

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: A case of post-COVID hepatitis in a 21-old-male is presented with flow charts of liver enzyme and SARC-Cov-2 antibodies in your manuscript. This case is very interesting and unique. Though liver biopsy was not done, the possibility of immune hepatitis can be considered. At the present time, we have to collect the COVID related data about hepatocyte injury.

Author response: We thank the reviewer for the useful comments.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: I have some concerns regarding the presented case report of COVID-19 related hepatitis. I am not sure if the Authors could categorize that case as post-COVID complication. SARS-CoV-2 was still detected by PCR till 24th day of hospitalization parallel to the peak of transaminases elevation.

Author response: We agree with the reviewer's comment and our initial diagnostic assumption was also that liver cytolysis could also have occurred during COVID disease per se, as can be seen from Table 2, where we discussed potential etiologies of the increased liver enzymes. However, upon further evaluation and reassessment of the case, it became apparent that all signs and symptoms of COVID had remitted at day 4, with the patient meeting the definition for clinical remission and no further symptom progression. Indeed, PCR was still positive for SARS-CoV-2 virus at day 24, but based on our experience since, this was probably just an artefactual finding due to the high sensitivity of the PCR test, particularly given the fact that the very next day the PCR was negative. Unfortunately, because this happened relatively early on in the pandemic, we do not have quantitative viral load data, but it is reasonable to assume that in the absence of any clinical signs of COVID and with a negative RT-PCR from both nasopharyngeal swabs and peripheral blood the very next day, cytolysis was not due to the virus itself, but rather to the immune response following the acute injury having occurred 20 days earlier. For this reason and after interdisciplinary consultation, we decided to interpret this as a post-COVID complication. These clarifications have also been added to the Abstract and manuscript full text, please see below the changes made:

Abstract: "The liver enzyme increase occurred 20 days after the complete clinical remission of COVID-19 and ALT dynamics paralleled the increase in total anti-SARS-CoV-2 antibodies."

Full text: "The remaining hypothesis, and the final diagnosis in our case, was post-COVID immune hepatitis, which occurred 20 days after the complete clinical remission of COVID-19 and paralleled a rapidly increasing titer of total anti-SARS-CoV-2 antibodies".

Was the interleukin-6 (IL-6) value checked only once? The Authors wrote „We also checked the interleukin-6 (IL-6) value at that time point". You speculate that the cytokine storm caused by excessive immune response induced by the virus may also be one of the pathways of liver damage. It will be essential to provide a kind of evolution scheme on cytokine values comparing with liver function tests.

Author response: Thank you for the comment. We agree that more information is needed and we have now added a Table providing the full results of the laboratory tests, including the repeated determination of IL-6.

References have to be extended. So far, there have been reported many studies regarding liver involvement during COVID-19. You need to cite them in Discussion.

Author response: Thank you for the comment. We agree that there are several studies reporting on liver involvement during COVID-19. However, most of these studies generally report hepatocytolysis during the acute phase of the infection, while in our reported cases, this occurred 20 days after complete clinical resolution. We have now extended the Discussion section and added further references, as suggested, including:

(China): Fan, Z., et al., *Clinical features of COVID-19-related liver functional abnormality*. Clin Gastroenterol Hepatol, 2020. **18**(7): p. 1561-1566.

(USA): Hajifathalian, K., et al., *Gastrointestinal and hepatic manifestations of 2019 novel coronavirus disease in a large cohort of infected patients from New York: clinical implications*. Gastroenterology, 2020. **159**(3): p. 1137-1140 e2.

(France): Chaibi, S., et al., *Liver function test abnormalities are associated with a poorer prognosis in Covid-19 patients: Results of a French cohort*. Clin Res Hepatol Gastroenterol, 2020.

Del Zompo, F., et al., *Prevalence of liver injury and correlation with clinical outcomes in patients with COVID-19: systematic review with meta-analysis*. Eur Rev Med Pharmacol Sci, 2020. **24**(24): p. 13072-13088.

The expanded Discussion now includes the following information: “Hepatocytolysis can be a relatively common feature of COVID-19, but it generally occurs during the acute phase of the infection, with a French cohort study reporting that up to 36.3% of patients had abnormal liver function tests [2], similar to the rates of 31.6% [3] and 37.2% [4] reported from China, with even higher rates 62% reported from the USA [5]. However, most of these clinical observations come from patients with moderate, severe or critical forms of disease, since this is the patient population that most often requires management in the hospital. Liver cytolysis has also been associated with more extensive lung lesions during the acute phase of COVID-19 [3]. However, while the overall prevalence of liver cytolysis in patients with COVID-19 appears to be quite high, reported at 46.9% in a pooled meta-analysis [6], relatively fewer cases display high-grade cytolysis, i.e., only 6.4% of the patients from the French cohort had ALT levels above 5 times the upper normal limit [2]. Because of the fact that in Romania at the time when our case occurred, hospital isolation was mandatory for all patients testing positive for SARS-CoV-2, we were able to detect this biochemistry finding, an ALT level 15 times the upper normal limit in a patient who had had mild COVID. Furthermore, ALT levels above 5 times the upper normal limit in COVID-19 are associated with a poor prognosis, specifically: significantly higher risk of severe lung involvement, intensive care admission, and death [2, 6]. This was not the case in our patient, where an even higher ALT level was not associated with worsening of COVID, and it occurred after remission of all clinical signs and symptoms for 20 days.”

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This is a case report that is straightforward and describes a situation that has not been documented before. It is a relevant contribution to the growing literature on covid-19.

Author response: We thank the reviewer for the useful comments.

4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript’s language will meet our direct publishing needs.

Author response: The manuscript has now been checked by a colleague who is a medical doctor and native-English speaker for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability. We now hope that the manuscript's language will meet the journal's publishing needs.

5 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) *Science editor:* 1 Scientific quality: The manuscript describes a case report of the transient immune hepatitis as a late post-COVID complication. The topic is within the scope of the WJCC. (1) Classification: Two Grades B and Grade D; (2) Summary of the Peer-Review Report: A case of post-COVID hepatitis in a 21-old-male is presented with flow charts of liver enzyme and SARC-Cov-2 antibodies in your manuscript. This case is very interesting and unique. The questions raised by the reviewers should be answered; and

Author response: The questions from the reviewers have been answered above and all requested changes have been implemented in the revised manuscript

(3) Format: There is 1 table and 2 figures. A total of 3 references are cited, including 3 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A and two Grades B. No language editing certificate was provided.

Author response: The manuscript has now been checked by a colleague who is a medical doctor and native-English speaker for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability. We now hope that the manuscript's language will meet the journal's publishing needs.

3 Academic norms and rules: Written informed consent of treatment was not provided.

Author response: We have now added the informed consent.

No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an unsolicited manuscript. No financial support was obtained for the study. The topic has not previously

been published in the WJCC. 5 Issues raised: (1) The "Author Contributions" section is missing. Please provide the author contributions;

Author response: We have now added the "Authors contributions section", according to the journal's instructions.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Author response: We have now added the Figures as editable PowerPoint files.

(3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

Author response: PMID and DOI numbers have been added in the reference list.

(4) The "Case Presentation" section was not written according to the Guidelines for Manuscript Preparation. Please re-write the "Case Presentation" section, and add the "FINAL DIAGNOSIS", "TREATMENT", and "OUTCOME AND FOLLOW-UP" sections to the main text, according to the Guidelines and Requirements for Manuscript Revision.

Author response: We have now written the "Case Presentation" section according to the Guidelines for Manuscript Preparation, and added the required section headers and subheaders.

6 Recommendation: Conditional acceptance.

Author response: We thank the editor for the recommendation. We have revised the manuscript according to all comments from the peer reviewers and editors and we now hope that the revised manuscript can be accepted for publication in its revised form.

(2) Editorial office director:

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Author response: We thank the editor for the recommendation. We have revised the manuscript according to all comments from the peer reviewers and editors and we now hope that the revised manuscript can be accepted for publication in its revised form.