

Manuscript title: Drug-induced liver injury and COVID-19: use of artificial intelligence and the updated RUCAM in clinical practice

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Article type: Original Research

Dear Artificial Intelligence in Gastroenterology Editorial Office,

Thank you for giving us the opportunity to submit a revised draft of our manuscript titled “Drug-induced liver injury and Covid-19: use of artificial intelligence and the updated RUCAM in clinical practice”. We appreciate the time and effort that you and the reviewers have dedicated to provide your valuable feedback on the manuscript. The reviewer's comments were helpful and relevant for the paper's improvement. We have incorporated some of the suggestions made by the reviewers. Please check below our responses to the reviewers' comments and concerns.

In addition, the manuscript was submitted to a new review in the English language.

REVIEWER 1

Comments	Author's response
1. This article focuses on the updated RUCAM for assessing hepatotoxicity causality in COVID-19, which has significant clinical implications. However, it is essential to differentiate whether liver damage is attributed to the novel coronavirus itself or to medication use.	<p>There is no consensus on the exact cause of the liver injury in COVID-19 patients. We added the sentence in the second paragraph of the introduction section: “Pathophysiology possibilities of liver injury in COVID-19 vary from direct infection by SARS-CoV-2, hypoxic changes, systemic inflammation, exacerbation of underlying disease and adverse drug reactions.” to elucidate all the possible mechanisms of liver damage.</p> <p>In our analysis, we could suggest that DILI was present in patients who the RUCAM assessment could be applied, but as RUCAM itself currently does not consider Covid-19 as exclusion, it was not possible to affirm, using a retrospective methodology, that Covid-19 was not involved in the damage.</p> <p>In the discussion section, page 15, we reinforce the sentence “COVID-19 itself has been associated with transaminase elevation either caused by viral direct damage, hypoxemia, or multisystem inflammatory syndrome”. We discuss the possibility of adding the Covid-19 hypothesis in the RUCAM tool as we believe that the lack of differentiation between Covid-19 and DILI as the cause of the damage is, in fact, a finding of the study that should be further investigated.</p>
2. This study is a retrospective study with a	Missing data is a known limitation of

<p>small number of cases, and there were significant differences in basic conditions such as patient age. Additionally, the clinical data of the included patients were incomplete, and it cannot be ruled out that other causes, such as hepatitis virus infection, could lead to abnormal liver function. Therefore, the conclusion proposed in this study is not sufficiently supported.</p>	<p>retrospective studies, although it does not invalidate the insights it can provide. In addition, absence of relevant clinical information in electronic medical records (EMR) for a considerable number of patients brings attention to the quality of healthcare systems worldwide, as it usually appears as a limitation of studies of this nature. However, EMR are essential sources of information when conducting pharmacoepidemiology studies such as our study.</p> <p>Also, we analyzed differential diagnosis of patients and excluded the ones with liver injuries defined by other etiologies such as viral hepatitis, alcoholic hepatitis, hepatocellular carcinoma, autoimmune hepatitis, cytomegalovirus, leptospirosis, Epstein Barr, hemolytic diseases, among other hepatobiliary disorders. As DILI is a rare adverse reaction, patients' samples will vary, mainly when considering idiosyncratic DILI.</p> <p>In addition, section 5 of the RUCAM assessment causality tool considers decreasing DILI score as the patient presents other diseases such as sepsis, cancer, shock, hypotension, autoimmune disease and other hepatic conditions. Thus, if the patient presents DILI as high probable, probable or possible, all the other causes were analyzed.</p> <p>The absence of some relevant clinical information in our study was a finding to be considered and is elucidated in our conclusion "Our study shows that DILI has a rare incidence in COVID-19 inpatients and the absence of relevant clinical information on EMR may underestimate DILI rates. " Finally, we consider that even though we have a small number of confirmed cases of DILI, the methodological rigor of our study applying the RUCAM to confirm cases is a differential when comparing to other publications, as we have seen that some articles do not apply causality assessment methods to confirm DILI, concluding the diagnosis by only excluding other causes, which leads to a bigger sample.</p>
<p>3. The paragraph 6 of the manuscript suggests utilizing lower cutoff points, such as ALT values one to three times the ULN, instead of five times the ULN. This recommendation takes into account the common practice of using medications off label. However, it remains debatable whether this basis is adequately rigorous or not.</p>	<p>Authors accepted the suggestion. We included more information regarding the comparison of laboratory threshold criteria in drug-induced liver injury detection algorithms, in paragraph 6 of the "discussion" section. As demonstrated in the literature, when detecting DILI using artificial intelligence (AI), it is preferable to use cut-offs lower than $5 \times > \text{ULN}$ as the technology will overcome the time consuming disadvantage of screening a higher number of patients. In rare</p>

	adverse drug reactions, it is important to not miss any case, even the ones that will not need clinical intervention besides monitoring signs and symptoms.
4. Is the basis for the appeal sufficiently rigorous in the sixth paragraph of the manuscript, which suggests using lower cutoff points such as ALT one to three times the ULN instead of five times the ULN, considering that many medicines are used off-label?	Authors accepted the suggestion. We included more information regarding the comparison of laboratory threshold criteria in drug-induced liver injury detection algorithms, in paragraph 6 of the “discussion” section. As demonstrated in the literature, when detecting DILI using artificial intelligence (AI), it is preferable to use cut-offs lower than 5x > ULN as the technology will overcome the time consuming disadvantage of screening a higher number of patients. In rare adverse drug reactions, it is important to not miss any case, even the ones that will not need clinical intervention besides monitoring signs and symptoms. ALT 5x>ULN is important when considering the risk benefit of stopping suspected drug treatment.
5. The manuscript mentions a new RUCAM score, but it does not provide specific details about the upgrades. Could you please enumerate the upgrades to enhance its reference value?	Authors accepted the suggestion. We added the sentence “The updated version of RUCAM was completed by additional criteria to establish DILI with high degree of certainty, such as, clarification of ambiguous questions related to alcohol use, exclusion of non-drug causes as check-list of differential diagnosis” to the manuscript.” page 6

REVIEWER 2

Comments	Author's response
The author should ensure that the references cited in the introduction and related work section are thoroughly addressed in the reference section.	All references cited in the text have been revised. Included references are highlighted.
The introduction should provide an extended version of the abstract, with elaboration on the key points and supportive ideas and references.	Authors accepted the suggestion. We modified the abstract as well as the introduction, so the idea of the article could be easy and concise for readers to understand. All modifications are highlighted in the text.
Lastly, the conclusion section needs revision to provide a more insightful and comprehensive summary of the manuscript. Deep Convolutional Neural Network Architecture to Detect COVID-19 from Chest X-Ray Images.	Authors accepted the suggestion. We included two paragraphs exploring the possibilities of artificial intelligence application in COVID-19. Modifications are highlighted in the text. We also included the suggested references to make the AI and COVID-19 clearer for the

<https://doi.org/10.24996/ijis.2023.64.5.38>
Artificial intelligence for COVID-19: A Short
Article.
<https://doi.org/10.24203/ajpnms.v10i1.6961>

readers. AI specifically applied to DILI
detection is still a field to be investigated.