A concept for causality assessment and causal inference of adverse events cases

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Dear Editor,

Causality assessment of adverse drug events is essential in pharmacovigilance to assess the relationship between the medicine and the event.[1,2] Regulatory authorities recommend using standardized methods for causality assessment.[3,4] The World Health Organization-Uppsala Monitoring Center (WHO-UMC) system offers generalized criteria for establishing causal relationships.[3] In contrast, the Roussel Uclaf Causality Assessment Method (RUCAM) provides a specialized system to assess Drug-Induced Liver Injury (DILI) cases. We systematically reviewed the literature and verified that these systems are among the best tools currently available for signal detection and causality assessment. In 2020, the Council for International Organizations of Medical Sciences (CIOMS) considered the RUCAM a gold standard for DILI causality assessment.[5] Both causality assessment criteria apply to the case report by Kassid *et al.*; they reported a case of flutamide-induced hepatotoxicity in a 75-year-old Iraqi male with prostatic adenocarcinoma (Table 1 and Figure 1).[6] Kassid *et al.* did not use any causality assessment criteria in their report.

Kassid *et al.* reported a case of prostate adenocarcinoma for which the patient had a radical prostatectomy. Later, he developed an acute liver failure and a subsequent multi-organ failure, after which he died (Figure 1). Kassid *et al.* diagnosed the patient with flutamide-induced acute liver failure (ALF).[6] Nevertheless, when applying the WHO-UMC criteria, we found that the diagnosis is unlikely to be «certain», but it can be «possible» (Table 2). The patient had additional risk factors for ALF because he was 75 years old with long-standing hypertension. Besides, according to the Food and Drug Administration's DILI Rank Dataset, the utilized drugs – Candesartan and Goserelin – possess DILI concerns.[7] There have been rare incidents of clinically apparent DILI associated with Candesartan therapy; Goserelin therapy can also lead to mild hepatic enzymes elevation in 3-5% of patients.[8] Therefore, we cannot rule out Drug-Drug Interaction (DDI) in Kassid *et al.*'s case. On the other hand, the RUCAM system assigns points for seven domains, and the summative score reflects the likelihood that the hepatic injury is due to a specific medicine; these categories are: excluded (<1 point), unlikely (1-2

points), possible (3-5 points), probable (6-8 points) or highly probable (>8 points).[4] Kassid *et al.*'s case scored six, which fits under the category «probable» (Table 3).

Unfortunately, neither the WHO-UMC criteria nor the RUCAM system offers inferential statistics for causality assessment concerning adverse events (AE) because it deals with critically analyzing individual cases. Nonetheless, these criteria – for instance, the WHO-UMC criteria – offer a scale of measurement from the lowest probability (unclassifiable) to the highest (certain); the scale is ordinal and has six levels. Accordingly, we may consider the ordinal scale of the criteria as the dependent (outcome) variable for causality assessment. Further, case reports represent sequential cross-sections of data across time. Therefore, if we collect a reasonable number of cases reporting the same AE concerning the same medicine, having similar demographic and socio-economic backgrounds, and possessing comparable temporality (*i.e.*, within the same month or the same season), then we may consider these cases as an approximation of a single sample for which we can run the regression analysis. Our concept suggests compiling cases of similar temporal (time), spatial (place), and patient attrib-

Table 1. Summary of medications.

Drug	Dose in the reported case	Duration of use in the reported case	Standard therapeutic dose*	Drug's half-life*	Reported drugs' interaction*
Flutamide	500 mg/day for 1 month, then 750 mg/day	Two months	750 mg/day	6 hours	None
Goserelin	Unknown	Single dose	3.6 mg depot once every 28 days	2-4 hours	None
Candesartan	16 mg/day	Unknown	32mg/day	9 hours	None

*The Electronic Medicines Compendium (EMC; Datapharm Ltd.) was consulted concerning the reference values. Available from: https://www.medicines.org.uk/emc/

Table 2. World Health Organization-Uppsala Monitoring Center causality categories.

Category	Evaluation Criteria*	Kassid *et al.*
Certain	• 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 pharmacologic phenomenon) • Rechallenge satisfactory, if necessary	Not applicable
Probable, or likely	• 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	Not applicable
Possible	• 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	Applicable
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide a plausible explanation	Not applicable
Conditional, or unclassified	• Event or laboratory test abnormality • More data for proper assessment is needed, or • Additional data under examination	Not applicable
Unassessable, or unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because the information is insufficient or contradictory • Data cannot be supplemented or verified	Not applicable

*All points should be reasonably satisfied.

Table 3. The domains of the RUCAM scoring system.

Domain	Evaluation Criteria	Score	RUCAM Category*
1.	Time to onset	+2	
2.	Time course of liver injury	0	
3.	Risk factors	+1	
4.	Concomitant hepatotoxic drugs	-1	Probable
5.	Exclusion of other causes of liver injury	+2	
6.	Previous information on hepatotoxicity of the drug	+2	
7.	Development of repeated liver injury after drug re-administration	0	
Total score		6	

*RUCAM system categories are: excluded (<1 point), unlikely (1-2 points), possible (3-5 points), probable (6-8 points), or highly probable (>8 points).[4]

utes to solve the rarity issue that pharmacovigilance workers encounter with rare AE cases.

When applying the WHO-UMC criteria or the RUCAM system, we implicitly analyze most of these parameters qualitatively, not quantitatively. We propose to abridge the qualitative-quantitative gap by incorporating the mentioned variables into an ordinal regression model that can test the relationship between explanatory variables and an ordinal response variable. We can consider the causality likelihood grade as the dependent variable, and the independent variables (potential predictors) can include demographic variables, socio-economic parameters, dietary factors, other potential culprits (chemicals, illicit substances, medicines, and DDI), and pre-existing pathologies and comorbidities (liver, kidney, among others). Further, when sufficient data entry points (cases) exist, we can run Artificial Neural Networks (ANN) analysis.[9] However, there is usually a limited number of cases; nevertheless, when pharmacovigilance experts gain access to big data via national and international pharmacovigilance databases, such as the WHO-UMC VigiLyze® and VigiFlow®, then they can analyze many AE cases using ANN.[10,11]

Pharmacovigilance employees implement conventional causality assessment methods to exclude all possible confounding factors. For instance, the national Iraqi Pharmacovigilance Center receives daily reports from healthcare providers (HCPs) and marketing authorization holders (MAHs). Guidelines for reporting by HCPs and MAHs exist, and pharmacovigilance specialists transfer these data into the VigiFlow® database. Experts search for new safety concerns, analyze data, and recommend regulatory actions to the authorities. Our causal inference concept not only complements conventional causality assessment in pharmacovigilance but also mandates rechecking the raw data for the individual cases and incorporating these into the causal inference analysis (ordinal regression and ANN). Analytics can yield statistical significance, predictors' importance, and effect size. The proposed concept can offer leverage concerning AE cases that readers might consider biased or irrational; it also applies to analyzing Adverse Events Following Immunization (AEFI), which can be further enhanced using data optimization methods.[12,13]

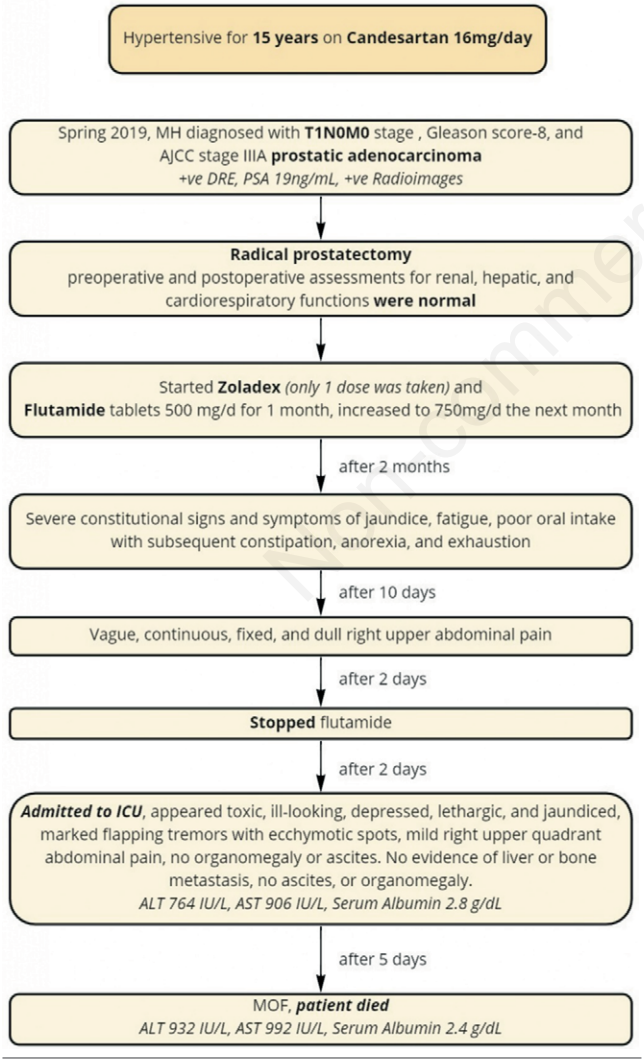

Figure 1. Flowchart of the case report by Kassid *et al.* (2022). The authors created the flowchart with Miro online tool.

Our letter critically analyzed Kassid *et al.*'s case using the RUCAM and the WHO-UMC system; both agreed concerning the uncertainty of Flutamide-induced ALF. Further, we introduced a concept for robust causal inference of collective AE cases reporting the same medicine by deploying regression analytics and ANN while relying on a valid causality assessment system. The proposed concept is feasible to implement (requires a simple background in data science), beneficial to integrate by pharmacovigilance experts, and may guide future research, including experimental studies (based on inference from causality assessment). Another advantage relates to AEs that are fatal or infrequent, for instance, in rare dermatological conditions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. These rare, fatal, and difficult-to-predict conditions can manifest idiosyncratically due to specific drugs; therefore, researchers cannot conduct experimental studies by inducing such harmful conditions in humans; on the other hand, it is not practical due to the rarity issue. In summary, the conjugate use of causality assessment systems and causal inference can extrapolate a superior level of evidence concerning AE cases.

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