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The characteristics and clinical outcome of drug-induced liver injury in a Chinese hospital

A retrospective cohort study

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Abstract

The aim of this cohort study was to determine the characteristics and clinical outcome of 287 patients with drug-induced liver injury (DILI) in a Chinese hospital.

Between January 2008 and January 2013, individuals who were diagnosed with DILI were selected. The complete medical records of each case were reviewed, and factors for the outcome of patients with DILI were extracted and analyzed using univariate and multivariate analysis.

Two hundred eighty-seven cases identified as DILI were included in the study. A total of 105 different drugs were considered to be related to the hepatotoxicity. The main causative group of drugs was Chinese herb (n = 111). Liver failure developed in 9 (3.1%) patients, and 2 died (0.7%). Overall, complete recovery occurred in 92 (32.1%) patients. Univariate analysis and binary logistic regression analysis identified the digestive symptoms, jaundice, total bilirubin (TBIL), and direct bilirubin (DBIL) as independent factors for the non-recovery of DILI. Then the prediction model, including digestive symptoms, jaundice, TBIL, and DBIL, was built by using binary logistic regression analysis again. Receiver operating characteristic curve validated the strong power (area under the curve (AUC) = 0.907) of prediction model for predicting the DILI non-recovery.

DILI is an important cause of liver test abnormalities, and Chinese herb represented the most common drug group. The factors such as digestive symptoms, jaundice, TBIL, and DBIL have effect on DILI outcomes. The prediction model, including digestive symptoms, jaundice, TBIL, and DBIL, established in this study is really an excellent predictive tool for non-recovery of DILI patients.

Abbreviations: ALF = acute liver failure, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DBIL = direct bilirubin, DILI = drug-induced liver injury, GGT = gamma-glutamyl transpeptidase, NAFLD = nonalcoholic fatty liver disease, NSAIDs = nonsteroidal anti-inflammatory drugs, RUCAM = Roussel Uclaf Causality Assessment Method, TBIL = total bilirubin, ULN = upper limit of normal.

Keywords: acute liver failure, drug-induced liver injury, hepatotoxicity, recovery, toxic hepatitis

1. Introduction

Drug-induced liver injury (DILI) is a serious common health problem in the general population.[1,2] It is the most common cause of acute liver failure (ALF) in the United States, accounting for more than 50% of cases;[3] thus DILI has been attracting increased attention over the past years.[4] The symptoms of DILI range from mildly elevated liver enzymes to severe hepatic damage requiring liver transplantation with poor transplant-free survival of the respective cases.[5] The epidemiology of DILI in the general population has not been well studied. According to reporting systems, the incidence rate of DILI in France and Spain was 14 and 34 cases per 100,000 individuals per year, respectively.[6,7] However, this number is likely underestimated because of the several limitations of the reporting systems.

To date, case reports and cohort studies have revealed numerous drugs that may cause hepatic damage. But only a minority of these medications have a dose-related and thus predictable hepatotoxicity,[8] as most of them display an idiosyncratic mode, either immune-mediated or metabolic.[9] Therefore, more studies are needed in order to quantify the risk of different drugs. In China, because of the huge population and multitude of drugs available, especially, the vast number of Chinese herbal medicines, DILI is becoming an increasingly serious health problem.[10] Many studies in China have revealed the drugs that lead to DILI and also involved the relevant clinical features and outcomes of DILI;[10–12] nevertheless, the results of

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these studies cannot well explain the relationships between clinical characteristics and outcomes of DILI. To further clarify the causes, clinical features, and outcomes of DILI in hospitalized patients, we conducted this study by retrospectively collecting the 5-year data of hospitalized patients diagnosed with DILI.

2. Materials and methods

2.1. Hospital

Huashan Hospital, one of the accredited agencies of Joint Commission International (JCI), is a tertiary hospital with 1216 beds and annual admission rate of about 20,000 patients. The hospital's hepatology department has 60 faculties and 120 inpatient beds, with an average annual admission of 3300 patients.

2.2. Patients

Between January 2008 and January 2013, a total of 287 consecutive patients diagnosed with DILI who were seen at Department of Infectious Diseases and Hepatology, Huashan Hospital, were retrospectively analyzed. The data were collected from hospitalized patients. A history, including the presence of medical illness, present and previous drug use, herbal remedies and mushroom intake, alcohol abuse, and drug addiction, was obtained for all patients and family members, if available. The final diagnoses and reasons for the inclusion and exclusion of the cases are shown in Fig. 1. Criteria for inclusion were age above 14 years; absence of confounding disease including acute (not the chronic) viral hepatitis (hepatitis A, B, C virus, cytomegalovirus, herpes simplex virus, and Epstein–Barr virus); convincing evidence of absent or minimal alcohol consumption, <15 g alcohol/day for women and <20 g alcohol/day for men; exclusion of other forms of liver disease including autoimmune, metabolic liver disease such as hemochromatosis, Wilson disease, α-1 antitrypsin deficiency, and biliary obstruction; exclusion of renal diseases and severe heart diseases (mild and moderate heart diseases included); and elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) threefold above upper limit of normal (ULN) or an elevation of total bilirubin (TBIL) higher than 2 mg dL^{-1}. Liver biopsies were available for evaluation in 36 patients with DILI.

2.3. Data collection and abstraction

Data were abstracted and recorded in a standard form by 2 investigators and then reviewed in duplicate by another 3 investigators, all of whom accepted training to familiarize themselves with the performance of the data form at the commencement of the study. We recorded data as follows: general information (sex, age, occupation, height, weight, etc.), the comorbidity, and complications; diagnosis at admission and discharge, disease history (including history of allergies), and drinking history; information about the drug suspected to have caused the liver injury; symptoms and signs; results of biochemical examinations, including ALT, AST, serum TBIL, direct bilirubin (DBIL), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), creatinine (Cr), and blood routine examination results the first time DILI was diagnosed; results of laboratory tests for other liver diseases (including hepatitis A, B, C, D, E virus, cytomegalovirus, Epstein–Barr virus,

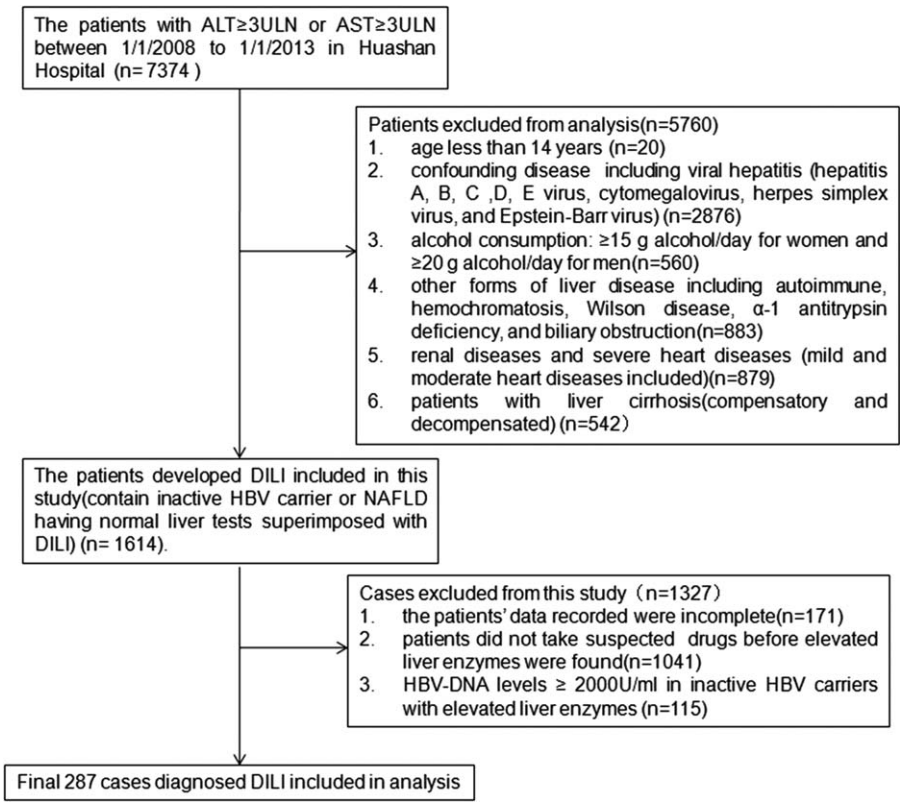

Figure 1. Flowchart summarizing the patient enrollment. ALT = alanine aminotransferase, AST = aspartate aminotransferase, DILI = drug-induced liver injury, NAFLD = nonalcoholic fatty liver disease, ULN = upper limit of normal.

and herpes virus infection, Wilson disease, autoimmune hepatitis, etc.); imaging and endoscopic results; and severity and outcome of DILI.

2.4. Ethics statements

All data were anonymously analyzed without individual patient consent due to the retrospective nature of the study. This study protocol was approved by the institutional review boards at Fudan University and Huashan Hospital.

2.5. Definition

After the data were collected, we rediagnosed all the patients according to the American College of Gastroenterology (ACG) clinical guidelines for the diagnosis and management of idiosyncratic DILI.[13] The diagnosis of DILI was based on the patient's history, clinical and biochemical characteristics, and histologic criteria, when available. The diagnosis was based on clinical suspicion, exclusion of other forms of liver disease, and consideration of the relationships between suspicious drug intake and onset of liver test abnormalities. Patients with underlying liver disease such as in inactive hepatitis B virus (HBV) carrier or nonalcoholic fatty liver disease (NAFLD) having normal liver tests were included into the study if they developed superimposed DILI. HBV-DNA levels in inactive HBV carriers with elevated liver enzymes were also checked using polymerase chain reaction to rule out HBV reactivation.

The definition and pattern of DILI (hepatocellular, cholestatic, or mixed) were characterized based on the International Consensus Meeting criteria for liver injury.[14,15] Hepatocellular pattern of DILI was defined as the ratio (R) of serum ALT (as a multiple of its ULN) to serum ALP (as a multiple of its ULN) greater than 5, cholestatic as R less than 2, and mixed as R greater than 2 to less than 5.[14,15] Interval between suspicious drug intake and DILI recognition was defined as the time to onset from the beginning of the drug/herb.

The most widely accepted definition of ALF includes evidence of coagulation abnormality, usually an International Normalized Ratio (INR) $\geq$1.5, and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of $<$26 weeks' duration.[16,17] Patients with DILI were defined as recovery when abnormal liver tests had returned to normal within 3 months for hepatocellular pattern of injury or within 6 months for cholestatic or mixed pattern of injury; if no recovery was observed and patients also did not develop into ALF, the patients were defined as chronicity.[7] Then ALF and chronicity patients were included into non-recovery group in this study.

2.6. Statistical analyses

Kruskal–Wallis test was used for group comparisons and Fisher exact test for categorical variables. Mean $\pm$ SD was given for continuous measurements. Frequencies and percentiles were given for categorical data. Influence of cancer, infection, antineoplastic agents, and antibiotics on the patterns of liver injury was assessed by using multinomial logistic regression analysis. Binary logistic regression was used to evaluate the factors associated with clinical outcome of DILI. Odds ratios (ORs) and 95% confidence intervals (CIs) of ORs were given. In addition, the predictive accuracy of TBIL, DBIL, and DBIL/TBIL for patients' outcome was assessed by receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC). A prediction model built by using significant variables obtained from binary logistic regression with $P < 0.05$. Then predictive power of the prediction model was also validated by ROC curve analysis. The optimal cutoff value was determined to maximize the sum of sensitivity and specificity. Differences were reported as statistically significant if the P value was less than 0.05. The data analyses were performed using SPSS 21.0 (IBM Corp., Armonk, NY) and Stata 12.0 (StataCorp., College Station, Texas).

3. Results

3.1. Study population

From January 2008 to January 2013, a total of 7374 new patients with liver test abnormalities were seen in our hospital. Of those, a total of 287 patients (male/female: 123/164; mean age: 50.70 $\pm$ 16.98 years, range: 14 to 81 years) (3.9%) fulfilled the criteria of DILI; female sex was slightly predominant (57.1%); and 45 (15.7%) had known underlying liver disease with NAFLD and inactive HBV carrier status. A total of 105 different drugs were potential candidates for the hepatotoxicity. Cholestatic pattern of liver injury was most commonly observed (100 of 287, 34.8%) followed by mixed pattern (98 of 287, 34.1%) and hepatocellular pattern (89 of 287, 31.0%). The median interval between suspicious drug intake and DILI recognition was 30 days (interquartile range: 18 to 87 days). The interval period showed no significant difference among these 3 patterns ($P=0.870$). Digestive symptoms (44.9%), dark urine (39.4%), fatigue (37.3%), and jaundice (16.4%) were the most frequent symptoms during admission. Digestive symptoms were more frequently associated with the hepatocellular pattern of injury ($P=0.027$) and jaundice seemed related to the cholestatic pattern of injury ($P=0.035$). No significant differences were observed between groups in terms of patient age, sex, and the presence of preexisting chronic liver disease ($P>0.05$). The demographics and clinical and laboratory characteristics of the 287 patients with DILI are shown in Table 1. As regards comorbidities, 42 patients had infection, 38 had cancer (detailed information about cancer can be seen in Table S1, http://links.lww.com/MD/B223), 28 had hypertension, 22 had autoimmune disease, 19 had diabetes mellitus, and 19 had hyperlipidemia. Among these complications, only cancer and infection were significantly different in 3 DILI patterns ($P=0.046$ and $P=0.045$).

3.2. Drug causality assessment in individual cases

In a total of 287 cases, the drug relationship according to the updated CIOMS scale was judged as at least "possible." A total of 105 different drugs or herbs were identified in these 287 patients as being related to liver injury. Table S2 (http://links.lww.com/MD/B223) exhibits the drug or herbs assessed as "possible," "probable," and "highly probable." Altogether, drugs of Chinese herbs (38.7%), antineoplastic agents (9.1%), nonsteroidal anti-inflammatory drugs (NSAIDs) (8.7%), and antibiotics (8.4%) were the groups represented the most (Table 1, Table S2, http://links.lww.com/MD/B223). Additionally, as shown in Table 1, Chinese herbs ($P=0.041$) and antineoplastic agents ($P=0.002$) were significantly correlated with patterns of DILI, while antibiotics showed no relationship with 3 DILI patterns. Moreover, the multinomial logistic regression analysis, in which the factors such as antineoplastic agents, antibiotics, cancer, and infection were respectively included, was performed to deeply confirm whether these 4 variables were independent factors which affect the patterns of DILI. Finally, our results showed that antineoplastic agents, antibiotics, cancer, and

Table 1

Characteristics of patients with DILI based on the type of liver damage.

Characteristics	Whole group (n = 287)	Hepatocellular (n = 89)	Cholestatic (n = 100)	Mixed (n = 98)	*P*
Mean age, y	50.70 ± 16.98	47.99 ± 15.56	52.12 ± 17.75	51.72 ± 17.31	0.203*
Female, n (%)	164 (57.1)	54 (60.7)	51 (51.0)	59 (60.2)	0.306#
Preexisting liver disease, n (%)	45 (15.7)	12 (13.5)	17 (17)	16 (16.3)	0.784#
Days between drug exposure and DILI recognition, median (IQR)	30 (18–87)	30 (15–78)	30 (14–90)	31 (21–60)	0.870*
Clinical presentation, n (%)					
Fever	35 (12.2)	12 (13.5)	12 (12)	11 (11.2)	0.892#
Digestive symptoms (nausea/vomiting/ anorexia/abdominal discomfort)	129 (44.9)	50 (56.2)	37 (37.0)	42 (42.9)	0.027#
Rash/pruritus	25 (8.7)	6 (6.7)	12 (12%)	7 (7.1)	0.350#
Fatigue/dizziness	107 (37.3)	38 (42.7)	30 (30.0)	39 (39.8)	0.161#
Jaundice	47 (16.4)	12 (13.5)	24 (24.0)	11 (11.2)	0.035#
Dark urine	113 (39.4)	43 (48.3)	36 (36.0)	34 (34.7)	0.113#
No clinical symptoms	65 (22.6)	13 (14.6)	24 (24.0)	28 (28.6)	0.069#
Laboratory parameters, mean value					
ALT (U/L)	636.76 ± 823.16	1378.28 ± 1134.11	205.95 ± 129.94	402.95 ± 250.33	<0.001*
AST (U/L)	386.10 ± 573.82	803.10 ± 854.22	143.56 ± 117.82	254.86 ± 238.94	<0.001*
ALP (U/L)	170.36 ± 174.63	134.24 ± 67.07	243.93 ± 264.617	128.09 ± 76.07	<0.001*
TBIL (μmol/L)	73.71 ± 102.09	77.31 ± 78.74	83.57 ± 119.02	60.38 ± 101.76	0.001*
DBIL (μmol/L)	44.13 ± 71.04	48.39 ± 53.25	51.77 ± 85.27	32.46 ± 68.36	<0.001*
GGT (U/L)	193.10 ± 203.35	153.65 ± 123.37	278.34 ± 271.02	141.94 ± 146.92	<0.001*
WBC (10^9/L)	6.04 ± 2.69	6.20 ± 3.24	5.96 ± 2.33	5.99 ± 2.50	0.947*
EOS (%)	3.14 ± 3.04	3.44 ± 3.63	3.04 ± 2.79	2.96 ± 2.67	0.863*
Autoimmune antibodies testing, positive, n (%)	17 (5.9)	6 (6.7)	5 (5.0)	6 (6.1)	0.875#
Duration of hospitalization, mean value, d	20.11 ± 17.72	20.45 ± 13.70	19.77 ± 21.08	20.13 ± 17.37	0.078*
Hospitalization costs, mean value, RMB, yuan	13,453.72 ± 12,324.77	16,635.12 ± 15,970.17	12,638.33 ± 11,398.38	11,396.51 ± 8344.94	0.013*
Comorbidity and complications, n (%)					
Hypertension	28 (9.8)	11 (12.4)	10 (10.0)	7 (7.1)	0.484#
Diabetes	19 (6.6)	3 (3.4)	10 (10.0)	6 (6.1)	0.182#
Hyperlipidemia	19 (6.6)	3 (3.4)	7 (7.0)	9 (9.2)	0.275#
Cancer	38 (13.2)	9 (10.1)	20 (20.0)	9 (9.2)	0.046#
Infection	42 (14.6)	14 (15.7)	8 (8.0)	20 (20.4)	0.045#
Autoimmune disease	22 (7.7)	8 (9.0)	7 (7.0)	7 (7.1)	0.852#
Epilepsy	6 (2.1)	2 (2.2)	1 (1.0)	3 (3.1)	0.594#
Heart disease	7 (2.4)	2 (2.2)	3 (3.0)	2 (2.0)	0.900#
Thyroid disease	12 (4.2)	3 (3.4)	5 (5.0)	4 (4.1)	0.854#
No complication	105 (36.6)	34 (38.2)	30 (30)	41 (41.8)	0.209#
Drugs, n (%)					
Chinese herbs	111 (38.7)	41 (46.1)	29 (29.0)	41 (41.8)	0.041#
Antineoplastic agents	26 (9.1)	3 (3.4)	17 (17.0)	6 (6.1)	0.002#
Nonsteroidal anti-inflammatory drugs	25 (8.7)	13 (14.6)	6 (6.0)	6 (6.1)	0.060#
Antibiotics	24 (8.4)	6 (6.7)	11 (11.0)	7 (7.1)	0.496#
Lipid-lowering drugs	17 (5.9)	4 (4.5)	4 (4.0)	9 (9.2)	0.239#
Antiepileptic drugs	13 (4.5)	4 (4.5)	5 (5.0)	4 (4.1)	0.953#
Antituberculosis drugs	11 (3.8)	2 (2.2)	3 (3.0)	6 (6.1)	0.335#
Thioureas	8 (2.8)	3 (3.4)	6 (3.0)	2 (2.0)	0.848#
Antifungals	8 (2.8)	3 (3.4)	3 (3.0)	2 (2.0)	0.848#
Antihypertensives	5 (1.7)	1 (1.1)	1 (1.0)	3 (3.1)	0.468#
Psychotropics	5 (1.7)	1 (1.1)	1 (1.0)	3 (3.1)	0.468#
Antidiabetics	4 (1.4)	1 (1.1)	2 (2.0)	1 (1.0)	0.813#
Others	30 (10.5)	10 (11.2)	12 (12.0)	8 (8.2)	0.510#

Mean value = mean ± SD.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DBIL = direct bilirubin, DILI = drug-induced liver injury, EOS = eosinophil, GGT = gamma-glutamyl transpeptidase, IQR = interquartile range, TBIL = total bilirubin, WBC = white blood cell.

* Kruskal–Wallis test.

Fisher exact test.

infection were all not correlated with DILI patterns (Fig. 2 and Table S3, http://links.lww.com/MD/B223).

3.3. Clinical characteristics of patients with ALF

Acute liver failure (ALF) based on American Association for the Study of Liver Diseases (AASLD) criteria[16] developed in 9 patients. Among these 9 patients, cholestatic was the most common pattern of injury (6 patients), 2 (1 hepatocellular pattern and 1 cholestatic pattern injury) died in the hospital, 3 were auto-discharged, and the remaining 4 patients (3 cholestatic pattern of injury and 1 mixed pattern of injury) became chronicity. All of the patients with ALF ranged from 16 to 62 years, 5 were male and 4 were female, and 3 had preexisting

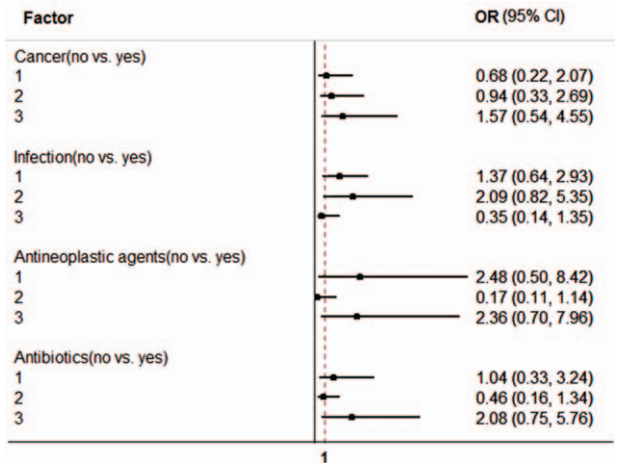

Figure 2. Influence of cancer, infection, antineoplastic agents, and antibiotics on the patterns of liver injury was evaluated by multinomial logistic regression analysis. 1 = hepatocellular vs mixed, 2 = cholestatic vs hepatocellular, 3 = mixed vs cholestatic.

liver disease. Table S4 (http://links.lww.com/MD/B223) shows detailed information of the 9 patients with ALF.

3.4. Univariate analysis and binary logistic regression analysis for factors associated with DILI outcomes

It is shown in Table 2 (univariate analysis) that non-recovery (including ALF and chronicity) developed in 195 patients (67.9%) (male/female: 81/114; mean age: 49.24 ± 16.79 years). Recovery occurred in 92 (32.1%) hospitalized patients within a mean of 20.38 ± 14.44 days (range: 7 to 180 days) after discontinuation of the implicated drug. Significant relationship was found between the characteristics (age, jaundice, ALP, TBIL, DBIL, hospitalization costs, diabetes, pattern of liver injury, and antineoplastic agents) and the development of different outcomes ($P < 0.05$). Other factors showed no association with patients' outcomes (Table 2).

In order to further investigate independent factors associated with prognosis of DILI patients, multivariate binary logistic regression analysis was performed, and the results (Fig. 3 and Table 3) showed that presence of digestive symptoms and jaundice on admission were associated with non-recovery (digestive symptoms: OR = 1.626, $P = 0.002$; jaundice: OR = 2.447, $P = 0.039$), which means patients with digestive symptoms (nausea/vomiting/anorexia/abdominal discomfort) and jaundice were more likely to become non-recovery compared with patients without digestive symptoms and jaundice. It is also clear from Table 3 and Fig. 3 that TBIL and DBIL were the independent factors related with DILI prognosis ($OR_{TBIL} = 1.011$, $\beta_{TBIL} = 0.011$, $P_{TBIL} = 0.002$; $OR_{DBIL} = 1.013$, $\beta_{DBIL} = 0.013$, $P_{DBIL} = 0.011$), suggesting that individuals with non-recovery had higher level of TBIL and DBIL.

3.5. ROC curve assesses efficacy of TBIL, DBIL, and DBIL/TBIL for predicting DILI non-recovery

We considered non-recovery (yes vs not) as final diagnosis; TBIL, DBIL, and DBIL/TBIL were respectively regarded as diagnostic indicators. Then ROC curves were plotted by SPSS 21.0 to evaluate the predictive power of TBIL (Fig. 4A), DBIL (Fig. 4B), and DBIL/TBIL (Fig. 4C) for DILI patients' non-recovery. The AUCs of the 3 ROC curves were 0.625, 0.621, and 0.615, severally (Fig. 4), and the 3 AUCs all were less than 0.70, indicating that TBIL, DBIL, and DBIL/TBIL did not have strong predictive power for DILI patients' prognosis.

3.6. Prediction model establishment

After plotting ROC curves, the independent factors such as digestive symptoms, jaundice, TBIL, and DBIL were together included into the binary logistic regression model again. Next, we built a prediction model and got the prediction probability for forecasting the clinical outcomes of DILI patients (each patient had a prediction probability, the details can be seen in Table S5, http://links.lww.com/MD/B223). Then we took the prediction probability as test variable and the actual classification of clinical outcome as state variable (non-recovery vs recovery), and finally the ROC curve was plotted again by using SPSS 21.0 to determine predictive power of the prediction model. As shown in Fig. 5, the AUC of this model for predicting non-recovery was 0.907, and optimal cutoff prediction probability was 0.558, suggesting that DILI patient whose prediction probability is greater than 0.558 can be considered as non-recovery outcome according to the result of ROC curve (Fig. 5).

4. Discussion

Establishing a diagnosis of DILI in an individual with elevated liver injury tests is often compelled because of the complete definition criteria of DILI. In fact, misdiagnosis and missed diagnosis for hospitalized patients are common, and there are still no standard diagnostic criteria for DILI in China. Most of the diagnoses are based on the physicians' individual ability and experience, and the Roussel Uclaf Causality Assessment Method (RUCAM) causality assessment[18] is seldom used. Therefore, in this study, DILI diagnosis in each case was made on the basis of clinical assessment, biochemical parameters, and histologic evaluation when available. Complete recovery after the implicated drug withdrawal is an important diagnostic criterion for DILI. We also ruled out other causes of liver injury in the final analysis. As seen in Table 1, female sex showed slight predominance, cholestatic pattern of liver injury was most commonly observed (34.8%), followed by mixed pattern (34.1%), which was conflicted with other studies that showed hepatocellular as the most commonly observed pattern in individuals with DILI.[3,7] Hundreds of drugs available on the market have been implicated in hepatotoxicity. Antibiotics and NSAID are the most widely used medications worldwide.[1,6] As seen from our investigation, Chinese herbs represented the main causative group, followed by antineoplastic agents, NSAIDs, and antibiotics (Table 1), which is inconsistent with the results reported in earlier studies.[3,7,19] Therefore, the cholestatic pattern of liver injury was predominant in our series maybe due to the most common drug leading to the DILI. As the main causative group in our study, Chinese herbs were relevant with 3 DILI patterns (Table 1, $P = 0.041$) and they may lead the cholestatic pattern of liver injury to become predominant. However, the mechanism of how Chinese herbs affect the pattern of DILI still remains unknown and needs to be further studied.

In addition, epidemiological studies have established that increasing BMI (kg/m^2) is associated with increased all-cause mortality,[20,21] and obesity is designated as a disease by American Medical Association. The prevalence of obesity is increasing worldwide in both developed and developing

Table 2

The association between patients' outcomes and clinical characteristics (univariate analysis).

Factor	Non-recovery (n = 195)[†]	Recovery (n = 92)	P[*]
Age, y, mean ± SD	49.24 ± 16.79	53.82 ± 17.06	0.015
Sex, male, n (%)	81 (41.5)	42 (45.7)	0.525
Days between drug exposure and DILI recognition, median (IQR)	30 (15–89)	31 (20–84)	0.695
Preexisting liver disease, n (%)	33 (16.9)	12 (13.0)	0.488
Clinical presentation, n (%)			
Fever	23 (11.8)	12 (13.0)	0.847
Digestive symptoms (nausea/vomiting/ anorexia/abdominal discomfort)	80 (41.0)	49 (53.3)	*0.057*
Rash/pruritus	20 (10.3)	5 (5.4)	0.261
Fatigue/dizziness	67 (34.4)	40 (43.5)	0.151
Jaundice	40 (20.5)	7 (7.6)	0.006
Dark urine	73 (37.4)	40 (43.5)	0.366
No clinical symptoms	45 (23.1)	20 (21.7)	0.880
Laboratory parameters, mean ± SD			
ALT (U/L)	671.41 ± 919.90	563.34 ± 563.50	0.966
AST (U/L)	411.34 ± 629.22	332.57 ± 431.90	0.207
ALP (U/L)	185.52 ± 202.37	138.23 ± 83.66	0.022
TBIL (μmol/L)	85.16 ± 112.80	49.44 ± 68.95	0.001
DBIL (μmol/L)	52.68 ± 79.38	26.01 ± 44.05	0.001
GGT (U/L)	204.81 ± 217.63	168.28 ± 167.56	*0.062*
WBC (10^9/L)	6.26 ± 2.90	5.59 ± 2.14	0.151
EOS (%)	3.18 ± 3.11	3.05 ± 2.91	0.534
Autoimmune antibodies testing, positive, n (%)	9 (4.6)	8 (8.7)	0.187
Duration of hospitalization, mean ± SD, d	19.97 ± 19.11	20.38 ± 14.44	0.145
Hospitalization costs, mean ± SD, RMB, yuan	14,548.17 ± 13,382.91	11,133.96 ± 9357.92	0.019
Comorbidity and complications, n (%)			
Hypertension	16 (8.2)	12 (13.0)	0.206
Diabetes	9 (4.6)	10 (10.9)	0.047
Hyperlipidemia	14 (7.2)	5 (5.4)	0.579
Cancer	27 (13.8)	11 (12.0)	0.713
Infection	31 (15.9)	11 (12.0)	0.475
Autoimmune disease	14 (7.2)	8 (8.7)	0.641
Epilepsy	5 (2.6)	1 (1.1)	0.668
Heart disease	3 (1.5)	4 (4.3)	0.216
Thyroid disease	10 (5.1)	2 (2.2)	0.349
No complication	66 (33.8)	39 (42.4)	0.189
Pattern of liver injury, n (%)			0.019
Hepatocellular	64 (32.8)	25 (27.2)	
Cholestatic	75 (38.5)	25 (27.2)	
Mixed	56 (28.7)	42 (45.7)	
Suspected drugs, n (%)			
Chinese herbs	70 (35.9)	41 (44.6)	0.194
Antineoplastic agents	23 (11.8)	3 (3.3)	0.025
Nonsteroidal anti-inflammatory drugs	19 (9.7)	6 (6.5)	0.502
Antibiotics	20 (10.3)	4 (4.3)	0.111
Lipid-lowering drugs	11 (5.6)	6 (6.5)	0.792
Antiepileptic drugs	7 (3.6)	6 (6.5)	0.361
Antituberculosis drugs	8 (4.1)	3 (3.3)	0.729
Thioureas	6 (3.1)	2 (2.2)	0.665
Antifungals	6 (3.1)	2 (2.2)	0.665
Antihypertensives	2 (1.0)	3 (3.3)	0.332
Psychotropics	4 (2.1)	1 (1.1)	0.675
Antidiabetics	2 (1.0)	2 (2.2)	0.596
Others	19 (9.7)	11 (12.0)	0.544

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DBIL = direct bilirubin, EOS = eosinophil, GGT = gamma-glutamyl transpeptidase, IQR = interquartile range, SD = standard deviation, TBIL = total bilirubin, WBC = white blood cell.

[*] *P* value: categorical variables—Fisher exact test, continuous variables—Kruskal–Wallis test.

[†] Non-recovery = chronicity + acute liver failure.

nations,[22] and the China Health and Nutrition Survey[23] reports that adult overweight prevalence nearly tripled from 1991 (11.7%) to 2009 (29.2%), leading to increasing concern in the public. Chinese herbal medicine is broadly accepted as safe and effective medication in China for the treatment of various ailments including obesity. They are believed to have effects on weight loss and other components of the metabolic syndrome, but good quality data on efficacy and side effects are

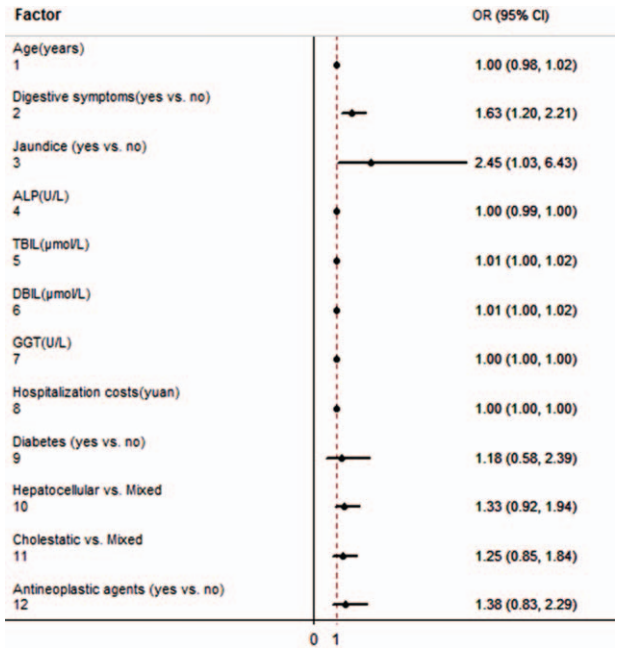

Figure 3. Factors associated with non-recovery of drug-induced liver injury (DILI) patients after adjusting the confounders. 1 to 12 represent the serial numbers.

lacking.[24,25] So obese patients are likely to take these so-called "safe" and "natural" products for losing weight, and a part of them may result in liver injury.[26]

Several antibiotics have the potential to cause liver injury. The exact incidence of antibiotic-related liver injury is unknown. In this study, the percentage of antibiotic-related liver injury was 8.4% (24/287). Antibiotic-induced liver injury represents all patterns of liver injury and one antibiotic may cause more than one pattern of injury.[27,28] Several reasons can explain antibiotics as common implicated drug group related to hepatotoxicity, such as the high consumption of antibiotics in the general population, lax prescription policies concerning antibiotics in most countries including China, and also infection and inflammation increase the susceptibility of the liver to some drugs.[29] NSAIDs is also a common cause of DILI in our study, which was similar to the results reported in the Western countries and the United States.[3,6,7] Also, in this analysis, antineoplastic agents (26/287) seemed to be one main cause of DILI, the reason for this may be the increased incidence of cancer in China.[30] Furthermore, data of Table 1 reveal that antineoplastic agents, cancer, and infection have influence on the patterns of DILI. However, the comorbidity may be just the condition which drug was used (cancer: antineoplastic agent; infection: antibiotics) rather than itself that make different patterns of DILI. Therefore, we performed multinomial logistic regression analysis to confirm the influence of cancer, infection, antineoplastic agents, and antibiotics on the patterns of liver injury, and the results indicated that these 4 factors were not correlated with DILI patterns (Fig. 2 and Table S3, http://links.lww.com/MD/B223).

The manifestation was mild in most of the patients, and some patients were even asymptomatic. Besides, the liver function of the patients rapidly improved after the hepatotoxic drugs were discontinued. These findings suggest that early detection of abnormal liver function and timely discontinuation of the drugs are very imperative. ALF developed in approximately 3.1% (9/287) of individuals with DILI in this study, and cholestatic pattern of injury was predominant (6/9) in patients with ALF (Table S4, http://links.lww.com/MD/B223). Earlier studies conducted in Spain and in the United States[3,7] were evaluated to identify the risk factors for the development of ALF in individuals with DILI. Female sex, pattern of liver injury, and serum bilirubin level on admission were identified as risk factors for the development of ALF in the Spain Cohort study,[7] but not in the US study.[3] In this study, because of the limitation of the ALF patients' number (only 9), the risk factors for the development of ALF were really hard to identify. The data from Spain[7] showed that the mortality rate of DILI was approximately 5.38% and the recovery patients accounted for the most percentage in the DILI series. Whereas, according to our research, the mortality rate of DILI was merely 0.697% (2/287), which showed the favorable prognosis and all of the mortality was liver related. Moreover, the number of recovery patients was lower than non-recovery

Table 3

Factors for non-recovery studied by binary logistic regression.

Factor*	Univariate analysis		Multivariate analysis	
	P	*β*	OR (95% CI)	*P*
Age (continuous)	0.015	0.006	1.001 (0.978–1.022)	0.114
Digestive symptoms (nausea/vomiting/anorexia/ abdominal discomfort) (yes vs no)	0.057	0.486	1.626 (1.196–2.212)	0.002
Jaundice (yes vs no)	0.006	0.895	2.447 (1.031–6.432)	0.039
ALP (U/L) (continuous)	0.022	0.004	1.001 (0.993–1.004)	0.293
TBIL (μmol/L) (continuous)	0.001	0.011	1.011 (1.004–1.021)	0.002
DBIL (μmol/L) (continuous)	0.001	0.013	1.013 (1.003–1.023)	0.011
GGT (U/L) (continuous)	0.062	0.001	1.001 (0.997–1.002)	0.197
Hospitalization costs (yuan) (continuous)	0.019	0.001	1.001 (0.998–1.003)	0.602
Diabetes (yes vs no)	0.047	0.162	1.176 (0.578–2.393)	0.655
Pattern of liver injury	0.019			
Hepatocellular vs mixed		0.288	1.334 (0.919–1.937)	0.129
Cholestatic vs mixed		0.222	1.249 (0.847–1.841)	0.262
Antineoplastic agents (yes vs no)	0.025	0.321	1.378 (0.829–2.291)	0.217

Set recovery group as reference.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DBIL = direct bilirubin, GGT = gamma-glutamyl transpeptidase, TBIL = total bilirubin, WBC, white blood cell.

* Factors for continuous variables, the odds ratio represents that the possibility of recovery or chronicity changes n-fold with one unit.

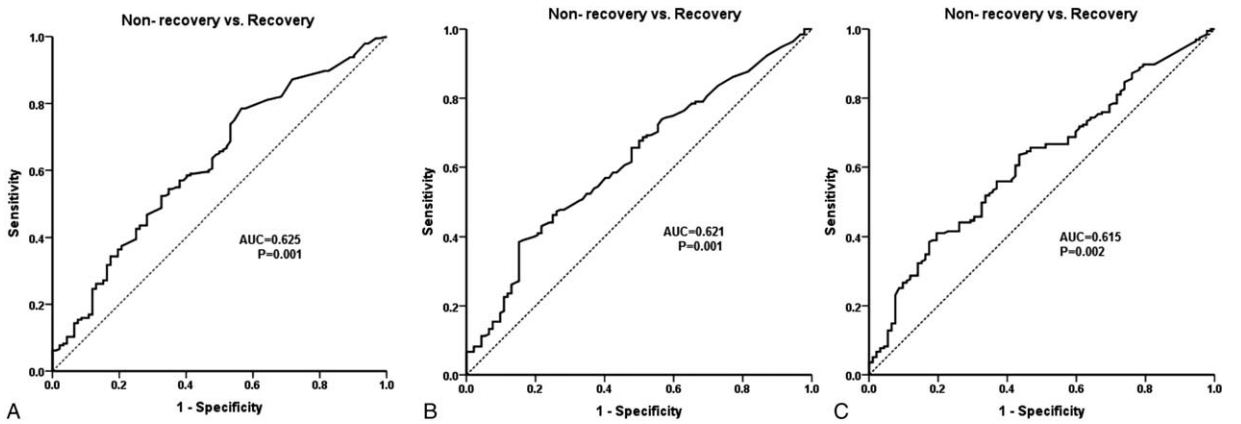

Figure 4. Receiver operating characteristic (ROC) curves with TBIL (A), DBIL (B), and DBIL/TBIL (C) for predicting the non-recovery in drug-induced liver injury (DILI) patients. *P* value was calculated by the Delong test. DBIL = direct bilirubin, TBIL = total bilirubin.

patients in this study. Thus, compared with the Western series, our DILI series had low complete recovery and low mortality, and this phenomenon may be attributed to the different race of the patients in the Western and our study. The property difference between the Western and Chinese patients may lead to the different clinical outcomes. The influence of racial difference on the prognosis of DILI patients needs to be identified by a multiethnic study in the future.

In our research, 15.7% (45/287) of DILI individuals had preexisting liver disease. NAFLD and inactive HBV carrier status were the most common diagnoses among these preexisting liver diseases. It has been reported that NAFLD conveys a nearly fourfold increase of DILI risk in middle-aged patients,[31] which deserves great attention by physicians when treating NAFLD patients to avoid drugs with potential hepatotoxicity. Our data also demonstrated that preexisting liver disease in patients with DILI did not affect the patients' prognosis (non-recovery vs recovery) (Table 2). Additionally, it can be seen from this study that non-recovery developed in 67.9% (195/287) of the individuals, and overall complete recovery occurred in 92 patients (32.1%) (Table 2). Although predictable factors associated with the clinical outcomes of DILI patients have been investigated in many countries,[3,6,7,19,32] the reliable data from China still seem lacking. Therefore, in this investigation, we further explored the risk factors related to DILI outcomes (non-recovery vs recovery). On our univariate analysis, the presence of jaundice on admission, age, ALP, TBIL, DBIL, hospitalization costs, diabetes, pattern of liver injury, and antineoplastic agents were associated with non-recovery or recovery of DILI patients (Table 2).

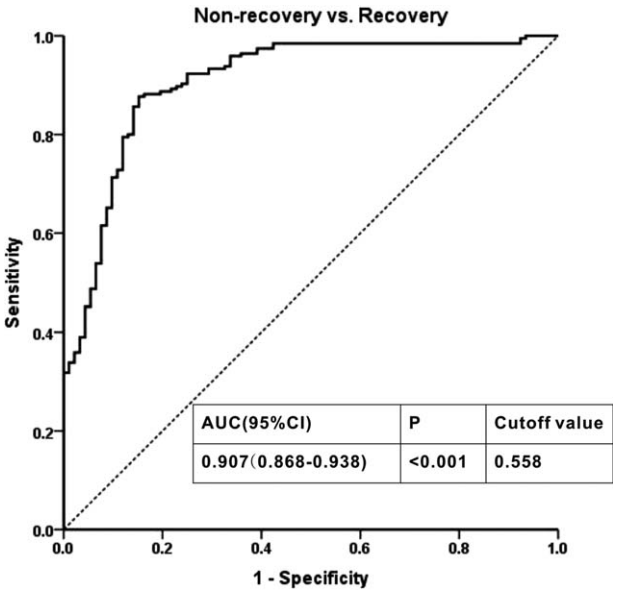

Figure 5. Receiver operating characteristic (ROC) curve for determining the predictive power of the prediction model including digestive symptoms, jaundice, TBIL, and DBIL. *P* value was calculated by the Delong test. DBIL = direct bilirubin, TBIL = total bilirubin.

As univariate analysis (Fisher exact test and Kruskal–Wallis test) could hardly manage the interference existed among these variables, in order to identify the independent factors for recovery and non-recovery, a multivariate analysis must be used to determine the authenticity and validity of the prognostic factors detected from the univariate analysis. After that, binary logistic regression analysis was performed and the results demonstrated that digestive symptoms, jaundice, TBIL, and DBIL were independent factors for the non-recovery and recovery. As shown in Table 3 and Fig. 3, the groups with digestive symptoms and jaundice may have 1.626 and 2.447 times possibility of DILI non-recovery compared with their counterpart groups without digestive symptoms and jaundice. As TBIL and DBIL were continuous variables, the odds ratio just represented that the possibility of non-recovery or recovery change n-fold with one unit. Thereby, to further investigate the role of TBIL and DBIL in predicting DILI outcomes, we combined TBIL and DBIL together, and took DBIL/TBIL as a new factor for the prognosis of DILI patients. TBIL, DBIL, and DBIL/TBIL were respectively regarded as test variable, and then 3 ROC curves were plotted to evaluate the predictive power of these 3 variables (TBIL, DBIL, and DBIL/TBIL) for DILI patients' outcomes (non-recovery vs recovery). Regrettably, the results from the ROC curve analyses indicated that TBIL (AUC = 0.625), DBIL (AUC = 0.621) and DBIL/TBIL (AUC = 0.615) did not have strong power for predicting non-recovery of DILI patients (Fig. 4). In order to seek a reliable method to predict the non-recovery of DILI patients, we ultimately developed a prediction model composed of the 4 variables (digestive symptoms, jaundice, TBIL, and DBIL)

by using binary logistic regression analysis again. The strong power of the prediction model for predicting the non-recovery of DILI patients can be described by the ROC curve (AUC = 0.907, $P < 0.001$) (Fig. 5). The cutoff value of prediction probability (0.558) was also determined by ROC curve. Notably, the patient with prediction probability greater than 0.558 was considered as non-recovery in our study.

In conclusion, on the basis of the results of this study, DILI is one of the important causes of liver test abnormalities. Chinese herbal medicine was the main cause of DILI in hospitalized patients in China, followed by antineoplastic agents, NSAIDs, and antibiotics. Digestive symptoms, jaundice, TBIL, and DBIL were identified as independent factors associated with recovery and non-recovery. Furthermore, the prediction model, including digestive symptoms, jaundice, TBIL, and DBIL, firstly built in our study can be an excellent tool to predict non-recovery in DILI patients.

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