Hepatology International (2024) 18:384–419
https://doi.org/10.1007/s12072-023-10633-7

GUIDELINES

Chinese guideline for the diagnosis and treatment of drug-induced liver injury: an update

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Received: 7 October 2023 / Accepted: 18 December 2023 / Published online: 24 February 2024

Abstract

Drug-induced liver injury (DILI) is an important adverse drug reaction that can lead to acute liver failure or even death in severe cases. Currently, the diagnosis of DILI still follows the strategy of exclusion. Therefore, a detailed history taking and a thorough and careful exclusion of other potential causes of liver injury is the key to correct diagnosis. This guideline was developed based on evidence-based medicine provided by the latest research advances and aims to provide professional guidance to clinicians on how to identify suspected DILI timely and standardize the diagnosis and management in clinical practice. Based on the clinical settings in China, the guideline also specifically focused on DILI in chronic liver disease, drug-induced viral hepatitis reactivation, common causing agents of DILI (herbal and dietary supplements, anti-tuberculosis drugs, and antineoplastic drugs), and signal of DILI in clinical trials and its assessment.

Keywords Drug · Herbal and dietary supplements · Liver injury · Guideline · Management · Diagnosis · Treatment · Prevention · Phenotypes · Prognosis

Abbreviations

ACLF	Acute-on-chronic liver failure
AIH	Autoimmune hepatitis
ALF	Acute hepatic failure
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibody
AST	Aspartate aminotransferase
AT-DILI	Anti-tuberculosis drug-induced liver injury
ATT	Anti-tuberculosis treatment
BSEP	Bile salt export pump
CIOMS	Council for International Organizations of Medical Sciences
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug–drug interaction
DDInter	Drug–drug interaction database
DI-AIH	Drug-induced autoimmune hepatitis
DI-ALH	Drug-induced autoimmune-like hepatitis
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DRESS	Drug reaction with eosinophilia and systemic symptoms
ERCP	Endoscopic retrograde cholangiopancreatography
ETV	Entecavir
FDA	Food and drug administration
GGT	Gamma-glutamyl transpeptidase
anti-HBc	Hepatitis B virus core antibody
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HBVr	Hepatitis B virus reactivation
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDS	Herbs and dietary supplements
HILI	Herbal medicines induced liver injury
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMs	Herbal medicines
HSCT	Hematopoietic stem cell transplantation

Extended author information available on the last page of the article

HSOS	Hepatic sinusoidal obstruction syndrome
ICIs	Immune checkpoint inhibitors
IDILI	Idiosyncratic DILI
INR	International normalized ratio
irAEs	Immune-related adverse events
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NAC	*N*-Acetylcysteine
NAFLD	Non-alcoholic fatty liver disease
NAs	Nucleotide analogues
NAT	*N*-Acetyltransferase
PA	Pyrrolizidine alkaloid
RCT	Randomized controlled trial
RM	Reactive metabolites
RUCAM	The Roussel Uclaf causality assessment method
SALF	Subacute liver failure
SEOP	Structured expert opinion process
TAF	Tenofovir alafenamide fumarate
TBil	Total bilirubin
TCM	Traditional Chinese medicine
TDF	Tenofovir disoproxil
TMF	Tenofovir amibufenamide
ULN	Upper limit of normal

Background

Drug-induced liver injury (DILI) refers to liver injury caused by prescription or over-the-counter drugs such as chemicals, biologic agents, and Chinese patent medicines as well as products such as herbal medicines (HMs), natural drugs, health products, dietary supplements, or their metabolites, excipients, contaminants, and impurities. The early detection, diagnosis, prognosis, management, and prevention of DILI is challenging owing to the following factors: complex drug classes causing liver injury; differences in prescribing habits; limitations in the understanding of population heterogeneity, mechanisms of injury, risk factors, and phenotypes; and lack of specific diagnostic biomarkers and effective interventions.

Since the publication of the last Chinese guideline for DILI in 2017, research in the field of DILI has greatly progressed, with new ideas and evidence being proposed. Liver injury caused by the use of herbal and dietary supplements (HDS) and herbal medicines (HMs) has been a global concern, especially in Asian and African countries where such complementary and alternative medicine (CAM) are frequently used and recently in western countries where HDS-DILI has also increased. Moreover, with the recent approval of targeted therapies and immune checkpoint inhibitors (ICIs), new challenges such as immune-mediated ICI-related hepatotoxicity have been posed in the field of DILI. In this context, we have addressed some specific issues in this update regarding chronic DILI and various specific phenotypes of DILI, DILI with pre-existing liver disease, drug-induced reactivation of hepatitis virus, and DILI signal in clinical trials and assessment in this document which is not covered by the 2017 guideline. International organizations such as the European Association for the Study of the Liver, the American College of Gastroenterology, the Asian Pacific Association for the Study of the Liver, the International Council for Organization of MedicalSciences (CIOMS) and American Association for the Study of Liver Disease have all published or updated clinical practice guideline for DILI in the past 3 years.

We organized experts to update the DILI guideline based on the evidence of the latest research advances. The guideline aims to provide clinicians with professional guidance on DILI detection, diagnosis, and management. It is also applicable to practitioners of pharmaceutical companies and drug regulatory agencies involved in new drug development, drug evaluation, and pharmacovigilance. However, this guideline cannot cover or address all issues of DILI diagnosis and treatment arising in clinical practice and are not mandatory standards. Therefore, clinicians should be fully aware of the latest relevant studies in clinical practice and make treatment decisions accordingly. This guideline will be updated in due course as research progresses.

The guideline has been developed according to the basic processes and procedures of guideline development promulgated by authoritative academic organizations worldwide. All experts who wrote the guideline signed a conflict-of-interest statement. The methodology of evidence assessment used in the production of the guideline was based on the 2011 Oxford centre for evidence-based medicine levels of evidence and grades of recommendation (Tables 1, 2). All evidence collection and assessment were performed by the Health Data Science Institute of Lanzhou University, an independent third party.

Overview of DILI

Epidemiology

Incidence in the general population

The actual incidence of DILI in the general population is often difficult to determine. Owing to differences in study methods, study populations, diagnostic criteria, and prescribing habits, currently reported general population-based epidemiologic data vary widely among countries, and the actual incidences may be under-reported [1]. Population-based prospective studies in France and Iceland showed that the annual incidence of DILI in the general population was

Table 1 Oxford centre for evidence-based medicine 2011 levels of evidence

Level	Description
1	Systematic review of randomized trials, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect
2	Individual randomized trial or (exceptionally) observational study with dramatic effect
3	Non-randomized controlled cohort/follow-up study
4	Case-series, case-control, or historically controlled studies
5	Mechanism-based reasoning

Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size

PICO participants, interventions, comparisons, outcomes

Table 2 Oxford centre for evidence-based medicine 2011 grades of recommendation

Grade	Description
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Grades of recommendation is technically based on OCEBM 2011, but final decision on certain recommendations is made considering specific circumstances during clinical practice

13.9/100,000 and 19.1/100,000, respectively [2, 3], and the annual incidence in the United States, Spain, and Sweden was < 4.0/100,000 [4–6]. In Asia, the annual incidence of DILI in the general Korean population is approximately 12/100,000 [7]. The estimated annual incidence in China is at least 23.80/100,000, which is higher than that in other countries and has been increasing annually [8].

Incidence in hospitalized patients

The incidence of DILI in hospitalized patients is approximately 1–6% and is significantly higher than in the general population [1]. DILI is an important etiology of unexplained liver injuries. It accounts for approximately 2–10% of patients who present with jaundice [9], 11.3% of patients hospitalized for severe acute liver injury [10], and 2.7% of total hospitalized patients with liver diseases [11]. Although DILI is not leading cause of acute liver failure (ALF) in Asian and African countries, and acetaminophen (APAP) is neither the leading cause of DILI in India nor China, the proportion of DILI in ALF has been increasing in the western countries. It is estimated that approximately 50% of ALF cases are caused by APAP in the US and UK [12].

Drugs causing DILI

At least 1000 drugs have been reported to cause liver injury. Detailed information on these drugs is available on the LiverTox (www.livertox.org) and Hepatox (www.hepatox.org) websites [13, 14]. The drugs that cause liver injury vary across countries and regions owing to the epidemiology of the primary disease, variations in prescribing habits, and population heterogeneity [15]. In Asian countries, such as South Korea [7], Malaysia [16], Thailand [17], Singapore [18], Taiwan [19], India [20], and China [8], anti-TB drugs, herbal and alternative medications such as traditional Chinese medicine (TCM), and antibiotics are the leading causes of DILI. The most common drugs that cause liver injury in China include TCM, HDS, anti-TB drugs, antineoplastic agents, and immunomodulators [8]. Meanwhile, the importance of antibiotics, and non-steroidal anti-inflammatory drugs such as APAP should not be overlooked since these are still the commonest causing agents of DILI in most western countries [21].

DILI classification

Direct, idiosyncratic, and indirect DILI

DILI can be classified as direct, idiosyncratic, or indirect based on its mechanisms [22]. Table 3 shows the clinical characteristics and associated causative agents. Although most drugs cause liver injury through specific mechanisms, some drugs can induce liver injury through numerous mechanisms.

Hepatocellular, cholestatic, and mixed DILI and R ratio

The *R* ratio is calculated from the initial abnormal liver biochemical results and reflects the pattern of abnormal

Table 3 Clinical characteristics of intrinsic, idiosyncratic, and indirect DILI and associated drugs

	Intrinsic	Idiosyncratic	Indirect
Mechanism of injury	Intrinsic toxicity of drug or drug metabolites	Idiosyncratic host metabolic or immune reaction	Indirect liver injury caused by drugs altering liver or host immune status
Dependency on dose	Dose dependent	Usually independent, although a dose threshold may be required	Unknown
Latency	Usually short (several days)	Various (days to years)	Delayed (several months)
Clinical phenotype	Hepatocellular, cholestatic, mixed, and specific phenotype	Hepatocellular, cholestatic, mixed, and specific phenotype	Hepatocellular, cholestatic, mixed, and specific phenotype
Examples	Acute hepatitis	Acute hepatitis, mixed or cholestatic hepatitis	Acute hepatitis, reactivation of hepatitis virus, DI-ALH, ICI-related hepatotoxicity, fatty liver disease
Common suspect drug	APAP, amiodarone, niacin, methotrexate, etc	Amoxicillin–clavulanate, cephalosporins, isoniazid, nitrofurantoin, minocycline, fluoroquinolones, macrolide antibiotics, ketoconazole, leflunomide, fenofibrate, amiodarone, statins, lisinopril, phenytoin, etc	Antineoplastic agents, corticosteroid, monoclonal antibodies (e.g., anti-tumor necrosis factor, anti-CD20 monoclonal antibody, ICI), protein kinase inhibitor

APAP acetaminophen, *DI-ALH* drug-induced autoimmune-like hepatitis, *DILI* drug-induced liver injury, *ICI* immune checkpoint inhibitors

biochemistry. Based on the *R* ratio, acute DILI can be classified as follows: (1) hepatocellular: $R \geq 5$, (2) cholestatic: $R \leq 2$, and (3) mixed: $2 < R < 5$ [23]. R = (alanine aminotransferase [ALT]/upper limit of normal [ULN])/(alkaline phosphatase [ALP]/ULN). Aspartate aminotransferase (AST) can be used as a substitute if ALT is unavailable. The initial *R* ratio may change as the liver injury progresses. Dynamic monitoring of the *R* ratio helps to thoroughly understand and determine the evolution of liver injury.

Recommendation 1: Abnormal initial liver biochemistry results should be used to calculate *R* ratio in suspected acute DILI episodes. R = (ALT/ ULN])/(ALP/ ULN). AST can be used as a substitute if ALT is unavailable. (2, C).

Clinical phenotype

The clinical phenotype of DILI is complex and includes almost all known types of acute, subacute, and chronic liver injuries. Mild cases can present with mild or moderate elevations in liver enzyme levels. Severe cases can progress to ALF or subacute liver failure (SALF). Hepatocellular injury accounts for 42–59% of DILI cases and is the most common clinical phenotype, which presents with an acute-hepatitis-like significant elevation of ALT or AST level following administration of the suspected drug. Cholestatic injury is also a typical phenotype and accounts for 20–32% of DILI cases, which present with ALP or gamma-glutamyl transferase (GGT) elevation. Approximately 7–24% of acute DILI cases can transition to chronic injury, which presents with signs of chronic DILI [3, 5, 21, 24, 25]. Furthermore, certain drugs can induce specific phenotypes of DILI which are discussed in a later section [23, 26].

Risk factors

The known risk factors can be classified as drug- or host-related. There is insufficient evidence suggesting that currently reported drug- and host-related risk factors can increase all-cause susceptibility to iDILI [1, 27].

Drug-related risk factors

Drug properties raising the risk of hepatotoxicity: (1) Dose and lipophilicity: In direct DILI, the risk of liver injury is dose dependent. Idiosyncratic DILI (iDILI) is largely dose-independent, although some studies have suggested that a dose threshold is usually required [28, 29]. High lipophilicity of a drug may increase the risk of iDILI [30]. A drug with high lipophilicity (log of octanol–water partition coefficient, Log$P > 3$) and daily dose > 100 mg, referred to as the "rule-of-two," may be associated with an increased risk of iDILI [31]. (2) Reactive metabolites (RM): The in vivo formation of RM plays an important role in iDILI pathophysiology, and integration of RM into the new "rule-of-two" model can precisely predict the risk and severity of iDILI [31]. (3) Drugs affecting the bile salt export pump (BSEP) and mitochondrial function: Drugs that affect both adenosine triphosphate-dependent BSEP and mitochondrial function are associated with an increased risk of DILI. Hepatotoxicity of cyclosporin A, bosentan, troglitazone, and imatinib

are probably associated with inhibition of BSEP function [32–34].

Drug interactions: Concomitant use of certain drugs may increase the risk of hepatotoxicity. Concomitant drugs can modulate the metabolism of other drugs through induction, inhibition, or substrate competition, and particularly the CYP 450 reaction, thus affecting the individual risk of iDILI [35]. The concomitant use of CYP 450-enzyme-inducing anticonvulsant drugs, such as carbamazepine and phenytoin, has also been reported to increase the risk of valproic acid-induced hepatotoxicity. Similarly, rifampin, a strong CYP inducer, has been demonstrated to increase the incidence of hepatotoxicity when administered together with isoniazid as an anti-TB treatment [36, 37].

Host-related risk factors

Non-genetic factors: (1) Age: Age is not a general risk factor for DILI. However, older age is associated with an increased risk of liver injury induced by isoniazid, amoxicillin–clavulanate, and nitrofurantoin [38–40]. (2) Sex: There is insufficient evidence suggesting that female are at a higher risk of DILI than men. However, female are more susceptible to minocycline- and nitrofurantoin-induced autoimmune hepatitis (AIH) than are male [41]. (3) Alcohol (ethanol) consumption and pregnancy: Study have shown that heavy alcohol consumption is not a risk factor for worse outcomes in iDILI [42]. However, high alcohol consumption increases the risk of liver injury induced by certain drugs such as APAP, isoniazid, methotrexate, and halothane. DILI during pregnancy is rare because of conservative drug use. Tetracycline is currently the only known drug to increase the risk of DILI development during pregnancy [43]. (4) Comorbidity: Limited evidence suggests that comorbidities increase the risk of developing DILI. Current evidence does not support the opinion that diabetes or obesity increase susceptibility to all-cause DILI [5], although they may increase the risk of liver injury induced by certain drugs such as tamoxifen and methotrexate [44, 45].

Genetic factors: Polymorphisms in drug-metabolizing enzymes, transporters, and human leukocyte antigen (HLA) may be important determinants of DILI. Genetic polymorphism of the CYP 450 enzyme may be associated with an increased risk of liver injury induced by certain drugs [46, 47]. HLA polymorphisms associated with certain drugs have also been reported [1]. A recent genome-wide association study suggested that a missense variant (rs2476601) in protein tyrosine phosphatase non-receptor type 22 can increase the risk of liver injury induced by various drugs (e.g., amoxicillin–clavulanate, terbinafine, flucloxacillin, and haloperidol) [48]. It is important to note that the currently reported genetic polymorphisms (HLA or non-HLA) associated with an increased risk of drug-specific DILI may also be associated with certain physiologic or other diseases; thus, further validation is required before its clinical use.

Diagnostic approach

Clinical presentation

The clinical presentation of DILI is usually nonspecific, similar to that of other acute and chronic liver diseases. Patients with acute hepatocellular injury can present with symptoms ranging from asymptomatic to jaundice (e.g., yellow skin, and/or icterus and dark urine). Non-specific gastrointestinal symptoms such as fatigue, loss of appetite, rejection of greasy food, pain in the liver, and upper abdominal discomfort may also occur. Patients with obvious cholestasis may present with jaundice, pale stools, and pruritus. Patients with disease progression to ALF/SALF may present with jaundice, coagulopathy, ascites, and encephalopathy. Patients with specific phenotypes such as eosinophilia and systemic symptoms (DRESS syndrome) may present with various symptoms such as fever, rash, and other extrahepatic symptoms [49, 50].

Laboratory tests

Liver biochemistry test and diagnostic threshold: liver biochemistry test profile includes determinations of ALT, AST, ALP, GGT, total bilirubin (TBil), direct bilirubin, and albumin. Serum ALT, AST, and ALP levels are the markers of liver injury, whereas TBil, albumin, and international normalized ratio (INR) are markers of severity.

The threshold of liver biochemistry should meet any one of the following criteria for acute DILI: (1) ALT $\geq 5 \times$ ULN; (2) ALP $\geq 2 \times$ ULN (particularly accompanied by an increased GGT level with bone disease ruled out); (3) ALT $\geq 3 \times$ ULN and TBil $\geq 2 \times$ ULN [26, 51].

Patients who do not meet these criteria and are adjudicated as drug-induced by the causality assessment can be defined as those with drug-induced abnormal liver biochemistry. It should be noted that the above criteria are only applicable to the diagnosis of acute DILI and not to chronic or specific-phenotype DILI.

Excluding alternative etiologies: See Table 4 for laboratory tests used to exclude alternative etiologies.

Imaging

Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are commonly used for the diagnosis and differential diagnosis of various liver diseases, including DILI. All patients suspected of having DILI should undergo an abdominal ultrasound. CT, MRI, and endoscopic ultrasound can be performed depending on the clinical context.

Table 4 Laboratory tests/imaging used to exclude alternative causes in diagnosis of DILI

Disease	Laboratory test/imaging
Hepatotropic virus infection	
Hepatitis A	Anti-HAV IgM
Hepatitis B	HbsAg, anti-HBc, HBV DNA
Hepatitis C	Anti-HCV, HCV RNA
Hepatitis E	Anti-HEV IgM and IgG
Non-hepatotropic virus infection	
CMV	Anti-CMV IgM and IgG
HSV	Anti-HSV IgM and IgG
EBV	Anti-EBV IgM and IgG
Autoimmune liver disease	
Autoimmune hepatitis	ANA and ASMA titer, serum IgG, IgA, and IgM
PBC	AMA (especially AMA-M2) tier, serum IgG, IgA, and IgM
Alcoholic liver disease	History of alcohol use, GGT, MCV
Non-alcoholic fatty liver disease	Ultrasound or MRI
Other diseases	
Hypoxic/ischemic liver disease	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI
Bile duct disease	Ultrasound or MRI, ERCP (depends on clinical context)
Wilson disease	Ceruloplasmin
Hemochromatosis	Ferritin, transferrin saturation
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

ANA anti-nuclear antibody, *ASMA* anti-smooth muscle antibody, *anti-HBc* anti-HBV core antibody, *CHF* congestive heart failure, *CMV* cytomegalovirus, *DILI* drug-induced liver injury, *EBV* Epstein–Barr virus, *ERCP* endoscopic retrograde cholangiopancreatography, *HAV* hepatitis A virus, *HbsAg* HBV surface antigen, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HEV* hepatitis virus, *HSV* herpes simplex virus, *Ig* immunoglobulin, *MCV* mean corpuscular volume, *MRI* magnetic resonance imaging

Magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) may be considered if necessary.

Liver biopsy

Liver biopsy can provide valuable histopathological information that may help clarify the diagnosis of DILI when it is difficult to exclude competing etiologies [52]. The histologic features of DILI are complex and include almost all pathologic changes in the liver. According to the injured target cell in the liver (e.g., hepatocytes, cholangiocytes, endothelial cells of the sinusoids, and the intrahepatic venous system), the presence of inflammatory necrosis, cholestasis, hepatocyte steatosis, steatohepatitis-like changes, vasculitis and vasculopathy, different degrees of fibrosis, cirrhosis, tumors, and various acute or chronic lesions may be observed in liver biopsy. The type of injured target cell at the onset of DILI largely determines the clinical phenotype. Currently, there is no uniform histologic scoring system for DILI. See Online Resource 1 for the common histopathological phenotypes of DILI [25, 53, 54].

Recommendation 2: In the baseline assessment and regular monitoring during drug therapy, a liver biochemistry test should include ALT, AST, ALP, GGT, TBil, direct bilirubin, and albumin. INR could be added if necessary. (3, B).

Recommendation 3: The threshold of liver biochemistry should meet any one of the following criteria for acute DILI: (1) ALT $\geq 5 \times$ ULN, (2) ALP $\geq 2 \times$ ULN (accompanied by an increased GGT level with bone disease ruled out), and (3) ALT $\geq 3 \times$ ULN and TBil $\geq 2 \times$ ULN. (4, B).

Recommendation 4: All patients suspected of having DILI should undergo an abdominal ultrasound. The use of additional imaging studies (e.g., CT, MRI, MRCP, or ERCP) depends on the clinical context. (3, B).

Diagnosis and differential diagnosis

Detection of suspected DILI

Regular monitoring of liver biochemistry is important for detecting suspected DILI cases, particularly for patients using drugs with known hepatotoxicity or among high-risk

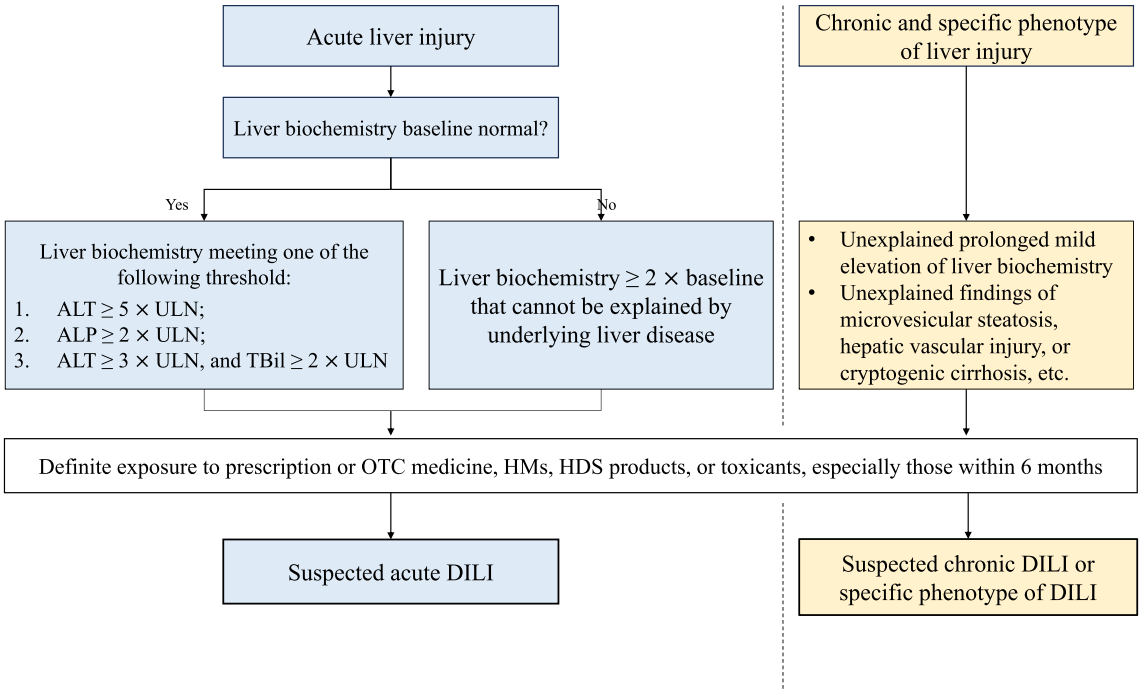

Fig. 1 When to suspect DILI. *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *DILI* drug-induced liver injury, *HM* herbal medicine, *HDS* herbal and dietary supplement, *OTC* over-the-counter, *TBil* total bilirubin, *ULN* upper limit of normal

populations. Figure 1 illustrates the circumstances when DILI should be suspected. The possibility of DILI should be considered if one of the following occurs: (1) in patients with normal baseline liver enzymes, ALT/AST, ALP, or TBil significantly increases and meets the criteria of acute DILI after administration of a drug; (2) in patients with abnormal baseline liver enzymes, liver enzymes double the baseline level or significant deteriorating liver function that cannot be explained by underlying liver disease after administration of a drug; (3) patients present obvious symptoms of liver disease after administration of a drug; (4) patients with an unknown cause of liver injury or liver disease, particularly with other common causes being ruled out.

History taking

A detailed and thorough medical history, including medication history, is crucial for causality assessment and diagnosis. Information about an accurate history of exposure to a suspected drug, a temporal relationship between drug exposure and suspected DILI event, clinical course of suspected DILI event and its evolution after rechallenge or dechallenge, history of liver injury or liver disease, and laboratory tests that help rule out competing etiologies, are important. Usually, DILI occurs within the first 6 months after starting a new medication; however, there are exceptions. Table 5 shows the minimum information required during history taking for patients with suspected DILI.

Recommendation 5: DILI should be suspected under any of the following circumstance: (1) significant increase in ALT, AST, ALP, and TBil after administration of a drug; (2) in patients with abnormal baseline liver enzymes, liver enzymes double the baseline level or significant deterioration of liver function that cannot be explained by underlying liver disease after administration of a drug; (3) patients present with obvious symptoms of liver disease after administration of a drug; and (4) patients with unknown cause of liver injury or liver disease, particularly in cases with other common causes ruled out. Patients with an unclear medication history should be followed up in detail to confirm a history of exposure to suspected drugs or toxic chemicals.

Recommendation 6: For suspected DILI cases, the minimum data for diagnosis or causality assessment should include: (1) start and stop date of the suspected drug; (2) history of previous exposure and reaction to the suspected drugs and/or drugs of the same class; (3) concomitant medication and reaction; (4) date of suspected DILI onset, evolution of clinical course after rechallenge or dechallenge, and prognosis; (5) comorbidity and underlying liver diseases or history of liver injury; and (6) exclusion of competing causes of liver injury. (4, B).

Table 5 Minimum information required during history taking for suspected DILI patients

Domain	Information	Comment
Demography	Sex, age, and ethnicity	Especially information associated with competitive cause
History of alcohol use	Past vs. present; estimated grams per day/week; duration	Especially history associated with suspected DILI episode; exclude possibility of alcoholic liver disease
History of allergy	If present	Especially drug allergy
Suspect drug	Trade name/generic name	Complete list of medications, biologic products, or HDS products within 6 months prior to onset
	Start/stop time	Course of treatment/time of exposure
	Dose/route of administration	Daily dose/oral, intravenous, intramuscular, etc
	Previous exposure and reaction/previous exposure to similar drugs and reaction	Evaluate possible rechallenge or certain cross reactivities
Concomitant medication	Same as "suspect drug" domain	Evaluate and exclude possible DILI caused by concomitant medication
History of suspected DILI episode	Time of onset	Evaluate if there is definite and reasonable temporal relationship between suspect drug
	Latency	Time from start and stop dates to first onset
	Signs and symptoms	Presence of liver disease-related or extrahepatic signs and symptoms, and time of presentation
	First abnormal liver biochemistry	Date, results, assess classification of liver injury and features
	Dechallenge/rechallenge	Recovery/evolution after discontinuation, timepoint and reaction of rechallenge (if available)
	Laboratory test/imaging that excludes competitive cause of liver injury	Biomarkers of viral hepatitis; antibodies of AIH and serum IgG, ultrasound ± Doppler, CT or MRI ± MRCP
	Liver biopsy (if done)	Timepoint of biopsy, and histologic features associated with DILI events
	Clinical outcome	Recovery, improvement, or other clinical outcome events and its timepoint
Comorbidity	Primary disease	Evaluate or rule out the possibility of liver injury due to progression of primary disease
	Chronic liver disease	Identify history of concomitant chronic liver disease, treatment, and current status to screen cause of suspected DILI episode and assess its association with increased risk of DILI caused by certain drug
	Other underlying disease	Especially systemic disease associated with competitive cause, or concomitant disease associated with increased risk of DILI caused by certain drug
History of liver injury	History of DILI and clinical outcome	Identify suspect drug
	History of other liver disease/liver injury	Assess the correlation with suspected DILI episode

CT computed tomography, *DILI* drug-induced liver injury, *HDS* herbal and dietary supplements, *IgG* immunoglobulin G, *MRCP* magnetic resonance cholangiopancreatography, *MRI* magnetic resonance imaging

Principles of diagnosis and differential diagnosis

Principles of diagnosis: DILI remains a diagnosis of exclusion based on a detailed history, clinical manifestations, serum biochemistry, imaging, and liver biopsy, owing to the lack of specific diagnostic biomarkers. Based on the principle of relationship evaluation of adverse drug reactions, diagnosis of DILI relies heavily on the following: (1) definite and reasonable temporal relationship between drug exposure or dechallenge and change in liver biochemistry; (2) clinical and/or pathologic manifestations (phenotype) of liver injury consistent with known hepatotoxicity of the suspect drug; (3) significant improvement or recovery after discontinuation of the drug or tapering of dose; (4) positive rechallenge; (5) liver injury with competing causes and activity/recurrence of underlying liver disease already excluded,

and injury cannot be explained by concomitant medication/therapy or primary disease.

Differential diagnosis: The differential diagnosis of patients with suspected DILI can be based on the clinical classification or phenotype of liver injury. Other common liver diseases that present with the same type of liver injury should be excluded first. Figure 2 shows the diagnostic algorithm for suspected DILI. If necessary, liver biopsy should be considered to acquire important information for differential diagnosis.

Although in most cases, the diagnosis of DILI cannot be made solely based on pathology, liver biopsy is of great value for providing information on the histopathological type, area, and severity of injury. Recent studies suggest that liver biopsy can significantly affect the score of Roussel–Uclaf causality assessment method (RUCAM) [52]. Liver biopsy is recommended in the following cases [27]: (1) competing etiologies of liver injury cannot be ruled out, particularly when immunosuppression therapy is planned in suspected AIH cases; (2) persistent increase of liver biochemical tests or deterioration of liver function after discontinuation of suspect drug; (3) peak ALT does not decrease > 50% in 30–60 days in hepatocellular type, or peak ALP does not decrease > 50% in 30–60 days in cholestasis type after discontinuation of suspect drug; (4) persistent liver biochemistry is abnormal for > 180 days with suspected chronic liver disease or chronic DILI; (5) suspected DILI with pre-existing liver disease, the etiology of which cannot be determined; (6) onset of liver injury after organ transplantation (e.g., liver, bone marrow).

XXX

Recommendation 7: In suspected hepatocellular or mixed DILI, competing etiologies resulting in ALT

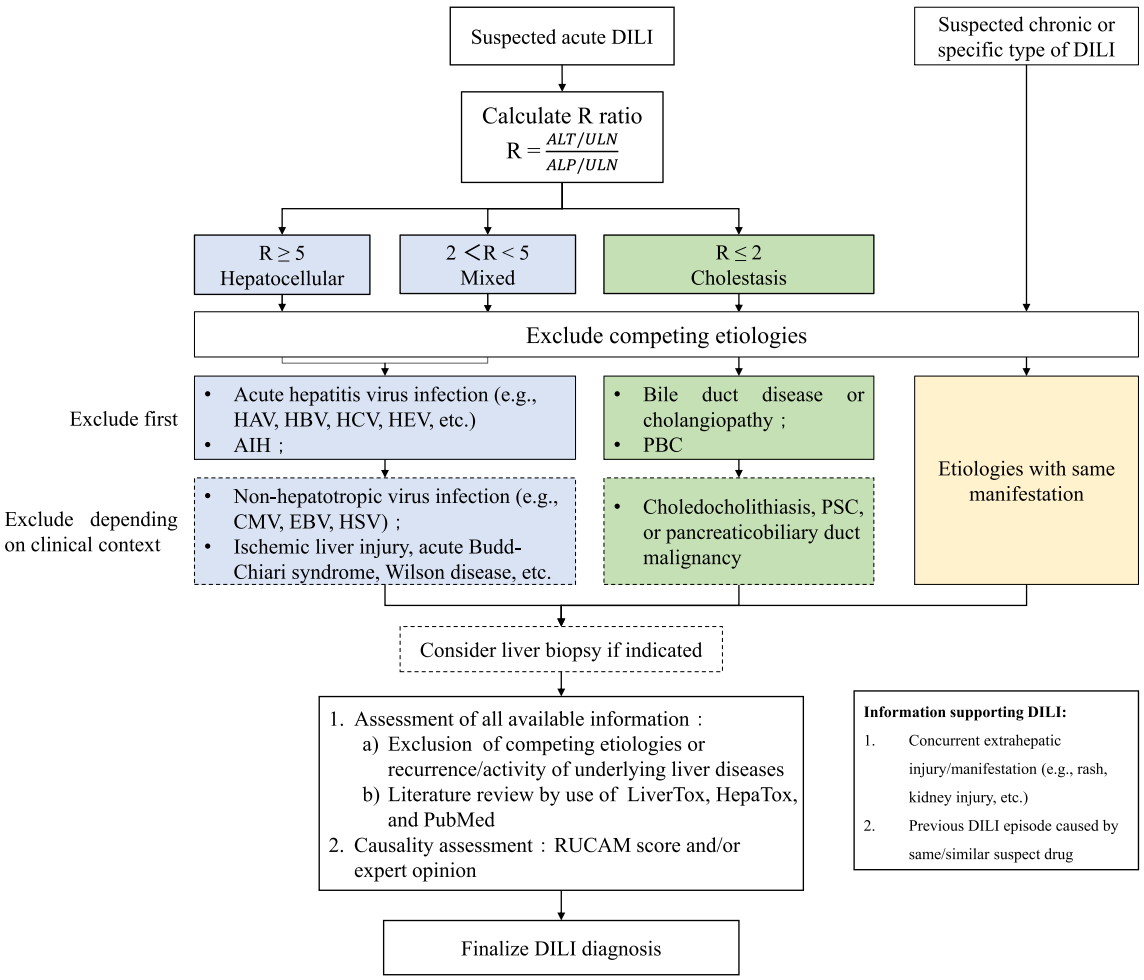

Fig. 2 Diagnostic algorithm for suspected DILI. *AIH* autoimmune hepatitis, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *CMV* cytomegalovirus, *DILI* drug-induced liver injury, *EBV* Epstein–Barr virus, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HEV* hepatitis virus, *HSV* herpes simplex virus, *PBC* primary biliary cholangitis, *PSC* primary sclerosing cholangitis, *RUCAM* Roussel Uclaf causality assessment method, *TBil* total bilirubin, *ULN* upper limit of normal

elevation such as acute hepatitis virus infection and AIH should be excluded first. Non-hepatotropic virus infection, ischemic liver injury, acute Budd–Chari syndrome, and Wilson disease may be excluded depending on the clinical context. (4, B).

Recommendation 8: In suspected cholestasis DILI, competing etiologies resulting in ALP/GGT elevation such as cholangiopathy and primary biliary cholangitis should be excluded first. Choledocholithiasis, primary sclerosing cholangitis, and pancreaticobiliary duct malignancy may be excluded depending on the clinical context. (4, B).

Recommendation 9: Liver biopsy is recommended in the following cases: (1) competing etiologies of liver injury, particularly AIH, cannot be ruled out; (2) after discontinuation of suspected drug, increasing levels of liver enzyme, peak ALT does not decrease > 50% in 30–60 days in hepatocellular injury, or peak ALP does not decrease > 50% in 180 days in cholestatic type; (4) persistent liver biochemical abnormality for > 180 days with suspected chronic liver disease or chronic DILI, the cause of which cannot be determined; (5) liver injury after organ transplantation. (4, B).

Causality assessment

Causality assessment is the key to DILI diagnosis and can be used to determine whether a drug is the cause of liver injury. Although some methods have been reported to assess causality in adverse drug reactions, including DILI, the value of non-liver-specific methods are limited [55, 56].

RUCAM: The RUCAM causality assessment score includes seven distinct domains [57]. The updated score was published in 2016 [58], but remains to be validated. Although there are some ambiguities regarding how to score certain sections as well as suboptimal reliability, RUCAM can provide systematic and framed guidance for the assessment of patients with suspected DILI and is the most widely used tool [26, 27, 51, 59]. It should be noted that RUCAM should not be the only basis for diagnosing DILI. In certain clinical scenarios (e.g., TCM/HDS-DILI, DILI caused by multiple suspected drugs, DILI in patients with pre-existing liver disease, and evaluation of hepatotoxicity in clinical trials of new drugs), rote use of the RUCAM score may result in misdiagnosis or missed diagnosis owing to lowered reliability.

Revised Electronic Causality Assessment Method (RECAM): RECAM is a recently reported evidence-based update with similar diagnostic efficacy to RUCAM but better precision and reliability because of its increased objectivity and clarity since it is an electronic algorithm integrated with LiverTox likelihood category [60]. The original criteria of risk factors in RUCAM is removed in RECAM for lack of diagnostic value, so is competing medications to encourage assessment of each culprit drug. It demonstrated a better overall agreement with expert opinion and greater sensitivity for detecting patients in extreme DILI diagnostic categories (e.g., highly likely/probable; unlikely/excluded). However, this method requires external validation from regions other than US and Spain since it was developed based on case data from Drug-Induced Liver Injury Network (DILIN) and the Spanish DILI Registry [61]. In addition, its reliability in herb-induced liver injury (HILI) remains unknown since there is still insufficient data regarding these HMs/HDS.

Expert opinion: Expert opinion is an important causality assessment method for the diagnosis of DILI. For individuals with suspected DILI, expert opinion is a professional adjudication made after considering all currently known relevant information. The advantages of expert opinion include the ability to account for different or rare-specific phenotypes of DILI, thereby achieving a more detailed differential diagnosis. Prospective research conducted in the DILIN used a structured expert opinion process (SEOP) for causality assessment [62]. Although the SEOP overcomes some shortcomings of the RUCAM score, it is not externally validated and is not suitable for daily clinical practice because of its complex procedures. The SEOP may be used in situations such as DILI studies, clinical trials of new drugs, or when the RUCAM score is not applicable or shows significantly lowered reliability. The likelihood of DILI can be divided into five probability groups: definite, > 95% likelihood; highly likely, 75–95% likelihood; probable, 50–74% likelihood; possible, 25–49% likelihood; and unlikely, < 25% likelihood [62].

Rechallenge

A positive rechallenge is defined as the recurrence of liver injury after exposure to the same drug, accompanied by an ALT > 3 × ULN [26, 63]. In clinical practice, most rechallenges are performed unintentionally or because of their importance in the treatment of the primary disease. A positive rechallenge is the most powerful evidence in the causality assessment of suspected DILI and helps in a definite diagnosis. However, rechallenge may result in a rapid and severe liver injury that may progress to ALF, particularly when the initial exposure has already caused liver injury fulfilling Hy's law or when the liver injury after initial exposure is due to immune-related reactions. Therefore, rechallenge with the suspected drug should be avoided unless the anticipated benefit is high for severe or life-threatening conditions with no alternative therapy.

The standard format of diagnosis

A complete diagnosis of DILI should include diagnosis, clinical classification, clinical course, RUCAM score, expert opinion results, and severity. For example:

- DILI, hepatocellular, acute, RUCAM score: 9 (definite), grade 3.
- DILI, cholestatic, chronic, RUCAM score: 7 (definite), grade 2.
- DILI, cholestatic, chronic, RUCAM score: 4 (possible); expert opinion: highly likely, grade 3.

Recommendation 10: The RUCAM score is recommended as the primary method for causality assessment. In scenarios such as suspected liver injury caused by two or more suspected drugs, suspected TCM/HDS-DILI, suspected DILI in patients with pre-existing liver disease, and evaluation of hepatotoxicity in clinical trials of new drugs, causality assessment in combination with expert opinions is recommended. (3, B).

Recommendation 11: Clinicians are strongly advised to remind patients to avoid re-exposure to the same suspected drug, particularly if the initial exposure caused severe liver injury. (4, A).

Severity and prognosis

Grading severity

After the diagnosis of acute DILI, the assessment of severity should be performed according to the CIOMS DILI Working Group criteria:

Grade 1 (Mild): ALT $\geq 5 \times$ ULN or ALP $\geq 2 \times$ ULN and TBil $< 2 \times$ ULN.

Grade 2 (Moderate): ALT $\geq 5 \times$ ULN or ALP $\geq 2 \times$ ULN and TBil $\geq 2 \times$ ULN or symptomatic hepatitis.

Grade 3 (Severe): ALT $\geq 5 \times$ ULN or ALP $\geq 2 \times$ ULN and TBil $\geq 2 \times$ ULN or symptomatic hepatitis and at least one of the following criteria:

- INR ≥ 1.5
- Ascites and/or encephalopathy, disease duration < 26 weeks, and absence of underlying cirrhosis
- Other organ failures are considered to be due to DILI.

Grade 4 (Fatal): Death or liver transplantation due to DILI.

Prognosis, natural history, and follow-up

Most patients with acute DILI can recover from liver injury with a good prognosis within 6 months of discontinuation of the suspected drug. However, a small number of patients can become critically ill or progress to ALF/SALF requiring liver transplantation or even death. Studies have shown that approximately 10% of cases that fulfill Hy's law will progress to ALF [5, 64], and is associated increased mortality or need for liver transplantation [65–68]. The proportion of patients with fatal adverse clinical outcomes varies from country to country owing to differences in study design, methods, and populations [8]. There are several models available to predict prognosis. The ALF study group models based on etiology and coma severity can predict transplant-free survival in ALF [69]. The novel DI-ALF-5 model was developed to predict transplant-free survival in non-APAP DI-ALF [70]. Another validated model incorporating the Model for End-Stage Liver Disease score, the serum albumin level, and the Charlson comorbidity index as parameters may be useful in predicting the 6-month risk of death in patients with DILI [71]. Some patients may present with chronic manifestations after an acute DILI episode, which eventually transforms into chronic liver injury as a clinical outcome.

Therefore, all patients with acute DILI should be followed up consistently until the liver injury recovers or until clinical outcome events are reached (e.g., chronicity, ALF, liver transplantation, or death).

Recommendation 12: Hy's law can be used to assess potentially serious hepatotoxicity in clinical trials of new drugs and to help clinicians identify patients with DILI at risk for ALF. (3, B).

Recommendation 13: All patients with acute DILI should be followed up consistently until the liver injury recovers or a clinical outcome event is reached (e.g., chronicity, ALF, liver transplantation, or death). (4, C).

Chronic DILI and specific phenotypes

Chronicity of acute DILI and delayed recovery

Liver biochemistry in approximately 7–13% of patients may not return to normal or baseline levels 6 months or 1 year after an acute DILI episode, which indicates that acute liver injury may develop into a chronic injury or delayed recovery [8]. Older age, dyslipidemia, and acute episode severity are risk factors for chronic injury and delayed recovery [75]. High TBil and ALP levels in the second month after an acute DILI episode and the biochemical nonresolution-6 model may help predict the risk of chronic injury and delayed recovery [26, 72]. In addition, evidence shows that the

cholestatic type is more prone to the development of chronic injury and delayed recovery than other types and requires more time for recovery [21, 73]. Prolonged cholestasis with progressive reduction of the interlobular bile ducts can lead to vanishing bile duct syndrome with a poor prognosis [74].

Chronic DILI

Drug-induced chronic liver injury with laboratory, imaging, and histologic evidence of chronic liver inflammation, liver fibrosis, cirrhosis, or portal hypertension is the basis for the clinical diagnosis of chronic DILI. Clinically, some cases with chronic DILI develop from the chronicity of acute DILI, however, some might be a specific phenotype caused by drugs (e.g., drug-associated fatty liver disease [75], drug-induced fibrosis/cirrhosis, nodular regenerative hyperplasia [76], drug-induced autoimmune-like hepatitis [DI-ALH], and peliosis hepatis [77]). Some patients with chronic DILI may develop varying degrees of liver fibrosis or cirrhosis despite discontinuation of the suspected drug, which is an important etiology of cryptogenic cirrhosis. Some patients may present with unexplained chronic liver injury, chronic hepatitis, or even cirrhosis at their first medical visit [78]. Patients with chronic DILI should be managed with long-term follow-up and regular assessment of the risk of disease progression, similar to the management of other chronic liver diseases [79]. Whether noninvasive transient elastography technology such as FibroScan and FibroTouch are suitable for the management of chronic DILI requires investigation; nevertheless, they might be used as adjunct measures to regularly assess the progression of liver fibrosis in clinical practice [80].

> Recommendation 14: Failure to recover from liver injury within 6 months after acute DILI suggests an increased risk of delayed recovery or chronic injury. Chronicity should be considered one of the clinical outcomes of acute DILI. Patients with cholestasis have a higher risk of chronicity or delayed recovery. (3, B).
> Recommendation 15: Laboratory, imaging, and histologic evidence of chronic liver inflammation, liver fibrosis, cirrhosis, or portal hypertension after drug exposure are the basis for the clinical diagnosis of chronic DILI, including the chronicity of acute DILI and specific phenotypes. (4, B).
> Recommendation 16: Noninvasive diagnostic techniques such as FibroScan and FibroTouch might be used as adjunct measures to regularly assess the progression of liver fibrosis in clinical practice. (4, C).

Specific phenotypes

Although specific drug-induced phenotypes of DILI are rare, clinicians should be aware of the possibility of after ruling out other common etiologies for specific phenotypes of liver injury. Table 6 shows the common specific phenotypes of DILI [81, 82].

The terminology used to describe DILI with autoimmune features, such as DILI with autoimmune features and DI-ALH, varies. The most commonly used term is drug-induced AIH (DI-AIH). However, it is unclear whether the different terminologies represent different prognoses. According to the latest international consensus, DI-ALH is the preferred terminology [41]. Differential diagnosis of DI-ALH and AIH is difficult in clinical practice because of their similar clinical features and laboratory results. Unlike AIH, most cases of DI-ALH rarely relapse in the long-term follow-up after the discontinuation of corticosteroid or immunosuppressive therapy [83, 84], which is the key information that indicates the probability of DI-ALH, particularly for patients with a history of classical drug exposure. In a few patients with DILI with autoimmune features, of which the natural history is the same as that of AIH, drug may cause a "trigger effect" as a precipitating factor that drives autoimmune injury. Therefore, patients with DILI with autoimmune features require long-term follow-up and should be tested using standardized autoantibody assays, such as indirect immunofluorescence, to avoid false-positive and false-negative results interfering in diagnosis and management. Notably, DILI in AIH also presents with liver injury with autoimmune features, but it belongs to the category of DILI with pre-existing liver disease. In most cases, the mechanism of injury differs from that of DI-ALH which is under the category of indirect DILI and should be distinguished.

In China, vascular liver diseases such as HSOS and hepatic vein occlusive disease (caused by the consumption of plants containing pyrrolizidine alkaloids [PA] such as *Gynura segetum*) are common [85]. Although the exact mechanism of PA-HSOS remains known, the destruction of hepatic sinusoidal endothelial cells in the liver acinus by toxic metabolites of PA and long persistence of PA metabolites especially pyrrole protein adducts in vivo may play an important role in the toxicity [86–88].

The most used diagnostic criteria for PA-HSOS, known as the "Nanjing criteria," [89] are as follows: A history of PA-containing plant consumption, exclusion of other known causes, and confirmation using pathologic examination or observation of three of the following: (1) abdominal distention and/or pain in the liver area, hepatomegaly, and ascites; (2) elevated TBil or other liver biochemistry abnormalities; and (3) classic characteristics on contrast CT or MRI (e.g., hepatomegaly, "map-like" liver, or "mottle-like" enhancement). The Nanjing criteria have recently been clinically validated in a retrospective cohort and demonstrated excellent performance with a sensitivity and specificity of 95.35% and 100%, in which the study also highlighted the importance of differential diagnosis from Budd-Chiari syndrome

Table 6 Specific phenotype of DILI and associated drugs

Phenotype	Clinical features	Associated drugs
Immune-mediated liver injury		
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)	Drug-induced hypersensitivity involving multiple organs with fever, rash, eosinophilia, and other extrahepatic manifestations. Liver injury often occurs within a short period of time or even within 1 to 2 d after drug administration. The mortality is up to 10%. Rechallenge is extremely risky	Carbamazepine, phenytoin and phenobarbital, minocycline, allopurinol, abacavir, and nevirapine
Drug-induced autoimmune-like hepatitis (DI-ALH)	Mostly seen in female, which can lead to acute, subacute, and chronic liver injury, and rarely progress to ALF. Present with laboratory and/or histologic evidence of autoimmune features. Corticosteroids are effective and usually no recurrence after discontinuation	Methyldopa, minocycline, nitrofurantoin, statins, diclofenac, halothane, indomethacin, infliximab, interferon
ICI-related hepatotoxicity	Usually occurs 4 to 12 weeks after the start of treatment. Most patients present with ICI-related hepatitis with some present with ICI-related cholangitis, and a few may present with other specific clinical phenotypes such as nodular regenerative hyperplasia	Various ICIs
Hepatocellular steatosis		
Acute fatty liver	A clinical syndrome of liver and other organ failure with extensive microvesicular steatosis. It is mainly seen in children with Reye's syndrome due to salicylates. Acute liver enzyme elevation and jaundice may be preceded by rapidly progressive organ failure	Amiodarone, diphenylamine, stavudine, valproic acid and zalcitabine
Drug-associated fatty liver disease	Drug-induced macrovesicular or microvesicular steatosis with or without inflammation and fibrosis. Usually found by imaging studies or liver biopsy	Amiodarone, methotrexate, tamoxifen, fluorouracil, irinotecan, corticosteroids, haloperidol, and lomitapide
Bile duct injury		
Secondary sclerosing cholangitis	Clinical, biochemical, imaging and/or histologic presentation highly resembles PSC. ERCP is a commonly used diagnostic method. No available specific treatment, but endoscopic treatment may improve symptoms in some patients. Liver transplantation is required in advanced patients	Amiodarone, atorvastatin, amoxicillin-clavulanate, gabapentin, infliximab, 6-mercaptopurine, sevoflurane, and venlafaxine
Ductopenic syndrome/vanishing bile duct syndrome (VBDS)	Caused by continuous progressive destruction of small intrahepatic bile ducts due to drugs or long-term cholestasis. Characterized by bile duct reduction and cholestasis, the clinical presentation is moderate to severe acute cholestasis or mixed liver injury. Early histology may show acute cholangitis, cholestasis, and reduced or absent bile ducts in the confluent area (bile duct reduction > 50%). In the chronic phase, various degrees of liver fibrosis are seen. The prognosis is poor and liver transplantation is often needed	Azathioprine, androgens, amoxicillin-clavulanate, carbamazepine, chlorpromazine, erythromycin, estradiol, flucloxacillin, phenytoin, terbinafine, and trimethoprim-sulfamethoxazole

Table 6 (continued)

Phenotype	Clinical features	Associated drugs
Liver vascular injury		
Hepatic sinusoidal obstruction syndrome (HSOS) or hepatic vein occlusive disease (HVOD)	Drug-induced injury of the vascular endothelium of the hepatic blood sinuses, small hepatic veins, and interlobular veins, which in turn forms microthrombi that block the blood sinuses, causing intrahepatic stasis, impaired liver function and portal hypertension	Oxaliplatin, busulfan, cyclophosphamide, herbs containing pyrrolizidine alkaloids, *gemtuzumab ozogamicin*
Nodular regenerative hyperplasia (NRH)	One of causes of non-cirrhotic portal hypertension. Vascular endothelial and vascular injury are the driving factors for its development. Most NRH occurs after prolonged (> 6 months) or multiple (> 6 courses) dosage. The sensitivity and specificity of MRI can reach 75% to 80%. Histology is characterized by extensive vascular lesions leading to diffuse nodule formation in the liver parenchyma	Azathioprine, busulfan, bleomycin, cyclophosphamide, chlorambucil, cytarabine, carmustine, doxorubicin, 6-thioguanine and oxaliplatin
Other		
Granulomatous hepatitis	Caused by a variety of factors such as infection, inflammation, immune factors, and drugs. Mainly confirmed by liver biopsy	Allopurinol, phenytoin, quinidine, methyldopa, sulfonamides, BCG, amoxicillin-clavulanate, mesalazine, etanercept, rosiglitazone, mebendazole, vemurafenib, norfloxacin, pyrazinamide, and ICIs
Liver fibrosis/cirrhosis	Diagnosed by liver biopsy or imaging studies	Methotrexate, isoniazid, methyldopa, papaverine
Liver tumor	May present with hepatocellular adenomas, HCC, cholangiocarcinoma, and hemangiosarcoma. The dose and duration of oral contraceptive use are associated with the risk of adenoma. Adenomas may regress after discontinuation, but the likelihood decreases with prolonged exposure	Anabolic androgens, oral contraceptives

ALF acute liver failure, *BCG* Bacillus Calmette–Guérin vaccine, *DILI* drug-induced liver injury, *ERCP* endoscopic retrograde cholangiopancreatography, *HCC* hepatocellular carcinoma, *ICIs* immune checkpoint inhibitors, *MRI* magnetic resonance imaging, *PSC* primary sclerosing cholangitis

due to similar imaging features [90]. Pyrrole protein adducts detected in the patient's blood have a retrospective significance for diagnosis [91].

Stepwise therapy with anticoagulants (low-molecular-weight heparin and/or warfarin) and transjugular intrahepatic portosystemic shunt (TIPS) is currently the recommended standard therapy, which has been confirmed in multiple retrospective studies [89]. Recently developed Drum Tower Severity Scoring (DTSS) system integrating the levels of ALT, TBil, fibrinogen, and peak portal vein velocity was reported to predict the outcome of anticoagulation therapy in PA-HSOS [92]. Patients with a score of 4–6 were defined as mild and anticoagulation along with follow-up every other week is recommended. Patients with a score of 7–10 were defined as moderate, and patients with a score of 11–16 were defined as severe for whom direct TIPS is recommended. Nonetheless, external validation from a prospective cohort is needed to achieve high-level evidence. Pretreatment with high-dose chemotherapy after hematopoietic stem cell transplantation (HSCT), chemotherapy for solid tumors, and post-transplantation immunosuppressive therapy are also important causes of HSOS. The Baltimore or modified Seattle criteria may be referred to as the relevant diagnostic criteria. Currently, defibrotide is the recommended therapy [93–95].

Recommendation 17: Liver biopsy and long-term follow-up are recommended for patients diagnosed with DILI with autoimmune features. (2, B) Close monitoring is recommended after the discontinuation of corticosteroids. The likelihood of DI-ALH increases in the absence of relapse. (3, B).

Recommendation 18: The Nanjing criteria can be used to diagnose PA-induced HSOS, and stepwise anticoagulant-TIPS therapy is currently recommended as an effective management strategy. (2, B).

Recommendation 19: The Baltimore or modified Seattle criteria can be used to diagnose pretreatment with high-dose chemotherapy after HSCT, chemotherapy for solid tumors, or post-transplantation immunosuppression therapy-induced HSOS. Defibrotide can be used as a treatment, if available. (4, C).

DILI with pre-existing liver disease

DILI with pre-existing liver disease is not rare because of the high global prevalence of non-alcoholic fatty liver disease (NAFLD) and the heavy burden of hepatitis B virus (HBV) infection and NAFLD in China [21]. In the United States and China, 10% and 23% of patients with DILI have underlying liver disease, respectively [8, 21]. Several studies have shown that patients comorbid with HBV, and hepatitis C virus (HCV) infection are at greater risk of developing DILI during anti-TB therapy and highly active antiretroviral therapy for human immunodeficiency virus (HIV) infection while active HBV infection may be associated with fatal cases [19, 96–100]. However, due to various confounding factors in most retrospective cohorts, the risk of HBV or HCV infection remains in doubt. Similarly, some small-sample-size studies suggest that NAFLD may increase the risk of all-cause DILI [101–103]. However, in populations with chronic liver disease including NAFLD, the risk of statin-induced DILI did not increase [104–106]. Therefore, there is insufficient evidence to suggest that an underlying liver disease increases the risk of all-cause DILI. The increased risk of hepatotoxicity of certain drugs in this population may be associated with specific drugs or impaired liver function due to underlying liver diseases, particularly the latter. For example, in patients with Child–Pugh class B and decompensated cirrhosis (class C), the hepatotoxicity of protease inhibitors for hepatitis C and obeticholic acid for primary biliary cholangitis is significantly increased [107, 108]. Current evidence suggests that decompensated cirrhosis may affect drug metabolism in the liver and hepatocyte regeneration after acute liver injury, which may increase the risk of critical illness or prolong the time to recovery [100, 109–111]. Therefore, drugs (e.g., protease inhibitors, obeticholic acid, and etc.) for which there is evidence that the underlying liver disease is likely to increase the risk of DILI, particularly in decompensated cirrhosis, should be prescribed with extreme caution, and decisions should be made after fully assessing the possible benefits and risks.

Making a diagnosis of DILI in patients with pre-existing liver disease is challenging when identifying the actual etiologies of liver injury. The diagnosis of DILI should be established with caution in this population. Patients with suspected DILI need to be excluded, at a minimum, from other more common etiologies, and activity or recurrence of underlying liver disease. For example, liver injury in patients infected with HBV under good control who had a history of suspect drug with potential hepatotoxicity does not necessarily attribute to the activity of hepatitis B and possibility of DILI should be considered. The RUCAM score may have reduced reliability in this setting and expert opinion may be useful for making a comprehensive judgment after obtaining detailed information about the suspected drug, liver injury, and underlying liver disease.

DILI patients with pre-existing liver disease have reported to demonstrate an increased risk of 6-month mortality at 4.5% in validation cohort and 8.5% in discovery cohort in a DILIN study [71]. Therefore, major measures to control this risk are prescribing potentially hepatotoxic medications with caution, close monitoring, and early detection of liver injury. Patients who need to use potentially hepatotoxic medications should undergo a complete liver biochemistry test before therapy begins,

and the frequency of monitoring should be determined or adjusted according to the level of risk. In patients with abnormal baseline liver enzyme levels, DILI should be suspected when the liver enzyme levels reach double the baseline level or reach the threshold for acute DILI during monitoring. Other causes of liver injury should be investigated, and the activity or recurrence of the underlying liver disease should be evaluated for early recognition and detection of DILI.

Recommendation 20: Patients with underlying chronic liver disease, particularly those with severely impaired liver function, should be evaluated for benefits/risks before prescribing potentially hepatotoxic drugs, and a monitoring plan should be developed and adjusted according to the level of risk during treatment. (5, C) Other etiologies, recurrence or activity of the underlying liver disease should be excluded when establishing the DILI diagnosis. (4, B).

Drug-induced reactivation of hepatitis virus

HBV reactivation (HBVr) is more common among cases of drug-induced reactivation of hepatitis virus because of the heavy HBV burden in China. Reactivation is caused by risk drugs such as immunosuppressants, high-dose glucocorticoids, cytotoxic chemotherapeutic agents, anti-CD20 monoclonal antibody, and anti-tumor necrosis factor drugs that alter the original liver and immune status of HBV-infected patients or carriers, leading to increased viral replication and immune-mediated liver injury. Patients may present with a significant elevation in ALT levels with or without jaundice, positive HBV DNA, or increased viral load compared with pre-exposure to risky drugs and may progress to ALF and even death in severe cases.

The common drugs that cause HBVr include several classes of antineoplastic agents and immunomodulators. Other certain therapies including HSCT and direct-acting antivirals may also cause HBVr. Therapies are classified into high, intermediate, low, and uncertain risk groups according to the risk level for HBVr [112] (Table 7).

Immunosuppressive therapy such as chemotherapy is usually suspended once HBVr occurs, owing to possible severe clinical outcomes, thereby delaying the treatment of the primary disease. Therefore, prior to the administration of immunosuppressants or other related risky drugs, patients should undergo routine screening for HBV surface antigen (HBsAg) and anti-HBV core antibody (anti-HBc), plus HBV DNA if either is positive [113]. Patients with serum evidence (positive HBsAg or anti-HBc) of HBV infection or carriers should be managed as a population at risk of HBVr if they: (1) receive chemotherapy for various hematologic malignancies and solid tumors, (2) receive immunosuppressive therapy for various autoimmune diseases, or (3) receive solid organ transplantation or HSCT.

Stratified management of high-risk drugs and patients can effectively reduce the incidence of HBVr. For patients at high or intermediate risk of HBVr, prophylactic antiviral therapy is recommended prior to treatment with relevant risk medications, with preference given to nucleoside analogs (NAs) with a high barrier to resistance, such as entecavir (ETV), tenofovir disoproxil (TDF), tenofovir alafenamide fumarate (TAF), and tenofovir amibufenamide (TMF) [114, 115]. Lamivudine is not recommended as the first-line treatment because it increases the risk of drug resistance. For patients previously treated with lamivudine, TDF, TAF, or TMF are preferred, but ETV is not recommended. Conventional prophylactic antiviral therapy is not recommended for patients at low risk of HBVr. However, ALT, serum markers of HBV infection (HBsAg and anti-HBc), and HBV DNA should be monitored every 1–3 months during treatment, and patients showing signs of HBVr during monitoring should be promptly administered antiviral therapy. If close monitoring is not available, prophylactic antiviral therapy should be administered, even if the risk of reactivation is low. When the risk of HBVr is uncertain, the use of prophylactic antiviral treatment requires comprehensive judgment by the clinician [116].

Usually, antiviral therapy should be maintained for 6–12 months after chemotherapy or immunosuppressive therapy are completed. However, in patients treated with B-cell monoclonal antibodies or HSCT, NAs should be maintained for at least 18 months after completion of immunosuppressive therapy. The discontinuation of NAs may result in HBV relapse. Therefore, discontinuation should be performed under the guidance of hepatologist, and follow-up should be continued for 12 months after discontinuation of antiviral therapy, during which time HBV DNA and liver biochemistry should be monitored every 1–3 months [116].

Recommendation 21: Prior to the administration of immunosuppressants or drugs that increase the risk of HBVr, patients should undergo routine screening for HBsAg, anti-HBc, and HBV DNA (if either is positive). (1, A).

Recommendation 22: For patients at intermediate to high-risk of HBVr, prophylactic antiviral therapy is recommended. Patients at low risk do not need prophylactic antiviral therapy but require close monitoring during therapy. Prophylactic antiviral therapy should

Table 7 Risk level of therapies causing HBV reactivation

Risk level	Therapy	Serum biomarker	
		HbsAg positive/anti-HBc positive	HbsAg negative/anti-HBc positive
High (> 10%)	Antineoplastic agents	Anthracyclines: doxorubicin, epirubicin, daunorubicin, etc ICIs: nivolumab, pembrolizumab, atezolizumab, ipilimumab TKIs: imatinib, nilotinib, dasatinib, erlotinib, gefitinib, oshitinib, afatinib, etc	
	Immunomodulators	Anti-CD20 monoclonal antibodies: rituximab, ofatumumab, Obinutuzumab High potency anti-TNF drugs: adalimumab, infliximab, golimumab, certolizumab High-dose corticosteroid therapy: ≥ 20 mg/day for ≥ 4 weeks	Anti-CD20 monoclonal antibodies
	Others	Direct-acting antivirals for HBV/HCV co-infection (Note: except for non-cirrhotic patients with HBsAg < 10 IU/ml) Allogeneic and autologous HSCT	Allogeneic HSCT
Intermediate (1–10%)	Antineoplastic agents	Cytotoxic chemotherapy agents (expect for anthracyclines)	Anthracyclines
	Immunomodulators	Less potent anti-TNF drug: etanercept Moderate dose corticosteroid therapy: 10–20 mg/day for ≥ 4 weeks	High potency anti-TNF drugs
	Others	Protease inhibitors	Autologous HSCT
Low (< 1%)	Antineoplastic agents	Methotrexate, azathioprine	Cytotoxic chemotherapy agents (expect for anthracyclines); TKIs
	Immunomodulators	Low-dose corticosteroid therapy: < 10 mg/day	High-dose corticosteroid therapy: ≥ 20 mg/day; Less potent anti-TNF drug
	Others	Non-cirrhotic patients with HBsAg < 10 IU/ml receiving direct-acting antivirals for HBV/HCV co-infection	Protease inhibitors Direct-acting antivirals for HCV infection
Uncertain (no relevant clinical studies available)		Novel biologic products such as abatacept, tocilizumab, ibrutinib, alemtuzumab, natalizumab, ocrelizumab, and ublituximab-xiiy	ICIs

anti-HBc anti-HBV core antibody, *CTLA-4* T-lymphocyte antigen 4, *HBV* hepatitis B virus, *HbsAg* HBV surface antigen, *HCV* hepatitis C virus, *HSCT* hematopoietic stem cell transplantation, *ICIs* immune checkpoint inhibitors, *TKIs* tyrosine kinase inhibitors, *TNF* tumor necrosis factor, *PD-1* programmed cell death 1, *PD-L1* programmed cell death ligand 1

be administered if close monitoring is impossible. (2, A).

Recommendation 23: NAs with high barriers to resistance, such as ETV, TDF, TAF, and TMF, are the first-line antiviral therapies for hepatitis B. (1, A).

Recommendation 24: Antiviral therapy should be maintained for 6–12 months after chemotherapy and immunosuppressive therapy are completed. In patients treated with B-cell monoclonal antibodies or HSCT, NAs should be maintained for at least 18 months after the completion of immunosuppressive therapy. Discontinuation of antiviral therapy should be performed under the guidance of hepatologist, and follow-up should be continued for 12 months after discontinuation of antiviral therapy, during which time HBV DNA and liver biochemistry should be monitored every 1–3 months. (4, C).

Common DILI etiologies

HDS

Epidemiology

The actual incidence of HDS-DILI remains unclear because of the lack of high-quality epidemiologic data. HDS-DILI in Asia is mainly associated with HMs, termed HILI [59]. HMs are the leading cause of DILI in many Asian countries such as Korea [7], Thailand [17], and Singapore [18], and accounts for 27.5%, 41.5%, and 61.4% respectively. The

proportion are reported to be 13.9% and 6% in India and Japan, respectively [20, 117]. In China, this proportion has been reported to be approximately 20–30% [118–120]. Traditional medicine has a long history in Asia and is widely used for the prevention and treatment of various diseases. Owing to the misconception that HMs are "natural and non-toxic," many patients are unaware of their risk of liver injury, resulting in an under-reported use of HMs/HDS during clinical visits. In addition, the absence of proper labeling on the medicine as a common phenomenon has made it hard for physicians to pinpoint the exact culprit ingredient [121], all of which have created obstacles to conduct rigorous studies. *Withania somnifera*, *Curcuma longa*, *Psoralea corylifolia*, and etc. are associated with hepatotoxicity in traditional Indian Ayurvedic herbs [122]. In China, HMs such as *Polygonum multiflorum*, *Tripterygium wilfordii*, *Dioscorea bulbifera*, *Cullen corylifolium*, *Senecio scandens*, *Epimedium*, *Gynura japonica*, and their decoctions or patent medicines have been reported to potentially cause liver injury. See Online Resource 2 for the reported HMs that may cause liver injury.

The incidence of HDS-DILI is rapidly increasing worldwide and is becoming a key concern for academics and regulatory agencies. The etiology of HDS-DILI in Western countries differs significantly from that in Asia. HDS-DILI in Western countries is associated with dietary supplements, particularly those used for bodybuilding. In the US, HDS accounts for approximately 20% of DILI cases, ranking second [123], and 8–16% in Europe and Latin America [3, 124, 125].

Regulatory measures

HDS are not strictly regulated as drugs by regulatory agencies in most countries. For example, HDS are primarily regulated as dietary supplements in Europe and the United States. In China, HMs include TCM plants, herbal decoctions, extracts, formula granules, Chinese patent medicines, folk herbs, and dietary supplements or foods containing TCM components, all of which are regulated differently. For example, Chinese patent medicine is regulated according to drug approval; products containing TCM components are regulated as dietary supplements; and TCM plants, folk herbs, and folk self-picked herbs are regulated as agricultural products. Quality control and safety assessment significantly differ across regulatory categories of HMs, which has brought great challenges to the prevention, clinical evaluation, and management of HILI; this is also one of the reasons why HDS-DILI, including HILI, is rapidly increasing worldwide.

Risk factors

The risk factors for HILI are similar to those for liver injury caused by other drugs, such as chemicals and biologic agents, including drug- and host-dependent risk factors. However, the following HILI-specific risk factors may cause liver injury [126–133]: (1) quality of products: different places of origin and improper preparation may cause differences in components, thereby increasing the risk of hepatotoxicity; (2) identical names but different substances, counterfeit drug misuse, mixing, or adulteration; (3) environmental contaminants, such as pesticide residues, heavy metals, and chemical fertilizers in the soil and water sources during the cultivation process of TCM plants; (4) unreasonable or incompatible formulation; (5) irrational use of HDS: inappropriate prescription, off-label use, overdose, repeated use, and prolonged course of treatment (particularly, repeated use of Chinese patent medicines with herbal decoction or other patented Chinese medicines can increase the dose of a single ingredient with potential hepatotoxicity, thus increasing the risk of HILI). Most Chinese patent medicines and decoctions are formulated with multiple components. Therefore, their composition is extremely complex, and drug interactions between different ingredients are unclear, which is one of the important reasons for the adverse effects of HMs and the risk of HILI. In addition, in China, TCMs are often used in combination with chemical drugs and biologic agents or with dietary supplements and food containing further TCM components. These interactions between TCM, chemical drugs, and dietary supplements are complex and may cause systematic pharmacokinetic changes by altering the absorption, distribution, metabolism, and excretion of medicinal components, resulting in adverse effects including hepatotoxicity and nephrotoxicity [132].

Clinical phenotypes and diagnosis

Most patients with HDS-DILI or HILI present with hepatocellular injury and elevated ALT levels. However, some HDS products or HMs may also cause cholestatic or mixed types and even some specific phenotypes such as PA-HSOS. Multiple studies from Asia, Europe, and Latin-America have shown that liver injury caused by HMs/HDS is more severe than that caused by other drugs, with a higher risk of death or requirement of liver transplantation [120, 124, 134]. These findings are consistent with long-term trends in suspected drugs, clinical characteristics, and clinical outcomes in adult patients with drug-induced ALF (DI-ALF) reported in the US over the past 20 years [135]. In China, a large cohort study suggests that HDS accounts for 57% of drug-induced ALF [70]. Therefore, physicians have to be alert to rapid progression of HDS-DILI/HILI to ALF.

Similar to DILI, the diagnoses of HDS-DILI or HILI are based on an exclusion strategy. A history of exposure to suspected HMs or HDS is the cornerstone of diagnosis [123]. However, many patients tend to assume that these products are "natural and non-toxic" and do not actively inform clinicians about the history of exposure. Therefore, patient education and proactive inquiries can encourage patients to provide a history of exposure to certain products, which is crucial for the correct diagnosis of HDS-DILI or HILI [27]. Although the RUCAM score is recommended for the causality assessment of DILI, it is not specifically designed for HDS-DILI or HILI. Owing to the complexity of the composition of HDS or HMs, the possibility of unlabeled ingredients, the lack of warnings on adverse reactions (including hepatotoxicity in the instructions of some HDS or HM products), and frequent combination with other drugs, it is difficult during clinical practice to define which HDS or HM ingredients are associated with liver injury and which herbs have increased hepatotoxicity in the context of the formulation. Therefore, the RUCAM score may show reduced reliability in the causality assessment of suspected HDS-DILI or HILI [27]. The integrated evidence-chain method [136] emphasizes excluding concomitant chemical drugs and sourcing the suspected herb, which is theoretically helpful in defining HDS-DILI or HILI. However, in the current situation of widespread concomitant use of HMs with chemical drugs and dietary supplements in clinical scenarios, most of the components of HMs are complex and difficult to source. The identification of families and genera, the exclusion of counterfeit products, and the identification and detection of relevant metabolites or specific biomarkers remain unresolved challenges in dealing with most HMs. Therefore, the diagnostic efficacy and practicability of this method in clinical practice must be further evaluated and validated [59]. The RUCAM score, combined with expert opinion, may be the best current practical causality assessment method for establishing a diagnosis of HDS-DILI or HILI [27, 59]. An expert opinion can lead to a comprehensive judgment based on all available information. Positive rechallenge, the presence of typical features or phenotypes of liver injury known to be associated with specific HMs, and significant improvement in liver injury after dechallenge may add weight to the diagnosis.

Risk management

HILI-specific risk management measures include the following: (1) Identify the ingredients of TCM plants, herbal decoction pieces, and excipients; specify the material basis; regulate the source of origin and standard of quality control; and limit the content of the relevant risk substances. (2) Ensure the rationality of the formulation and avoid unreasonable or incompatible formulations. (3) Avoid irrational use of HMs or HDS products such as incorrect prescription, off-label use, overdose, and prolonged courses of treatment. (4) Avoid unnecessary concomitant HMs or HDS products, particularly repeated use of different HMs that cause an increase in the dose of a single potentially hepatotoxic ingredient. (5) Evaluate patients requiring products containing HMs with known hepatotoxic ingredients for overall benefit/risk before prescribing other HMs, HDS products, or chemical agents alone or in combination. (6) Strengthen scientific education and medication guidance to prevent individuals from collecting and taking HMs on their own.

Recommendation 25: The irrational use of HDS, such as inappropriate prescription, off-label use, overdose, prolonged course of treatment, inappropriate formulation, and unnecessary concomitant/repeated use of HMs or HDS products that causes an increase in the dose of a single potentially hepatotoxic ingredient, should be avoided. Scientific education should be strengthened to prevent people from collecting, purchasing, and consuming HMs on their own, particularly those that do not follow medicinal food homology. (4, C).

Recommendation 26: For patients suspected of having HILI/HDS-DILI, a detailed investigation of the history of exposure to HMs should be conducted, and clinicians should actively ask or encourage patients to provide their history of exposure to HMs or HDS products. (4, B).

Recommendation 27: Patients who require HMs containing known hepatotoxic ingredients or have a history of HILI should be evaluated for overall benefit/risk before therapy and should be closely monitored during therapy. (5, C).

Recommendation 28: For patients suspected of having HILI/HDS-DILI, the RUCAM score combined with expert opinion is the recommended causality assessment method. (4, B).

Recommendation 29: For patients suspected of having HILI/HDS-DILI who have concomitant use of other HMs, HDS products, and chemical drugs, a positive rechallenge, the presence of typical features or phenotypes of liver injury known to be associated with specific HMs, and significant improvement in liver injury after dechallenge may add weight to the diagnosis of specific HM-induced liver injury. (5, B).

Anti-TB drugs

Epidemiology

The incidence of TB is higher in Asian countries than in Western countries, which increases the incidence of anti-TB DILI (AT-DILI), another characteristic of DILI in Asian countries. The incidence of AT-DILI is 9.5–10.6% in China and 3.8–10.0% in India [137]. In China, AT-DILI accounted for 22–31.3% of the investigated cases of DILI [119]. Therefore, AT-DILI is the most common cause of DILI and a common cause of ALF and acute-on-chronic liver failure (ACLF) in Asian countries [138, 139]. Among the common first-line anti-TB drugs, isoniazid, rifampin, and pyrazinamide are highly hepatotoxic, and cases of significant hepatotoxicity have been reported with ethambutol. Second-line drugs such as ethionamide, protionamide, and aminosalicylate are also highly hepatotoxic.

Risk factors

The currently reported risk factors for AT-DILI include old age; female sex; Asian ethnicity; HBV, HCV, or HIV infection; and concomitant use of multiple hepatotoxic anti-TB treatments (ATT) [51, 59] Genetic polymorphisms may be associated with an increased risk of AT-DILI in people carrying the HLA-B*52:01 allele and in ultraslow metabolizers carrying NAT2*6 or NAT2*7 variants [140].

Clinical characteristics and diagnosis

Usually, AT-DILI occurs within the first 2 months of ATT, but the risk of liver injury persists throughout the course of treatment [141, 142]. Studies suggest that indicators of impaired liver function such as TBil, INR, and albumin are more severe in patients with AT-DILI than in those with DILI caused by other drugs [138]; however, additional studies are needed for validation. The prognosis of AT-DILI is usually favorable; however, only a small number of patients progress to ALF or ACLF.

The overall diagnostic approach for AT-DILI is the same as that used for liver injury induced by other drugs. The diagnosis should exclude the possibility of DILI caused by other concomitant potentially hepatotoxic drugs such as anti-inflammatory analgesics, antibiotics, HDS products, or HMs. The diagnosis of AT-DILI in patients with both TB and pre-existing liver disease requires exclusion of the influence of the underlying liver disease. Liver injury due to hepatic TB usually presents with cholestasis due to biliary obstruction caused by infiltration of the liver parenchyma or lymph node enlargement, which differs from the usual presentation of AT-DILI and should be differentiated or excluded when establishing the diagnosis of AT-DILI.

Monitoring and management

Liver biochemistry tests and regular monitoring for nonspecific symptoms are important measures of risk management that help in the early detection of AT-DILI and should be performed throughout the course of ATT. All patients receiving ATT should undergo tests for liver biochemistry and hepatitis B and hepatitis C biomarkers before therapy to obtain baseline data. For patients with risk factors such as long-term alcohol consumption, HBV/HCV/HIV infection, concomitant hepatotoxic drugs, and abnormal baseline liver enzyme levels, monitoring every 2 weeks for the first 2 months after starting ATT and every 4 weeks thereafter is an acceptable frequency. For patients without risk factors, the frequency of monitoring can be reduced but should be increased if new nonspecific symptoms appear [59, 143].

When ATT is restarted after recovery from liver injury, the treatment regimen should be carefully evaluated. If severe liver injury with jaundice or ALF develops after the initial ATT, reuse of the same ATT regimen should be strictly restrained. For patients who present with mild elevation of liver enzymes after ATT, although most can tolerate the reintroduction of first-line drugs, a comprehensive assessment of benefits/risks should be performed before planning to use the same ATT regimen, and the frequency of monitoring should be increased during treatment.

Recommendation 30: All patients should undergo baseline tests for HBsAg (plus HBV DNA if positive), anti-HCV, liver biochemistry, and abdominal ultrasound. (1, A).
Recommendation 31: Non-specific symptoms of liver disease should be regularly monitored for the early detection or identification of potential AT-DILI. (3, B).
Recommendation 32: For patients without risk factors, liver biochemistry should be monitored every month during ATT. (4, C) For patients with risk factors, liver biochemistry should be monitored every 2 weeks for the first 2 months after starting ATT and every 4 weeks thereafter until the completion of treatment. (2, B).
Recommendation 33: Rechallenge with the suspect drug should be avoided if severe liver injury accompanied by jaundice or ALF occurs after ATT. (4, B) A comprehensive assessment of benefits/risks should be performed before the reintroduction of an ATT, and the frequency of monitoring should be increased during treatment if only asymptomatic mild liver biochemical abnormality arise after initial exposure. (2, B).

Antineoplastic agents

Epidemiology

Antineoplastic agents are important causes of DILI. In Western countries, antineoplastic agent-induced liver injury accounts for 5–8% of DILI. Approximately 10% and 8.34% of DILI cases in China and Japan, respectively, are caused by antineoplastic agents [1]. Traditional chemotherapeutic agents, large- or small-molecule targeted drugs, and the newly available ICIs can cause liver injury. In clinical trials, the incidence of all-grade liver injury due to different small-molecule targeted drugs such as tyrosine kinase inhibitors is reportedly 5–55% [144–149]. Sunitinib, lapatinib, pazopanib, regorafenib, ponatinib, pexidartinib, and idelalisib are targeted drugs that have been assigned box warnings for hepatotoxicity by the United States Food and Drug Administration (FDA) [150, 151]. The incidence of ICI-related hepatitis depends on the class of drugs, dose, and whether they are used as monotherapy or combination therapy [152, 153]. The incidence of any grade of ICI-related hepatitis is usually < 10% with monotherapy, and the incidence of liver injury induced by cytotoxic T-lymphocyte antigen 4 inhibitors is higher than that induced by programmed cell death 1 inhibitors, particularly at high doses. The incidence of any grade of ICI-related hepatitis in combination therapy is higher than that in monotherapy, for both the combination of two ICIs and a combination of an ICI with targeted therapy [152].

ICI-related hepatotoxicity

ICI-related hepatotoxicity usually occurs in the first 4–12 weeks or after the administration of 1–3 doses [154]. Most patients present with hepatocellular ICI-related hepatitis, which is characterized by a significant elevation in ALT or AST levels [155], and some present with cholestatic or mixed type. In addition, patients may present with ICI-related cholangitis characterized by a significant elevation in ALP or GGT levels [156]. A small number of patients may present with a specific clinical phenotype, such as nodular regenerative hyperplasia [157].

More than half of patients with ICI-related hepatotoxicity have extrahepatic immune-related adverse events (irAEs) [158], and a low titer of anti-nuclear antibody may be detected in a small number of patients [155]. Although rare, ALF may occur in 0.1–0.2% of patients [159–162]. The histologic features of ICI-related hepatitis may be of great importance for its diagnosis and management, which can help reveal the histopathological phenotype of liver injury and the presence of liver metastasis, and provide the histologic information needed to distinguish AIH or DILI [155, 163]. Liver biopsy is recommended for patients in whom suspected or ICI-related hepatotoxicity cannot be completely ruled out, particularly for those who do not respond well to corticosteroid therapy.

Liver injury caused by classical chemotherapy and targeted therapy is usually either intrinsic or idiosyncratic. However, ICI-related hepatotoxicity is an indirect form of DILI [22, 152]. The exact mechanism remains unknown, but autoimmune-like inflammation caused by overactivation of the immune system is currently under speculation, and genetic susceptibility may also play an important role [155, 164]. Possible risk factors for ICI-related hepatotoxicity include organ transplantation, comorbidity with autoimmune disease, history of ICI-induced irAEs, high doses of ICIs (particularly cytotoxic T-lymphocyte antigen 4 inhibitors), combination therapy with multiple ICIs, or a combination of an ICI with targeted therapy [165–167].

Management of ICI-related hepatotoxicity should include assessment before treatment (Fig. 3), monitoring during treatment, diagnosis (Fig. 4), treatment, and follow-up. Based on the severity of the hepatotoxicity, clinicians need to determine whether to continue, hold, or permanently discontinue ICIs and whether to initiate corticosteroid or immunosuppressive therapy (Fig. 5). Most patients with grade ≥ 3 ICI-related hepatitis respond well to high-daily-dose corticosteroids (1–2 mg/kg day methylprednisolone or equivalents) without relapse after discontinuation. However, a recent study suggested that low-daily-dose

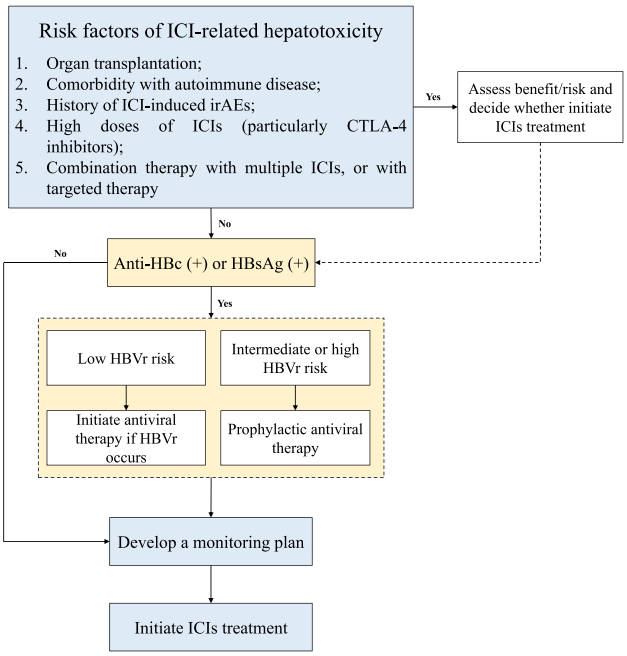

Fig. 3 Baseline assessment before ICIs treatment. *anti-HBc* hepatitis B virus core antibody, *CTLA-4* cytotoxic T-lymphocyte antigen 4, *HBsAg* hepatitis B virus surface antigen, *HBVr* hepatitis B virus reactivation, *ICI* immune checkpoint inhibitor, *irAE* immune-related adverse event

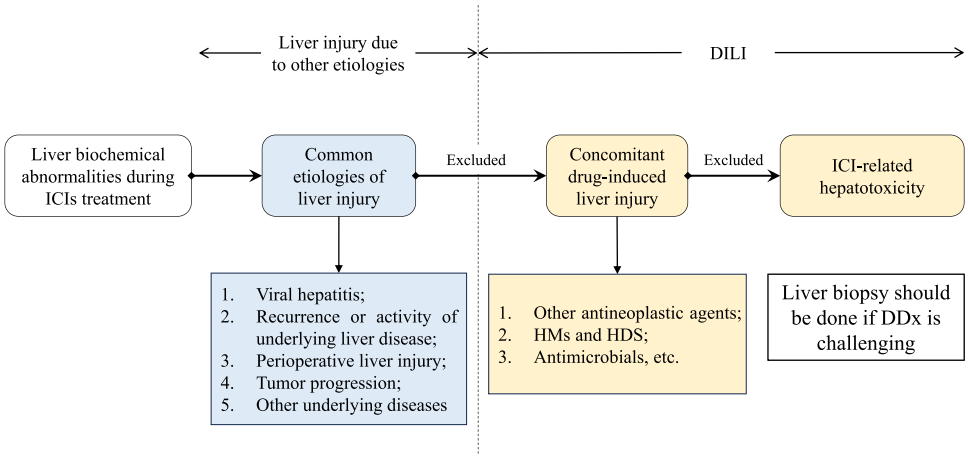

Fig. 4 Diagnostic algorithm for ICI-related hepatotoxicity. *DDx* differential diagnosis, *HDS* herbal and dietary supplement, *HM* herbal medicine, *ICI* immune checkpoint inhibitor

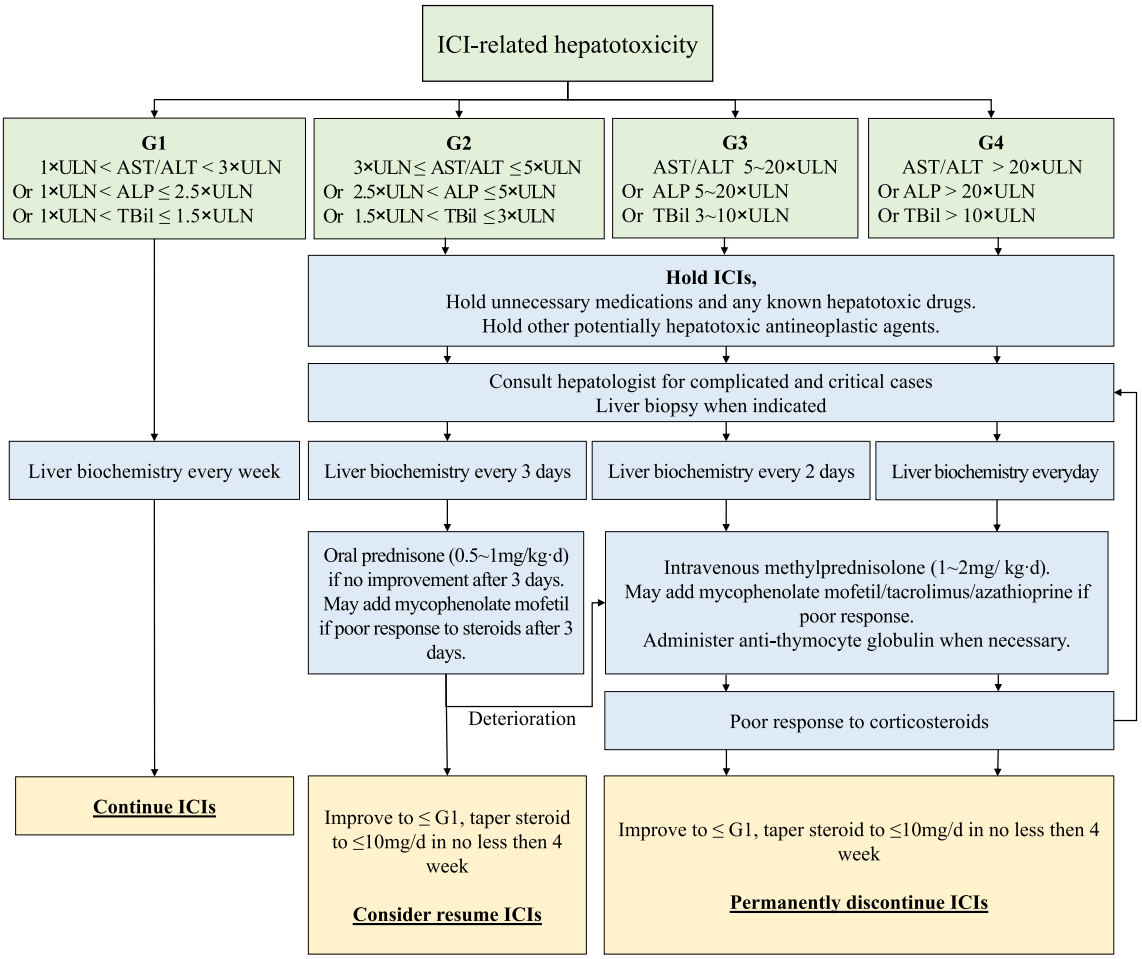

Fig. 5 Algorithm for the management of ICI-related hepatotoxicity. *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ICIs* immune checkpoint inhibitors, *TBil* total bilirubin, *ULN* upper limit of normal

corticosteroids (< 1.5 mg/kg day methylprednisolone or equivalent) provide similar outcomes with lower risks of corticosteroids related adverse reaction than higher-dose regimens [168]. Of note, whether to permanent discontinuation of ICIs grade 3 ICI-related hepatotoxicity is currently still under debate [169, 170], safe reintroduction in sporadic cases have been reported [171]. A few patients, particularly those with cholestasis or ICI-related cholangitis, may respond poorly to corticosteroids, for whom immunosuppressants such as mycophenolate mofetil, tacrolimus, and azathioprine may be added [169, 170, 172]. Infliximab is not recommended as salvage therapy after failure of corticosteroid therapy. We recommend a consensus by a multidisciplinary team that includes hepatologists on the diagnosis and differential diagnosis of ICI-related hepatotoxicity, the dose/course of corticosteroid therapy, and restarting ICI therapy after recovery.

Special considerations in diagnosis of antineoplastic agent-induced liver injuries

The diagnostic approach for all antineoplastic agent-induced liver injuries is the same as that used for liver injury induced by other drugs. During the diagnosis of suspected liver injury caused by antineoplastic agents, the following should be ruled out: (1) liver or biliary metastasis or infiltration of tumor; (2) progression of hepatocellular carcinoma and biliary tract or ampullary tumor; (3) perioperative liver injury due to recent surgery or interventional therapy; (4) influence of other diseases; (5) possibility of concomitant drug-induced (e.g., anti-infectious drugs, HMs, nutritional support, and palliative adjuvant therapy) liver injury. Because of the similar characteristics of liver biochemical abnormality and clinical presentations, although challenging, it is important to determine which is the suspected drug during combined therapy of ICIs with targeted therapy because this is a deciding factor for subsequent antineoplastic regimens and deciding whether to use immunosuppressive therapy. A liver biopsy may provide important information for the differential diagnosis. In addition, patients who do not develop liver injury with the previous regimen and develop liver injury after the administration of the latter regimen have an increased likelihood of the latter causing DILI. The presence of irAEs in other organs may also contribute to the diagnosis of ICI-related hepatotoxicity. Significant improvement and recovery from liver injury after discontinuation of a single agent in the combination regimens (dechallenge) may help clarify the suspected agent.

It should be noted that the severity grading of liver injury caused by antineoplastic drugs is usually based on a single liver biochemical marker according to the Common Terminology Criteria for Adverse Events in clinical trials of antineoplastic drugs [173], which is different from the DILIN or international DILI severity grading and may not truly reflect the clinical severity of liver-related adverse events [152].

Risk management

Recommendations for DILI risk control in patients with tumors include the following: (1) All patients should undergo regular liver biochemistry tests before, during, and after treatment. (2) The frequency of monitoring can be adjusted according to the risk level of drug hepatotoxicity, presence of known risk factors, and severity and evolution of liver injury. (3) Clinical decisions regarding antineoplastic regimens (monotherapy or combination therapy), choice of specific agents, and whether to delay or discontinue therapy should be made after a careful assessment of potential benefits/risks based on liver biochemistry at baseline or during monitoring. (4) Antineoplastic therapy should be restarted with caution. If grade ≥ 3 liver injury or severe liver injury with jaundice or ALF occurred after the initial exposure, reintroduction of the same regimen should be strictly restrained. Although most patients can tolerate reintroduction of treatment only if mild asymptomatic liver biochemical abnormalities develop after antineoplastic therapy, the benefits and risks of reintroduction should be evaluated under the guidance of hepatologist before reuse of the same antineoplastic regimen, and the frequency of monitoring should be increased during treatment. (5) All patients at intermediate to high risks of reactivation of viral hepatitis should be conventionally screened for HBV and HCV and administered prophylactic or therapeutic antiviral therapy depending on the risk level before receiving antineoplastic agents. (6) For patients at risk of liver metastasis, contrast-enhanced MRI or CT is recommended before antineoplastic therapy.

> Recommendation 34: Minimum assessment before antineoplastic therapy should include: (1) liver biochemistry test; (2) contrast abdominal MRI or CT in patients at risk of liver metastasis or liver/biliary tract tumor; (3) concomitant underlying liver disease and other systemic diseases; and (4) previous antineoplastic regimen with history of hepatotoxicity. (4, B).
> Recommendation 35: Monitoring frequency during and after treatment can be adjusted according to the risk level of drug hepatotoxicity, the presence of known risk factors, and the severity and evolution of liver injury. (3, B).
> Recommendation 36: The diagnosis of suspected antineoplastic agent-induced liver injury should rule out liver or biliary metastasis and infiltration, perioperative liver injury, and the possibility of concomitant drug-induced liver injury. (4, C).
> Recommendation 37: For patients with risk factors for ICI-related hepatotoxicity such as organ transplantation, comorbidity with autoimmune disease, and a history of irAEs, ICI-containing antineoplastic regimens should be

developed with caution, and close monitoring is required during treatment. (4, B).

Recommendation 38: Clinicians need to determine whether to continue, hold, or permanently discontinue ICIs and initiate corticosteroid therapy based on the severity of hepatotoxicity. Infliximab is not recommended as salvage therapy after failure of corticosteroid therapy. The diagnosis and management of complicated and critical patients should be performed by a multidisciplinary team that includes hepatologist. (2, C).

Recommendation 39: When ICIs are combined with targeted therapy, liver biopsy is recommended when ICI-related hepatotoxicity cannot be diagnosed or excluded, when there are other causes of liver injury (including DILI), or when the differential diagnosis is difficult. (4, B) The presence of irAEs in other organs may add weight to the diagnosis of ICI-related hepatotoxicity. (4, C).

Recommendation 40: If grade ≥ 3 liver injury or severe liver injury with jaundice or ALF occurs after antineoplastic treatment, reintroduction of the suspected drug should be avoided. (4, B) If only asymptomatic mild liver biochemical abnormalities arise after initial exposure, the benefits and risks of reintroduction should be evaluated, and the frequency of monitoring should be increased during treatment. (2, B).

New biomarkers

Biomarkers can be classified into different categories such as risk prediction, diagnosis, and prognosis based on their clinical application. Development of new biomarkers for DILI will help in (1) early detection of DILI in nonclinical research on new drug development and monitoring of DILI in clinical trials; (2) identification of common mechanisms of DILI and specific mechanisms of specific drugs; (3) early detection and diagnosis of DILI in clinical practice; (4) prediction of the risk, prognosis, and the achievement of risk-control goals for precision medicine and stratified management; and (5) development of drugs for DILI treatment. When developing an ideal biomarker, its sensitivity, specificity, positive predictive value, and negative predictive value should be considered to ensure overall accuracy.

Multiple potential biomarkers of DILI have been identified. MicroRNA-122 is a hepatocyte-specific miRNA that is elevated in the plasma of patients with APAP overdose before the ALT level is elevated and is considered able to predict the onset of liver injury at an early time point [174]. The mitochondrial matrix enzyme glutamate dehydrogenase is a biomarker of mitochondrial injury. Its potential value in confirming or excluding hepatocellular injury in cases of elevated ALT levels from a suspected extrahepatic origin (e.g., muscle) has been evaluated [26, 175]. High mobility group box 1, a damage-associated molecular pattern molecule, has been reported to be associated with the pathogenesis of DILI [176]. Cytokeratin 18, macrophage colony-stimulating factor receptor 1, and osteopontin have also been identified as DILI biomarkers that predict a poor prognosis [177]. In addition, several potential biomarkers associated with the risk of liver injury caused by specific drugs or HMs have been reported, such as HLA-B*35:01, immune factors, and metabolic markers that may be associated with the risk of Polygonum multiflorum-induced liver injury [178–180]. Although advances in omics have provided new methods for the development of DILI biomarkers, and progress has been made [181], the analysis of biomarkers and clinical validation are necessary steps for biomarker evaluation by regulatory agencies. Therefore, currently reported biomarkers have yet to be clinically validated for approval, and studies using large DILI cohorts are required for biomarker validation, highlighting the importance of collaborative DILI registry studies [181, 182].

DILI signal in clinical trials and assessment

In randomized controlled trials (RCT), an imbalance in liver enzyme levels between the trial and placebo (or positive control) groups or the presence of severe DILI cases in the trial group, characterized by elevated bilirubin, jaundice, and/or coagulation dysfunction accompanied by obvious symptoms of liver disease, are the two major signals that the trial drug has potential hepatotoxicity [51]. Early detection and assessment of potential hepatotoxicity signals of new drugs are not only beneficial for risk control and prognosis but also have a great influence on the subsequent strategy of new drug development.

Signal detection

Hy's law Cases fulfilling Hy's law in clinical trials have both predictive and prognostic value for the risk of hepatotoxicity associated with new drugs. Finding one to two such cases in clinical trials is considered highly predictive that the drug has a higher risk of causing ALF when administered to a larger population. The FDA is at present rigorously applying Hy's law to screen for potentially hepatotoxic drugs [183].

Non-Hy's law To detect the risk of DILI early during the development of a new drug, it is important not only to ensure that Hy's-law cases are properly identified but also to look for other potential signals throughout the process [183]. In clinical trials, the possibility of DILI should be suspected in participants with no history of liver disease, normal liver biochemistry at baseline, and ALT and/or AST levels exceeding $3 \times$ ULN (hepatocellular type) or

ALP > 1.5 × ULN after drug administration [51]. If the participant has a history of liver disease and abnormalities of ≥ 2 × ULN in liver biochemistry at baseline, exceeding twofold the average baseline value after drug administration may be considered a threshold for close monitoring [51]. Because DILI in patients with chronic liver disease is usually severe, conservative thresholds should be used in this population, particularly for new drugs that have been identified in nonclinical and preclinical studies as having a potential risk for DILI. The frequency of liver enzyme elevation is a necessary but not definitive indicator of the likelihood of severe DILI in individuals exposed to specific new drugs. The magnitude of elevation in transaminase levels after drug administration may be a better indicator of severe DILI than the frequency of elevation, with higher peaks (10–15 × ULN) indicating specificity. A more definite sign of severe hepatotoxicity is the presence of elevated liver enzyme levels accompanied by elevated TBil levels after drug administration [183].

Signal assessment

In clinical trial databases, the presence of Hy's-law cases in the trial group or a higher incidence of ALT or AST levels exceeding ≥ threefold the ULN in the trial group than in the control or placebo group usually indicates that the trial drug is potentially hepatotoxic. The presence of one or more cases of fatal liver injury, such as ALF, death, or liver transplantation, is a sign of severe hepatotoxicity. The following criteria may be helpful in assessing whether the trial drug may pose a high-risk of DILI [51, 183]: (1) a higher proportion of patients in the trial group with ALT elevations of ≥ 3 × ULN than the control group; (2) some participants in the trial group with significant ALT elevations of 5 × ULN, 10 × ULN, or 20 × ULN compared with the control group; (3) after excluding other causes of liver injury, one or more patients in the trial group with hepatocellular injury accompanied by TBil ≥ 2 × ULN. For new drugs suspected of causing cholestatic liver injury, the incidence of ALP > 1.5 × ULN, > 2 × ULN, and > 3 × ULN in each group should be compared to determine whether the trial drug is hepatotoxic.

Signal follow-up

During safety monitoring in clinical trials, once an elevation in ALT, AST, and/or ALP levels is detected, the test should be repeated within 48–72 h for confirmation [183]. If the presence of liver injury is confirmed, the participant should be closely monitored, followed up, and screened for the cause of liver injury. The frequency of follow-up depends on the risk of hepatotoxicity associated with the new drug and severity of liver injury. Regardless of whether the cause of liver injury is ultimately defined as new drug-related, follow-up of participants presenting with adverse events should be maintained until the liver injury recovers or a clinical outcome event is reached (e.g., chronicity, ALF, liver transplantation, or death).

Diagnosis and management in individual participants

The diagnostic approach for DILI in individual participants in clinical trials may follow the recommendations of the guideline. In most cases, the risk of DILI and the associated risk factors for new drugs in the clinical development phase are unknown, information and literature on previous liver injury caused by these drugs are limited, and once participants in clinical trials develop a liver injury, they are usually not rechallenged. Therefore, the reliability of the RUCAM score for causality assessment in clinical trials of new drugs may be lowered, and a combination with expert opinions may be a better option [51, 183]. In addition, in clinical trials, the severity of liver-related adverse events, including DILI, is usually assessed using the Common Terminology Criteria for Adverse Events, which may not accurately reflect the clinical severity of DILI [51]. The threshold for treatment discontinuation after DILI episodes in clinical trials can be found in the FDA guideline [183].

Treatment

The major goals of DILI treatment include: (1) promoting early recovery from liver injury; (2) preventing deterioration or chronicity of liver injury, avoiding clinical outcome events such as ALF, chronic DILI, or even cirrhosis, and ultimately reducing the risk of all-cause or liver-associated mortality; (3) reducing the impact of DILI on the treatment of primary diseases. The following general principles can help clinicians implement appropriate treatment and management measures [184].

Discontinuation of the suspected drug

Discontinuation and avoidance of suspected drugs are the most important measures for treating liver injury and constitute the basic principles of DILI treatment. Liver injury in most acute DILI cases is self-limiting after discontinuation of the suspected drug. A small number of patients become critically ill or develop chronic injuries that require other therapies. The thresholds for treatment discontinuation in clinical trials suggested by the FDA guideline are as follows: (1) ALT or AST > 8 × ULN; (2) ALT or AST > 5 × ULN for more than 2 weeks; (3) ALT or AST > 3 × ULN and

(TBL > 2 × ULN or INR > 1.5); (4) ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) [183]. This threshold is designed for clinical trials and is only used as a reference in clinical practice. Some patients may not recover immediately from liver injury after discontinuation of the suspected drug, and clinicians should continue to closely follow-up and collect relevant information to decide whether to take other treatment measures. Once the drug is discontinued, the patient should not be exposed to it again.

Reasonable choice of medication

In addition to the necessary supportive treatment, medications should be appropriately selected based on research evidence. The drugs commonly used in the treatment of DILI include the following:

N-Acetylcysteine

N-Acetylcysteine (NAC) is the only antidote approved by the FDA for the treatment of APAP-induced intrinsic DILI. In a randomized placebo-controlled trial of adult non-APAP ALF (including DILI as the etiology), intravenous NAC improved transplant-free survival in early stage ALF with grade I–II coma [185]. However, no significant benefits were observed with NAC in pediatric non-APAP-induced ALF [186]. Currently, NAC is accepted for the treatment of adult patients with drug-induced ALF and should be administered as early as possible at a dose of 50–150 mg/kg day.

Corticosteroids

The conventional use of corticosteroids for DILI is not supported by a high-level of evidence. Similarly, we have no definite evidence suggesting that corticosteroids can improve the survival of patients with DI-ALF or the prognosis of cholestatic DILI or vanishing bile duct syndrome. While some studies have suggested that corticosteroids ameliorate liver injury [187–191], others have suggested that they increase adverse events without significant benefits [192, 193]. Therefore, corticosteroids should not be used as a conventional therapy for DILI. The indications should be strictly controlled, and the possible benefits and risks should be fully assessed before administration. Immune-mediated DILI with hypersensitivity or autoimmune features (e.g., DRESS syndrome, DI-ALH, and ICI-related hepatotoxicity) is an indication for corticosteroid use. The dose for DRESS is recommended to be 1 mg/kg of methylprednisolone, while 40–60 mg/d prednisone taper over 1–3 months may improve normalization of liver enzyme for iDILI [82, 191]. However, there is no standardized dose or duration for iDILI. The regimen is usually empirical and at the discretion of each physician.

Other drugs indicated for liver injury

Unlike other countries, a wide range of drugs is commonly used in China for the treatment of elevated liver enzymes of various etiologies. Regardless of the mechanism, they can be classified into two categories: those that lower ALT and/or AST levels and those that lower ALP and/or GGT levels.

Magnesium isoglycyrrhizinate (MgIG) and bicyclol are recommended for acute hepatocellular or mixed DILI accompanied by a significant ALT elevation. Currently, MgIG is the only drug indicated for acute DILI. It has been shown to promote ALT and AST normalization in patients with acute DILI when administrated intravenously 200 mg/day for at least 2 weeks [194]. Bicyclol is the first oral drug indicated for acute DILI registered for clinical trial. In a phase II trial, bicyclol effectively reduced level of aminotransferase in patients with acute DILI and promoted recovery from liver injury when given 25 or 50 mg 3 times a day [195].

Evidence of the efficacy of other drugs in DILI is mostly provided by small-sample-size RCTs or retrospective real-world studies. However, the exact efficacy remains to be confirmed by a high-level of evidence [196]. Given the favorable safety of these drugs, for patients with mild to moderate hepatocellular and mixed DILI without jaundice, oral or intravenous drugs such as glycyrrhetinic acids [197] (e.g., diammonium glycyrrhizinate, compound glycyrrhizin), silybin [198], glutathione, polyene phosphatidylcholine [199], and Chinese patent medicine [200, 201] (e.g., Hugan tablets, Wuling capsule) can be used to reduce ALT levels. For patients with cholestatic DILI, particularly those with severe, cholestatic, or mixed DILI with delayed recovery, ursodeoxycholic acid or *S*-adenosyl methionine may be used to reduce ALP levels.

There is no evidence suggesting better efficacy of a combination of two or more of these drugs. Therefore, a combination of two or more drugs that reduce ALT levels is not recommended for the treatment of liver injury. Despite the lack of evidence, it is acceptable to choose one drug that primarily reduces ALT levels and another that improves the symptoms of cholestasis in mixed DILI.

The prophylactic use of these drugs for liver injury to reduce the occurrence of DILI in the context of high-risk drug therapies such as antineoplastic therapy and ATT is not well documented. Therefore, conventional prophylactic treatments are not recommended for all patients. However, for patients with risk factors such as previous liver injury after initial exposure, comorbidity with underlying liver disease, and drugs with clear evidence of DILI, prophylactic

treatment should be considered based on a comprehensive assessment of risk. Drugs that have been studied with large sample sizes and have better pharmacoeconomic evidence such as bicyclol [202, 203], MgIG [204–207] and other drugs are preferred [208–210].

Liver transplantation in DI-ALF/ACLF

The overall prognosis of DI-ALF/ACLF is poor, with 24% or 27.1% transplant-free survival. Liver transplantation can significantly increase survival by up to 66.2% [66, 211, 212]. Therefore, liver transplantation is currently the most effective treatment for patients with DI-ALF and ACLF. L-ornithine-L-aspartate may be beneficial for the treatment of hyperammonemia in critical cases or liver failure [213–217]. Studies have suggested that an artificial liver (e.g., plasma replacement therapy or a double plasma molecular absorption system) may improve transplant-free survival [218].

Recommendation 41: Once DILI occurs, the suspected drug should be promptly discontinued. The threshold for the discontinuation of clinical trials issued by the FDA can be referred to. (4, A).
Recommendation 42: Intravenous NAC should be administered as early as possible to adult patients with DI-ALF and SALF. NAC is not recommended for pediatric patients. (2, B).
Recommendation 43: There is no high-level evidence that favors or contradicts the conventional use of corticosteroids for DILI. (4, C) Corticosteroids should be administered with caution. Immune-mediated DILI with hypersensitivity or autoimmune features (e.g., DRESS syndrome, DI-ALH, and ICI-related hepatotoxicity) is an indication for corticosteroid use. (3, B).
Recommendation 44: Magnesium isoglycyrrhizinate and bicyclol are recommended for acute hepatocellular or mixed DILI accompanied by a significant ALT elevation. (1, A).
Recommendation 45: Glycyrrhetinic acid (e.g., diammonium glycyrrhizinate, compound glycyrrhizin), silibinin, glutathione, polyene phosphatidylcholine, or Hugan tablets can be used in patients with mild to moderate hepatocellular DILI with ALT or AST elevation. (4, C) Ursodeoxycholic acid or S-adenosyl methionine can be used in patients with cholestatic DILI. (4, C) A combination of two or more drugs that reduce ALT levels is not recommended for the treatment of liver injury. (4, B).
Recommendation 46: In the context of high-risk drug therapies such as antineoplastic therapy and ATT conventional prophylactic treatment is not recommended for every patient. (2, B) However, for patients with risk factors such as previous liver injury after initial exposure and comorbidity with underlying liver disease, prophylactic treatment could be considered. (4, C).
Recommendation 47: Liver transplantation is recommended for critically ill patients with DI-ALF/SALF/ACLF. (2, B) An artificial liver (e.g., plasma replacement therapy, double plasma molecular absorption system) may be an option. (4, C) L-ornithine-L-aspartate may be beneficial for the treatment of hyperammonemia in critical cases or in those with liver failure. (4, C).

Prevention, management, and future

Challenges in DILI prevention

The DILI prevention and treatment situation in China is serious, mainly for the following reasons: (1) China is becoming an aging society with a huge population taking multiple medications for multiple morbidities; (2) widespread irrational medication use; (3) healthcare providers other than hepatologists are unfamiliar with the diagnosis and management of DILI; (4) the post-market surveillance of pharmaceutical companies is poorly developed; (5) lack of public awareness concerning drug safety, particularly DILI. Therefore, effective DILI prevention is a systemic program that requires scientific and reasonable control of potentially hepatotoxic drugs by regulatory agencies (e.g., suspension of sale or direct withdrawal, revision of drug instructions, restriction on use), establishment of risk management by pharmaceutical companies (e.g., establishment of a pharmacovigilance department, development of proper strategies for surveillance and risk management, active research, revision of drug instructions, and communication of risk information), risk management of DILI in clinical practice by healthcare providers (e.g., regular monitoring during treatment, early detection of DILI, proper diagnosis, decision to discontinue or taper the dose of drug), and public education on drug safety and the rational use of medication.

Rational use of medication

Healthcare providers should assess or identify potential risk factors for DILI or at-risk patients, fully weigh benefits/risks, and avoid prescribing hepatotoxic drugs. The LiverTox and Hepatox websites provide healthcare providers and the public with information on several hepatotoxic drugs. Clinical pharmacists should be a part of the healthcare team to ensure the administration of reasonable formulations and avoid incompatibilities. Drug–drug interactions (DDIs) should be avoided to reduce the risk of DILI. For example,

the combination of orally targeted drugs with CYP3A4 inhibitors (e.g., erythromycin and itraconazole) may lead to increased blood levels of targeted drugs and increase the risk of DILI. The DDInter covers approximately 240,000 DDI drugs reviewed and revised by clinical pharmacists, providing practical information on mechanisms of action, severity, potential risks, and drug-switching options [219]. For drugs with a narrow safety window or for specific high-risk drugs, therapeutic drug monitoring can be performed when necessary. For instance, during anti-infection therapy with vancomycin and anti-epileptic treatment with lamotrigine, standardized therapeutic drug monitoring can reduce the toxicity caused by the irrational use of medication [220]. In addition, inappropriate medication habits may increase the risk of DILI. For example, catechol and caffeine in tea and coffee beverages can lead to increased concentrations of drugs metabolized by CYP2E1, such as acyclovir and quinolone. Grapefruit juice can increase the concentration of immunosuppressants, statins, and other drugs metabolized by CYP3A4. Therefore, clinicians and pharmacists should strengthen public education on the rational use of medications and educate patients on the importance of taking medications as instructed.

Recommendation 48: Healthcare providers should assess or identify potential risk factors for DILI or at-risk patients, fully weigh the benefits/risks, and avoid prescribing hepatotoxic drugs. Regular monitoring should be performed to facilitate early detection of DILI during treatment. (4, B).

Recommendation 49: Clinical pharmacists should be a part of the healthcare team to reduce the risk of DILI by reviewing drug combinations, reminding patients of potential drug interactions, and monitoring plasma concentrations when necessary. Public education on health and the rational use of medication should be strengthened. Moreover, patients should be educated on the importance of following instructions on taking medications and to correct harmful medication habits. (4, B).

Recommendation 50: Healthcare professionals and the public could visit the LiverTox and Hepatox websites to learn more about hepatotoxic drugs and to increase awareness of DILI. (4, B).

Table 8 Major directions for future research in DILI

Direction	Comment
Mechanistic studies	Basic research on common pathogenesis of DILI should be continuously carried out to discover potential therapeutic targets
Genomic studies and prospective cohorts	Advances in genomic studies in DILI cohort may provide more insight into HLA or non-HLA associated genetic susceptibility of all-cause DILI or DILI caused by certain drug in different population. Further validation by well-designed prospective large cohorts is needed to translate current findings into clinical use of DILI prediction and prevention
Diagnosis and causality assessment	Diagnostic biomarkers need to be further developed and validated by translational studies to identify genuine DILI in clinical practice since such markers are still not approved by the authorities Development of causality assessment method that integrates evaluation of multiple suspect drugs, pre-existing liver disease, and HMs or HDS is required to improve accuracy and reliability of these tools
Prediction of prognosis	Discovery of biomarkers and development of models to predict prognosis of DILI are needed to timely distinguish severe DILI cases from self-limited ones
Common etiologies	
HMs and HDS	Rigorous cohort studies are imperative to evaluate the epidemiology, clinical features, and prognosis of HILI and HDS-DILI Methods and technology to identify single hepatotoxic ingredients or chemical within HMs and HDS is the cornerstone of promoting relevant study
ICIs	More basic research is required to reveal the underlying immune mechanism of ICI-related hepatotoxicity. Meanwhile, further real-world study shall improve the knowledge of epidemiology, clinical features, outcomes, and etc. in ICI-related hepatotoxicity in various post-market clinical settings. Moreover, rationale of ICI reintroduction after G3 hepatotoxicity need to be explained further by relevant studies
Therapeutic drug	Interventional RCT studies are needed to evaluate efficacy of specific drug on clinical outcomes of DILI

DILI drug-induced liver injury, *HDS* herbal and dietary supplement, *HILI* herb-induced liver injury, *HM* herbal medicine, *HLA* human leukocyte antigen, *ICI* immune checkpoint inhibitors, *RCT* randomized controlled trial

Future directions

Despite recent progress in the field of DILI, there still remains a large amount of unmet clinical needs. Future research should focus more but not only on proposed directions shown in Table 8. Of note, pharmacoepidemiologic studies, large prospective registries, cohort studies, and establishment of large DILI databases are the foundations on which relevant results can be translated.

Definitions of terminology

Intrinsic DILI

Intrinsic DILI is caused by the direct toxicity of a drug or its metabolites and is dose dependent. Liver injury can occur in individuals who reach a certain dose threshold or exposure level and is predictable.

Idiosyncratic DILI

iDILI occurs in a small proportion of people exposed to certain drugs and is widely considered dose-independent and unpredictable based on known mechanisms of action. iDILI is mainly associated with unique host factors such as metabolic and immune idiosyncrasies.

Indirect DILI

DILI caused by drugs that alter pre-existing liver diseases (e.g., chronic viral hepatitis or fatty liver disease) or host immune status, such as viral hepatitis reactivation caused by high-dose corticosteroids or certain monoclonal antibodies and immune-mediated liver injury caused by immune activation (e.g., ICI-induced liver injury, DI-ALH).

R ratio and new R ratio

R = (ALT/ULN)/(ALP/ULN); AST can be used as a substitute for ALT, if ALT data are unavailable. The new R ratio is calculated using the higher value of either ALT or AST.

Rechallenge

Re-exposure to the same suspect drug after recovery from DILI.

HBV reactivation

HBV reactivation is defined as HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive patients with an increase in HBV DNA ≥ 2 log IU/mL from baseline while receiving immunosuppressive or other associated risk medications, individuals with negative HBV DNA at baseline becoming positive, or HBsAg changing from negative to positive.

Hy's law

A case of Hy's law is defined as hepatocellular DILI with the following three criteria being met: (1) Serum ALT or AST ≥ 3 × ULN and TBil ≥ 2 × ULN; (2) No cholestasis (ALP ≥ 2 × ULN) at onset; (3) Exclusion of other reasons (e.g., viral hepatitis, massive alcohol intake) to explain the combination of increased ALT/AST and TBil levels.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12072-023-10633-7.

Acknowledgements The authors are grateful to Jiyao Wang (Zhongshan Hospital, Fudan University), Hui Zhuang (School of Basic Medical Sciences, Peking University), Dekai Qiu (Renji Hospital, Shanghai Jiaotong University School of Medicine), Chengwei Chen (the 905th Hospital of Chinese PLA Navy), Xiaoyuan Xu (First Hospital of Peking University), and Minde Zeng (Renji Hospital, Shanghai Jiaotong University School of Medicine) who served as advisors; Zijun Wang, Ling Wang, Hui Lan, Hui Liu, Hairong Zhang, Juanjuan Zhang, Yaolong Chen, Junxian Zhao, and Hongfeng He from Institute of Health Data Science, Lanzhou University who assisted with the methodologic process. We also wish to thank Yang Ding (Shengjin Hospital Affiliated to China Medical University), Wenjin Ding (Xinhua Hospital, Shanghai Jiaotong University School of Medicine), Yuecheng Yu (General Hospital of Chinese PLA East Command), Xiaozhong Wang (Fourth Affiliated Hospital of Xinjiang Medical University), Xiaoqing Liu (Beijing Union Hospital), Jiajun Liu (First Hospital Affiliated to Xiamen University), Yongguo Li (First Affiliated Hospital of Harbin Medical University), Jun Li (First Affiliated Hospital of Nanjing Medical University), Tinghong Li (Tianjin Third Center Hospital), Lei li (Beijing Youan Hospital Affiliated to Capital Medical University), Changqing Yang (Shanghai Tongji Hospital), Dongliang Yang (Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science & Technology), Li Yang (Shanghai Tongji Hospital), Yuan Yang (First Affiliated Hospital of Xian Jiaotong University), Zhengsheng Zou (Fifth Medical Center of Chinese PLA General Hospital), Xiaoen Xin (Qinghai Fourth People's Hospital), Jing Zhang (Beijing Youan Hospital), Lungeng Lu (Shanghai First People's Hospital), Kunyan Hao (81st Hospital of Chinese PLA), Yanqin Hao (First Hospital of Shanxi Medical University), Yuemin Nan (Third Hospital of Hebei Medical University), Yunsong Qian (Ningbo Second Hospital), Zuxiong Huang (Mengchao Hepatobiliary Hospital of Fujian Medical University), Haifang Cao (Qinghai Fourth People's Hospital), Zhen Peng (Henan People's Hospital), Qingchun Fu (Shanghai Public Health Clinical Center), Lei Fu (Xiangya Hospital of Zhongshan University), and Xiaoyu Wen (The First Bethune Hospital of Jilin University) for their contribution to the manuscript. This guideline was developed in collaboration with the Technology Committee on DILI Prevention and Management, Chinese Medical Biotechnology Association, and Study Group on Drug-Induced Liver Disease, Chinese Society of Hepatology, Chinese Medical Association. We give special thanks to Shiying Yu (Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science & Technology), Jiabo Wang (Capital Medical University), Guohong Deng (The Southwest Hospital of AMU), Kewei Sun (First Affiliated Hospital of Hunan University of

Chinese Medicine), Rong Sun (Second Hospital of Shandong University), Xiuhui Li (Beijing Youan Hospital, Capital Medical University), Zhimin Yang (Center for Drug Evaluation, National Medical Products Administration), Xiaohe Xiao (Fifth Medical Center of Chinese PLA General Hospital), Haibo Song (Center for Drug Evaluation, National Medical Products Administration), Yueqiu Gao (Shuguang Hospital, Shanghai University of Traditional Chinese Medicine), Li Zhang (Dongfang Hospital, Beijing University of Chinese Medicine), Shun Lu (Shanghai Chest Hospital), Jian Hou (Renji Hospital, Shanghai Jiaotong University School of Medicine), Jin Gu (Shanghai Pulmonary Hospital), Tao Han (People's Hospital of Nankai University), and Limei Zhao (Shengjin Hospital Affiliated to China Medical University) for their external review for the manuscript. The authors also thank Jing Li, Wei Zhong, Xiaohong Lei, and Aiping Cao for their great assistance in developing this document.

Author contributions All authors contributed to the conception and design of the document. All authors have read and approved the final manuscript.

Funding This work was supported by the National Key R&D Program of China (Grant number 2022YFC3502101), the Major Project of National Thirteenth Five Plan (Grant number 2017ZX09304016), and the National Natural Science Foundation of China (Grant numbers NSFC 81970513 and NSFC 82270619), all to Yimin Mao.

Data availability Not applicable.

Declarations

Conflict of interest Yimin Mao, Shiwu Ma, Chenghai Liu, Xiaoyan Liu, Minghua Su, Dongliang Li, Yiling Li, Gongying Chen, Jun Chen, Jinjun Chen, Jingmin Zhao, Xiaoyan Guo, Jieting Tang, Yuzheng Zhuge, Qing Xie, Wen Xie, Rongtao Lai, Dachuan Cai, Qingxian Cai, Yang Zhi and Xiaoyun Li have no relevant financial or non-financial interests to disclose.

Informed consent in studies with human subjects and animal studies This article does not contain any studies with human or animal subjects.

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