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Assessment of cholestasis in drug-induced liver injury by different methods

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Abstract

Cholestasis in drug-induced liver injury (DILI) can be assessed by biochemical and pathologic methods, but the agreement between the 2 methods remains unclear.

The aim of this study was to identify the accurate method for assessment of cholestasis in DILI.

The DILI standard established and revised by the Council for International Organizations of Medical Sciences (CIOMS) (*R* values were calculated by liver function at different time points), cholestatic liver disease guideline (European Association for the Study of the Liver, EASL), and liver pathology were used to assess, compare, and analyze the cholestasis in 133 patients with DILI.

The *R* values at different time points in CIOMS standard had no statistical difference for the assessment of cholestatic DILI ($a=0.05$, $\chi^2=1.51$, $P=.679$). There were statistical differences among the results of CIOMS, EASL, and pathology ($a=0.05$, $\chi^2=99.97$, $P<.001$). EASL standard had no statistical difference with pathology ($a=0.003$, $\chi^2=8.00$, $P=.005$).

CIOMS and EASL standards based on biochemical parameters underestimated cholestatic DILI, as compared to liver pathology.

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase, CIOMS = Council for International Organizations of Medical Sciences, DBIL = direct bilirubin, DILI = drug-induced liver injury, EASL = European Association for the Study of the Liver, γ-GT = gamma-glutamyltranspeptidase, NR = new R, RUCAM = Roussel Uclaf Causality Assessment Method, SABC = streptavidin–biotin complex, TBA = total bile acid, TBIL = serum total bilirubin, UDCA = ursodeoxycholic acid.

Keywords: biochemistry, cholestasis, drug-induced liver injury, histology, pathology

1. Introduction

Drug-induced liver injury (DILI) is a liver disease caused by drugs or other metabolites during drug application.[1] The diagnosis mainly depends on exclusive methods, and the Roussel Uclaf Causality Assessment Method (RUCAM) scale is the most commonly used method.[2,3] Based on the type of injury in target cells, DILI can be divided into hepatocyte type, cholestasis type, mixed type, and liver blood vessel type (which is rarely seen and was not enrolled in the present study).[4] The cholestasis-type DILI tends to be chronic,[5–7] so its accurate assessment is especially important.

The Council for International Organizations of Medical Sciences (CIOMS) has proposed and revised the assessment standards of hepatocellular injury-type, cholestasis-type, and mixed-type DILI,[8–10] in which *R* values are calculated by serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP). Cholestasis exists in both cholestasis and mixed-type DILI (defined as cholestatic DILI), so the standard can be used to assess the existence of cholestasis. Recently, new *R* (NR) has been proposed, which is calculated by the higher value between ALT and aspartate transaminase (AST).[11] However, in majority of the studies, the 1st liver biochemical parameter obtained after hospitalization was used to calculate the *R* value in CIOMS standard[12] (defined as *R* value on admission), and the relevant indices might change with disease progression. Whether cholestasis could be accurately assessed by *R* value on admission remains unclear. To ensure the relative objectivity of the data, ALT peak value and ALP peak value during hospitalization were used to calculate the *R* value (*R* peak value). The ALT and ALP values when total bilirubin peaked were also used to calculate the *R* value (defined as TR in this study).[12] Whether the 4 *R* values show consistent agreement on cholestatic DILI and their correlations with liver pathology remain unclear.

Second, cholestasis caused by different pathogenesis can be assessed by Clinical Practice Guidelines: Management of cholestatic liver diseases (European Association for the Study of the Liver, EASL)[13,14] (EASL standard), which includes cholestasis caused by DILI.

Finally, although the manifestations of DILI liver pathology are similar to various liver diseases, it remains the gold standard for evaluating liver injury caused by drugs.[15,16] It can relatively accurately evaluate the existence of cholestasis in liver. Herein, CIOMS standard (including *R* value on admission, NR, *R* peak value, TR) and EASL standard were used to assess the existence of cholestasis, as compared to liver pathology. Furthermore, they were also used to assess whether the standards based on biochemical parameters could relatively accurately indicate cholestasis in liver.

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LZ contribution was the same as co-first author.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (ethical approval number: No 8 2015).

Informed consent was obtained from all individual participants included in the study.

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This study provides theoretical basis for exploring noninvasive diagnostic model to accurately assess cholestatic DILI, as well as improve prognosis.

2. Materials and methods

2.1. Case collection

A total of 205 patients with DILI were hospitalized in the Second People's Hospital of Tianjin between January 2015 and January 2017. The RUCAM was used for DILI diagnostic criteria.[2] The evaluation standards were as follows: highly probable: >8 points; probable: 6 to 8 points; possible: 3 to 5 points; unlikely: 1 to 2 points; excluded: ≤0 point. The patients with RUCAM score ≥6 who simultaneously underwent liver pathology examination were enrolled in this study. The exclusion criteria were patients with cytomegalovirus, EB virus, and coxsackie virus infections, viral hepatitis (HAV, HBV, HCV, HDV, HEV), autoimmune liver disease, alcoholic liver disease, hereditary liver disease, and biliary obstruction. Finally, 133 cases were enrolled in this study, and all patients signed informed consent. The study was approved by the Ethics Committee of Tianjin Second People's Hospital. The research method is illustrated in Figure 1.

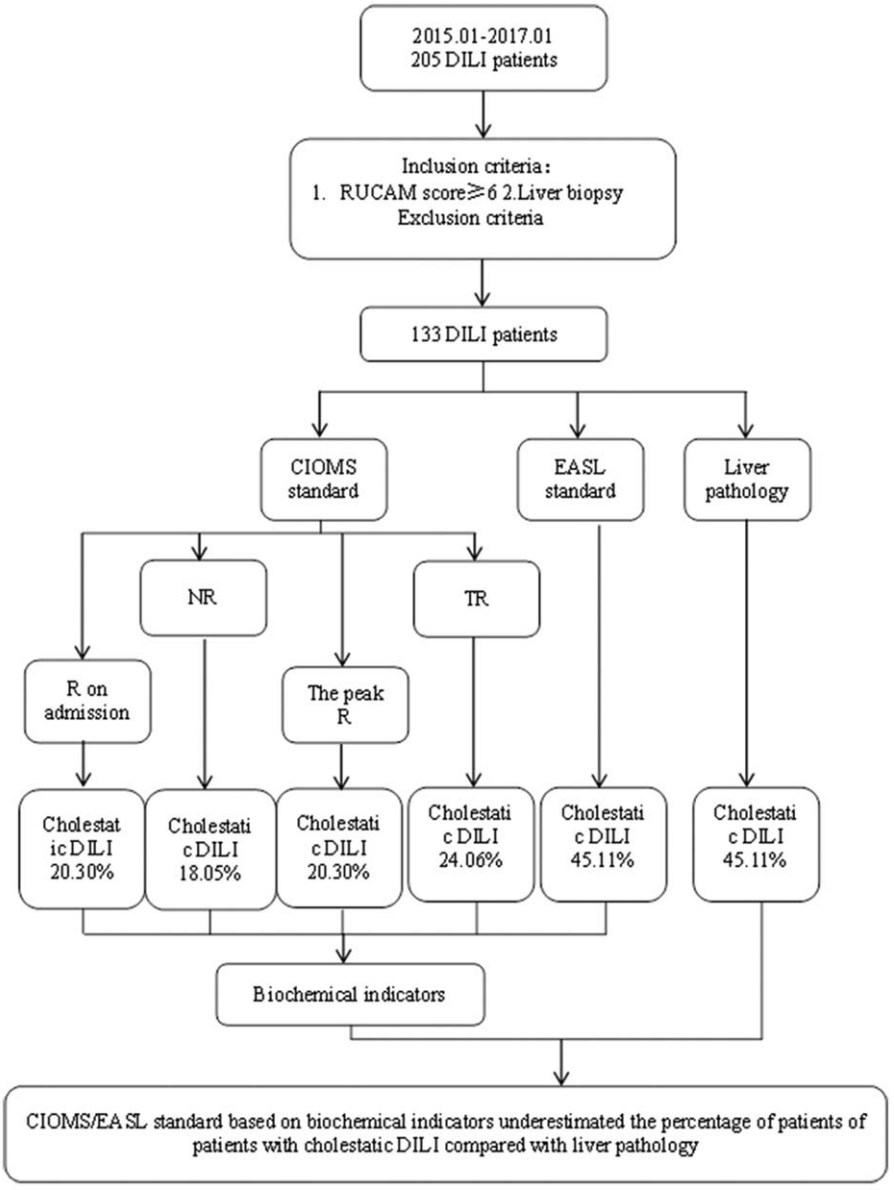

Figure 1. Data were collected from 205 patients with drug-induced liver injury (DILI) who were admitted to Tianjin Second People's Hospital between January 2015 and January 2017. Patients with Roussel Uclaf Causality Assessment Method (RUCAM) scores of ≥6 who had undergone liver biopsy were included in this study. Exclusion criteria were complications including infection with cytomegalovirus, EB virus or coxsackievirus, viral hepatitis (HAV, HBV, HCV, HDV, HEV), autoimmune liver diseases, alcoholic liver disease, hereditary liver diseases, and bile duct obstruction. In the end, a total of 133 patients were included in this study. Three different sets of diagnostic criteria for cholestatic DILI were used separately to classify 133 patients with DILI into 2 groups: those with cholestatic DILI and those with noncholestatic DILI. The 3 sets of criteria were: the diagnostic criteria established by the Council for International Organizations of Medical Sciences (CIOMS) (including different *R* value), the diagnostic criteria in the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: management of cholestasis liver diseases, and liver pathology, respectively. Then, the percentages of those with cholestatic DILI were compared to explore the accuracy of the 3 sets of diagnostic criteria. Compared with that of cholestatic DILI using the pathologic diagnostic criteria, the incidence of cholestatic DILI diagnosed using the CIOMS/EASL criteria was underestimated.

2.2. Biochemical parameters

Fasting blood samples (2 mL) were taken within 24 hours after hospitalization and weekly to measure ALT, AST, ALP, gamma-glutamyltranspeptidase (γ-GT), serum total bilirubin (TBIL), direct bilirubin (DBIL), and total bile acid (TBA) using an automatic biochemistry analyzer (Hitachi-7180). The reagents were purchased from Wako Pure Chemical Industries, Ltd and BioSino Bio-Technology & Science Inc.

2.3. Liver pathology examination

Liver pathology examination was completed within 1 week after hospitalization. Liver biopsy was conducted under the guidance by B ultrasound with a Bard liver biopsy gun (16 G), and 1.5 to 2.5 cm long hepatic tissues were taken, including at least 4 portal areas. The hepatic tissue was fixed with 10% formaldehyde, embedded with paraffin, sliced into 5 μm sections, and stained by hematoxylin and eosin and Masson. The fibrosis degree and pathologic features were observed under a microscope. The hepatocellular iron deposition was observed by Prussian blue staining. In situ expression of HBsAg and HBcAg was detected by streptavidin–biotin complex (SABC), and CK19 expression was detected by immunohistochemistry to observe bile duct hyperplasia.

2.4. Reference standard for cholestatic DILI

Patients were classified into 2 groups: those with cholestatic DILI and those with noncholestatic DILI. Classification was independently based on 3 different sets of diagnostic criteria:

1. Cholestasis of patients with DILI was assessed by CIOMS standard[3]: hepatocellular-type: ALT ≥ 3 ULN and $R \geq 5$; cholestasis-type: ALP ≥ 2 ULN and $R \leq 2$; mixed-type: ALT ≥ 3 ULN, ALP ≥ 2 ULN and $2 < R < 5$, where the R value = (actual ALT/ALT ULN)/(actual ALP/ALP ULN), the ULN denotes the upper limit of normal. In this standard, the cholestatic DILI included cholestasis-type and mixed-type DILI. R value on admission was calculated using ALT and ALP values within 24 hours after admission. NR value was calculated from the higher value between ALT and AST. R peak value was calculated from the peak values of ALT and ALP during hospitalization. TR was calculated from the ALT and ALP when TBIL peaked.
2. Based on the EASL standard (2009),[13] when ALP > 1.5 ULN and γ-GT > 3 ULN, the existence of cholestasis should be considered.
3. Liver pathology[14,17,18]: The pathologic manifestations of cholestasis include cholestasis in hepatocytes, feathery degeneration associated with capillary dilatation, and bile thrombus formation. In severe cholestasis, the bile capillary containing bile thrombus was centered, and the hepatocytes showed gland alveolus-like arrangement forming bile wreath. The hypertrophied Kupffer cells in hepatic sinusoid took up bile, and interlobular bile duct cholestasis associated with bile thrombus was formed in the portal area. In the absence of the above manifestations, cholestasis could be excluded. The liver biopsy specimens were examined by the pathologists at our hospital, and sent to Prof Wang or Prof Hu for consultation.

2.5. Follow-up

The patients were followed-up once every 1 to 3 months. A total of 133 patients were followed up for >1 year.

2.6. Prognosis evaluation

Based on the guidelines for the diagnosis and treatment of DILI, chronic DILI was defined as DILI occurring after 6 months with continuous abnormal serum ALT, AST, ALP, and TBIL, or imaging and histologic evidences of portal hypertension or chronic liver injury.[4] However, some experts have recently proposed that it is more appropriate to define chronic DILI at 1 year.[19]

2.7. Statistical methods

The SPSS 17.0 was used to analyze the data. Measurement data were expressed as the mean ± standard deviation and median. Enumeration data were tested using the Chi-squared test. $P < .05$ was considered to indicate statistically significant difference. For determining the percentage of patients with cholestatic DILI, the rate of concordance between the CIOMS or EASL criteria and the pathologic diagnostic criteria were calculated using the formula $(a+d)/(a+b+c+d)$.

3. Results

3.1. General information

Among the 133 patients with DILI, there were 51 males (38.35%) with average age of 41.03 ± 12.12 years, and 82 females (61.65%) with average age of 49.23 ± 11.66 years. The medication duration of patients was 5 to 120 days (median = 30 days), and the withdrawal duration was 2 to 60 days (median = 16 days) (Table 1). Among patients with DILI caused by the different drugs, 65 (48.87%) were caused by herbal medicines. Thus, priority was given to DILI caused by herbal medicines.

3.2. Manifestations of liver pathology in patients with DILI

The liver pathology manifestations in 133 patients with DILI included hepatocellular injury, cholestasis, etc. Hepatocyte

Table 1

The basic characteristics of patients.

Column	Cases, n (%)
Gender	
Male	51 (38.35)
Female	82 (61.65)
Symptom	
Fatigue	75 (56.39)
Jaundice	80 (60.15)
Nausea	11 (8.27)
Poor appetite	57 (42.86)
Abdominal distention	12 (9.02)
Fevered	5 (3.76)
Rash	3 (2.26)
Itching	2 (1.50)
Asymptomatic	6 (4.51)
Drug types (etiology)	
Herb	65 (48.87)
Antitumor drugs	14 (10.52)
Antituberculosis drug	10 (7.52)
Nonsteroidal anti-inflammatory drug	10 (7.52)
Diary supplement	9 (6.77)
Drug used treatment cardiovascular diseases	8 (6.00)
Antibiotics	7 (5.26)
Drug used treatment thyroid gland diseases	4 (3.00)
Psychiatric drug	5 (3.76)
Immunosuppressants	2 (1.5)

Table 2

Pathologic manifestations in the 133 patients with drug-induced liver injury.

Pathologic changes	n (%)
Hepatocyte injury	
Hepatocyte swelling	133 (100.00)
punctate and focal necrosis	130 (97.74)
Acidophilic degeneration	129 (96.99)
Interface inflammation	89 (66.92)
Infiltration of mixed inflammatory cells	85 (63.91)
Steatosis	73 (54.89)
Apoptotic bodies	66 (49.62)
Central phlebitis	29 (21.80)
Bridging necrosis	11 (8.27)
Cholestasis	
Cholestasis in hepatocytes	82 (61.65)
Bile duct proliferation	71 (53.38)
Ductular reaction	70 (52.63)
Bile plugs	51 (38.35)
Fibrosis	100 (75.19)
Waxy deposits	51 (38.35)
Deposition of brown pigments	18 (13.53)

swelling was the most common manifestation in hepatocellular injury, and hepatocyte cholestasis was the most common manifestation in cholestasis. All patients had different degrees of hepatocellular injury, with or without cholestasis. There were 50 patients with hepatocellular injury alone (37.59%), and 83 patients with hepatocellular injury and cholestasis (62.41%). The occurrence of different pathologic injuries is shown in Table 2.

3.3. Assessment of cholestasis of patients with DILI by different standards

The CIOMS standard (including *R* value on admission, NR, *R* peak value, TR), EASL standard, and liver pathology were used to assess the cholestasis of 133 patients with DILI. Cholestatic DILI accounted for *R* value on admission: 20.30% (27/133), NR: 18.05% (24/133), *R* peak value: 20.30% (27/133), and TR: 24.06% (32/133); EASL: 45.11% (60/133) in different methods, respectively, and 62.41% (83/133) in liver pathology. Different *R* values in CIOMS standard had no statistical difference in cholestatic DILI ($\alpha=0.05$, $\chi^2=1.51$, $P=.679$). There were statistical differences among CIOMS standard (including different *R* values), EASL, and liver pathology ($\alpha=0.05$, $\chi^2=99.97$, $P<.001$). The pairwise comparison showed no statistical difference among different *R* values in CIOMS standard, or between EASL standard and liver pathology (Fig. 2).

Liver pathology was used as a gold standard to calculate the diagnosis accordance rate with other methods. The results showed that the accordance rates of *R* value on admission with liver pathology, NR value with liver pathology, *R* peak value with liver pathology, TR with liver pathology, and EASL standard with liver pathology were 41.35%, 42.11%, 41.35%, 39.10%, and 51.13%, respectively (Table 3).

3.4. Prognosis analysis

The follow-up duration of 133 patients with DILI was >1 year. Based on the guidelines for the diagnosis and treatment of DILI, 24 patients progressed to chronic DILI (18.05%), of which 15 patients had cholestasis in liver pathology (15/24, 62.5%). If 1 year was used to define chronic DILI, 9 patients progressed to chronic DILI (6.77%), of which seven had cholestasis in liver pathology (7/9, 77.78%).

4. Discussion

With the continuous expansion of drugs, herbs, and dietary supplements as well as target population, the incidence of DILI has been steadily increasing.[15,20] In the guidelines for the diagnosis and treatment of DILI, cholestasis-type DILI easily progresses to chronicity.[4–6] Although cholestatic DILI has relatively lower

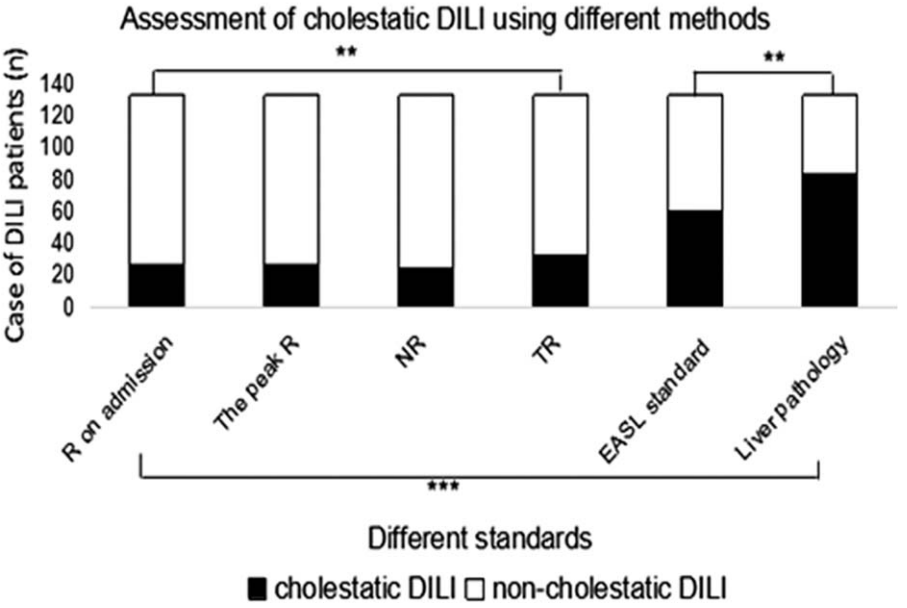

Figure 2. Cross axes represented different criteria or method. Longitudinal axis said the cases of patients with DILI. **Results with no statistical difference. ***Results with significant statistical difference.

Table 3

The rate of concordance between the CIOMS/EASL criteria and the pathologic diagnostic criteria in terms of the percentage of patients with cholestatic DILI.

Methods	Pathologic criteria		Consistency rate
	Cholestatic DILI	Noncholestatic DILI	
CIOMS criteria			
R on admission			
Cholestatic DILI	16	11	41.35
Noncholestatic DILI	67	39	
NR	15	9	42.11
Cholestatic DILI			
Noncholestatic DILI	68	41	
The peak *R*	16	11	41.35
Cholestatic DILI			
Noncholestatic DILI	67	39	
TR	17	15	39.10
Cholestatic DILI			
Noncholestatic DILI	66	35	
EASL criteria	39	21	51.13
Cholestatic DILI			
Noncholestatic DILI	44	29	

The rate of concordance between *R* on admission and liver pathology was 41.35%; the rate of concordance between NR and liver pathology was 42.11%; the rate of concordance between the peak *R* value and liver pathology was 41.35%; the rate of concordance between TR and liver pathology was 39.10%; the rate of concordance between EASL criteria and liver pathology was 51.13%.
CIOMS = DILI standard established and revised by the Council for International Organizations of Medical Sciences, DILI = drug-induced liver injury, EASL = cholestatic liver disease standard recommended by European Association for the Study of the Liver, NR = new *R*, TR = *R* peak value.

fatality, the risk of progression to chronic DILI is relatively high. Thus, accurate assessment of cholestatic DILI is closely related to prognosis. CIOMS standard was initially used in this study to assess cholestatic DILI (including different *R* values). Although the new edition of RUCAM scale redefines the type of DILI,[21] it is not universally accepted.[22] Hence, previous CIOMS standard was used in this study. Besides, the calculation time point of *R* values in CIOMS is an important issue during the disease course. Although there is no specified regulation in the standard, most of the investigations have calculated the *R* values based on the initial ALT and ALP levels obtained after hospitalization.[12] The calculation does not include AST level related to hepatocellular injury and γ-GT level related to cholestasis. Besides, the changes of relevant indices during liver disease progression is not considered, which may lead to misdiagnosis of liver injury. Therefore, in this study, *R* value on admission (ALT and ALP were obtained within 24 hours after hospitalization), NR value (the higher value between ALT and AST), *R* peak value (ALT and ALP peak values during hospitalization), TR (ALT and ALP when TBIL peaked) were used to assess the condition. The results indicated no statistical difference in the proportion of cholestatic DILI using different *R* values, and DILI associated with cholestasis was significantly lower than noncholestatic DILI (Fig. 2). The potential reasons are as follows: First, NR value was calculated based on the higher value between ALT and AST. The increase in ALT or AST suggested hepatocellular injury, which further reduced the detection efficiency of the standard on cholestasis. Second, *R* peak value was calculated using ALT and ALP peak values during hospitalization, but the increase in ALT level was often much higher than ALP in liver injury, which was not high enough to cause significant change of *R* peak value. Although most of the liver protecting treatments after hospitalization mainly decrease ALT and AST levels with less influence on ALP, it influences the accuracy of *R* peak value to a certain extent. This is the reason for the consistent results of assessment by *R* value on admission or *R* peak value. Finally, TR was calculated by ALT and ALP when TBIL reached its peak. Although the elimination of bilirubin has a certain relationship with metabolism of cholestasis, the liver-protecting drugs would significantly reduce TBIL, and further influence TR diagnosis. Therefore, there was no statistical difference in the proportion of cholestatic DILI using different *R* values.

Secondly, in CIOMS standard, ALP ≥2 ULN and $R \leq 2$ were defined as cholestasis-type DILI, and ALT ≥3 ULN, ALP ≥2 ULN, and $2 < R < 5$ were defined as mixed-type. There are corresponding diagnostic criteria for EASL on cholestatic liver disease. Therefore, EASL standard was also used to assess the cholestasis of 133 patients with DILI in this study. In contrast to *R* value in CIOMS, EASL standard only enrolls cholestasis-related ALP (γ-GT was to ensure that the increase in ALP was from liver), and eliminates the influence of sharp increase in ALT on ALP. Thus, in EASL standard, the proportion of cholestatic DILI was higher than that of CIOMS (Fig. 2), and had no statistical difference with the assessment results of liver pathology (α=0.003, $\chi 2 = 8.00$, $P = .005$). The diagnostic accordance rate between EASL standard and liver pathology on cholestatic DILI was higher than that between CIOMS and liver pathology (Table 3).

Finally, the DILI liver pathology is characterized by multiple injury targets and nonspecificity. However, some liver histologic change mode or combination of modes may have a certain DILI specificity.[22] Although liver pathology is an invasive detection as compared to other diagnostic methods, it is relatively visual, accurate and objective, and can be used as a gold standard for evaluating DILI.[15,16] The liver pathology in our study indicated that all the patients had different degrees of hepatocellular injury. No patient had cholestasis alone. Those with both hepatocellular injury and cholestasis accounted for up to 62.41%, which was much higher than those with cholestasis assessed by CIOMS and EASL standards (Fig. 2). Therefore, CIOMS and EASL standards based on biochemical parameters underestimated cholestatic DILI, which suggested that the biochemical diagnostic methods of cholestatic DILI were faulty. Hence, it is necessary to explore a noninvasive diagnostic method that could more accurately assess DILI and cholestasis.

The follow-up results indicated that if six months were used as an assessment standard for chronic DILI in the Guidelines for the

diagnosis and treatment of DILI, 24 patients (24/133, 18.05%) progressed to chronic DILI, of which 15 showed cholestasis in liver pathology (15/24, 62.50%). If 1 year was used to define chronic DILI, 9 patients progressed to chronic DILI (6.77%), of which seven had cholestasis (7/9, 77.78%). Therefore, patients with cholestatic DILI progressed more easily to chronic DILI.

In this study, CIOMS and EASL standards were found to underestimate the existence of cholestasis, whereas liver puncture could more accurately judge the presence of DILI and find out the patients with cholestasis, especially those who had bile duct deficiency, or even developed vanishing bile duct syndrome. Previous studies have shown a poor prognosis for drug-related vanishing bile duct syndrome.[23,24] And the early use of high dose ursodeoxycholic acid (UDCA) may help to improve the prognosis of patients with cholestatic DILI.[25] The prognosis of some patients with drug-related bile duct deficiency may be improved by the early use of UDCA, glucocorticoids and immunosuppressants.[26] In addition, because cholestatic DILI is prone to chronicity, following tips may be very important to improve patients' prognosis: patients with cholestasis should be treated in the early stage and then followed up more frequently, and treatment plans should be adjusted in time according to the patient's condition. Therefore liver puncture, at present, is necessary for early diagnosis, treatment, follow-up and prognostic evaluation of patients with DILI.

5. Conclusion

In summary, CIOMS and EASL standards based on biochemical parameters underestimated the existence of cholestasis in patients with DILI. Since DILI associated with cholestasis tends to progress to chronicity,[4] liver pathology, as a gold standard, could accurately assess the DILI cholestasis, which is helpful to understand the occurrence and identification of DILI. Therefore, pathologic examination of patients with DILI is important. Diagnostic indices and methods that could more accurately assess DILI should be explored in the future.

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Author contributions

Jia Li and Mindan Xing conceived and supervised the study; Jia Li, Mindan Xing and Lu Zhai designed experiments; Mindan Xing, Lu Zhai, Zengli Xu, Jun Wen, and Min Gao collected data; Mindan Xing, Lu Zhai and Qian Li analysed data; Mindan Xing, Jia Li, Lu Zhai and Jun Wen wrote the manuscript; Jia Li, Min Gao, and Mindan Xing made manuscript revisions. All authors reviewed the results and approved the final version of the manuscript.

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