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Pathological Features Associated with Severity of Drug-Induced Liver Injury: A Hospital-Based Retrospective Study

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Drug-induced liver injury; Pathology; Severity; Influencing factors

1. Abstract

1.1. Aims: To investigate the correlation between severity and pathological features of Drug-Induced Liver Injury (DILI), and the independent factors of pathological features affecting the severity of the disease were explored.

1.2. Methods: In this single-center retrospective observational study, patients were divided into mild group and moderate-severe group depending on clinical severity classification. Subsequently, we analyzed the differences between the two groups using univariate analysis. Finally, the factors with $P<0.05$ were included in multivariate logistic regression analysis to determine the independent predictive factors.

1.3. Results: 93 cases were finally enrolled (58 cases in the mild group and 35 cases in moderate-severe goup). There were no differences in baseline characteristics between the two groups (all $P>0.05$). There were differences in lobular activity grade, confluent necrosis, neutrophil rate, hepatocellular cholestasis rate, canalicular cholestasis rate, bile duct injury rate, fibrosis stage and eosinophil rate between mild and moderate-severe groups (all $P<0.05$). It was concluded that neutrophil (OR = 41.843, 95%CI 6.572～266.401), eosinophil (OR = 0.022, 95%CI 0.003～0.139), bile duct injury (OR = 3.960, 95%CI 1.044～15.018) and fibrosis (OR = 2.889, 95%CI 1.526～5.471) were independent influencing factors in patients with moderate-severe DILI (all $P<0.05$). Eosinophil was a protective factor.

1.4. Conclusions: There were correlations between severity and pathological features of DILI. Neutrophil, bile duct injury, fibrosis and eosinophil were independent factors affecting the severity of DILI. Neutrophil, bile duct injury and fibrosis were associated with higher severity DILI, and eosinophil was more likely to appear in lower severity DILI.

2. Introduction

Drug Induced Liver Injury (DILI) is the liver damage caused by various drugs and their metabolites. With the accelerated development of new drugs and the increasing types of clinical drugs, the incidence of DILI also rises accordingly [1, 2].

Patients with mild DILI can only have abnormal biochemical indicators without clinical symptoms, and severe cases may lead to acute liver failure or even death [3, 4]. It is also the main reason for drug approval failure and withdrawal from the market.

There is a lack of specific biomarkers to support diagnosis of DILI. Therefore, DILI remains an exclusive diagnosis, and American and European guidelines recommended Roussel Uclaf Causality Assessment Method (RUCAM) as the preferred method for formally assessing the causal relationship between drugs and liver injury [5-7].

Liver biopsy is not used routinely for clinical evaluation of the condition, but histopathology plays an irreplaceable role in providing direct diagnosis and treatment. The correlation between clinical classification and pathological features of patients with DILI has been reported in literatures at home and abroad [8, 9]. Moreover, specific histological patterns or characteristics can predict the prognosis of DILI [10, 11]. However, there are few studies on the correlation between the severity and pathological features of DILI, this study analyzed the correlation between them to explore the independent factors associated with severity of DILI.

3. Patient Selection

The patients diagnosed with DILI using liver biopsy at the Third People's Hospital of Shenzhen between March 2014 and July 2021 were included in this single-center, retrospective, observational study.

The inclusion criteria were as follows: (1) a causal relationship between suspected drug exposure and liver-related symptoms or biochemical abnormalities; (2) a Roussel Uclaf Causality Assessment Method (RUCAM) score ≥6; and (3) results of liver biopsy supporting the diagnosis of DILI. The exclusion criteria were as follows: (1) liver injury caused by viral hepatitis, alcoholic liver disease, autoimmune liver disease, or genetic metabolic factors; (2) poor score or classification of liver biopsy; and (3) incomplete clinical data. The study design adhered to the 1975 Declaration of Helsinki and was approved by the internal review board of the Third People's Hospital of Shenzhen (approval number:2021-007-02), which waived the requirement for informed consent due to the retrospective nature of this study.

4. Study Design

Data were obtained using the electronic medical record system, which included sex, age, body mass index, common diseases, use of drugs suspected to cause liver injury, serum biochemical indicators, and pathological data.

The severity of DILI was determined by Diagnosis and treatment guideline on drug-induced liver injury: (1) Mild: elevated ALT and/or ALP, but TBIL <2.5 times the upper limit of normal(ULN) and INR <1.5; (2) Moderate: elevated ALT and/or ALP, and TBIL >= 2.5 times the ULN or INR >= 1.5; (3) Severe: elevated ALT and/or ALP, and TBIL >= 5 times the ULN; (4) Acute liver failure: elevated ALT and/or ALP, and TBIL >= 10 times the ULN or daily elevation >= 17.1 mumol/L, and INR >2 or prothrombinactivity (PTA) <40%, ascites or hepatic encephalopathy may occur or other organ failures due to DILI; (5) Fatal death or liver transplantation due to DILI [12].

This criterion classifies severity into six grades: none (grade 0), mild (grade 1), moderate (grade 2), severe (grade 3), acute liver failure (grade 4), fatal/transplanted (grade 5). Grades 0-1 were classified as the mild group, while grades 2-5 were classified as the moderate-severe group in this study.

Liver biopsies were reviewed and re-scored by an experienced pathologist (Guang-de Zhou). Liver biopsy tissues were stained with hematoxylin-eosin, reticular fiber, Masson's trichrome, iron, copper, and immunohistochemical staining for CK7, CK19, and CD34, and then microscopically observed and analyzed. Each biopsy sample contained an average of 10 portal vein regions. The pathological observation items included inflammation and necrosis (spotty necrosis, interface hepatitis, confluent necrosis, bridging necrosis, and massive or submassive necrosis), hepatocellular cholestasis, canalicular cholestasis, lipogranulomas, bile pigment granules, bile duct injury, ductal paucity, vascular injury, and infiltration of inflammatory cells (eosinophils, neutrophils, and plasma cells). Inflammation was assessed using the Scheuer scoring system [13], which scores inflammation according to portal/periportal and lobular activity; each section was separately scored (0–4 points). The degree of fibrosis was assessed using the METAVIR scoring system, which categorizes liver fibrosis into 0–4 stages [14].

5. Statistical Analysis

Continuous variables are expressed as mean ± standard deviations or medians (upper quartile, lower quartile), while classified variables are expressed as counts (percentages). For the statistical analysis, an independent-samples t-test was used for continuous variables presenting normal distribution. The Mann–Whitney U test was used for two non-normally distributed datasets. The chi-square test was used to compare the classified data between the different groups.

Patients were divided into mild group and moderate-severe group depending on clinical severity classification. Subsequently, we analyzed the differences between the two groups using univariate analysis. Finally, the factors with $P<0.05$ were included in multivariate logistic regression analysis to determine the independent predictive factors. In all analyses, statistical significance was set at $P<0.05$. All analyses were performed using IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA).

6. Results

93 patients with DILI were included (Figure 1), 58 cases (62.4%) in the mild group and 35 cases (37.6%) in the moderate-severe group, shown in Table 1.

The criteria in the guideline are based on serum biochemical indicators and prognosis to classify the severity of DILI. The comparison of serum biochemical indicators between mild group and moderate-severe group was shown in Table 2.

There were no significant differences in gender, age, body mass index, smoke, alcohol, basic medical history and suspected liver injury drugs between the two cohorts, shown in Table 3.

Moderate-severe group was associated with higher degrees of lobular

activity (3(2, 4) vs. 2 (1.75, 3); P<0.001), fibrosis stage (2(1, 3) vs. 1(1, 2); P=0.024) than mild group. Moderate-severe group was more likely to have increased confluent necrosis (28.57% vs. 1.72%; P<0.001), neutrophils(77.14% vs. 48.28%; P=0.006), hepatocellular cholestasis (40% vs. 12.07%; P=0.002), canalicular cholestasis (22.86% vs. 3.45%; P=0.003), bile duct injury(62.86% vs. 37.93%; P=0.02), less likely to show eosinophils (34.29%vs. 60.34%; P=0.015) than mild group, shown in Table 4.

The above factors with P<0.05 were included in multivariate logistic regression analysis to determine the independent predictive factors.

Multivariate logistic regression analysis indicated that neutrophil (odds ratio [OR= 41.843, 95% confidence interval [CI]: 6.572–266.401, P<0.001), bile duct injury (OR=3.96, 95% CI: 1.044–15.018, P=0.043), fibrosis (OR=2.889, 95% CI: 1.526–5.471, P=0.001) and eosinophil (OR=0.022, 95% CI: 0.003–0.139, P<0.001) were independent factors affecting the severity of DILI. Neutrophil, bile duct injury and fibrosis were associated with higher severity DILI, and eosinophil was more likely to appear in lower severity DILI, shown in Table 5.

Table 1: Characteristics of 93 Patients With DILI Undergoing Biopsy

Feature	n=93
Age, years (mean ± standard deviation)	45.82±13.82
Male (N, %)	41(44.09)
BMI (kg/)	22.86±3.23
Causality process completed	
Definite (N, %)	21(22.58)
Very likely (N, %)	67(72.04)
Probable (N, %)	5(5.38)
Possible (N, %)	0
Unlikely (N, %)	0
Clinical severity classification	
None (N, %)	0
Mild (N, %)	58(62.3)
Moderate (N, %)	1(16.1)
Severe (N, %)	8(8.6)
Acute liver failure (N, %)	12(12.9)
Fatal/transplanted (N, %)	0

Table 2: Comparison of serum biochemical indexes between mild group and moderate-severe group

	Mild group (n=58)	Moderate-severe group (n=35)	*P*-value
ALB, g/L	42.11±5.34	38.01±3.58	＜0.001
TBIL, μmol/L	14.45(9.58,22.85)	117.9(75.4,266.2)	＜0.001
DBIL, μmol/L	6(3.5,11.65)	76.7(52.23,171.53)	＜0.001
IDIL, μmol/L	8.45(4.83,10.88)	36.75(23.98,78.05)	＜0.001
TBA, μmol/L	10.4(5.23,30.2)	153.6(89.7,257.95)	＜0.001
ALT, IU/L	209.5(119.75,468.8)	523(224,932)	0.001
AST, IU/L	102(63.75,261.75)	503(125,833.3)	＜0.001
ALP, IU/L	133(96.5,183)	183(129,324)	0.008
GGT, IU/L	180.55(101.25,373.5)	236(116,354)	0.374
PT, s	12.91±1.00	14.75±4.27	0.017
PTA, %	107.70±20.49	92.74±27.82	0.004
INR	0.98±0.10	1.16±0.46	0.024
PLT, × 10^9/L	204.62±67.89	226.46±102.67	0.268
IgE, IU/mL	52.4(13.19,145.55)	69.26(10,196.6)	0.941
WBC, × 10^9/L	5.54±1.78	5.50±2.48	0.923
HGB, g/L	134.83±20.47	130.31±17.70	0.282
PLT, × 10^9/L	204.62±67.89	226.46±102.67	0.268
Eosinophils, × 10^9/L	0.12(0.07,0.21)	0.1(0.02,0.17)	0.102
Eosinophils, %	2.3(1.58,3.63)	1.8(0.8,3.1)	0.054
EGFR, ml/min	101.81±16.22	103.77±20.15	0.627

Table 3: Baseline characteristics of mild group and moderate- severe group

	Mil dgroup(n=58)	Moderate-severe group(n=35)	*P*-value
Gender			
Male	28(48.28)	13(13.14)	0.295
Female	30(51.72)	22(62.86)	
Age, years	44.81±13.04	47.49±15.08	0.369
BMI, kg/	23.04±3.48	22.39±2.73	0.36
Smoking	2(3.45)	2(5.71)	1
Alcohol use	3(5.17)	2(5.71)	1
AIDS	11(18.97)	3(8.57)	0.174
Hypertension	11(18.97)	5(14.29)	0.562
Diabetes	2(3.45)	3(8.57)	0.557
Hyperlipidemia	5(8.62)	5(14.29)	0.611
Suspected liver injury drugs			
Herbal products	32(53.45)	25(74.29)	0.119
Anti-AIDS drugs	11(18.97)	3(8.57)	0.174
Antipyretic Analgesics	6(10.34)	4(11.43)	1
Drugs acting in the metabolic/endocrine system	5(8.62)	2(5.71)	0.913
Immunosuppressive drug	2(3.45)	3(8.57)	0.557
Antibiotic	4(6.9)	0	0.289

Table 4: Correlation between pathological features and clinical severity

	Mild group(n=58)	Moderate-severe group(n=35)	*P*-value
Lobular activity	2(1.75, 3)	3(2, 4)	0.001
Portal/periportal activity	2(1, 2)	2(1, 2)	0.453
Spotty necrosis	53(91.38)	34(97.14)	0.509
Confluent necrosis	1(1.72)	10(28.57)	0.001
Bridging necrosis	7(12.07)	4(11.43)	1
Massive or submassive necrosis	1(1.72)	2(5.71)	0.653
Interface hepatitis	32(55.17)	22(62.86)	0.467
Eosinophils	35(60.34)	12(34.29)	0.015
Neutrophils	28(48.28)	27(77.14)	0.006
Plasma cells	18(31.03)	15(42.86)	0.248
Hepatocellular cholestasis	7(12.07)	14(40)	0.002
Canalicular cholestasis	2(3.45)	8(22.86)	0.003
Lipogranulomas	6(10.34)	3(8.57)	1
Bile pigment granules	6(10.34)	7(20.00)	0.321
Bile duct injury	22(37.93)	22(62.86)	0.02
Ductal paucity	3(5.17)	2(5.71)	1
Vascular injury	22(37.93)	20(57.14)	0.071
Sinusoidal dilation	2(3.45)	3(8.57)	0.557
Lipogranulomas	2(3.45)	1(2.86)	1
Fibrosis stage	1(1, 2)	2(1, 3)	0.024

Table 5: Multivariate logistic regression analysis of independent factors affecting moderate-severe DILI

	P-value	*OR*(95%*CI*)
Eosinophils	0.001	0.022(0.003-0.139)
Neutrophils	0.001	41.843(6.572-266.401)
Hepatocellular cholestasis	0.095	3.377(0.808-14.108)
Bile duct injury	0.043	3.96(1.044-15.018)
Fibrosis stage	0.001	2.889(1.526-5.471)

CI denotes confidence interval; *OR* denotes odds ratios

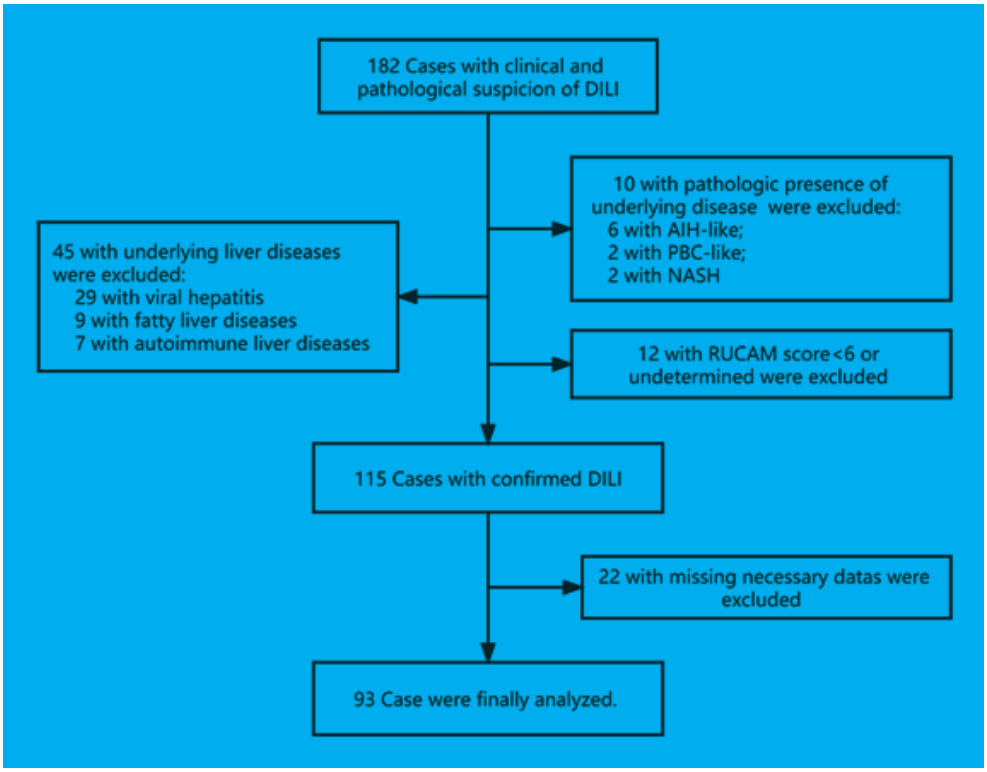

Figure 1: Comparison of pathological features between mild group and moderate-severe group

7. Discussion

7.1. Relationship between the severity of DILI and neutrophils

Neutrophils were shown to be the main component of liver infiltration in DILI in an immunohistochemical study of liver tissue by Gerussi et al [15]. When liver injury occurs, hepatocyte necrosis products will trigger liver inflammation and release neutrophil chemokines such as CXC-chemokine ligand 1 (CXCL1) and CXC-chemokine ligand 2 (CXCL2) and CXC-chemokine ligand 8 (CXCL8), these chemokines can bind to neutrophil receptors and rapidly attract neutrophils into the liver, It leads to the infiltration of inflammatory cells and the production of reactive oxygen species, which causes hepatocyte injury and death. Neutrophil infiltration in liver tissue is the main cause of moderate and severe liver injury [16].

7.2. Relationship between the severity of DILI and bile duct injury

According to studies made at home and abroad, more than 30 drugs can cause bile duct injury, mainly including Chinese herbal medicine, anti infective drugs, hypoglycemic drugs, anti-tumor drugs, proton pump inhibitors and other drugs [17].

Bile duct injury can lead to bile duct loss, and a large number of studies about DILI have shown that patients with bile duct loss have a poor prognosis [11, 18, 19]. When clinical manifestations or biochemical indicators show that cholestasis is prolonged or continuously aggravated, it often indicates drug-induced vanishing bile duct syndrome (D-VBDS). Recently, Li et al. [20] confirmed that the prognosis of D-VBDS was related to bile duct injury by comparing the liver pathology of 31 patients with good prognosis and 14 patients with poor prognosis. The prognosis of patients with a wide range of bile duct disappearance was poor.

Bile duct injury can lead to cholestasis, and DILI with cholestasis can easily progress to chronic [11, 21], and severe cases may progress to biliary cirrhosis and liver failure [22].

Early use of ursodeoxycholic acid, glucocorticoid and immunosuppressant can improve the prognosis of bile duct injury [23, 24]. However, early bile duct injury is not necessarily accompanied by cholestasis, and serological indicators or imaging may not provide accurate evidence of early bile duct injury. Therefore, liver biopsy is particularly important for the diagnosis of early bile duct injury.

7.3. Relationship between the severity of DILI and fibrosis

Chronic DILI caused by furantoin, isoniazid and other drugs may lead to fibrosis [25]. Our study showed that liver fibrosis was positively correlated with the severity of DILI, similar to the results of Kleiner et al. [8]. Other studies showed that the degree of fibrosis was also an independent factor affecting the 6-month prognosis of patients with DILI [10]. The higher the degree of fibrosis, the worse the prognosis.

The stage of liver fibrosis has significant clinical significance. The mortality caused by liver fibrosis of different causes may vary, but regardless of the cause, liver-related mortality increases exponentially with increasing fibrosis stage, and the incidence of hepatocellular carcinoma also increases [26].

7.4. Relationship between the severity of DILI and eosinophils

Eosinophils contribute to the progression of inflammation and are extremely important cells during immune and allergic reaction. In a

mouse model of immune-mediated hepatitis induced by concanavalin A, eosinophils accumulate in the liver and lead to hepatocyte death [27], and the immunohistochemical study of Pham et al. [28] showed that cationic protein released by eosinophils can lead to hepatocyte injury in patients with DILI. Based on the above studies, it can be speculated that eosinophils also play a pathogenic role in DILI.

However, our study showed that eosinophil infiltration in the liver was more common in mild DILI. Kleiner et al. [8] reached the same conclusion by analyzing the liver pathological sections of 128 patients with DILI, indicating that eosinophils have not only negative effects in the occurrence and development of DILI.

We speculate that this may be because the clinical symptoms of patients with eosinophil infiltration are more significant, mostly manifested as fever and rash, so patients seek medical treatment more quickly, stop liver damage drugs more timely, and the severity of liver injury is less. Some pathological experts believe that the occurrence of eosinophil infiltration may be related to the time of liver biopsy. More eosinophils can be seen in the pathological sections with later biopsy, while the patients with later biopsy usually have a longer treatment course and better recovery. Therefore, the role of eosinophils in DILI is still controversial and needs to be further explored.

Our study had a few limitations, the sample size was small, few patients with liver failure were included in this study, with insufficient studies of critically ill patients.

In conclusion, there are some correlations between severity and histological manifestations of DILI. Neutrophil, bile duct injury, fibrosis and eosinophil were independent factors affecting the severity of DILI. Neutrophil, bile duct injury and fibrosis were associated with higher severity DILI, and eosinophil was more likely to appear in lower severity DILI. This shows that histopathology can assist clinicians in judging the severity of DILI and guiding treatment in patients whose serological indicators are insensitive or whose serological indicators have recovered due to late treatment time. It also alerts clinicians to treat patients with bile duct injury or neutrophil infiltration in liver pathology more aggressively.

References

1. Shen T, Liu Y, Shang J, et al. Incidence and Etiology of Drug-Induced Liver Injury in Mainland China. Gastroenterology. 2019; 156(8): 2230-2241.e11.
2. Yang M, Li Z, Dou D. Can Retrospective Studies Confirm Causes of Drug-Induced Liver Injury?. Gastroenterology. 2019; 157(5): 1436-1437.
3. Devarbhavi H, Patil M, Reddy VV, et al. Drug-induced acute liver failure in children and adults: Results of a single-centre study of 128 patients. Liver Int. 2018; 38(7): 1322-1329.
4. Andrade RJ, Lucena MI, Fernández MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period [published correction appears in Gastroenterology. 2005 Nov;129(5):1808]. Gastroenterology. 2005; 129(2): 512-521.
5. Rockey DC, Seeff LB, Rochon J, et al. Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf causality assessment method. Hepatology. 2010; 51(6): 2117-2126.
6. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR. Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. Am J Gastroenterol. 2021; 116(5): 878-898.
7. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; Clinical Practice Guideline Panel: Chair:; Panel members; EASL Governing Board representative:. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019; 70(6): 1222-1261.
8. Kleiner DE, Chalasani NP, Lee WM, et al. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. Hepatology. 2014; 59(2): 661-670.
9. HE WP, XU B, WANG HF, et al. Correlation between clinical classification and histopathology in drug-induced injury. Chin Hepatol. 2010; 15(4): 241-243.
10. Tian QJ, Zhao XY, Wang Y, et al. Histologic pattern is better correlated with clinical outcomes than biochemical classification in patients with drug-induced liver injury. Mod Pathol. 2019; 32(12): 1795-1805.
11. Bonkovsky HL, Kleiner DE, Gu J, et al. Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements. Hepatology. 2017; 65(4): 1267-1277.
12. The Study of Drug Induced Liver Disease of Chinese Medical Association. Diagnosis and treatment guideline on drug-induced liver injury. Chin J Hepatol. 2015; 23(11): 810-820.
13. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol. 1991; 13(3): 372-4.
14. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1996; 24(2): 289-293.
15. Gerussi A, Natalini A, Antonangeli F, et al. Immune-Mediated Drug-Induced Liver Injury: Immunogenetics and Experimental Models. Int J Mol Sci. 2021; 22(9): 4557.
16. Czepielewski RS, Jaeger N, Marques PE, et al. GRPR antagonist protects from drug-induced liver injury by impairing neutrophil chemotaxis and motility. Eur J Immunol. 2017; 47(4): 646-657.
17. Reau NS, Jensen DM. Vanishing bile duct syndrome. Clin Liver Dis. 2008; 12(1): 203-x.
18. Zhao H, Xie W. Bile duct deficiency and vanishing bile duct syndrome associated with idiosyncratic drug-related liver injury: rare and poor prognosis. Chin Hepatol. 2017; 22(7): 576-577.
19. Gökçe S, Durmaz O, Celtik C, et al. Valproic acid-associated vanishing bile duct syndrome. J Child Neurol. 2010; 25(7): 909-911.
20. YE LH, WANG CK, ZHAO LL, et al. Clinicopathological features and prognostic analysis of 45 cases with drug-vanishing bile duct syndrome[J]. Anhui Med Pharm J. 2019; 23(10): 2073-2077.
21. Xing M, Zhai L, Li J, et al. Assessment of cholestasis in drug-induced liver injury by different methods. Medicine (Baltimore). 2019; 98(6):

e14399.

22. Ma WT, Liu QZ, Yang JB, et al. A Mouse Model of Autoimmune Cholangitis via Syngeneic Bile Duct Protein Immunization. Sci Rep. 2017; 7(1): 15246.
23. Ma X, Qiu DK. Progress in diagnosis and treatment of cholestatic liver disease. Chin J Clin Gastroenterol. 2009; 21(3): 141-143.
24. Sun Y, Zhao XY, Jia JD. Progress in diagnosis and treatment of drug associated vanishing bile duct syndrome. Chin Hepatol. 2014; 5: 360-362.
25. Dakhoul L, Ghabril M, Chalasani N. Drug-induced chronic liver injury. J Hepatol. 2018; 69(1): 248-250.
26. Berumen J, Baglieri J, Kisseleva T, et al. Liver fibrosis: Pathophysiology and clinical implications. WIREs Mech Dis. 2021; 13(1): e1499.
27. Louis H, Le Moine A, Flamand V, et al. Critical role of interleukin 5 and eosinophils in concanavalin A-induced hepatitis in mice. Gastroenterology. 2002; 122(7): 2001-2010.
28. Pham BN, Bemuau J, Durand F, et al. Eotaxin expression and eosinophil infiltrate in the liver of patients with drug-induced liver disease. J Hepatol. 2001; 34(4): 537-547.