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Archives of Gastroenterology Research Editorial

DILI, HILI, RUCAM Algorithm, and AI, the Artificial Intelligence: Provocative issues, Progress, and Proposals

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Abstract

Artificial Intelligence (AI) principles published in 1956 included the recommendation to use algorithms for solving complex processes. The creation of the Roussel Uclaf Causality Assessment Method (RUCAM) was published in 1993 with integration of an intelligent algorithm to solve issues of causality assessment in cases of complex suspected drug induced liver injury (DILI) cases. Other causality assessment methods (CAMs) published before the era of AI and RUCAM followed rather general principles without precise and valid algorithm. From 2014 to 2019, 46,266 RUCAM based DILI cases have been published worldwide. The future of RUCAM, now to be used as the updated RUCAM published in 2016 that also includes herb induced liver injury (HILI), is encouraging and will help determine DILI and HILI case features more accurately and allow for better data comparision among countries.

Keywords: Algorithm; Artificial Intelligence; AI; Liver injury; Drug induced liver injury; Herb induced liver injury; RUCAM

Artificial Intelligence (AI) techniques represent a fascinating, provocative, and challenging discipline, are pervasive and of global importance. The European Commission summarized the current state in a White Paper on AI issues released on 19 February 2020, discussing various AI concepts that revolutionized many complex processes [1]. Inital tools were algorithms, and more recently also software programmes are used with increasing tendency [1-3]. AI as a special term was created in 1956, when John McCarthy, a professor of Mathematics at Darmouth College, proposed a research project [2] with the objective to simplify complex processes. The principle was to provide tools enabling input of data into a black box that systematically evaluates incoming data and fosters output of clear results such as diagnosis in complex diseases [3]. At the time when AI concepts had been developed, the focus was on algorithms applied mostly manually prior to helpful software availability.

It was only in the early nineties that these provocative, innovative tools of AI principles including algorithms were introduced as a diagnostic algorithm to simplify complex processes assessing causality in drug induced liver injury (DILI). This led to the establishment of the Roussel Uclaf Causality Assessment Method (RUCAM) published in 1993 [4,5], with an update reported in 2016 that is now the preferred version to be used in future DILI cases and herb induced liver injury (HILI) cases [6]. Since then, RUCAM has an excellent run not only in the DILI community but also among the HILI experts [7-17] including those of the US who obviously accept now RUCAM as a valuable diagnostic algorithm and causality assessment method (CAM) for liver injury cases [18,19]. However, some criticism has been raised in Letters to the Editor [20-22] concerning the recent publication in Gastroenterology [19] with a concomitant rebuttal [23]. The high appreciation of the RUCAM algorithm is also substantiated by the 46,266 DILI cases all assessed for causality by RUCAM and published worldwide between 2014 and 2019 [24]. Such high case numbers were not achieved by other CAMs. Indeed, most of them are not suitable for assessing causality in DILI cases being subjective because they are based on a mere variable opinion, dependent on the previous experience of assessors, not validated with a gold standard, not liver specific, and finally not providing

causality gradings derived from scored key elements (Table 1) [6,19,25,26]. Due to these weaknesses, most of the other CAMs will likely not survive the next few years. Additional information on RUCAM was provided in other publications [27,28], associated with the encouragement to substantially improve the reporting of RUCAM based DILI cases in the future and additional recommendations to strictly adhere to the instructions outlined in the updated RUCAM and, in particular, to follow a prospective study design to ensure data completeness and reliable high causality gradings [6].

Clearly defined core elements **Individually scored items**	**RUCAM**	**MV**	**TKK**	**DILIN**	**Expert Opinion**	**Naranjo**	**WHO**
• Worldwide use for assessing causality in liver injury by drugs	+	o	o	o	o	o	o
• Time frame of latency period	+	+	?	?	o	o	o
Scored item	+	+	o	o	o	o	o
• Time frame of dechallenge	+	+	?	?	o	o	o
Scored item	+	+	o	o	o	o	o
• Recurrent ALT or ALP increase	+	o	o	?	o	o	o
Scored item	+	o	o	o	o	o	o
• Risk factors	+	o	o	?	o	o	o
Scored items	+	o	o	o	o	o	o
• All comedications	+	o	o	?	o	+	o
Scored items	+	o	o	o	o	+	o
• Individual comedication	+	o	o	?	o	o	o
Scored item	+	o	o	o	o	o	o
• Exclusion of alternative causes	+	+	o	?	o	o	o
Scored items	+	+	o	o	o	o	o
• Markers of HAV, HBV, HCV, HEV	+	o	o	?	o	o	o
Scored items	+	o	o	o	o	o	o
• Markers of CMV, EBV, HSV, VZV	+	o	o	?	o	o	o
Scored items	+	o	o	o	o	o	o
• Cardiac hepatopathy	+	+	o	?	o	o	o
Scored item	+	?	o	o	o	o	o

• Liver and biliary tract imaging	+	+	o	?	o	o	o
Scored item	+	?	o	o	o	o	o
• Doppler sonography of liver vessels	+	o	o	?	o	o	o
Scored item	+	o	o	o	o	o	o
• Prior known hepatotoxicity of drug	+	+	o	?	o	+	o
Scored item	+	+	o	o	o	+	o
• Unintentional reexposure	+	+	o	?	o	+	o
Scored item	+	+	o	o	o	+	o
• Laboratory hepatotoxicity criteria	+	+	o	+	o	o	o
• Laboratory hepatotoxicity pattern	+	+	+	?	o	o	o
• Hepatotoxicity specific method	+	+	+	+	o	o	o
• Structured, liver related method	+	+	+	o	o	o	o
• Quantitative, liver related method	+	+	+	o	o	o	o
• Validated method (gold standard)	+	o	o	o	o	o	o

Core elements of the updated RUCAM as compared with other CAMs, which are actualized and adapted from a previous report [6]. References and additional details were published previously [6,25]. Considered are RUCAM, the MV scale from the report of Maria and Victorino, the TKK scale named after the first three authors Takikawa, Takamori, Kumagi et al., the DILIN method of the Drug Induced Liver Injury Network, the unspecified expert opinion-based method also known as global introspection method, the Naranjo scale based on the report of Naranjo et al., and the WHO method from the WHO database. The symbol "+" shows that this specific item is published, and the symbol "o" indicates lacking publication, whereas the symbol "?" refers to uncertain documentation.

Abbreviations: ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HEV: Hepatitis E Virus; HSV: Herpes Simplex Virus; RUCAM: Roussel Uclaf Causality Assessment Method); VZV: Varicella Zoster Virus

Table 1: Core elements of the updated RUCAM as compared with other causality assessment methods in use for drug induced liver injury.

The value of RUCAM algorithm can be traced back to its remarkable specificities (Table 2) [4-6,25-28]. RUCAM was the first method ever clearly defining DILI characteristics including liver injury pattern, liver test (LT) thresholds, and re-exposure criteria [4,5]. RUCAM is objective, structured, validated, quantitative, transparent, user friendly, and specifically designed for liver injury by assessing liver injury elements, for which individual scores are attributed [6]. Authors used RUCAM smoothly in their 46,266 DILI cases and problems were not reported [24], confirming once again its user-friendly use [6].

RUCAM specificities
Basic features
• Validated method (gold standard) based on cases with positive reexposure test results, providing thereby a robust CAM
• Worldwide use with 46,266 DILI cases assessed by RUCAM published 2014-2019, outperforming thereby any other CAM
• Assesses causality in DILI and HILI cases perfectly and reproducibility
• A typical intelligent diagnostic algorithm in line with artificial intelligence (AI) concepts
• A diagnostic algorithm for objective, robust causality assessment
• Assessment is user friendly, cost effective with results available in time and without needing expert rounds that often provide subjective and fragile, arbitrary opinions based on own experience, a method that cannot be validated alone by definition
• Transparency of case data and clear result presentation
• Suitable for reevaluation by peers and any of other interested parties such as national regulatory agencies international registries, and pharma companies
• Mandatory application for DILI cases if to be used for establishing new robust diagnostic biomarkers
• High causality gradings with complete data
• With prospective case data collection best results obtainable
Clearly defined key elements
Individually scored elements
• Time frame of latency period Scored key element
• Time frame of dechallenge Scored key element
• Recurrent ALT or ALP increase Scored key elements
• Risk factors Scored key element
• Individual comedications Scored key elements
• Exclusion of alternative causes Scored key elements
• Markers of HAV, HBV, HCV, HEV Scored key elements
• Markers of CMV, EBV, HSV, VZV Scored key elements
• Cardiac hepatopathy Scored key element
• Liver and biliary tract imaging Scored key elements
• Doppler sonography of liver vessels Scored key element
• Prior known hepatotoxicity of drug Scored key element
• Unintentional reexposure Scored key element
Other important specificities
• Laboratory based hepatotoxicity criteria
• Laboratory based hepatotoxicity pattern

• Hepatotoxicity specific method
• Structured, liver related method
• Quantitative, liver related method, based on scored key elements
Abbreviations: AI: Artificial Intelligence; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; CAM: Causality Assessment Method; CMV: Cytomegalovirus; DILI, Drug Induced Liver Injury; EBV: Epstein Barr Virus; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HEV: Hepatitis E Virus; HILI: Herb Induced Liver Injury; HSV: Herpes Simplex Virus; RUCAM, Roussel Uclaf Causality Assessment Method; VZV: Varicella Zoster Virus.

Table 2: Summarized characteristics of RUCAM.

RUCAM is a quantitative diagnostic algorithm coupled to a scoring system that includes seven key elements individually scored, which by summing provide a final score and causality grading: score ≤0, excluded causality; 1-2, unlikely; 3-5, possible; 6-8, probable; ≥9, highly probable [6]. For future DILI and HILI case characterization, only cohorts of cases with probable or highly probable causality gradings should be included in studies.

Based on thorough case analyses, three types of liver injury pattern emerged that showed striking differences of their clinical features and courses, with focus on challenge, dechallenge, and re-exposure characteristics [4-6]. Using results from laboratory analyses of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) rather than from liver histology, these three types were classified as hepatocellular injury, cholestatic liver injury, and mixed liver injury. Due to the variability of their clinical features, specific key items and individual scores had to be defined for each of the three liver injury types. Subsequent analyses led to the conclusion that for causality assessment, only two instead of three RUCAM versions are necessary, one for the hepatocellular injury and the other one for the cholestatic liver injury and the mixed liver injury with its predominant cholestatic features as outlined earlier [4-6].

In line with recommendations presented in the updated RUCAM, liver injury is defined by increased serum activities of liver tests (LTs) with the following thresholds [6]: ALT of at least 5 x ULN (upper limit of normal) and/or of alkaline phosphatase (ALP) of at least 2 x ULN provided ALP is of hepatic origin, both best assessed simultaneously on the day of first presentation of suspected liver as outlined in 2016 [6]. In the original RUCAM of 1993, ALT thresholds of 2 x ULN were lower [4,5] but these values should not be used anymore to ensure exclusion of cases reflecting unspecific, clinically not relevant liver injury like liver adaptation, a more frequent cause of liver injury such as nonalcoholic steatohepatitis (NASH), or simple LT abnormality [6]. These current ALT and ALP threshold values of 2016 [6] are also considered as relevant in China [29]. For sake of comparability, in future publications of DILI and HILI, these thresholds should be used and mentioned in the method section. In fact, actual threshold information is often lacking in DILI and HILI publications.

Another specificity of the RUCAM algorithm is the inclusion of results from unintentional re-exposure tests, but prerequisite for case inclusion is the application of strict criteria before and during re-exposures [6]. A positive re-exposure test result is a hallmark of DILI and HILI and recognized by a maximum achievable score of 3 in RUCAM. Clearly, re-exposure test is unintentional since intentional test is unethical due to high risks of severe outcome of liver injury. Results of re-exposure tests using defined criteria have rarely been reported in the HILI cases [6]. However, high causality gradings in DILI are easily achievable without the need of re-challenge [24], but claimed positive re-exposure test results from re-exposures have rarely been confirmed following reassessment due to absence of strict criteria [30,31]. For instance, among 34 HILI cases with initially reported positive re-exposure tests, 61.8% of the cases actually fulfilled established test criteria, with negative tests in 17.6% and uninterpretable tests in 20.6% of the cases [31].

RUCAM algorithm considers alternative causes in a transparent approach [6]. This is needed because many published DILI or HILI cases are not true DILI or HILI but such cases could be attributed to alternative causes [24,32-35]. The same issues occurred in cohorts with inclusion of true HILI cases and other liver diseases unrelated to herbal use but due to alternative causes that led inevitably to wrong descriptions of HILI features and conclusions [32], flaws also described for cohorts of suspected DILI but again with supporting evidence of alternative causes [24,33-35].

There are no valid diagnostic biomarkers perhaps with the exception of few drugs and herbs [36,37], which could have assisted RUCAM based DILI and HILI cases, due to a tricky dilemma after EMA correctly and officially

retracted its Letter of Support as external studies had been misconducted [36]. Clearly, new biomarkers must have been validated by RUCAM based DILI cases [24,28,36,37].

Based on current knowledge and experience, proposals have been made to improve evaluations using the updated RUCAM algorithm [28], in line with suggestions for improved case management by RUCAM algorithm (Table 3). Substantial progress is evident by searching for automatic RUCAM algorithms in DILI using electronic medical records (EMRs) and which should be encouraged [28]. The incorporation of the updated RUCAM in an electronic program would accelerate the evaluation process of large case numbers and likely reduces interrater variability. This approach was successful [28], with a high agreement between the automatized RUCAM and manual RUCAM scoring [38]. Another attempt to build a RUCAM based automated algorithm to be used in pharmacovigilance [39] appeared promising [28].

RUCAM has an excellent run internationally in assessing causality for DILI cases, attributed to its well accepted use worldwide and outperforming over other non-RUCAM CAMs. Quality of RUCAM based DILI cases is good but not optimal in some cases. Therefore, in future studies the following points should be considered:
1. Recommendations as outlined in the updated RUCAM should strictly be followed when assessing DILI cases. These include prospective study design, adherence to LT thresholds, laboratory based case classification as hepatocellular injury or cholestatic injury, and application of the criteria for assessing cases with an unintentional reexposure. For case presentation, DILI cohorts must be separated from HILI cohorts, the use of the updated RUCAM should be mentioned. Combined application of RUCAM with other CAMs is discouraged. RUCAM based causality gradings must be attributed to each DILI case, and for final evaluation characterization and decision only cases with a probable or highly probable causality gradings should be taken into consideration.
2. Regulatory causality assessments are problematic in most DILI cases due to lacking use of a robust CAM such as RUCAM. Manufacturers and physicians that intend submitting spontaneous reports of assumed DILI to regulatory agencies are well advised to attach a RUCAM sheet with all relevant case data, scores of each key data element, and the final score with a causality grading. This allows regulatory reassessments and fair discussions with the stakeholders, preventing premature regulatory decision going public, potential loss of regulatory reputation, fruitless discussions in scientific journals, and court hearings.
3. The DILI community will lose information on DILI characteristics, if DILI case evaluations do not include the use of a robust CAM such as RUCAM. These DILI cases are without scientific value and waste of time and energy of the authors, aside from financial aspects if studies were supported by Governmental funds gathered from taxpayers.
4. The recommendations listed above should be included in national guidelines on diagnosis of DILI. This will ensure comparability of DILI case features among various countries.
5. Encouraged are papers on DILI and HILI of excellent quality with high RUCAM based causality gradings to be submitted to journals including Archives of Gastroenterology Research.

Table 3: Proposals for improved case management by RUCAM algorithm.

In conclusion, in accordance with IA concepts to use algorithms for solving issues in complex processes, RUCAM incorporated in 1993 a diagnostic algorithm to provide a robust tool for causality assessment in cases of DILI, known as complex diseases. In retrospect, RUCAM is indeed an intelligent algorithm closely related to the principles of artificial intelligence. With 46,266 RUCAM based DILI cases published, RUCAM is now the most commonly used diagnostic algorithm with a better worldwide performance compared with non-RUCAM methods.

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Conflict of interests

The author declares that he has no conflict of interests regarding this invited editorial.

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