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REVIEW

Methods for causality assessment of idiosyncratic drug-induced liver injury

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Abstract

The diagnosis of idiosyncratic drug-induced liver injury (DILI) is a challenging task due to the lack of specific features or definitive diagnostic tools. A minimum of clinical and pharmacological information is required, together with laboratory and imaging tests to exclude other causes of liver injury. Several standardized methods have been developed to support clinical judgement and establish causality assessment, the most widely used being the Roussel Uclaf Causality Assessment Method—RUCAM—and structured Expert Opinion. More recently, an evidence-based, revised RUCAM, Electronic Causality Assessment Method—RECAM—has been developed and, although still a work in progress, may replace RUCAM scoring in the future. International collaborative networks and ongoing research efforts are key to advancing biomarker qualification and validation and developing new in vitro patient-based methods that will help improve DILI diagnosis and move towards a personalized medicine approach.

KEYWORDS
causality assessment methods, hepatotoxicity, idiosyncratic drug-induced liver injury, RECAM, RUCAM, structured expert opinion

1 | INTRODUCTION

Idiosyncratic drug-induced liver injury (DILI) is a host-dependent, unpredictable, multi-faceted liver disorder due to the use of drugs, herbal and dietary supplements (HDS) that, although relatively rare, on the order of 14–19 cases per 100 000 population/year, can progress to death or liver transplantation in 4%–10% of individuals, and become chronic in 8%–17%.[1]

Indeed, DILI is one of the most challenging liver diseases faced by hepatologists due to the myriads of drugs with hepatotoxic potential used in clinical practice and the growing concern of HDS hepatotoxicity in registries.[2–5] New immunotherapeutic agents

Abbreviations: ADRs, adverse drug reactions; CDS, Clinical Diagnostic Scale; DDW-J, Digestive Disease Week-Japan Scale; DILI, idiosyncratic drug-induced liver injury; DILI-CAT, Computer-Assisted DILI Causality Assessment Tool; DILIN, the US Drug-Induced Liver Injury Network; DLST, drug-induced lymphocyte stimulation test; HDS, herbal and dietary supplements; RECAM, Revised Electronic Causality Assessment Method; RECAM-J 2023, Japanese-adapted RECAM 2023; RUCAM, Roussel Uclaf Causality Assessment Method; WHO-UMC, World Health Organization Uppsala Monitoring Centre Causality Assessment.

including biologics, and especially immune checkpoint inhibitors, associated with immune-mediated adverse reactions including liver injury, are emerging forms of DILI that pose new challenges to physicians.[6]

Prospective DILI registries established over the past 30 years have proven invaluable in advancing the study of the epidemiology, phenotypic characterization, risk factor identification, and prognosis of DILI and have contributed to patient stratification and the establishment of a systematic DILI diagnostic approach. Moreover, the collection of serial biological samples has allowed genotypic characterization, biomarker development and deepens the knowledge of the underlying mechanisms in DILI.[7–9]

1.1 | Definition and recommendations for DILI causality assessment

To establish the likelihood of drug causality—to determine with reasonable confidence the strength of the association between the administration of a particular drug or HDS and the occurrence of the observed adverse outcome—each case of DILI requires an individualized, complete evaluation and relies on clinical acumen and the quality of the data provided to make a differential diagnosis.

There are a number of premises that need to be considered when assessing causality:

Correct diagnosis and causality assessment of DILI is essential. Unrecognized or delayed diagnosis of DILI may favour progression to death, liver transplantation or chronic liver injury. Therefore, accurate detection and diagnosis of DILI is critical for making important decisions, such as prompt withdrawal of otherwise effective medications or initiation of supportive care. In addition, accurate diagnosis and reporting of DILI cases helps to prevent unintentional rechallenge.[10] In fact, in a recent analysis of Spanish and Latin American DILI registries, failure to make an accurate diagnosis or to record it in the patient's medical history was the most common cause of patient re-exposure to the offending drug. Interestingly, self-medication against medical advice, mainly with HDS, accounted for the 10% of positive rechallenge episodes.[11]

However, a definitive diagnosis of DILI is generally not possible to make. The assessment of DILI can be challenging due to several characteristics. This complexity is compounded by a lack of awareness and incomplete understanding of the condition, similar to other rare diseases. It is known that DILI can mimic any acute or chronic liver disease, that the phenotypic expression in DILI is quite heterogeneous as drugs do not have a consistent signature, and that there is a lack of pathognomonic biochemical parameters, histopathological picture or imaging findings.[10] Although research into the discovery and qualification of DILI-specific biomarkers has yielded interesting results, these have not yet been fully translated into the clinic, making it very difficult to predict, diagnose and treat DILI.[12–14]

DILI diagnosis is further complicated by several confounding factors. Pre-existing liver disease or the underlying treated condition that may itself be associated with liver abnormalities complicates the diagnosis of hepatotoxicity.

The concomitant use of multiple drugs with overlapping temporal sequences and known hepatotoxic potential further confounds the clinical picture. In addition, compounds that are traditionally considered safe, such as over-the-counter, or illicit drugs, can contribute to the complexity of DILI diagnosis. Progression to acute liver failure, the need for liver transplantation, or even death, make diagnosis more urgent, but also more challenging.[15] Atypical presentations, such as drug-induced autoimmune-like hepatitis, or progression to chronicity, add another layer of difficulty to the diagnosis of DILI.[16]

The key to attributing causality of DILI is to collect accurate and complete information prospectively (it is difficult, if not impossible, to do so retrospectively). A thorough clinical and pharmacological history is a critical step in the evaluation of a hepatic event. If a drug or botanical compound is suspected, its hepatotoxic potential and signature should be evaluated. Nevertheless, data on the drug's risk of DILI are not always readily available or accessible. Several databases and applications have been created to compile information on the hepatotoxic potential and characteristics of drugs and HDS. 'LiverTox' is an open access authoritative website developed by Jay Hoofnagle, who was the driving force, with the support of various DILI experts (http://livertox.nih.gov), which provides comprehensive data on the hepatotoxic risk assessment of over 1000 drugs and 60 HDS derived from an extensive literature review of all published DILI cases over the past five decades.[17] Using this repository, Björnsson & Hoofnagle developed 'The likelihood score', that describes the likelihood of a given drug being associated with DILI, ranging from A to E. The score is based on the number of cases published in the literature, so it is more accurate for drugs that have

Key points

- Causality assessment methods provide a structured, objective and uniform approach for determining the likelihood of drug involvement in suspected idiosyncratic drug-induced liver injury (DILI) cases. Liver-specific scales should be used.
- The structured expert opinion process is the preferred approach for clinical drug development and cases with atypical DILI phenotypes.
- The Revised Electronic Causality Assessment Method is an evidence-based computerized scale and validated scoring system that reduces subjectivity and improves precision and is better than Roussel Uclaf Causality Assessment Method at the diagnostic extremes, although it is still a work on progress.
- A single instrument may not be able to capture all forms of DILI presentations unless there is a dynamic incorporation of drug-specific emerging data.

been used extensively over a longer period, and less accurate for more recently approved drugs and HDS that have not been widely used.[17]

Following this preliminary approach, the temporal relationship between drug use and liver injury onset, or the response to withdrawal of the suspected culprit drug must be assessed. In addition, one of the most important steps in DILI causality assessment is the exclusion of other causes of liver injury such as viral hepatitis, autoimmune liver disease, metabolic diseases such as hemochromatosis or Wilson's disease, metabolic dysfunction-asssociated steatotic liver disease, vascular disease, biliary obstruction, or tumours. Exclusion of these diseases requires imaging and blood tests including a full haematological and biochemical work-up, virological study, detection of autoantibodies and protein electrophoresis.[10]

Finally, some additional information can strengthen the diagnosis of DILI, such as the presence of hypersensitivity features (which occurs in less than 23% of patients),[8] compatible biopsy findings, or a positive rechallenge. The latter, can be considered the gold standard of DILI diagnosis, justified only when the drug is the only therapeutic option for a life-threatening condition.[18,19]

This step-by-step process of causality assessment described above has become the standard method for the evaluation of suspected DILI, which can be further supported by causality assessment methods.[20]

1.2 | Causality assessment methods to complement clinical judgement

A method for causality assessment in the context of DILI is defined as a systematic and unbiased framework for investigating putative DILI events. Several standardized decision systems have been developed for the assessment of adverse events, including liver-specific tools. The aim of these methods is to provide a standardized methodology to increase reliability and reproducibility in the assessment of DILI. These systems fall into three categories: expert judgement or global introspection, probabilistic approaches, and algorithms or scales.[21]

Despite the exploration of probabilistic methods in the context of hepatotoxicity, the need for accurate data derived from a large cohort of cases to model the probability distribution relevant to each parameter, coupled with the lack of methodological evaluation specific to hepatic adverse drug reactions (ADRs), limits the practicality of this modality in DILI scenarios.[22]

As there is no 'gold standard' for verifying DILI diagnosis, the validity of a diagnostic method—the ability to consistently discriminate between cases that are drug-related and those that are not—cannot be assessed. An expert opinion approach has been considered the gold-standard, although disagreements between experts have also questioned its validity.[23]

Another quality required of these instruments is reproducibility, which ensures an identical result regardless of who the user is or when the scale is used, in order to minimize subjective interpretations that depend on the quality of the data provided or the expertise of the rater. Therefore, well-defined criteria and a standardized minimum data set required to adequately assess causality in DILI are critical aspects that will lead to improved interobserver agreement (Figure 1). Indeed, causality assessment methods that rely on case-by-case information cannot distinguish valid from invalid cases, convert uncertainty into certainty, prove a drug-event relationship, or quantify a drug's contribution to the development of an adverse event, as the WHO rightly points out.[24] These methods cannot replace clinical judgement, but they can bring consistency to the diagnosis of DILI.

1.3 | General causality assessment methods

A recent review identified 21 eligible tools for assessing the causality of ADRs.[25] Among non-organ-specific systems, the Naranjo ADR Probability Scale and the World Health Organization (WHO)–Uppsala Monitoring Centre (UMC) Causality Assessment Criteria are the most frequently used methods for assessing causality in case reports (Table 1).[24,26]

The Naranjo scale is a general ADRs scale consisting of a simple questionnaire in which the sum of the results of 10 'yes' or 'no' items is translated into a probability score.[26] This method was designed for evaluation of predictable type A reaction in controlled trials and registration studies of new drugs, rather than in routine clinical practice. However, its simplicity has facilitated the generalization of its use, and even publications on DILI mention the probability results obtained with the Naranjo ADR Probability Scale.[27] Nevertheless, this scale has shown low sensitivity and reproducibility in the assessment of hepatotoxicity cases included in the Spanish DILI Registry, as it provides confusing criteria that leave room for individual interpretation and open questions that are not relevant to idiosyncratic DILI and is, therefore not recommended in this context.[28]

The WHO-UMC system, recommended by the Pharmacovigilance Program of India, provides 6 categories of likelihood, considering the basic evaluation criteria, including temporal relationship, biological plausibility and absence of other diseases or drugs, laboratory findings and de-challenge and re-challenge. Of note, the scale includes conditional/unclassified and unassessable/unclassifiable categories, which are applicable when additional information is either pending or lacking to assess the association (Table 1).[24]

Various studies have shown poor agreement between the two scales when assessing ADRs, which may indicate that the breadth of criteria provided by both scales allows for subjective interpretation that affects the final decision.[29]

1.4 | Organ-specific causality assessment methods in DILI

Several approaches to developing organ-specific methods for assessing causality in DILI have been published. One of the first was the

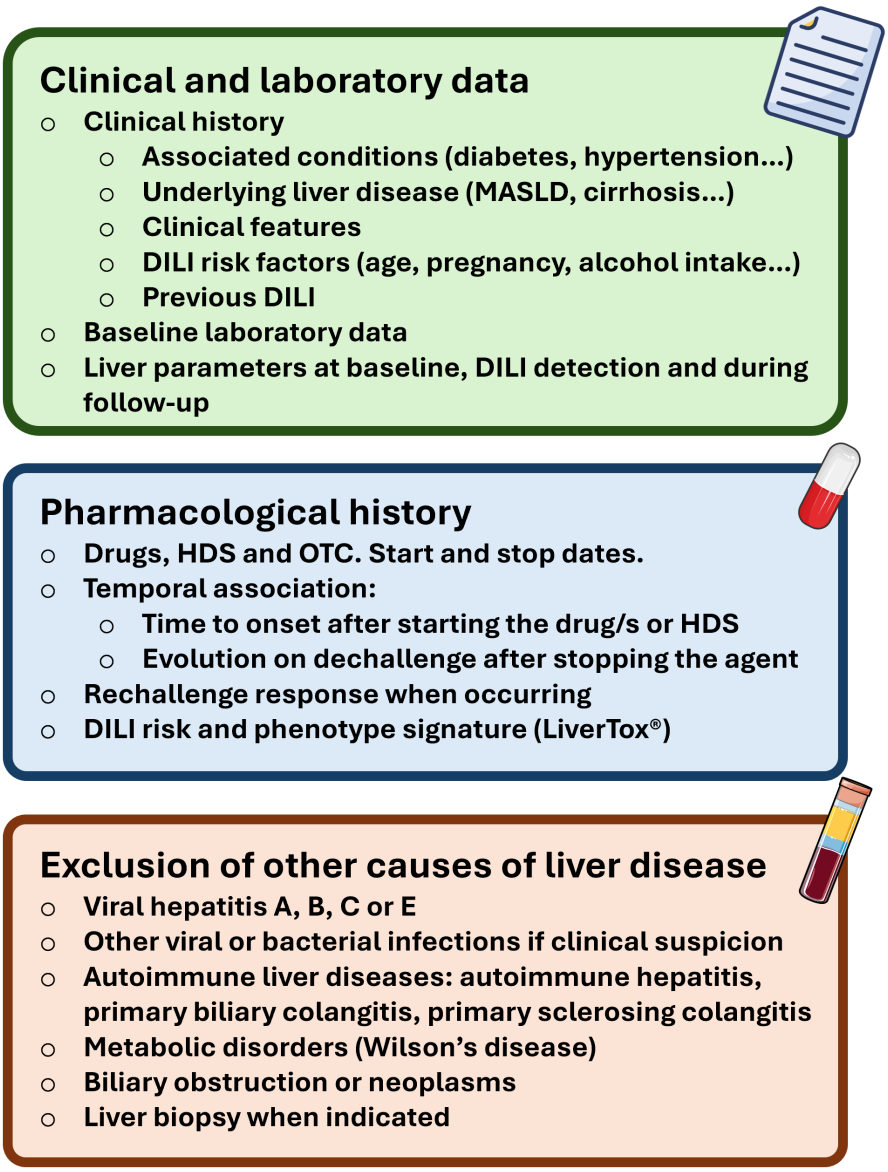

FIGURE 1 Minimum data set to be collected before applying causality assessment methods. DILI, drug-induced liver injury; HDS, herbal and dietary supplements; MASLD, metabolic dysfunction-associated steatotic liver disease; OTC, over-the-counter.

structured but complex Striker algorithm,[30] followed in the 1990s by the Roussel Uclaf causality assessment method (RUCAM), also known as the Council for International Medical Sciences Scale.[31–33] Other refinements have attempted to simplify, add new criteria, or adapt to country specificities, such as the Maria and Victorino or Clinical Diagnostic Scale (CDS),[34] the Computer-Assisted DILI Causality Assessment Tool (DILI-CAT)[35] and the Digestive Disease Week-Japan Scale (DDW-J).[36] More recently, the Revised Electronic Causality Assessment Method (RECAM)[37] has been launched (Figure 2).

The RUCAM scale involves weighted scoring of an event according to 7 distinct domains including the temporal relationship between exposure to a drug and the onset of liver injury and outcome after withdrawal (de-challenge), exclusion of other causes of liver injury, exposure to other drugs, risk factors such as sex, pregnancy or alcohol, previous evidence of adverse liver events induced by the suspected drug, and response to re-administration, if available. The sum of the scores (ranging from −10 to +14) translates into categories of probability of DILI (Table 2).[32] The reproducibility of the scale was evaluated by four experts in 50 suspected DILI cases, with agreement among two experts of 99%, 74% between three experts, although low agreement among four experts was reached (37%); and was further validated in 49 published DILI cases with positive re-challenge and 28 controls, showing a sensitivity of 86%, specificity of 89%, positive predictive value of 93%, and 78% of negative predictive value.[32,33] The RUCAM scale has been widely used for decades in the assessment of DILI in pre-clinical, clinical and investigational settings due to its advantages of improved validity, objectivity and higher reliability than clinical assessment. It has also been shown to be a good learning tool, providing a framework that systematizes the features to be considered for case ascertainment. However, disadvantages of the RUCAM scale include complexity and ambiguous instructions, arbitrary weighting of the criteria such as an overestimation of rechallenge, which is seldom done, lack of evidence-based risk factors, failure to consider ultra-short or long latency

TABLE 1 General adverse drug reactions causality assessment methods: the Naranjo Adverse Drug Reactions Probability Scale and the World Health Organization Uppsala Monitoring Centre Causality Assessment Criteria.

Naranjo ADR Probability Scale[26]		WHO-UMC causality assessment system[24]	
Assessment criteria	**Yes/no/unknown**	**Assessment criteria**	
Are there previous conclusive reports of this reaction?	+1/0/0	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary	Certain
Did the adverse event appear after the drug was given?	+2/−1/0	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required	Probable/likely
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1/0/0	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear	Possible
Did the adverse reaction reappear upon readministering the drug?	+2/−1/0	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations	Unlikely
Were there other possible causes for the reaction?	−1/+2/0	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination	Conditional/unclassified
Did the adverse reaction reappear upon administration of placebo?	-1/+1/0	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified	Unassessable/unclassifiable
Was the drug detected in the blood or other fluids in toxic concentrations?	+1/0/0		
Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose?	+1/0/0		
Did the patient have a similar reaction to the drug or a related agent in the past?	+1/0/0		
Was the adverse event confirmed by any other objective evidence?	+1/0/0		
Score	Definite ≥9 Probable 5–8 Possible 1–4 Doubtful ≤0		

Abbreviations: ADR, adverse drug reaction; UMC, Uppsala Monitoring Centre; WHO, World Health Organization.

periods for drugs with short or long half-lives, excessive penalty for concomitant hepatotoxic drugs, or omissions such as failure to consider liver histological findings.[20,39] In addition, it cannot discriminate between drugs with known hepatotoxic potential and the same temporal sequence, in patients with underlying liver disease, progression to fulminant liver failure, liver transplantation or death, or chronicity, or in atypical presentations, limiting causality assessment.[20] Advances in the identification and exclusion

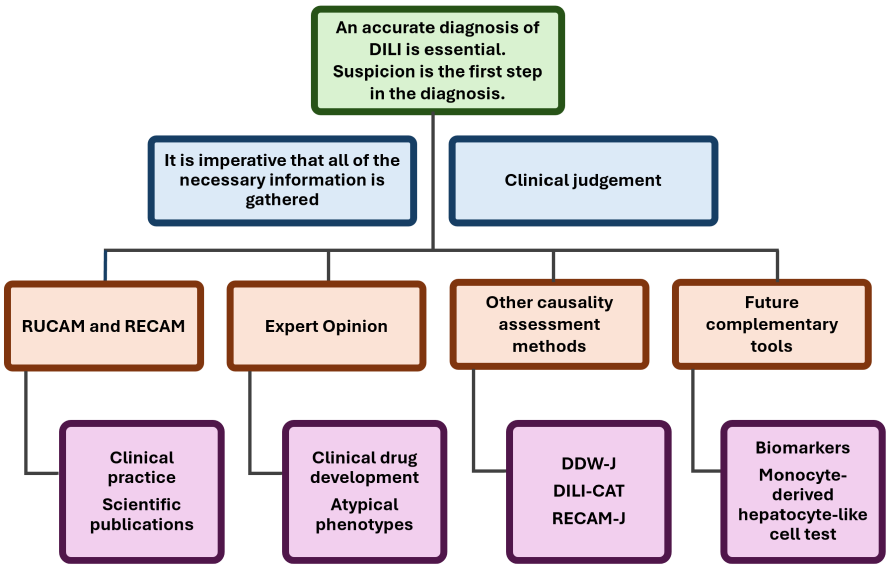

FIGURE 2 Approach to the diagnosis and causality assessment of idiosyncratic drug-induced liver injury. DILI, drug induced liver injury; DDW-J scale, Digestive Disease Week-Japan Scale; DILI-CAT, computer-assisted DILI causality assessment tool; RECAM, Revised Electronic Causality Assessment Method; RECAM-J 2023, A Japanese-adapted version of RECAM; RUCAM, Roussel Uclaf Causality Assessment Method.

TABLE 2 Organ-specific causality assessment methods in idiosyncratic drug-induced liver injury (DILI).

DILIN expert opinion process[38]	RUCAM[32]	RECAM[37]
Evidence for causality is 'highly unlikely' based on available information (<25%)	Time to onset Scoring differs according to the type of liver injury: hepatocellular versus cholestatic/mixed	Time to onset Domain 1a: onset after drug start and 1b: onset after drug stop
Causality is not supported by 'preponderance of evidence', but the possibility cannot be definitely excluded (25%–49%)	Dechallenge Scoring differs according to the type of liver injury: hepatocellular versus cholestatic/mixed	Domain 2: course dechallenge
Causality is supported by 'preponderance of evidence' implicating the drug, but the evidence cannot be considered definite or highly likely (50%–74%)	Exclusion of non-drug related causes	Domain 3: exclusion of competing diagnoses
Evidence for causality is 'clear and convincing' but not definite (75%–95%)	Previous information on hepatotoxicity (label and published cases)	Domain 4: DILI risk assessment based on the LiverTox likelihood categories
Liver injury is typical for the drug ('signature' or pattern of injury, timing of onset, recovery). Evidence for causality is 'beyond a reasonable doubt' (>95%)	Re-challenge	Domain 5: additional data, rechallenge, liver biopsy. Other causes: CMV, EBV, HSV, DRESS, SJS
	Risk factors Concomitant therapy	
Definite (>95%) Highly likely (75%–95%) Probable (50%–74%) Possible (25%–49%) Unlikely (<25%)	Sum of scores: >8 definite 6–8 probable 3–5 possible 1–2 unlikely <0 excluded	Sum of scores: ≥8: highly likely/high probable 7–4: probable 3 to −3: possible ≤−4: unlikely/excluded

Abbreviations: CMV, cytomegalovirus; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein–Barr virus; HSV, herpes simplex virus; RECAM, Revised Electronic Causality Assessment Method; RUCAM, Roussel Uclaf Causality Assessment Method; SJS, Stevens Johnsons Syndrome.

of other causes of acute liver disease over the last 30 years make RUCAM overdue.[39] Furthermore, RUCAM has never been developed or tested for use in HDS cases. These limitations may explain the inter- and intra-observer variability, even when used by DILI experts.[40] However, despite its ambiguity, RUCAM could be defined with clear guidelines to overcome ambiguity, and it can also be programmed in an application.

An 'updated RUCAM' was therefore developed to overcome some of the limitations of the original scale.[41] Modifications included new additional criteria, clarification of some ambiguous items, inclusion of the peculiarities of herbal-induced liver injury, and updating of the list of exclusion criteria, although a degree of subjectivity remains in the exclusion of these liver disorders.[41] Nevertheless, this modified scale retains risk factors of unclear value, included changes

that make it more complex and time-consuming, and it is not prospectively validated.

Several methods based on RUCAM have been published intending to improve this scale. The immunologists Maria and Victorino developed the CDS or Maria and Victorino Scale[34] and although the criteria have been simplified, the excessive weighting of extrahepatic or hypersensitivity features makes it less valid than RUCAM in DILI assessment.[42]

The DDW-J, a modification of the RUCAM scale, was developed in Japan.[36] Changes were made to the chronological criteria, the item of concomitant medications was removed, and an item on extrahepatic manifestations was included, where cases with positive drug-induced lymphocyte stimulation test (DLST) or eosinophilia scored positive.[43] The Japanese scale was shown to accurately diagnose DILI and was superior to the Maria and Victorino scale.[36] However, the DDW-J scale has not been generalized outside Japan because the DLST is not standardized worldwide and has not been shown to be consistent in diagnosing DILI due to all different types of drugs.[44]

The Pharmacovigilance-RUCAM is another improved algorithm; a standardized method based on RUCAM developed in the pharmacovigilance setting to support the assessment of suspected DILI by non-expert PV professionals in clinical trial records or electronic health records from a global PV database, but as the authors acknowledge, it needs prospective validation.[45] DILI-CAT is a data-driven diagnostic tool developed to characterize drug-specific signatures (latency, *R* value and AST/ALT ratio) in DILI adjudication using a robust computational framework.[35] The authors evaluated drug-specific DILI-phenotypes for amoxicillin-clavulanate, cefazolin (a culprit drug clustering in the US Drug-Induced Liver Injury Network [DILIN] registry), cyproterone acetate and *Polygonum multiflorum* using data from published case series, to develop DILI-CAT scores for each drug. However, phenotypic overlap between drugs precluded differentiation, as illustrated by amoxicillin-clavulanate and cefazolin.[35] As claimed by the authors, this approach could be of interest in the early development of new drugs, as has been shown for ximelagatran.[46]

Recently, the DILIN and the Spanish DILI Registry have collaborated to develop an objective, online and free computer program (https://dilirecam.com/) with a simplified scoring system, evidence-based criteria and refined weighting for wider applicability in the clinical setting, the RECAM. This method was redesigned using data from DILI cases due to single drugs included in these prospective registries and, where necessary, expert opinion and literature information.[37] The original RUCAM seven criteria were condensed into four domains, with a fifth domain added for additional data evaluation (when available) such as rechallenge, liver biopsy, specific atypical viral testing according to clinical context and presence of skin reactions with hypersensitivity features and organ involvement. The addition of histological data to the causality assessment process has been shown to reduce intermediate probabilities (more uncertain degrees of probability) and shift likelihood scores to higher or lower categories, thereby strengthening the causality assessment.[47]

Contrary to expectations, the distinction between hepatocellular and cholestatic/mixed injury was not necessary for latency (both from drug start & drug stop) and dechallenge scoring. The risk factors and concomitant drug items have been removed, an extended list of competing causes to be excluded has been added, and the drug DILI potential is now assessed using the Livertox® likelihood score.[48] Diagnostic testing is categorical and menu-driven to reduce interobserver variability.[37]

Unlike RUCAM, RECAMis evaluating one drug at a time without considering comedication, but a RECAM can be done for each drug. While this may result in different scores and degrees of likelihood, it is possible for some drugs to have the same score on the scale. This remains a limitation of current causality assessment methods. In addition, the potential for drug–drug interactions cannot be ignored. In the absence of a specific biomarker, attribution must be based on the drug combination.

As a novelty, the system displays red flag warnings when critical information is missing for the application of the scale, and the message urges the evaluator to obtain this data before proceeding or when a competing diagnosis is made and therefore the user should stop and consider the case excluded or unlikely. Indeed, with complete data at hand, this tool can be time-saving. Hayashi et al.[49] compared RECAM with RUCAM for correlation with expert opinion in 194 DILI cases from the Spanish and the DILIN registries. The area under the operator curves (AUC) for identifying at least a probable causality category was the same for RUCAM and RECAM, although RECAM showed better overall agreement with expert opinion (.62 vs. .56 weighted kappa, $p = .14$), and had greater sensitivity for extreme causality results. This semi-automated, computerized platform and validated scoring system covers a dynamic range of −6 to +20 points.[37]

A Japanese-adapted version of RECAM has recently been published with slight modifications in domains 3, 4 and 5.[50] As viral hepatitis is not an issue in Japan, missing viral data was common in retrospectively collected DILI cases in this country, and the sum of highly probable and probable cases reached only 206 out of 538 cases (38%). The authors propose a Japanese-adapted RECAM 2023 (RECAM-J 2023) without deduction of missing hepatitis virus markers. With this modification, the sum of highly probable and probable cases was increased to 421 (78%) and the RECAM-J 2023 was considered useful for the identification of suspected DILI in clinical practice.[50]

In a comparative study of the RUCAM and RECAM scales in five Chinese hospitals, where these scales were retrospectively applied to 481 DILI and 100 non-DILI patients, the overall agreement between the scales was low, with a weighted kappa of .54. Single conventional drugs were responsible for the injury in 63% of cases and HDS in the remaining 37% (*P. multiflorum* accounted for the 21.0% of HDS cases).[51] The authors found an overall better diagnostic performance of RECAM than RUCAM with a higher AUC (.947 (.926–.964) vs. .867 (.836–.893), $p = .0016$). Criteria responsible for the poorer agreement between the two scales were latency, hepatitis B exclusion criteria, and hepatotoxicity

information of the culprit drugs. In this study, the absence of anti-HBc IgM testing resulted in downgrading by the RECAM in patients with negative HBsAg. The authors suggested the need to refine the required criteria to exclude acute hepatitis B in areas endemic for hepatitis B such as Asia. RECAM and RUCAM were also applicable for not only conventional drugs but also herb-induced liver injury. Interestingly, in this study by Zhao et al.[51] both RECAM and RUCAM performed well in cases of correctly identified hepatotoxic herbs (*P. multiflorum*, Psoralen, Scutellariae radix and Cortex dictamni).

However, it is important to emphasize that the liver-specific scales do not capture the complexity of HDS-induced liver injury and are therefore not suitable for attributing causality in this context, as these products are frequently multi-ingredient and the toxic compound is often not identified or mislabelled.[3,5,52]

1.5 | Expert opinion-based methods

Expert judgement is the approach used to assess causality in large prospective DILI registries such as the Spanish, the Latin American, the European, or the DILIN.[9,38,53,54] Traditionally, the reliability of expert judgement is compromised by its inherent subjectivity and lack of uniformity, culminating in suboptimal reproducibility between experts.[21] In response to these limitations, the Spanish, LATINDILI and Pro-Euro DILI networks have combined the evaluation of suspected DILI cases by three experts and further assessment using causality scales, while the DILIN has developed a structured expert opinion process.[9,38,53,54] This protocol relies on the prospective evaluation of suspected DILI cases by expert hepatologists. The likelihood of assessment is articulated through a dual-faceted approach, using both a probabilistic percentage and a descriptive nomenclature[38] (Table 2). According to this scheme, events are classified as 'Definite' with a probability of more than 95% when the evidence is beyond a reasonable doubt; 'Highly Likely' with a probability of 75%–95% when the evidence of the drug as the cause of the liver toxicity is clear and convincing but not definitive; 'Probable' with a probability of 50% to 74% when the evidence supports the link between the drug and the liver injury; 'Possible' with a probability of 25% to 49%, with not conclusive evidence of DILI; 'Unlikely' with less than 25% of probability of DILI, with evidence of other causes of liver damage; and 'Not determinable' in cases with incomplete data.[23,38] Three experts evaluate the cases, and if there is complete agreement the results are accepted. However, in cases of disagreement, discrepancies are solved in a monthly teleconference, and if there is still no agreement, a vote is taken.[38]

When compared with RUCAM, the concordance between the two methods yielded a correlation coefficient of .42 and a low complete inter-rater agreement. Despite the demonstration of inter-observer variability with both instruments, the expert opinion approach resulted in superior inter-rater agreement and improved the likelihood score.[40] However, this method is hampered by subjectivity and limited reproducibility, making it unsuitable for clinical practice. The US DILIN Expert Opinion process has not been externally validated and requires expert judgement. However, it may be useful for investigational purposes, in the context of clinical trials, for HDS-induced liver injury, for specific DILI phenotypes and for the assessment of novel DILI cases.[55]

Finally, we summarize the information and recommendations regarding causality assessment methods for DILI diagnosis discussed in clinical practice guidelines and position papers in Table 3.

1.6 | DILI diagnostic biomarkers and 'in vitro' patient-based approaches

Research into DILI continues to be hampered by the lack of an objective, reliable laboratory tests that can reliably identify a specific drug or HDS as the cause of liver injury.[59]

International collaborative efforts such as the Safer and Faster Evidence-Based Translation consortium, followed by the Translational Safety Biomarker Pipeline, are enabling the development and implementation of novel safety biomarkers in clinical trials and early diagnosis of disease, although none of these have yet been shown to be DILI specific.[13,62] Recently, a tandem mass tag-based quantitative proteomic profiling identified FBP1, glutathione S-transferase A1, and leukocyte cell-derived chemotaxin 2 as potential serum biomarkers to discriminate acute DILI from acute non-DILI (AUC range: .65–.78). However, further technical and clinical validation of these promising biomarkers is required.[14]

All available genome-wide association studies have identified distinct HLA alleles that modulate the predisposition to DILI in association with specific drugs.[10,63] However, the rare occurrence of DILI in relation to a specific drug suggests that the positive predictive value of such associations is quite low. For example, the HLA-B*5701 genotype increases the risk of flucloxacillin-induced DILI by 80-fold, but it is estimated that only one in every 500 carriers of the genetic variant will develop liver injury after exposure to this antibiotic.[64] In fact, genomic biomarkers cannot predict an individual's risk of DILI before the drug is prescribed. In contrast, these genetic determinants confer a high negative predictive value, so that the absence of the specific polymorphism can be used to exclude the diagnosis of DILI, to differentiate between suspected culprit drugs taken at the same time, or for differential diagnosis with autoimmune hepatitis. Under this premise, the European Association for the Study of the Liver clinical practice guidelines recommend HLA genotyping only in clinical settings where it can assist in the diagnosis and management of hepatotoxicity.[10] In addition, the international DILI consortia have contributed to the construction of a polygenic risk score for amoxicillin-clavulanate susceptibility, which may also improve causality assessment.[65]

The development of an in vitro assay, MetaHeps®, using blood monocytes from the index patient differentiated to hepatocyte-like cells which exhibit increased cytotoxicity when cultured with the suspected drug, is an interesting patient-based approach to assess causality in idiosyncratic DILI.[66] While this test has shown promise

TABLE 3 Causality assessment methods listed and discussed in the latest Clinical Practice Guidelines and position papers in idiosyncratic drug-induced liver injury.

Causality assessment method	EASL clinical practice guideline[10]	ACG clinical guideline[56]	APASPL consensus guidelines[57]	ALEH position paper[58]	AASLD practice guidance[59]	Chinese guideline, CSH[60]
DILIN structured expert opinion,[38] 2009	Higher rates of inter-individual agreement and likelihood compared with RUCAM, although substantial inter-observer variability persists. It has not been externally validated but remains the mainstay for causality assessment of liver reactions that have not been fully characterized	Expert Opinion after a thorough evaluation for competing etiologies is the current gold standard. Not recommended for clinical practice since it is not widely available	Higher likelihood scores than the RUCAM scale in assessing causality. Major disadvantage: it has not been externally validated and hence, is not widely applicable.	NA	Advantages: it accounts for atypical cases, interrupted drug exposure, and liver histology in relationship to public literature. As useful as RUCAM, although rarely available in routine clinical practice.	Expert Opinion can account for different or rare-specific phenotypes of DILI. It overcomes some shortcoming of the RUCAM score but it is not externally validated and is not suitable for daily clinical practice because of its complex procedures.
RUCAM,[32] 1993	Cannot be used in 3%–24% cases due to inadequate information when evaluating retrospectively. Consistent application and ambiguities can be improved by agreeing criteria prior to its use. Value of risk factor domain is uncertain. Not widely used in clinical practice but used by most of studies. Provides a degree of objectivity. It can be improved.	Intended for use at the bedside or in clinic. Ambiguities on how to score certain sections of the RUCAM. Suboptimal retest reliability. Modest concordance with Expert Opinion.	Validated in events when DILI was suspected at onset and the final diagnosis was either DILI or other aetiology. Risk factor domain is controversial since it was not significantly different between the two groups. Its performance has been validated in DILI cases with positive re-challenge. American and European guidelines recommend the use of RUCAM as the preferred causality assessment method.	The most used DILI causality scale. It highlights the essential features for a DILI diagnosis. Also used for HDS and intoxicants. Limitations: No clear instructions for the scale; low diagnostic capacity when multiple drugs with same temporal relationship and when acute liver failure is one of the potential diagnoses.	Limitations: the relative weighting of its domain scores is not based on statistics or evidence. Additionally, consideration of alternative causes of liver injury may have been overlooked or unappreciated when the tools were first developed. There is little quality data to justify the inclusion of risk factors in RUCAM.	RUCAM frames guidance for the assessment of patients with suspected DILI In certain clinical scenarios (TCM/HDS-DILI, multiple suspected drugs, DILI with pre-existing liver disease and evaluation of hepatotoxicity in clinical trials of new drugs), RUCAM score may result in misdiagnosis.
RECAM,[37] 2022	NA	NA	NA	NA	RECAM is more rapid, standardized, objective, user-friendly, reproducible and reliable than RUCAM. Limitations: It has yet to be tested in other regions of the world apart from United States and Spain and it has not yet been tested in HDS cases. Its intra and inter-rater reliability needs to be determined.	Similar diagnostic efficacy to RUCAM but better precision and reliability because its objectivity and clarity. It demonstrated a better agreement with Expert Opinion and greater sensitivity for detecting patients in extreme likelihood categories. It requires external validation, and its reliability remains unknown in HDS DILI.

(Continues)

TABLE 3 (Continued)

Causality assessment method	EASL clinical practice guideline[10]	ACG clinical guideline[56]	APASPL consensus guidelines[57]	ALEH position paper[58]	AASLD practice guidance[59]	Chinese guideline, CSH[60]
Particularities of HDS or TCM as suspect agents in causality assessment	NA	Limitations: none of the scales have been developed and are not well suited to HDS. Significant variability in HDS ingredients (batch-to-batch), unlabelled ones, multiple components and contaminants may confound causality assessment.	Limitation: causality assessment methods were not developed for TCM/HDS. Labelled warning of hepatotoxicity usually does not exist on TCM/HDS. CFDA proposes to use the evidence-chained method, but it has not been validated and its effectiveness and practicability are not clear.[61]	NA	Special considerations: (i) HDS may contain ingredients not included (botanicals, chemicals pharmaceutical substances etc.) on the product label. (ii) HDS composition may change over time due to batch-to-batch variability. (iii) Latency to onset may be variable.	NA
Other comments	Decision tree or Bayesian model have not been formally validated.	Scoring systems should not be used as sole diagnostic tool but can be an adjunct to clinical impression to provide a framework to organize important areas of DILI history and tests, particularly for clinicians who do not see DILI frequently.	Assessment without a validated method leads to wide disagreements between assessors. Adoption of standardized causality assessment methods provides objectivity, accuracy and consistency to the assessment.	It is also expected to improve RUCAM, adding biomarkers or other criteria.	Limitations of non-expert Opinion methods: (i) multiple drugs in the same time frame may confound the assessment; (ii) an underlying chronic disease flare is not accounted for; (iii) they do not account evolving experience over time which add confidence to assessment.	Expert Opinion may be used in situations such as DILI studies, clinical trials of new drugs, or when the RUCAM score is not applicable.

Abbreviations: AASLD, American Association for the Study of the Liver; ACG, American College of Gastroenterology; ALEH, Latin American Association for the Study of the Liver; APASPL, Asia Pacific Association of Study of Liver; CFDA, China Food and Drug Administration; CSH, Chinese Society of Hepatology; DDW-J, Digestive-Disease-week Japan; DILIN, US Drug-Induced Liver Injury Network; EASL, European Association for the Study of the Liver; HDS, herbal and dietary supplements; MASLD, metabolic dysfunction-associated steatotic liver disease; RECAM, Revised Electronic Causality Assessment Method; RUCAM, Rousel Uclaf Causality Assessment Method; TCM, traditional Chinese medicine.

as a confirmatory assay in several studies, further refinement of the methodology and validation is required for its implementation in clinical practice.[59,67]

Research into mechanistic, genetic and epigenetic biomarkers, together with advances and requirements for the qualification of complex in vitro models such as human liver organoids that can capture patient characteristics and can recapitulate disease features, could be further incorporated into the causality assessment methods.

2 | CONCLUSIONS

While RECAM and expert opinion are currently the most reliable tools for assessing DILI causality, there is no single causality assessment tool that can capture the full heterogeneous presentation of DILI. The incorporation of drug-phenotype specificities and the discovery of new DILI biomarkers and laboratory diagnostic tools will further refine causality assessment in the future. Research is ongoing to overcome the limitations of current methods, while further validation of genetic testing is required before routine implementation can be recommended and we can move towards personalized medicine in DILI.

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REFERENCES

1. Andrade RJ, Chalasani NP, Björnsson ES, et al. Drug-induced liver injury. *Nat Rev Dis Primers*. 2019;5:1-22.
2. Navarro VJ, Khan I, Bjornsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. *Hepatology*. 2017;65(1):363-373.
3. Medina-Cáliz I, García-Cortés M, Gonzalez-Jimenez A, et al. Herbal and dietary supplement-induced liver injuries in the Spanish DILI registry. *Clin Gastroenterol Hepatol*. 2018;16(9):1495-1502.
4. Shen T, Liu Y, Shang J, et al. Incidence and etiology of drug-induced liver injury in mainland China. *Gastroenterology*. 2019;156(8):2230-2241.e11.
5. Bessone F, García-Cortés M, Medina-Caliz I, et al. Herbal and dietary supplements-induced liver injury in Latin America: experience from the LATINDILI network. *Clin Gastroenterol Hepatol*. 2022;20(3):e548-e563.
6. Pocurull A, Moreta MJ, Heitman D, et al. Anticancer drugs are the first cause of drug-induced liver injury in a reference hospital. *Liver Int*. 2024;44(2):286-292.
7. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. *Gastroenterology*. 2015;148(7):1340-1352.
8. Stephens C, Robles-Díaz M, Medina-Cáliz I, et al. Comprehensive analysis and insights gained from long-term experience of the Spanish DILI registry. *J Hepatol*. 2021;75(1):86-97.
9. Björnsson ES, Stephens C, Atallah E, et al. A new framework for advancing in drug-induced liver injury research. The prospective European DILI registry. *Liver Int*. 2023;43(1):115-126.
10. European Association for the Study of the Liver, Andrade RJ, Aithal GP, Bjornsson ES. EASL clinical practice guidelines: drug-induced liver injury. *J Hepatol*. 2019;70(6):1222-1261.
11. Pinazo-Bandera JM, Niu H, Alvarez-Alvarez I, et al. Rechallenge in idiosyncratic drug-induced liver injury: an analysis of cases in two large prospective registries according to existing definitions. *Pharmacol Res*. 2024;203:107183.
12. Church RJ, Watkins PB. Serum biomarkers of drug-induced liver injury: current status and future directions. *J Dig Dis*. 2019;20(1):2-10.
13. Cueto-Sanchez A, Niu H, Alvarez-Alvarez I, et al. Evaluation of diagnostic and prognostic candidate biomarkers in drug-induced liver injury vs. other forms of acute liver damage. *Br J Clin Pharmacol*. 2023;89(8):2497-2507.
14. Ravindra KC, Vaidya VS, Wang Z, et al. Tandem mass tag-based quantitative proteomic profiling identifies candidate serum biomarkers of drug-induced liver injury in humans. *Nat Commun*. 2023;14(1):1215.
15. Reuben A, Koch DG, Lee WM. Acute liver failure study G. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology*. 2010;52(6):2065-2076.
16. Andrade RJ, Aithal GP, de Boer YS, et al. Nomenclature, diagnosis and management of drug-induced autoimmune-like hepatitis (DI-ALH): an expert opinion meeting report. *J Hepatol*. 2023;79(3):853-866.
17. Bjornsson ES, Hoofnagle JH. Categorization of drugs implicated in causing liver injury: critical assessment based on published case reports. *Hepatology*. 2016;63(2):590-603.
18. Food and Drug Administration. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009. https://wwwfdagov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation
19. Hunt CM, Papay JI, Stanulovic V, Regev A. Drug rechallenge following drug-induced liver injury. *Hepatology*. 2017;66(2):646-654.
20. García-Cortés M, Stephens C, Lucena MI, Fernández-Castañer A, Andrade RJ. Causality assessment methods in drug induced liver injury: strengths and weaknesses. *J Hepatol*. 2011;55(3):683-691.
21. Arimone Y, Begaud B, Miremont-Salame G, et al. A new method for assessing drug causation provided agreement with experts' judgment. *J Clin Epidemiol*. 2006;59(3):308-314.
22. Zapater P, Such J, Perez-Mateo M, Horga JF. A new Poisson and Bayesian-based method to assign risk and causality in patients with suspected hepatic adverse drug reactions: a report

of two new cases of ticlopidine-induced hepatotoxicity. *Drug Saf*. 2002;25(10):735-750.
23. Hayashi PH. Drug-induced liver injury network causality assessment: criteria and experience in the United States. *Int J Mol Sci*. 2016;17(2):201.
24. World Health Organization, Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. 2013. https://www.who.int/publications/m/item/WHO-causality-assessment
25. Pradhan P, Lavallee M, Akinola S, et al. Causality assessment of adverse drug reaction: a narrative review to find the most exhaustive and easy-to-use tool in post-authorization settings. *J Appl Biomed*. 2023;21(2):59-66.
26. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245.
27. Garcia-Cortes M, Lucena MI, Andrade RJ, Camargo R, Alcantara R. Is the Naranjo probability scale accurate enough to ascertain causality in drug-induced hepatotoxicity? *Ann Pharmacother*. 2004;38(9):1540-1541.
28. Garcia-Cortes M, Lucena MI, Pachkoria K, et al. Evaluation of naranjo adverse drug reactions probability scale in causality assessment of drug-induced liver injury. *Aliment Pharmacol Ther*. 2008;27(9):780-789.
29. Shukla AK, Jhaj R, Misra S, Ahmed SN, Nanda M, Chaudhary D. Agreement between WHO-UMC causality scale and the Naranjo algorithm for causality assessment of adverse drug reactions. *J Family Med Prim Care*. 2021;10(9):3303-3308.
30. Striker B. *Drug-Induced Hepatic Injury*. 2nd ed.; Elsevier. 1992.
31. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol*. 1990;11(2):272-276.
32. Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol*. 1993;46(11):1323-1330.
33. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs—II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol*. 1993;46(11):1331-1336.
34. Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology*. 1997;26(3):664-669.
35. Tillmann HL, Suzuki A, Merz M, Hermann R, Rockey DC. A novel quantitative computer-assisted drug-induced liver injury causality assessment tool (DILI-CAT). *PLoS One*. 2022;17(9):e0271304.
36. Watanabe M, Shibuya A. Validity study of a new diagnostic scale for drug-induced liver injury in Japan-comparison with two previous scales. *Hepatol Res*. 2004;30(3):148-154.
37. Hayashi PH, Lucena MI, Fontana RJ, et al. A revised electronic version of RUCAM for the diagnosis of DILI. *Hepatology*. 2022;76(1):18-31.
38. Fontana RJ, Watkins PB, Bonkovsky HL, et al. Drug-induced liver injury network (DILIN) prospective study: rationale, design and conduct. *Drug Saf*. 2009;32(1):55-68.
39. Lewis JH. Causality assessment: which is best-expert opinion or RUCAM? *Clin Liver Dis (Hoboken)*. 2014;4(1):4-8.
40. Rockey DC, Seeff LB, Rochon J, et al. Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf causality assessment method. *Hepatology*. 2010;51(6):2117-2126.
41. Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. *Int J Mol Sci*. 2015;17(1):14.
42. Lucena MI, Camargo R, Andrade RJ, Perez-Sanchez CJ, Sanchez De La Cuesta F. Comparison of two clinical scales for causality assessment in hepatotoxicity. *Hepatology*. 2001;33(1):123-130.
43. Takikawa H, Takamori Y, Kumagi T, et al. Assessment of 287 Japanese cases of drug induced liver injury by the diagnostic scale of the international consensus meeting. *Hepatol Res*. 2003;27(3):192-195.
44. Whritenour J, Ko M, Zong Q, et al. Development of a modified lymphocyte transformation test for diagnosing drug-induced liver injury associated with an adaptive immune response. *J Immunotoxicol*. 2017;14(1):31-38.
45. Scalfaro E, Streefkerk HJ, Merz M, Meier C, Lewis D. Preliminary results of a novel algorithmic method aiming to support initial causality assessment of routine pharmacovigilance case reports for medication-induced liver injury: the PV-RUCAM. *Drug Saf*. 2017;40(8):715-727.
46. Hermann RP, Rockey DC, Suzuki A, Merz M, Tillmann HL. A novel phenotype-based drug-induced liver injury causality assessment tool (DILI-CAT) allows for signal confirmation in early drug development. *Aliment Pharmacol Ther*. 2022;55(8):1028-1037.
47. Ahmad J, Barnhart H, Bonacini M, et al. Value of liver biopsy in the diagnosis of drug-induced liver injury. *J Hepatol*. 2022;76(5):1070-1078.
48. National Institute of Diabetes and Digestive and Kidney Diseases. LiverTox. Clinical and Research Information on Drug-Induced Liver Injury. 2012. http://livertox.nih.gov
49. Hayashi PH, Lucena MI, Fontana RJ. RECAM: a new and improved, computerized causality assessment tool for DILI diagnosis. *Am J Gastroenterol*. 2022;117(9):1387-1389.
50. Tanaka A, Tsuji K, Komiyama Y, et al. RECAM-J 2023-validation and development of the Japanese version of RECAM for the diagnosis of drug-induced liver injury. *Hepatol Res*. 2024;54(6):503-512.
51. Zhao X, Wang Y, Lai R, et al. Validation of the revised electronic version of RUCAM for diagnosis of DILI in Chinese patients. *Hepatol Commun*. 2024;8(4):e0235.
52. Navarro V, Avula B, Khan I, et al. The contents of herbal and dietary supplements implicated in liver injury in the United States are frequently mislabeled. *Hepatol Commun*. 2019;3(6):792-794.
53. Andrade RJ, Lucena MI, Fernandez MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology*. 2005;129(2):512-521.
54. Bessone F, Hernandez N, Medina-Caliz I, et al. Drug-induced liver injury in Latin America: 10-year experience of the Latin American DILI (LATINDILI) network drug-induced liver injury in Latin America. *Clin Gastroenterol Hepatol*. 2024;S1542-3565(24)00605-0.
55. Hey-Hadavi J, Seekins D, Palmer M, et al. Overview of causality assessment for drug-induced liver injury (DILI) in clinical trials. *Drug Saf*. 2021;44(6):619-634.
56. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR. Practice parameters Committee of the American College of G. ACG clinical guideline: diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. *Am J Gastroenterol*. 2021;116(5):878-898.
57. Devarbhavi H, Aithal G, Treeprasertsuk S, et al. Drug-induced liver injury: Asia Pacific Association of Study of liver consensus guidelines. *Hepatol Int*. 2021;15(2):258-282.
58. Bessone F, Hernandez N, Tagle M, et al. Drug-induced liver injury: a management position paper from the Latin American Association for Study of the liver. *Ann Hepatol*. 2021;24:100321.
59. Fontana RJ, Liou I, Reuben A, et al. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. *Hepatology*. 2023;77(3):1036-1065.
60. Mao Y, Ma S, Liu C, et al. Chinese guideline for the diagnosis and treatment of drug-induced liver injury: an update. *Hepatol Int*. 2024;18(2):384-419.
61. Wang J, Ma Z, Niu M, et al. Evidence chain-based causality identification in herb-induced liver injury: exemplification of a well-known liver-restorative herb *Polygonum multiflorum*. *Front Med*. 2015;9(4):457-467.

62. Church RJ, Kullak-Ublick GA, Aubrecht J, et al. Candidate biomarkers for the diagnosis and prognosis of drug-induced liver injury: an international collaborative effort. *Hepatology*. 2019;69(2):760-773.
63. Daly AK. Genetics of drug-induced liver injury: current knowledge and future prospects. *Clin Transl Sci*. 2023;16(1):37-42.
64. Daly AK, Donaldson PT, Bhatnagar P, et al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet*. 2009;41(7):816-819.
65. Nicoletti P, Dellinger A, Li YJ, et al. Identification of reduced ERAP2 expression and a novel HLA allele as components of a risk score for susceptibility to liver injury due to amoxicillin-clavulanate. *Gastroenterology*. 2023;164(3):454-466.
66. Benesic A, Leitl A, Gerbes AL. Monocyte-derived hepatocyte-like cells for causality assessment of idiosyncratic drug-induced liver injury. *Gut*. 2016;65(9):1555-1563.
67. Benesic A, Rotter I, Dragoi D, et al. Development and validation of a test to identify drugs that cause idiosyncratic drug-induced liver injury. *Clin Gastroenterol Hepatol*. 2018;16(9):1488-1494.e5.

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