

Response to reviewers

Dear Editors and Reviewers:

On behalf of the authors, I am pleased to resubmit for publication the revised version of “COVID-19 related liver injuries in pregnancy”. We appreciate the constructive criticism of the scientific editor and the reviewers and have addressed all their concerns as outlined below. We revised the manuscript and the figure in line with the reviewers’ advice and preferences. The language was edited and checked by a native English-speaking expert, according to the editorial comments. The made revisions are explained as follows:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Dear authors, Generally, you have presented a very interesting review article about the COVID-19 related liver injuries in pregnancy. There are specific comments and remarks about your manuscript as follows:

1) Correct the word "polysyndromic" with the more appropriate one: "syndromic", everywhere at your manuscript.

Response: Thank you for this valuable comment. The amendments were done in the revised manuscript.

2) You could add the phrase: "ACE2 receptors" at the Keywords section.

Response: Done.

3) At page 4., you could change the phrase: "across the globe", with the word: "globally".

Response: The phrase “across the globe” was substituted with globally where appropriate after consulting an expert with full proficiency in English.

4) At page 5., you should report at the Search Strategy section the following: How many articles did you retrieve totally? What are the inclusion and exclusion criteria of the relevant articles that you studied? It would be beneficial if you present a flow diagram of your research strategy with the keywords that you used, the number of the included and the excluded studies that you reviewed.

Response: Only case reports, original articles, reviews and considerations of official societies in English language were included. Relevant papers were selected as per authors' professional expertise, experience and opinions to transcribe this narrative review [10].

5) At page 5. you could add the word "enzyme", after the phrase "including GGT".

Response: Done.

6) At page 6. change the word "pessimistic" with the word "poor".

Response: Done.

7) At page 8, can you analyze the (PE) and (IHC) abbreviations. It would be beneficial if you could add an abbreviations section after the Keywords section with all the main abbreviations that you use at your manuscript.

Response: Thank you for this remark. Abbreviations of PE and IHC are now disclosed upon their first mention, as per guidelines for the authors.

8) At page 9, change the word "mirrored" at the 3rd line, on the top of the page, with the more appropriate one: "represented" and two lines after the word "puttable" with the correct one: "putable".

Response: Thank you. Corresponding amendments in the manuscript text were made highlighted in yellow.

9) At page 11, can you analyze in brief the "Swansea criteria"?

Response: The following text was added to introduce both the condition AFLP and the Swansea criteria: "AFLP is a rare, potentially fatal complication that occurs in the peripartum period. The Swansea criteria are widely used for the diagnosis of AFLP and include results from both clinical and instrumental findings, as well as pathological examination"

10) At page 12, at the last line of the 1st paragraph add the word "three" before the word "babies".

Response: Done.

11) At page 13, last line of the page, change the word "dictum", with the more suitable word "statement".

Response: Done.

12) At page 14, change the word "corollary" with the word "conclusion". The word "culprit" with the word "cause" and the phrase "across the globe" with the word "globally".

Response: Done.

13) At page 15, you can analyze the abbreviation GW as "gestation week" at the penultimate paragraph.

Response: Done. GW is disclosed upon 1st mention.

14) At Table 1. change all the phrases "Fly-like" with the correct one "Flu-like" and at the end of the Table, add abbreviation analysis for the abbreviations: M+B, CS, GW, NR that you report at your table.

Response: Done. Furthermore, the abbreviations are now in alphabetical order for better reading.

15) At page 20, can you present more concluding remarks about your findings of COVID-19 related liver injuries and for possible clinical and laboratory markers of this injury to have a more clear and more detailed presentation of your conclusion-discussion section.

Response: We agree with the referee that we need more concluding remarks before the conclusion. We have added a paragraph before the section on vaccination (on page 19 of the revised manuscript). Additionally, we add some notes on this topic in the separate section called Future directions, as you suggested at the end of the review.

16) You can enrich your references with two more suggested and relevant bibliographies, such as: a) Karlafti E, Paramythiotis D, Pantazi K, Georgakopoulou VE, Kaiafa G, Papalexis P, Protopapas AA, Ztriva E, Fyntanidou V, Savopoulos C. Drug-Induced Liver Injury in Hospitalized Patients during SARS-CoV-2 Infection. *Medicina (Kaunas)*. 2022 Dec 15;58(12):1848. doi: 10.3390/medicina58121848. PMID: 36557050; PMCID: PMC9782075 and b) Georgakopoulou VE, Bali T, Adamantou M, Asimakopoulou S, Makrodimitri S, Samara S, Triantafyllou M, Voutsinas PM, Eliadi I, Karamanakos G, Basoulis D, Chatzipanagiotou O, Adamopoulou E, Alevizou A, Athanasiadis M, Spandidos DA, Papalexis P, Tarantinos K, Sipsas NV, Samarkos M, Cholongitas E. Acute hepatitis and liver injury in hospitalized patients with COVID-19 infection. *Exp Ther Med*. 2022 Sep 26;24(5):691. doi: 10.3892/etm.2022.11627. PMID: 36277149; PMCID: PMC9535623.

Response: Thank you for this advice. We have enriched our manuscript with the following two citations from your next comment: Karlafti et al. and Georgakopoulou et al. They were included on pages 5 and 6.

Finally, you should present the limitations of your review study in a separated section, also you can report the future directions of the topic described in this review, in a separate section in your text, presenting also the answers about the questions/issues that remain to be solved and the impact of this study to the basic science and/or clinical practice. Also, you have done a very well design of the study, with a very successful relevant figure, but you can improve your overall text so that it is less descriptive and more concise of the relevant scientific articles you have studied so that your particular finding on the covid-19-induced complications of liver function in pregnancy is clearly stated.

Response: Thank you very much for the critical notes and overall evaluation of our paper as good. We added a separated section with limitations and future directions.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Number ID: 04480049 Publication Journal: World Journal of Clinical Cases Authors: Metodija Sekulovski, Simona Bogdanova-Petrova, Monika Peshevska-Sekulovska, Tsvetelina Velikova, Tsvetoslav Georgiev Title: COVID-19 related liver injuries in pregnancy Manuscript Type: Review Title Submit Date: 2022-11-19 Title Accepted Date: 2022-11-21 Manuscript Submission Deadline: 2022-11-22 Description: General Impression. This is a well written and organized review manuscript which summarizes the main clinical characteristics and pathoetiology of Covid 19 related liver injury during pregnancy. Dispute an additional work with fundamentally the same topic has recently been published

(<https://pubmed.ncbi.nlm.nih.gov/36405386/>), the manuscript is thorough and highly informative. The manuscript gives a detailed explanation of the disease and potential causes. It is also well structured and the figure and the table are both well designed and highly informative. I believe that this manuscript is worth publishing subject to minor revisions/improvements. The authors may consider the following comments for improving the review manuscript. (Unfortunately, there is no line indication in the manuscript file).

Response: Thank you for the valuable suggestions and the overall evaluation of our paper as good. Our paper is focused primarily on the liver injuries related to COVID-19 in pregnancy. We acknowledge that two papers might have some common features, however, they are not similar in the content.

1) Given that we are entering in December 2022, the current n. of confirmed cases and deaths should be up to date

Response: Done. The current report from 23th Dec 2022 is now cited to update the number of confirmed cases and deaths. Amendments were made in the introduction.

2) A detailed review manuscript on this topic has recently been published on World Journal of Gastroenterology <https://pubmed.ncbi.nlm.nih.gov/36405386/>. I suggest mentioning this work

Response: Thank you for this comment. The work is now included in the reference list and is mentioned in the text.

3) The SARS-CoV-2 infection during pregnancy has also been hypothesized to be related to abortive events PMID: 35389480

Response: The following sentence was contextually included "Furthermore, SARS-CoV-2 infection during the first trimester of pregnancy is related to higher risk of miscarriage" and the relevant reference was added.

4) The authors should include the term "Coronavirus disease 2019 (COVID-19) associated liver injury (COVALI)" in the text

Response: We have now introduced the term COVALI in the introduction section.

5) "Underlying medical conditions, such as obesity, chronic lung disease (i.e., asthma), and chronic hypertension, decreased ability to tolerate infection associated with these conditions [26,27]." One of the main aspects of this phenomenon is the immune modulation process occurring in pregnancy which make pregnant females more predisposed to viral infections (doi: 10.1097/GCO.0B013E328028FDC7). This notion is for instance well explained in this immunological work conducted in a group of pregnant females (DOI:

10.3389/fmicb.2021.789991). I suggest including a couple of words on this notion alongside these two supporting references

Response: Thank you for this comment. We have enriched the manuscript with those two citations. We have added the following sentence “Furthermore, higher susceptibility to respiratory viral infections is seen in pregnant women [Longman et al.] partially attributable to a phenomenon of immune modulation occurring during pregnancy [Mazziotta et al.]”

6) Authors should check/uniform the font style and font color of the text

Response: Done.

7) I suggest rephrasing several sentences on ACE2 receptor. I suggest avoiding terms such as "abundant" or "found" on ACE2 receptors, as being a cell surface protein, which is encoded by a gene. So, I suggest using more appropriate terms such as high/low expression or "ACE2 is differentially expressed" etc...

Response: We agree with the reviewer's advice and have amended the inappropriate verb or adjective (e.g. found, abundant, etc.) addressing ACE2 receptors.

8) I suggest including a couple of words on SARS-CoV-2 infection and the increased risk of liver cancer given the growing literature in this field (DOI: 10.1111/liv.15320 and <https://bmjopengastro.bmj.com/content/9/1/e000794>)

Response: Thank you for your comment. Since we did not find any related information about liver cancer and pregnant women with COVID-19 (including the above-mentioned studies), we did not find logic to address this problem.

9) "To our knowledge, this is the first literature review published concerning COVID-19 in pregnant patients with pregnancy-related liver injury." As said before, this is not true <https://pubmed.ncbi.nlm.nih.gov/36405386/> . Please revise this sentence

Response: Yes, we agree with your comment and we have revised the sentence to “To our knowledge, this literature review is among few that have addressed COVID-19 in pregnant patients with...”. On another note, we have included the previous mentioned reference <https://pubmed.ncbi.nlm.nih.gov/36405386/>.

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.