World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

Check for updates

Evolution of causality assessment in drug-induced liver injury: From RUCAM to RECAM and emerging Artificial Intelligence applications

Fatima Rani [1,*], Shubham Biswas [1] and Saurabh Krishna Verma [2]

[1] *Department of Pharmacology and Therapeutics, King George's Medical University, Lucknow, U.P, India.*
[2] *Department of Pharmacology, Sarojini Naidu Medical College, Agra, U.P, India.*

World Journal of Biology Pharmacy and Health Sciences, 2026, 27(01), 053–062

Publication history: Received on 02 June 2026; revised on 09 July 2026; accepted on 11 July 2026

Article DOI: https://doi.org/10.30574/wjbphs.2026.27.1.0384

Abstract

Drug-induced liver injury (DILI) remains one of the most challenging adverse drug reactions to diagnose because of its heterogeneous clinical presentation and the absence of a definitive diagnostic test. Accurate causality assessment is therefore essential for patient management, pharmacovigilance, and regulatory decision-making. Over the past four decades, causality assessment has evolved from subjective expert judgment and general adverse drug reaction algorithms to structured liver-specific methods. The introduction of the Roussel Uclaf Causality Assessment Method (RUCAM) in 1993 marked a significant milestone by providing the first standardized and quantitative algorithm for evaluating suspected DILI. Although RUCAM remains the most widely accepted and extensively validated causality assessment tool, its limitations, including manual scoring, inter-observer variability, and restricted compatibility with electronic health records, prompted the development of the Revised Electronic Causality Assessment Method (RECAM). RECAM incorporates clearer definitions, improved standardization, and electronic implementation to enhance reproducibility and facilitate integration into modern clinical practice. More recently, artificial intelligence (AI) has emerged as a promising adjunct for DILI assessment through predictive modelling, automated data extraction, and clinical decision support. However, these technologies require further validation and should complement rather than replace structured causality assessment and clinical expertise. This review summarizes the evolution of DILI causality assessment from RUCAM to RECAM and critically compares their strengths and limitations. Further, it discusses the emerging role of AI in improving diagnostic accuracy and advancing evidence-based DILI management.

Keywords: Drug-induced liver injury; Causality assessment; RUCAM; RECAM; Artificial intelligence; Pharmacovigilance.

1. Introduction

Drug-induced liver injury (DILI) is an uncommon but clinically significant adverse drug reaction. It is one of the leading causes of acute liver failure. Therefore, DILI is an important reason for drug withdrawal during post-marketing surveillance.[1,2] A wide range of prescription medications, over-the-counter drugs, herbal medicines, and dietary supplements have been implicated in DILI, making it a growing concern for clinicians and regulatory agencies.[3]

The diagnosis of DILI is challenging because there is no specific diagnostic test or validated biomarker that can reliably establish causality.[1] Instead, diagnosis depends on a careful evaluation of the temporal relationship between drug exposure and liver injury, exclusion of competing causes, and assessment of clinical improvement after drug withdrawal.[3,4] The variable latency period, diverse patterns of liver injury, and frequent use of multiple medications further complicate diagnosis and increase the risk of misclassification.[2]

* Corresponding author: Fatima Rani.

Accurate causality assessment is essential for appropriate patient management, prevention of re-exposure, pharmacovigilance, and regulatory decision-making. However, reliance on clinical judgment alone often results in considerable inter-observer variability. This limitation prompted the development of structured causality assessment methods to improve objectivity and consistency.[5] Early algorithms, including the Naranjo algorithm and the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system, provided standardized approaches for evaluating adverse drug reactions but were not specifically designed for liver injury.[5,6]

The introduction of the Roussel Uclaf Causality Assessment Method (RUCAM) marked a major advance by providing the first liver-specific, structured algorithm for DILI assessment.[7] Although RUCAM became the most widely accepted causality assessment tool, several limitations encouraged the development of the Revised Electronic Causality Assessment Method (RECAM), which offers improved standardization and electronic implementation.[8,9] More recently, artificial intelligence (AI) has emerged as a promising tool to support DILI diagnosis through predictive analytics and clinical decision support systems.[10] This review discusses the evolution of causality assessment in DILI, focusing on the transition from RUCAM to RECAM and the emerging role of AI in improving diagnostic accuracy.

2. Evolution of Causality Assessment Before RUCAM

Adverse drug reactions (ADRs) have long been recognized as an important cause of morbidity and mortality. However, establishing a causal relationship between a drug and an adverse event has always been challenging because many clinical manifestations are nonspecific and may result from underlying diseases or concomitant therapies. Early causality assessment relied largely on expert clinical judgment, which often varied among clinicians due to differences in experience and interpretation.[11]

To improve consistency, several structured algorithms were developed during the 1980s. The Naranjo algorithm was one of the first widely accepted tools for assessing the probability of ADRs. It used a questionnaire-based scoring system that incorporated factors such as temporal association, dechallenge, rechallenge, alternative causes, and previous reports of toxicity.[5] Around the same time, the WHO-UMC system introduced a qualitative approach that classified ADRs into categories such as certain, probable, possible, unlikely, conditional, and unassessable.[6] These methods improved the standardization of ADR assessment and became widely used in pharmacovigilance programs.

Despite their utility, general ADR algorithms showed important limitations when applied to DILI. Liver injury often presents with variable latency periods, diverse biochemical patterns, and multiple competing etiologies that cannot be adequately addressed by generic assessment tools.[12] Furthermore, factors such as exclusion of alternative liver diseases, interpretation of liver-specific laboratory findings, and assessment of concomitant hepatotoxic drugs require disease-specific expertise. Studies evaluating the performance of the Naranjo algorithm in DILI demonstrated poor agreement with expert opinion and limited diagnostic accuracy, emphasizing the need for a dedicated liver-specific causality assessment method.[13]

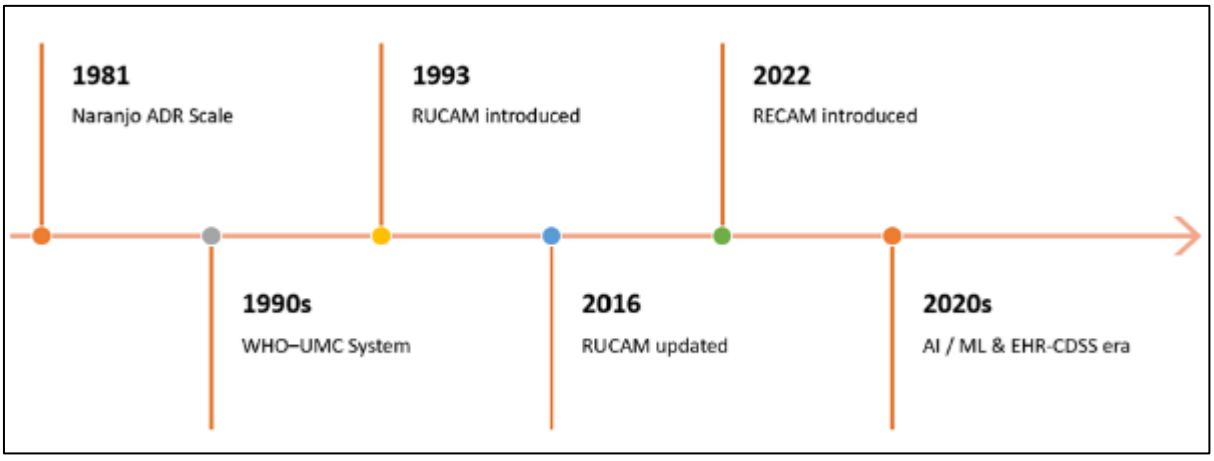

Figure 1 Evolution of causality assessment approaches in drug-induced liver injury. Naranjo and WHO–UMC are general adverse drug reaction causality assessment methods, whereas RUCAM and RECAM are liver-specific tools developed for the assessment of drug-induced liver injury.

Recognition of these limitations led to an international effort to develop a structured and quantitative algorithm specifically for DILI. This initiative resulted in the publication of the RUCAM in 1993, which introduced standardized criteria tailored to the unique clinical characteristics of liver injury.[7] RUCAM represented a significant shift from general ADR algorithms to disease-specific causality assessment and became the foundation for subsequent advances in DILI diagnosis. The evolution of causality assessment methods has been driven by advances in clinical knowledge and the need for standardized evaluation of suspected DILI. The evolution of causality assessment methods for suspected DILI is illustrated in **Figure 1**, and key characteristics of these methods are summarized in **Table 1**. These provide an overview of the transition from general ADR assessment tools to liver-specific algorithms.

Table 1 Evolution of Causality Assessment Methods for Drug-Induced Liver Injury.

Method	Type	Major Features	Limitations
Expert judgment	Clinical assessment	Flexible, clinician-driven	Subjective, poor reproducibility
Naranjo Algorithm	General ADR algorithm	Structured questionnaire	Not liver-specific
WHO-UMC System	General ADR algorithm	Global pharmacovigilance tool	Qualitative, limited utility in DILI
RUCAM	Liver-specific algorithm	Quantitative, standardized	Manual scoring, observer variability
RECAM	Electronic liver-specific algorithm	Standardized, electronic, improved reproducibility	Limited long-term validation

3. RUCAM: The Foundation of Liver-Specific Causality Assessment

3.1. Development and Principles of RUCAM

The absence of a reliable diagnostic test for drug-induced liver injury created an urgent need for a standardized method to establish causality. Before the early 1990s, clinicians relied primarily on expert judgment and general adverse drug reaction algorithms, both of which showed considerable variability and lacked specificity for liver injury.[5,6,11] Recognizing these limitations, an international panel of hepatologists, clinical pharmacologists, and regulatory experts developed the Roussel Uclaf Causality Assessment Method (RUCAM) through an international consensus process. First published in 1993, RUCAM became the first structured and liver-specific causality assessment tool for DILI.[7]

Unlike previous algorithms, RUCAM was designed specifically to account for the clinical characteristics of liver injury. It introduced a quantitative scoring system based on objective clinical and laboratory parameters, allowing clinicians to estimate the probability that a suspected drug was responsible for liver injury. This represented a major shift from subjective clinical judgment toward a more standardized and reproducible diagnostic approach.[7,15]

3.2. Components and Scoring System

RUCAM evaluates each suspected case using seven predefined domains that reflect the natural history of DILI. These include the time to onset after drug exposure, the clinical course following drug withdrawal, patient-related risk factors, concomitant medications, exclusion of alternative causes, previous evidence of hepatotoxicity associated with the suspected drug, and response to unintentional rechallenge.[7]

Each domain is assigned positive or negative points according to predefined criteria, and the cumulative score categorizes causality as excluded (≤0), unlikely (1–2), possible (3–5), probable (6–8), or highly probable (≥9).[14] Separate scoring systems are available for hepatocellular and cholestatic or mixed liver injury because these patterns differ in their clinical presentation and disease course.[16]

The structured design of RUCAM encourages systematic evaluation of every suspected case and reduces the likelihood that important clinical information will be overlooked. Consequently, it has become the most frequently used causality assessment method in DILI research, pharmacovigilance, and regulatory evaluation.[15,17]

3.3. Strengths of RUCAM

One of the greatest strengths of RUCAM is its transparency. The use of predefined scoring criteria allows different clinicians to evaluate cases using the same framework, thereby improving consistency compared with unstructured expert opinion.[15] Because each component contributes to the final score, the reasoning behind the causality assessment can be reviewed and reproduced by independent investigators.

RUCAM has also facilitated comparisons across clinical studies by providing a common diagnostic framework. Its widespread adoption has enabled standardized reporting of DILI cases in international registries, observational studies, and clinical trials.[18] Current clinical practice guidelines from major hepatology societies continue to recognize RUCAM as the most widely accepted structured method for assessing suspected DILI.[3,4]

The algorithm has undergone periodic refinement to improve clarity and standardization. The updated RUCAM published in 2016 clarified several definitions and strengthened recommendations for excluding alternative causes of liver injury.[14] These modifications improved consistency without altering the fundamental principles of the original scoring system.

3.4. Limitations and the Need for Revision

Despite its widespread use, several limitations have become evident over the past three decades. Accurate application of RUCAM requires comprehensive clinical information, including detailed medication histories, serial liver biochemistry, and thorough evaluation of competing liver diseases.[19] Incomplete documentation may reduce the reliability of the final score, particularly in retrospective studies.

Another challenge is the variability in interpreting certain domains, especially the exclusion of alternative causes and assessment of concomitant drugs. These components still require considerable clinical expertise and may contribute to inter-observer variability.[19] In addition, the increasing prevalence of polypharmacy, herbal medicine use, and complex multimorbidity has made causality assessment more difficult than when RUCAM was originally developed.[20]

Although RUCAM remains the most extensively validated liver-specific causality assessment method, its manual scoring process and limited compatibility with electronic health records restrict its routine implementation in modern clinical practice.[8] Recent studies have therefore focused on developing more standardized and electronically compatible approaches while preserving the evidence-based principles established by RUCAM.[9,21,22] These efforts ultimately led to the development of RECAM, which aims to improve reproducibility, simplify data interpretation, and facilitate digital integration.

4. RECAM: Advancing Causality Assessment in the Digital Era

4.1. Rationale for the Development of RECAM

Although RUCAM remains the most widely used causality assessment method for DILI, its application in routine clinical practice has highlighted several practical limitations. Manual scoring, dependence on complete clinical documentation, and variability in interpreting certain domains can affect reproducibility, particularly in patients with polypharmacy or multiple competing causes of liver injury.[19,20] These challenges, together with the increasing use of EHRs, created the need for a more standardized and electronically compatible causality assessment tool.

To address these limitations, investigators from the Drug-Induced Liver Injury Network (DILIN) developed the Revised Electronic Causality Assessment Method (RECAM). The revised algorithm was designed to improve consistency, simplify data interpretation, and facilitate electronic implementation while preserving the fundamental principles of structured causality assessment.[9,10]

4.2. Development and Key Features of RECAM

RECAM was developed using prospectively adjudicated DILI cases from the DILIN database. Unlike RUCAM, which was derived primarily through expert consensus, RECAM incorporated statistical analyses of a large, well-characterized clinical cohort to identify variables most strongly associated with DILI.[9] Several components of the original RUCAM were modified, while others were removed or redefined to improve objectivity and reduce ambiguity.

The revised algorithm simplifies the evaluation of alternative causes, provides clearer definitions for several clinical variables, and places greater emphasis on objective clinical evidence. It also minimizes reliance on subjective risk factors

that have limited predictive value. In addition, RECAM was specifically designed for computerized implementation, allowing automated calculations and reducing the possibility of manual scoring errors.[9,10]

An important advantage of RECAM is its compatibility with digital health systems. The structured format allows clinical information to be extracted more efficiently from electronic records, creating opportunities for integration with clinical decision support systems and future AI-assisted diagnostic platforms.[12]

4.3. Validation and Clinical Performance

Initial validation studies demonstrated that RECAM achieved good agreement with expert opinion and showed improved reproducibility compared with conventional manual assessment.[9] Subsequent external validation studies have further evaluated its performance in different populations.

A multicenter study from China demonstrated that the revised electronic algorithm could be successfully applied in routine clinical practice and supported its diagnostic utility in patients with suspected DILI.[21] Similarly, the Japanese RECAM-J study adapted and validated the algorithm for use in Japanese patients, demonstrating satisfactory diagnostic performance while emphasizing the importance of population-specific validation.[22]

Despite these encouraging findings, RECAM has not yet undergone the same degree of international validation as RUCAM. Most published studies have involved selected patient cohorts, and additional multicenter studies are needed to evaluate its performance across different ethnic groups, healthcare systems, and patterns of drug exposure.[21,22]

4.4. Current Role and Remaining Challenges

RECAM represents an important step toward modernizing causality assessment in DILI. Its electronic design, simplified scoring system, and improved standardization address several practical limitations of RUCAM and make it well suited for integration into contemporary clinical workflows.[9,10]

However, RECAM should currently be viewed as an evolution rather than a replacement for RUCAM. RUCAM continues to have the largest body of supporting evidence and remains the most widely accepted causality assessment method in clinical practice, regulatory evaluation, and published research.[15,18] Current hepatology guidelines also continue to recognize RUCAM as the standard structured algorithm for DILI assessment.[4,18]

Future studies should focus on prospective multicenter validation, evaluation in patients with complex polypharmacy and herbal medicine exposure, and integration with emerging biomarkers and artificial intelligence-based clinical decision support systems. These developments will determine whether RECAM can become the preferred causality assessment tool in routine clinical practice.

5. RUCAM versus RECAM: A Critical Comparison

The development of RECAM represents the latest milestone in the evolution of causality assessment for drug-induced liver injury. Although both RUCAM and RECAM share the common objective of providing a structured approach for evaluating suspected DILI, they differ considerably in their development methodology, scoring framework, and intended clinical application. Understanding these differences is important for selecting the most appropriate tool in both clinical practice and research.

RUCAM was developed through international expert consensus and introduced the first quantitative liver-specific algorithm for DILI assessment.[7] Its structured scoring system improved transparency and reproducibility compared with subjective clinical judgment and remains the most extensively studied causality assessment method. Over the past three decades, RUCAM has been widely adopted in clinical studies, pharmacovigilance programs, regulatory evaluations, and international guidelines, making it the current reference standard for structured DILI assessment.[15,18]

In contrast, RECAM was developed using prospectively adjudicated cases from the Drug-Induced Liver Injury Network and incorporated statistical analyses to identify variables that best predict causality.[9] The revised algorithm simplifies several assessment domains, provides clearer definitions for clinical variables, and was specifically designed for electronic implementation. These modifications aim to reduce inter-observer variability and improve reproducibility, particularly in routine clinical settings.[10]

Despite these improvements, RECAM has not yet accumulated the extensive body of evidence available for RUCAM. External validation studies from China and Japan have reported encouraging results, supporting its feasibility and diagnostic performance in different healthcare settings.[21,22] However, broader validation in diverse populations, including patients with polypharmacy, herbal medicine exposure, and pre-existing liver disease, remains necessary before RECAM can be considered a universal replacement for RUCAM.

Rather than viewing the two algorithms as competing tools, they should be regarded as complementary stages in the evolution of DILI causality assessment. RUCAM established the principles of standardized liver-specific evaluation and continues to provide a robust framework for clinical and regulatory practice. RECAM builds upon these principles by incorporating electronic compatibility, clearer definitions, and improved standardization, making it better suited for integration into modern healthcare systems. Future comparative studies, together with advances in biomarkers and digital health technologies, will determine the long-term role of each algorithm in routine clinical practice.

The principal differences between RUCAM and RECAM are summarized in **Table 2**.

Table 2 Comparative Features of RUCAM and RECAM for Causality Assessment in Drug-Induced Liver Injury

Feature	**RUCAM**	**RECAM**
Year introduced	1993	2022
Development	International expert consensus	DILIN-derived statistical model
Primary format	Manual scoring	Electronic/computerized scoring
Assessment approach	Quantitative algorithm	Revised quantitative algorithm
Clinical variables	Seven predefined domains	Revised and simplified domains
Alternative causes	Extensive evaluation	Simplified and standardized assessment
Polypharmacy	More challenging	Improved handling
Electronic compatibility	Limited	Designed for EHR integration
Reproducibility	Good but observer dependent	Improved standardization
Validation	Extensive international validation	Early external validation (China, Japan)
Current status	Most widely accepted and recommended	Promising emerging alternative

6. Emerging Applications of Artificial Intelligence in DILI Causality Assessment

Artificial intelligence (AI) has emerged as a promising tool for improving the diagnosis, prediction, and management of drug-induced liver injury. Rapid advances in machine learning, deep learning, and natural language processing have enabled the analysis of large clinical datasets that are difficult to interpret using conventional statistical methods. In DILI, AI has the potential to support clinicians by identifying patterns associated with hepatotoxicity, predicting causality, and improving the efficiency of pharmacovigilance systems.[23,24]

One of the earliest applications of AI has been the prediction of hepatotoxicity during drug discovery. Machine learning algorithms can analyze molecular structures, physicochemical properties, and toxicological data to identify compounds with a high risk of causing liver injury before clinical use.[25,26] More recently, graph neural networks and supervised chemical graph mining have demonstrated improved predictive performance by capturing complex structural relationships between drug molecules. These approaches may reduce late-stage drug failure and improve the safety profile of newly developed therapeutics.[27,28]

AI is also transforming clinical diagnosis by utilizing information from EHRs. Natural language processing (NLP) algorithms can extract relevant information from clinical notes, laboratory reports, and medication histories, enabling automated identification of patients with suspected DILI.[29] Such systems can improve case detection, facilitate pharmacovigilance reporting, and reduce the workload associated with manual chart review. Clinical decision support systems integrated into EHRs can further assist clinicians by generating alerts when patterns suggest possible DILI or when patients receive combinations of potentially hepatotoxic drugs.[12]

Another promising application is the integration of AI with structured causality assessment tools. Because RECAM was designed for electronic implementation, it provides an ideal framework for automated scoring using routinely collected clinical data.[9,10] AI algorithms could automatically retrieve relevant variables, calculate causality scores, identify missing information, and suggest alternative diagnoses. Such integration would improve consistency, reduce manual errors, and enable real-time clinical decision support. Nevertheless, clinical expertise remains essential because AI models depend on the quality of the underlying data and cannot fully account for complex clinical scenarios or atypical presentations.[24]

Recent studies have also explored AI models that predict the severity of DILI and identify patients at increased risk of poor outcomes.[30] When combined with emerging mechanistic biomarkers and structured causality algorithms, these models may facilitate earlier diagnosis, individualized risk stratification, and more effective patient management. However, most available AI models have been developed using retrospective datasets and require prospective multicenter validation before widespread clinical implementation.[23,24,30]

Rather than replacing clinical judgment, AI should be viewed as an adjunct to established causality assessment methods. The future of DILI diagnosis will likely depend on integrating structured algorithms such as RECAM with electronic health records, validated biomarkers, and explainable AI models that provide transparent and clinically interpretable recommendations. Such an approach has the potential to improve diagnostic accuracy while preserving the central role of clinician expertise in patient care.

7. Future Perspectives

The landscape of DILI causality assessment is evolving rapidly with advances in digital health technologies, biomarker discovery, and artificial intelligence. While RUCAM continues to serve as the most widely accepted structured algorithm, RECAM represents an important step toward a more standardized and electronically compatible approach. Future research should focus on validating RECAM across diverse populations, healthcare settings, and patterns of drug exposure to establish its generalizability and clinical utility.[9,21,22] Recent advances in digital health technologies have expanded the scope of DILI causality assessment beyond conventional algorithm-based approaches. Integration of EHRs, structured causality algorithms, clinical decision support systems (CDSS), and AI has the potential to improve diagnostic accuracy, facilitate earlier detection, and support standardized clinical decision-making. The conceptual workflow illustrating these complementary components is presented in **Figure 2**.

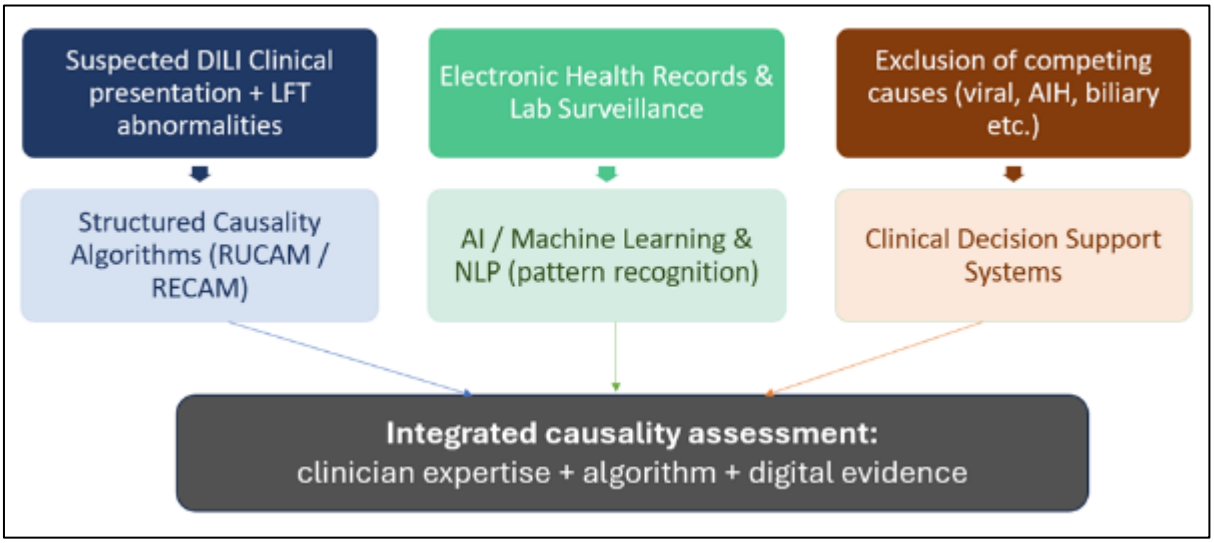

Figure 2 Integration of electronic health data, structured causality algorithms, and artificial intelligence in the diagnostic workflow of DILI.

The figure illustrates how electronic health records, laboratory surveillance, structured causality assessment tools (RUCAM/RECAM), clinical decision support systems, and artificial intelligence-based pattern recognition can be integrated to support comprehensive DILI causality assessment while complementing clinician expertise.

AI is expected to play an increasingly important role in the future of DILI diagnosis. Integration of AI with electronic health records and computerized causality assessment tools may enable automated identification of suspected DILI cases, real-time risk prediction, and decision support for clinicians.[23,29] Strengthening pharmacovigilance systems for herbal medicines and dietary supplements should remain a priority, particularly in countries where their use is widespread. Standardized causality assessment, improved adverse event reporting, and integration of digital health technologies may enhance the early recognition, monitoring, and reporting of herb-induced liver injury.[31] However, successful implementation will require high-quality datasets, transparent algorithms, external validation, and careful evaluation of ethical and regulatory considerations. AI should therefore be viewed as a tool that complements clinical expertise rather than replacing physician judgment.

The integration of validated biomarkers with structured causality assessment offers another promising direction. Mechanistic biomarkers such as microRNA-122, keratin-18, glutamate dehydrogenase, and high mobility group box-1 protein have shown potential for the early detection and prognostic assessment of DILI.[32–34] Although these biomarkers are not currently recommended for routine clinical practice, combining them with structured algorithms may improve diagnostic confidence, particularly in complex or equivocal cases.

Continued international collaboration will be essential to harmonize causality assessment methods and establish universally accepted diagnostic standards. Large prospective studies involving diverse patient populations are needed to compare existing algorithms, validate emerging technologies, and determine the most effective strategies for integrating clinical assessment, biomarkers, and AI into routine hepatology practice.

8. Conclusion

Accurate causality assessment remains the cornerstone of diagnosing drug-induced liver injury because no single clinical feature or laboratory test can definitively establish the diagnosis. Over the past four decades, causality assessment has evolved from subjective expert opinion and general adverse drug reaction algorithms to structured liver-specific methods. The introduction of RUCAM marked a major advance by providing a standardized and quantitative framework that improved consistency in clinical practice, pharmacovigilance, and research.

The development of RECAM reflects the next stage in this evolution. By incorporating clearer definitions, improved standardization, and electronic compatibility, RECAM addresses several practical limitations associated with manual causality assessment while maintaining the fundamental principles established by RUCAM. Although early validation studies have demonstrated encouraging results, broader prospective validation across different populations and healthcare systems is required before RECAM can be considered a universal alternative to RUCAM.

Artificial intelligence can further transform DILI causality assessment by enabling automated data extraction, predictive modelling, and integration with electronic health records. When combined with structured algorithms and emerging biomarkers, AI has the potential to improve diagnostic accuracy, facilitate early detection, and support individualized clinical decision-making. However, these technologies should complement rather than replace clinical expertise, as accurate diagnosis continues to require careful interpretation of patient history, laboratory findings, and exclusion of alternative causes.

In conclusion, the evolution from RUCAM to RECAM represents a significant step toward more objective, reproducible, and digitally integrated causality assessment. Continued collaboration among clinicians, researchers, regulatory agencies, and data scientists will be essential to refine existing algorithms, validate emerging technologies, and establish reliable, evidence-based strategies for the diagnosis and management of DILI.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Andrade RJ, Chalasani N, Björnsson ES, Suzuki A, Kullak-Ublick GA, Watkins PB, et al. Drug-induced liver injury. Nat Rev Dis Primers. 2019;5(1):58. doi:10.1038/s41572-019-0105-0.

[2] Hoofnagle JH, Björnsson ES. Drug-induced liver injury: types and phenotypes. N Engl J Med. 2019;381(3):264-273. doi:10.1056/NEJMra1816149.

[3] Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR. ACG clinical guideline: diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2021;116(5):878-898. doi:10.14309/ajg.0000000000001259.

[4] Fontana RJ, Liou I, Reuben A, Suzuki A, Fiel MI, Lee W, et al. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. Hepatology. 2023;77(3):1036-1065. doi:10.1002/hep.32689.

[5] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-245. doi:10.1038/clpt.1981.154.

[6] World Health Organization–Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment [Internet]. Uppsala (Sweden): WHO Collaborating Centre for International Drug Monitoring; 2018 [cited 2026 Jul 7]. Available from: https://who-umc.org/media/u4gjgxvv/who-umc-causality-assessment_new-logo.pdf

[7] 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. doi:10.1016/0895-4356(93)90101-6.

[8] Hayashi PH, Lucena MI, Fontana RJ, Björnsson ES, Aithal GP, Barnhart H, et al. A revised electronic version of RUCAM for the diagnosis of drug-induced liver injury. Hepatology. 2022;76(1):18-31. doi:10.1002/hep.32327.

[9] 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. doi:10.14309/ajg.0000000000001863.

[10] Li T, Kusko R, Thakkar S, Liu Z, Tong W. Predicting drug-induced liver injury with artificial intelligence—a minireview. In: Su TH, Kao JH, editors. *Artificial Intelligence, Machine Learning, and Deep Learning in Precision Medicine in Liver Diseases*. Cambridge (MA): Academic Press; 2023. p. 233-251. doi:10.1016/B978-0-323-99136-0.00012-X

[11] Meyboom RHB, Royer RJ. Causality classification in pharmacovigilance centres in the European Community. Pharmacoepidemiol Drug Saf. 1992;1:87-97.

[12] García-Cortés M, Lucena MI, Pachkoria K, Borraz Y, Hidalgo R, Andrade RJ. Evaluation of the Naranjo adverse drug reactions probability scale in causality assessment of drug-induced liver injury. Aliment Pharmacol Ther. 2008;27(9):780-789. doi:10.1111/j.1365-2036.2008.03655.x.

[13] Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. Drug Saf. 2008;31(1):21-37. doi:10.2165/00002018-200831010-00003.

[14] Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. Int J Mol Sci. 2016;17(1):14.

[15] Danan G, Teschke R. Drug-induced liver injury: why is the Roussel Uclaf Causality Assessment Method (RUCAM) still used 25 years after its launch? Drug Saf. 2018;41(8):735-743.

[16] Danan G, Teschke R. Roussel Uclaf Causality Assessment Method for drug-induced liver injury: present and future. Front Pharmacol. 2019;10:853.

[17] Teschke R, Danan G. Idiosyncratic drug-induced liver injury (DILI) and herb-induced liver injury (HILI): diagnostic algorithm based on the quantitative Roussel Uclaf Causality Assessment Method (RUCAM). Diagnostics (Basel). 2021;11(3):458.

[18] Devarbhavi H, Aithal G, Treeprasertsuk S, Takikawa H, Mao Y, Shasthry SM, et al. Drug-induced liver injury: Asia Pacific Association of Study of Liver consensus guidelines. Hepatol Int. 2021;15(2):258-282.

[19] Rockey DC, Seeff LB, Rochon J, Freston J, Chalasani N, Bonacini M, 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.

[20] Andrade RJ, Robles-Díaz M. Diagnostic and prognostic assessment of suspected drug-induced liver injury in clinical practice. Liver Int. 2020;40(1):6-17.

[21] Zhao X, Wang Y, Lai R, Wang X, Yu Y, Li M, et al. Validation of the revised electronic version of RUCAM for diagnosis of drug-induced liver injury in Chinese patients. Hepatol Commun. 2024;8(4):e0235.

[22] Tanaka A, Tsuji K, Komiyama Y, Tsuruya K, Kakisaka K, Tsutsui A, 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.

[23] Li T, Kusko R, Thakkar S, Liu Z, Tong W. Predicting drug-induced liver injury with artificial intelligence—a minireview. In: Su TH, Kao JH, editors. *Artificial Intelligence, Machine Learning, and Deep Learning in Precision Medicine in Liver Diseases*. Cambridge (MA): Academic Press; 2023. p. 233-251.

[24] Vall A, Sabnis Y, Shi J, Class R, Hochreiter S, Klambauer G. The promise of AI for DILI prediction. Front Artif Intell. 2021;4:638410. doi:10.3389/frai.2021.638410.

[25] Rao M, Nassiri V, Alhambra C, Snoeys J, Van Goethem F, Irrechukwu O, et al. AI/ML models to predict the severity of drug-induced liver injury for small molecules. Chem Res Toxicol. 2023;36(7):1129-1139. doi:10.1021/acs.chemrestox.3c00098.

[26] Ekins S, Lane TR, Urbina F, Puhl AC. *In silico* ADME/tox comes of age: twenty years later. Xenobiotica. 2024;54(7):352-358. doi:10.1080/00498254.2023.2245049.

[27] Lim S, Kim Y, Gu J, Lee S, Shin W, Kim S. Supervised chemical graph mining improves drug-induced liver injury prediction. iScience. 2023;26(1):105677. doi:10.1016/j.isci.2022.105677.

[28] Oh JH, Tannenbaum A, Deasy JO. Improved prediction of drug-induced liver injury literature using natural language processing and machine learning methods. Front Genet. 2023;14:1161047. doi:10.3389/fgene.2023.1161047.

[29] Ge J, Fontil V, Ackerman S, Pletcher MJ, Lai JC. Clinical decision support and electronic interventions to improve care quality in chronic liver diseases and cirrhosis. Hepatology. 2025;81(4):1353-1364. doi:10.1097/HEP.0000000000000583.

[30] Sridharan K, Balasundaram A, Kumar DT, Doss CGP. Evaluation of supervised machine learning algorithms and computational structural validation of single nucleotide polymorphisms related to acute liver injury with paracetamol. Curr Drug Metab. 2023;24(10):684-699. doi:10.2174/0113892002267867231101051310.

[31] Rani F, Biswas S, Mehrotra S, Singh S. Herbal and dietary supplement-induced hepatotoxicity: rethinking pharmacovigilance strategies in the Indian context. *J Popul Ther Clin Pharmacol.* 2025;32(9):559-567.

[32] Antoine DJ, Dear JW, Lewis PS, Platt V, Coyle J, Masson M, et al. Mechanistic biomarkers provide early and sensitive detection of acetaminophen-induced acute liver injury at first presentation to hospital. Hepatology. 2013;58(2):777-787. doi:10.1002/hep.26294.

[33] Church RJ, Kullak-Ublick GA, Aubrecht J, Bonkovsky HL, Chalasani N, Fontana RJ, et al. Candidate biomarkers for the diagnosis and prognosis of drug-induced liver injury: an international collaborative effort. Hepatology. 2019;69(2):760-773. doi:10.1002/hep.29802.

[34] Thulin P, Nordahl G, Gry M, Yimer G, Aklillu E, Makonnen E, et al. Keratin-18 and microRNA-122 complement alanine aminotransferase as novel safety biomarkers for drug-induced liver injury in two human cohorts. Liver Int. 2014;34(3):367-378. doi:10.1111/liv.12322.