N/A	257	149	53	33
339001	DILI	Methimazole/Metoprolol	31	46	34	204	N/A	317	147	77	28
335063	DILI	Cis-platinum	29	45	33	49	N/A	190	154	48	23
335027	DILI	Cis-platinum/Arsenic trioxide	91	90	217	343	N/A	68	48.4	51	30
321344	DILI	TCM(ingredient unknown)	27	177	68	60	229	374	279	40	26
320002	DILI	TCM (Ku-Huang herbal injection)	60	163	530	576	84	333	184	62	23
316007	DILI	Isoniazid/Pyrazinamide	142	342	217	N/A	N/A	345	292	61	27
309398	DILI	TCM(ingredient unknown)	465	281	82	93	99	277	159	60	32
309345	DILI	TCM(ingredient unknown)	300	385	27	85	69	135	83	37	20
309343	DILI	TCM(Sheng-Mai-Ying)	2583	573	59	216	458	182	80	52	30
309144	DILI	Amidopyrine compound	2841	901	58	201	220	106	43	53	30
309142	DILI	TCM(ingredient unknown)/Levofloxacin/Sulbactam	875	944	137	215	239	258	179	61	27
309136	DILI	Cold medication (details unknown)	105	132	37	47	56	258	221	38	28
308108	DILI	TCM(ingredient unknown)/Acarbose	174	217	219	252	226	320	204	43	23
289185	DILI	Esomeprazole	29	129	566	326	207	112	85	48	17
284044	DILI	Sulpiride	72	98	41	127	49	120	71	61	19
275046	DILI	Isoniazid/Ethambutol /Pyrazinamide/Rifampicin	322	433	47	184	83	331	209	56	28
274901	DILI	Imatinib	234	330	44	140	176	459	174	51	31
274886	DILI	TCM(ingredient unknown)	155	334	25	162	214	770	337	61	31
274819	DILI	Antituberculosis drugs (details unknown)	931	490	31	170	188	486	220	56	32

254050	DILI	TCM(ingredient unknown)	142	107	25	134	233	425	273	58	27
231293	DILI	TCM(ingredient unknown)	100	150	34	126	409	681	264	46	27
225001	DILI	Rifampicin	1444	3206	N/A	350	95	76	47	65	38
214007	DILI	TCM(ingredient unknown)/allopurinol	98	124	379	741	207	375	314	42	27
206016	DILI	TCM(ingredient unknown)	64	58	46	125	18	274	130	54	27
202010	DILI	TCM(ingredient unknown)	161	91	121	182	140	432	357	33	20
191059	DILI	TCM(Tu-San-Qi)	47	80	138	159	N/A	259	237	N/A	26
191057	DILI	Anti-tumor drugs(details unknown)	54	1701	1867	435	N/A	320	274	N/A	27
174064	DILI	TCM(Tu-San-Qi, yam chip)	73	128	127	124	175	391	281	45	32
161094	DILI	Rifampicin	288	55	38	121	N/A	267	83	51	28
146037	DILI	TCM(ingredient unknown)	404	177	37	78	162	373	186	54	37
146034	DILI	TCM(ingredient unknown)	455	267	36	167	N/A	342	157	69	26
144098	DILI	TCM(ingredient unknown)	230	111	26	109	246	228	123	54	31
140222	DILI	TCM(ingredient unknown)	82	187	34	258	307	427	280	69	29
140219	DILI	TCM(ingredient unknown)	12	88	33	84	138	486	164	53	33
140170	DILI	Propylthiouracil	46	50	N/A	N/A	N/A	102	79	53	29
140152	DILI	Antituberculosis drugs (details unknown)	795	1391	67	187	229	360	225	55	29
140141	DILI	TCM(ingredient unknown)	961	1811	382	173	52	656	404	53	32
140099	DILI	Isoniazid/Eethambutol/Pyrazinamide/Rifapentini	20	89	53	97	94	92	64	53	27
122002	DILI	Amlodipine	534	565	91	134	9	39	18	59	24
108036	DILI	Methylprednisolone	50	135	529	1275	23	1993	118	59	24
107014	DILI	TCM(ingredient unknown)	250	77	500	271	74	122	116	52	30
098074	DILI	TCM(ingredient unknown)	817	593	64	122	255	387	186	54	28
053166	DILI	Rifampicin/Isoniazid/Pyrazinamide/Ethambutol	299	189	39	107	N/A	312	143	42	28
050257	DILI	desensitizer (ingredient unknown)	712	54	196	189	280	427	270	47	31
050131	DILI	TCM(ingredient unknown)	150	124	140	146	247	581	312	53	33

050105	DILI	Ethambutol /Pyrazinamide/Rifampicin	124	140	80	154	132	352	174	49	19
048094	DILI	TCM (Radix euphorbiae lantu)	163	78	642	210	112	853	375	44	16
048092	DILI	TCM(Si-Xiao-Wan)	79	44	80	99	90	694	398	53	19
048089	DILI	Dexamethasone/TCM(ingredient unknown)	61	32	331	169	296	694	398	53	21
048071	DILI	TCM(Compound cantharidin capsule)	79	173	773	143	102	249	128	57	23
048020	DILI	TCM(ingredient unknown)	39	67	13	80	139	397	198	39	18
048019	DILI	TCM(Xiao-Cai-Hu-tang)	83	216	66	131	149	379	163	52	26
032004	DILI	Isoniazid/Ethambutol/Pyrazinamide/Rifampicin	1079	2541	76	158	160	273	117	65	25
027668	DILI	Antituberculosis drugs (details unknown)	339	337	91	185	333	429	143	41	28
021002	DILI	Methotrexate/Cyclophosphamide/Etoposide	30	125	163	422	N/A	169	165	37	19
019041	DILI	TCM(ingredient unknown)	192	213	60	156	226	364	216	77	21
016021	DILI	TCM(ingredient unknown)	1082	957	130	95	N/A	339	171	61	30
016008	DILI	Trazodone/Risperidone	2029	3189	188	5400	N/A	166	130	60	36
009057	DILI	TCM(ingredient unknown)	126	336	488	1246	238	528	487	39	22
008038	DILI	TCM(ingredient unknown)	41	83	33	44	289	492	375	45	30
007325	DILI	TCM(Tripterygium wilfordii)/Methylprednisolone	510	778	211	143	350	485	261	52	24
007123	DILI	Glucocorticoid/Ciclosporin/Mycophenolate	418	110	72	102	304	540	333	39	28
005082	DILI	TCM(ingredient unknown)	68	68	68	108	109	390	209	52	25
003664	DILI	TCM(ingredient unknown)	52	121	1433	932	76	494	371	64	28
003470	DILI	Isoniazid/Ethambutol/Pyrazinamide/Rifampicin	5	43	390	643	89	183	161	38	21
003435	DILI	Metoprolol/Warfarin/Sertraline	684	841	241	137	287	300	215	64	34
003277	DILI	Paracetamol/Pseudoephedrine	1147	493	1181	1503	254	547	433	54	29
003218	DILI	Isoniazid/Rifampicin/Pyrazinamide	127	136	125	179	276	445	343	55	27
003094	DILI	Pyrazinamide/Isoniazid/Rifampicin	161	64.7	90	172	234	409	125	66	37
003036	DILI	TCM(ingredient unknown)	496	242	65	149	219	533	385	53	36
140292	DILI	TCM(ingredient unknown)	228	325	226	149	327	388	254	75	33

DILI played a contributory role in these death cases (n=21)											
320029	respiratory failure, DILI	Cefotiam	32	45	121	250	6	15	6	63	32
335007	Acute lymphoblastic leukemia, DILI	Anti-tumor drugs(details unknown)	41	69	522	394	N/A	44	32	63	34
320006	Coronary heart disease, DILI	Levofloxacin	14	96	123	167	13	54	29	61	19
309237	Liver cirrhosis, DILI	TCM(ingredient unknown)	52	80	20	196	102	55	26	56	22
320003	Acute pancreatitis, DILI	TCM(Ai-Di injection)	27	46	560	516	15	9	3	68	32
287005	Cerebral infarction, DILI	TCM(ingredient unknown)/Warfarin/Trimetazidine	57	60	53	120	7	29	18	70	27
272084	Lung cancer, DILI	Cis-platinum	72	49	55	78	4	11	5	92	27
188070	Exfoliative dermatitis, Renal failure, DILI	Diclofenac	62	26	152	147	4	8	5	63	26
140255	Lung cancer, Diabetes, DILI	Gemcitabine	82	48	N/A	N/A	7	12	4	56	29
126033	Myocardial infarction, DILI	Adenosine Cyclophosphate	19	43	44	579	5	27	10	59	32
032329	TB, respiratory failure, DILI	Isoniazid/Ethambutol/Pyrazinamide/Rifampicin	183	189	116	253	4.7	13	11	59	30
027110	AIDS, opportunistic infections, DILI	Lamivudine/Stavudine/Efavirenz	144	248	328	405	N/A	27	5	55	19
013012	TB, respiratory failure, DILI	Antituberculosis drugs (details unknown)	79	141	116	458	N/A	22	11	56	24
008006	Pulmonary infection, heart failure, DILI	Teicoplanin/Clindamycin/Meropenem/moxifloxacin	93	83	175	201	2	28	17	56	32
007140	Intracranial infection, DILI	TCM/Cefepime/Ceftriaxone/midazolam/Valproic acid	560	398	188	81	12.7	31	28	46	13
003494	Gastric cancer, DILI	Anti-tumor drugs(details unknown)	160	56	225	133	5	20	11	58	36
001049	Prostatic cancer, DILI	Triptorelin/Bicalutamide/Zoledronic acid	81	132	273	490	N/A	40	7	51	26
320024	Intestinal tumor, DILI	Cefotiam	35	106	263	408	38	46	28	45	25
140194	Pulmonary infection, Septic shock, DILI	Antibiotic(details unknown)	47	116	N/A	232	239	61	46	60	24
001158	Septic shock, heart failure, DILI	TCM(ingredient unknown)	214	758	263	262	138	31	23	46	28
335008	Myeloid leukemia, DILI	Antineoplastic drug (details unknown)	263	305	586	310	N/A	27	18	67	30
DILI had no role in these death cases (n=9)											
335050	Acute myeloid leukemia	Hydroxycarbamide/Voriconazole/Biapenem/Teicoplanin	27	41	91	82	N/A	24	8	56	42
335003	Acute myeloid leukemia	Homoharringtonine/Cytarabine/Arsenic trioxide	18	12	50	55	N/A	5	3	51	28
335009	Acute non-gonobocytic leukemia, DIC	Voriconazole/Cytarabine/Homoharringtonine	59	17	73	55	N/A	14	8	53	33

284033	Pulmonary malignancy	Valproic acid	20	28	188	132	3	12	7	71	40
262001	cerebral infarction, acute rental failure	Anti-infectious agents (details unknown)	5	42	128	101	35	30	15	60	28
229046	Interstitial pneumonia, SLE, DIC	Methylprednisolone/Ganciclovir/Ciclosporin	34	22	457	124	23	20	8	48	24
216015	Breast cancer	Navelbine	37	31	56	103	5	18	6	62	34
111003	Chronic myelogenous leukemia	Methotrexate/Cytarabine	53	32	157	63	7	11	5	63	36
007184	Lung cancer	Navelbine/Cis-platinum/Cefotiam/Pantoprazole	35	51	79	98	1	12	6	67	33

Clinical indicators included serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBil), direct bilirubin (DBil), total bile acid (TBA), total protein (TP) and albumin (ALB). TCM, traditional Chinese medicines; TB, tuberculosis; DILI, drug-induced liver injury; SLE, systemic lupus erythematosus; DIC, disseminated intravascular coagulation; N/A, not available.

Supplementary Table 3. Comparison of latent periods among different clinical types of DILI and different categories of implicated drugs

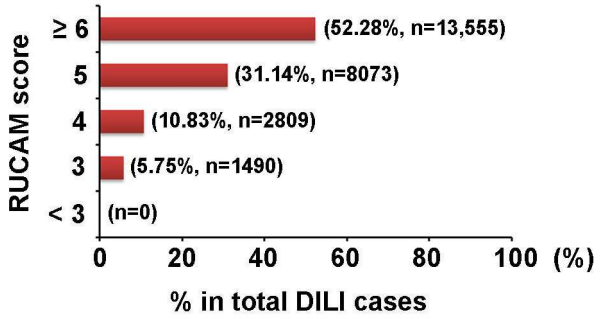
	Latent period (days) Median (IQR)	*P* value
Clinical types of DILI		**< .0001**
Hepatocellular injury (R≥5)	39.00 (20.00 - 82.00)	
Cholestatic injury (R≤2)	30.00 (11.00 - 70.00)	
Mixed injury (2<R<5)	31.00 (13.00 - 70.00)	
Origins of Implicated drugs		**< .0001**
Traditional Chinese medicines	44.00 (24.00 - 88.00)	
Western medications	30.00 (12.00 - 67.00)	
Classes of implicated drugs		**< .0001**
Single class	36.00 (17.00 - 75.00)	
Two classes in combination	32.00 (13.00 - 75.00)	
Three or more classes in combination	33.00 (13.00 - 71.00)	

Note: Between-group differences were assessed using the Kruskal-Wallis test. IQR, interquartile range. *P*-values (two-tailed) < .05 were considered significant.

Supplementary Table 4. The number (n) and proportion (‰) of DILI cases from all inpatients in seven geographical zones of mainland China

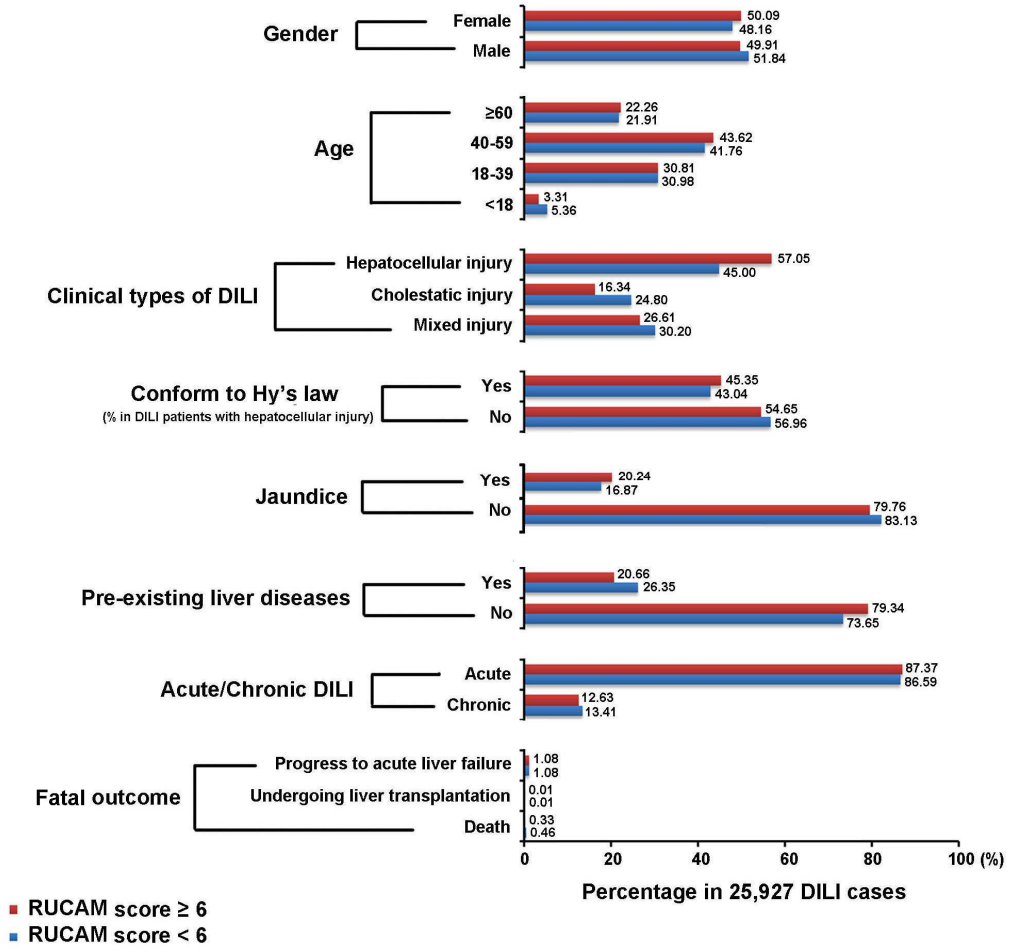
Geographic region	Inpatients (n)	DILI patients (n)	proportion of DILI (‰)	95% CI
Northeast China	1196360	1104	0.92	[0.87, 0.98]
North China	1162899	3197	2.75	[2.65, 2.84]
Eastern China	4719372	6573	1.39	[1.36, 1.43]
South China	186527	1218	6.53	[6.16, 6.90]
Central China	394783	505	1.28	[1.17, 1.39]
Northwest China	320533	480	1.50	[1.36, 1.63]
Southwest China	122258	614	5.02	[4.63, 5.42]
Total mainland China	8102732	13691	1.69	[1.66, 1.72]

Supplementary Figure 1



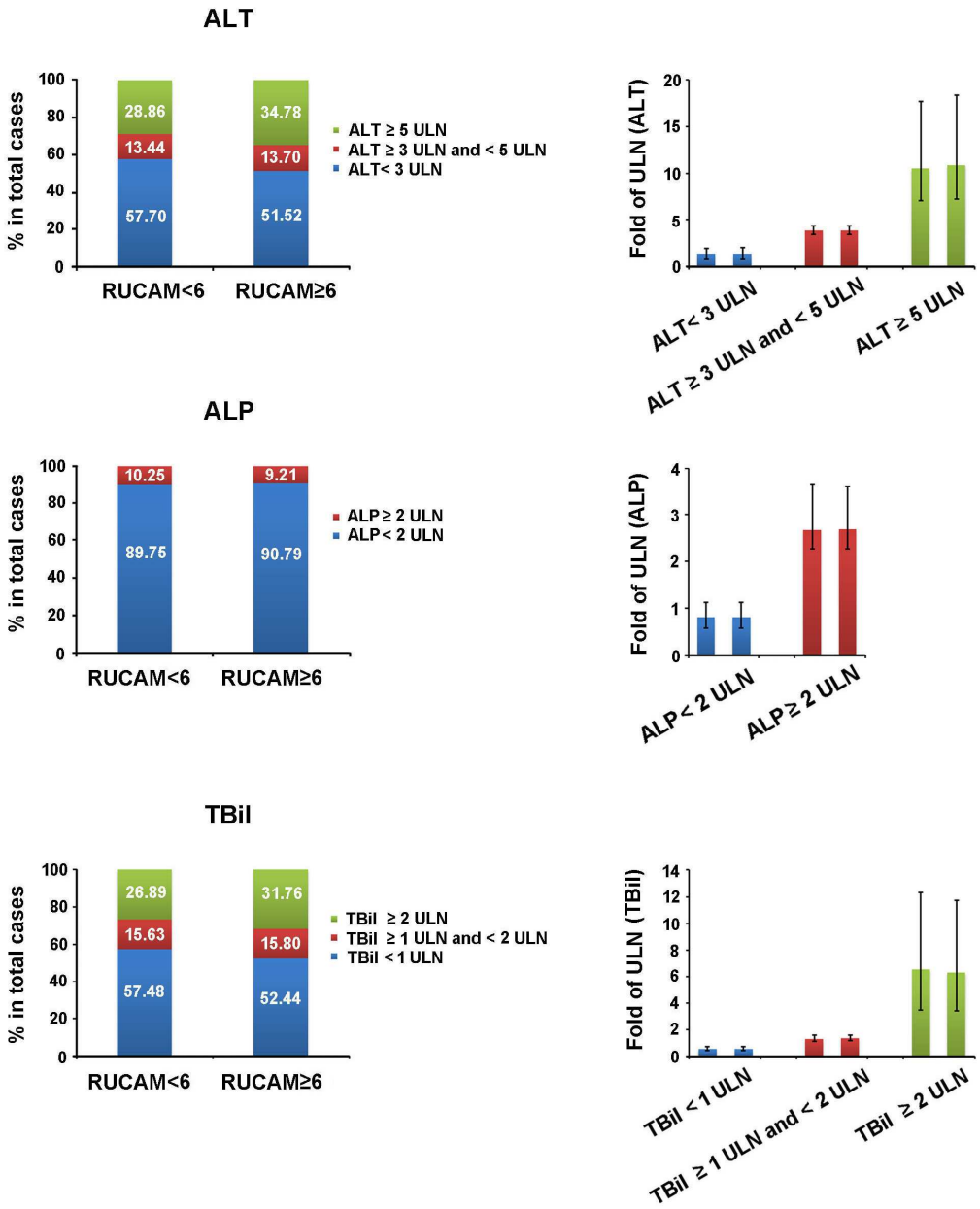
Supplementary Figure 1. The distribution of RUCAM scores of 25, 927 DILI cases collected in our study.

Supplementary Figure 2



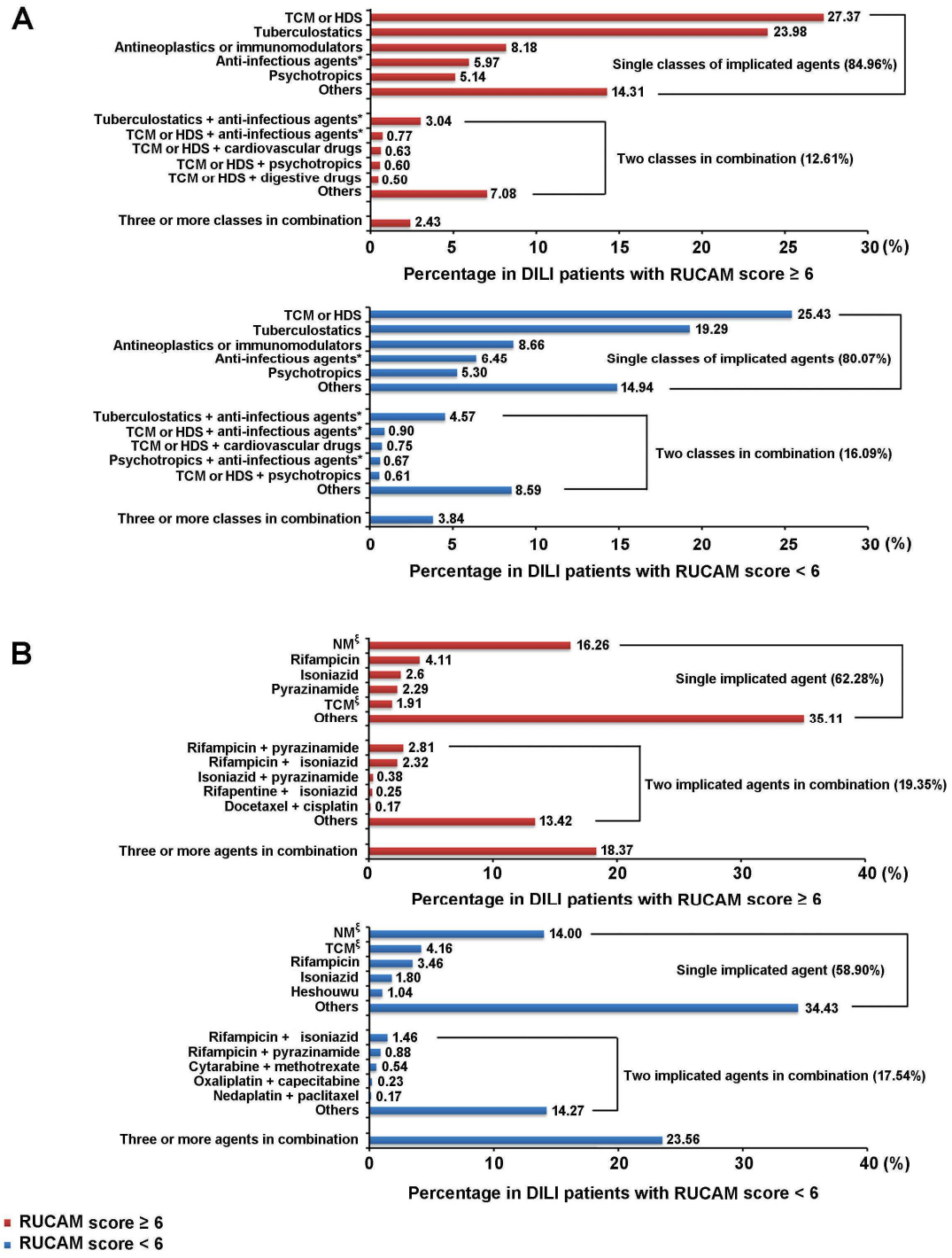
Supplementary Figure 2. Comparison of demographic and clinical features between two DILI subpopulations with RUCAM ≥6 and RUCAM <6.

Supplementary Figure 3



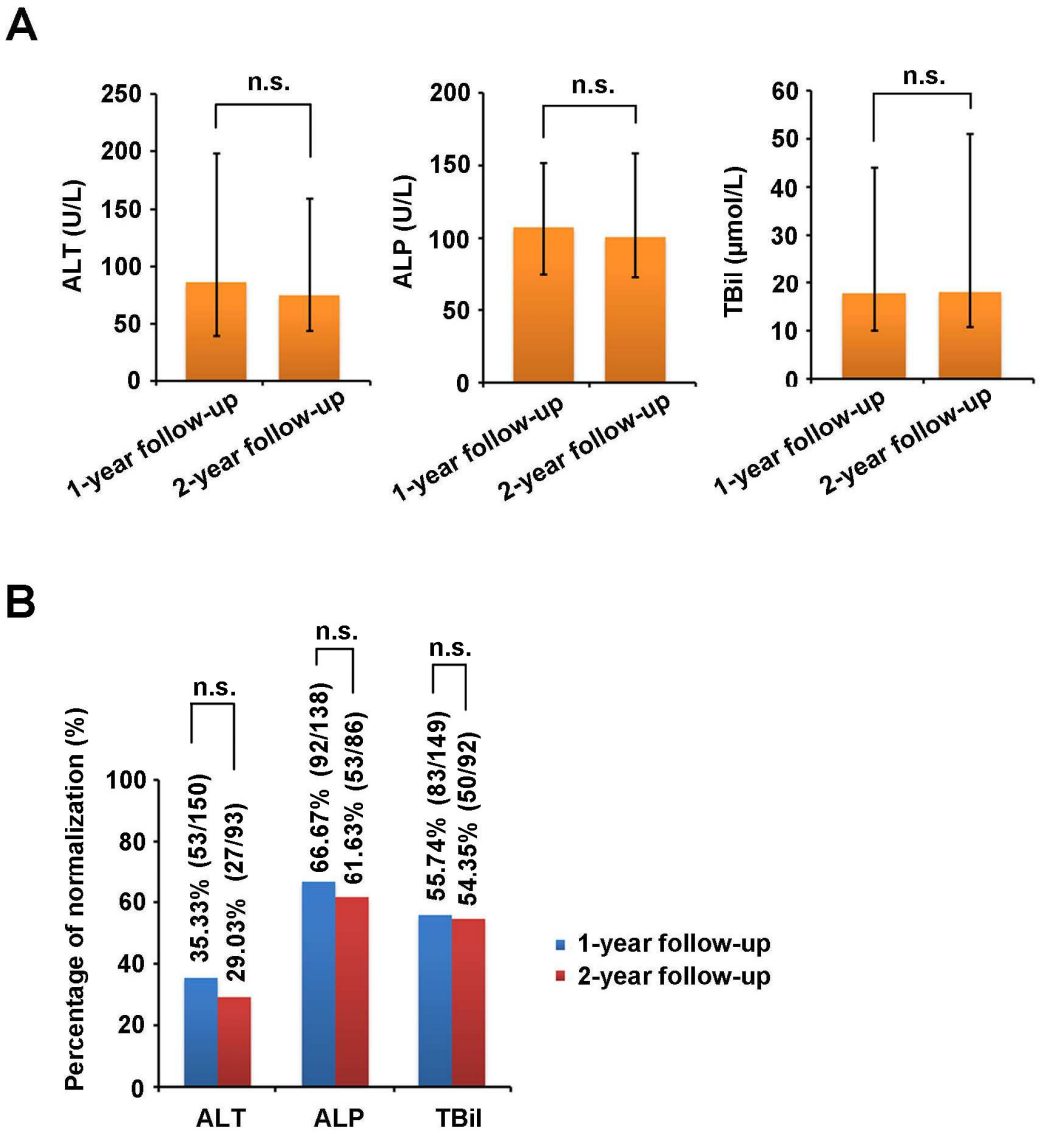
Supplementary Figure 3. Comparison of main liver function indicators between two DILI subpopulations with RUCAM ≥6 and RUCAM <6. Values of total bilirubin (TBil), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were indicated when abnormal hepatic biochemical indexes occurred for the first time and shown as median and interquartile range.

Supplementary Figure 4



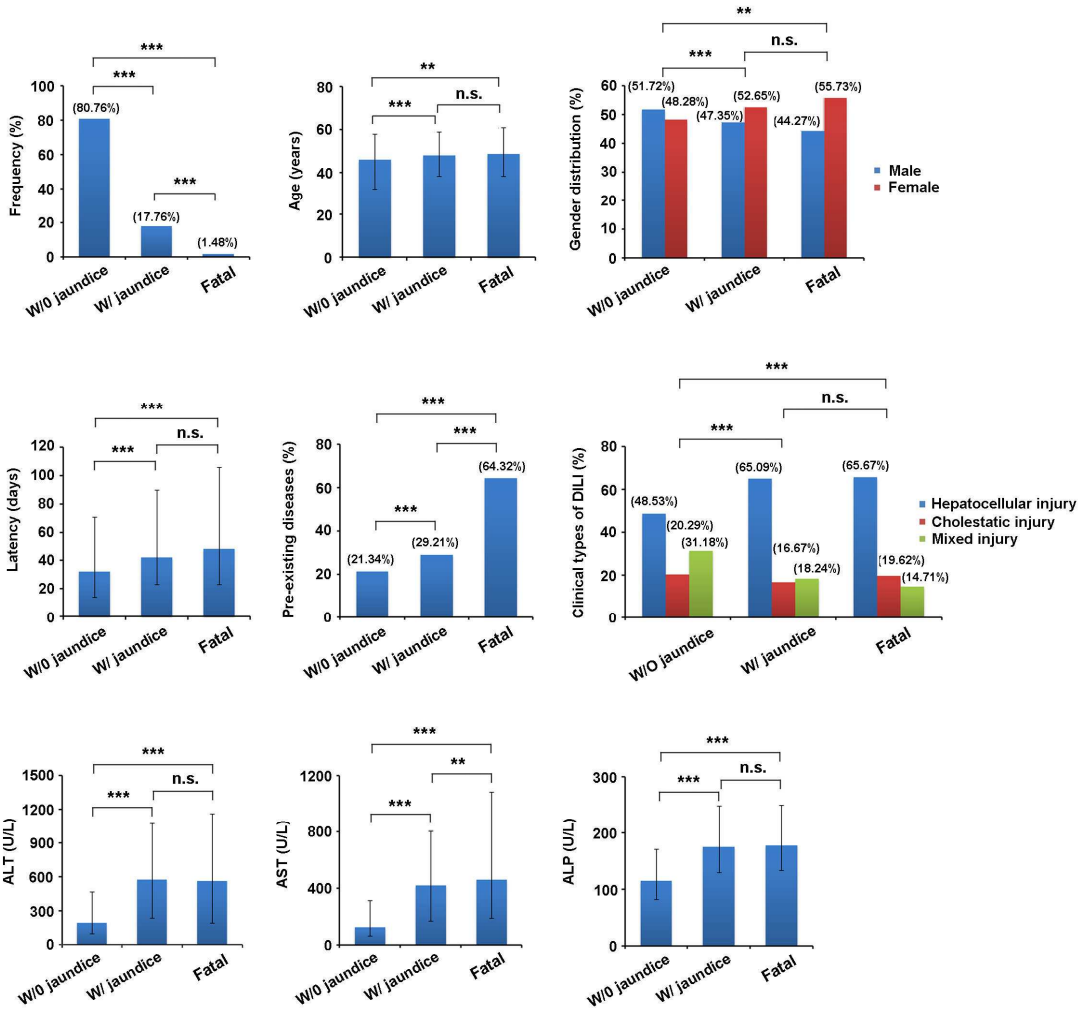
Supplementary Figure 4. Comparison of the implicated drug classes (A) and individual agents (B) between two DILI subpopulations with RUCAM ≥6 and RUCAM <6. *Anti-infectious agents included antibiotics, antiviral and antifungal drugs, but not anti-tubercular agents. §The detailed information is unknown.

Supplementary Figure 5



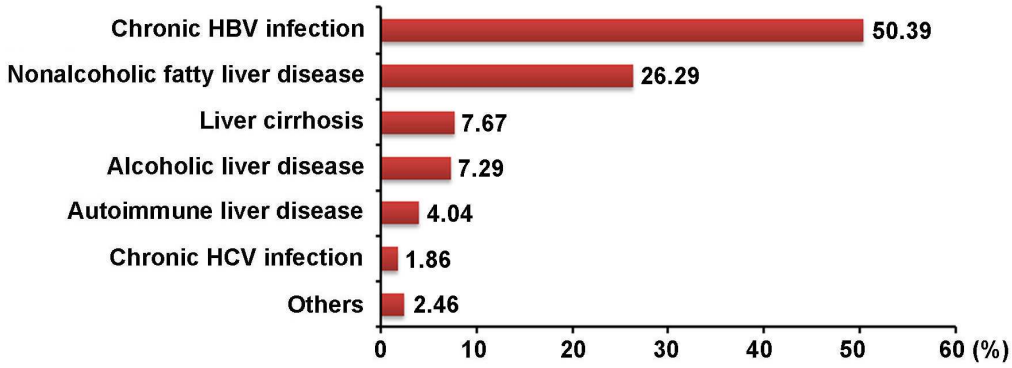
Supplementary Figure 5. Follow-up survey of some chronic DILI cases in the study. Values (A) and percentages of normalization (B) of ALT, ALP and TBil at the time points of 1- and 2-year follow-up for some of chronic DILI cases were presented. ALT, ALP and TBil were shown as median and interquartile range in (A). n.s., no significance.

Supplementary Figure 6



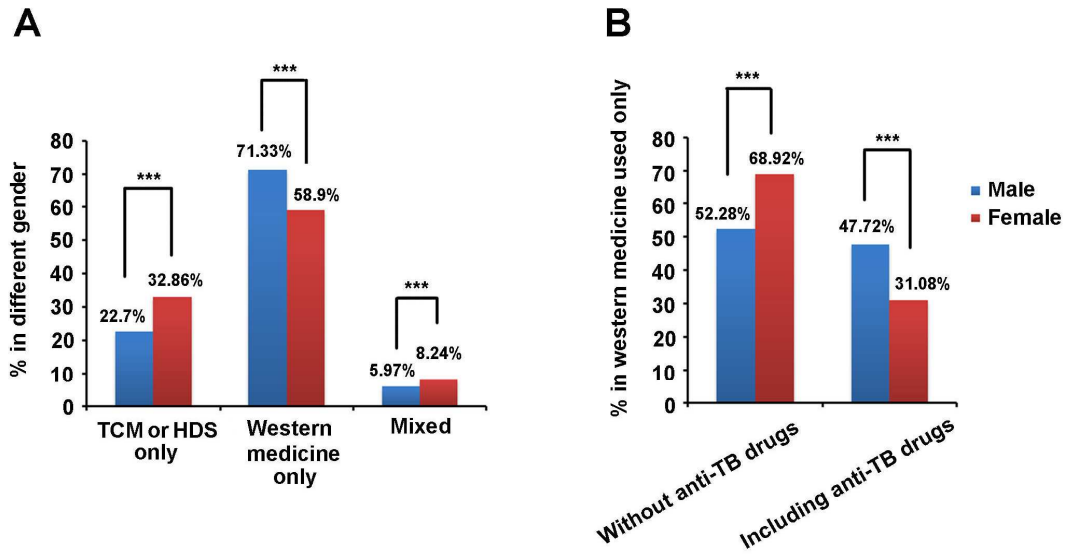
Supplementary Figure 6. Comparison of demographic and clinical features among DILI cases without jaundice (W/O jaundice, n=20,938), DILI cases with jaundice (W/ jaundice, n=4,605) and life-threatening ("fatal") DILI (n=384). Life-threatening DILI cases included 280 cases of progression to hepatic failure, 2 liver transplantations and 102 deaths. ALT/AST/ALP values used are the maximal values observed in each case during the course of the injury. Age, latency, ALT, AST and ALP values are shown as median and interquartile range (IQR) and between-group differences were assessed using either the Mann-Whitney U test or Kruskal-Wallis test. Category variables were analyzed with χ^2 test or Fisher's exact test where appropriate. *P*-values (two-tailed) < .05 were considered significant (*, $P < .05$; **, $P < .01$; ***, $P < .0001$). n.s., no significance.

Supplementary Figure 7



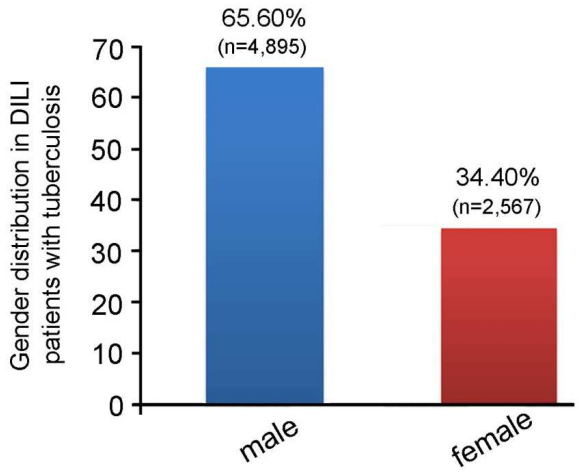
Supplementary Figure 7. The distribution of DILI cases with pre-existing liver diseases in the study.

Supplementary Figure 8



Supplementary Figure 8. Comparison of the implicated drug classes of DILI between men and women. (A) Comparison of frequencies of TCM or HDS used only, western medicine used only and mixed drugs used between two genders. (B) anti-TB drugs were more used by males than females. *P*-values (two-tailed) < .05 were considered significant (***, *P* < .0001).

Supplementary Figure 9



Supplementary Figure 9. Gender distribution in DILI patients with tuberculosis in our study. A total of 7, 594 cases were diagnosed as tuberculosis, in which gender information of 132 cases was missing or unknown.