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November 18, 2022

Dear Dr. Lian-Sheng Ma,

We are glad to have the opportunity to submit a revised draft of our manuscript entitled "COVID-19 and Liver Injury: A Review of Clinical Manifestations and Outcomes in Portuguese Patients" to the World Journal of Gastroenterology.

We are most grateful for the time and effort that you and the reviewers have dedicated to reading and examining our manuscript and for your insightful comments.

We analyzed each of the observations and were able to incorporate the changes needed to follow up on the recommendations and suggestions provided by the reviewers.

Below is a point-by-point response to the reviewers' comments and concerns.

Thank you for your consideration!

Yours Sincerely,



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## COMMENTS FROM REVIEWER 1

**Comment 1:** “The manuscript's title and abstract discuss focus on Portugal, while the manuscript itself has a small section about Portugal. As a reader, if I were to read the title and abstract of this manuscript, I would be misguided to expect a manuscript that discusses Portugal and COVID-19-related liver damage, when in turn, most of the manuscript is either not about liver (general impact of covid in health care services) or about Portugal (general association between liver damage and covid). Therefore, I suggest adapting the title and the abstract to reflect the manuscript.”

**Response:** Thank you for your comment. We agree with this and therefore, we modified the title of the manuscript to “The relation between COVID-19 with liver diseases and its impact on healthcare systems: the Portuguese case”.

**Comment 2:** “The authors use *infected* and *patient* interchangeably without describing whether the patient is in the community or hospitalized. Please clarify each statement or in general, whether the manuscript focuses more on the community rather than hospital patients.”

**Response:** Thank you for calling our attention to this use of words. We agree that interchanging the terms does not contribute to clear communication. When we mention “infected patient” we are referring to people in the community, who were COVID-19 positive but non-hospitalized. Individuals with COVID-19 who were hospitalized are referred to as ‘hospitalized’ in the text. For clarity, we have altered the text to use ‘individual’ or ‘person’ whenever the persons were COVID-19 positive but non-hospitalized.

**Comment 3:** Where it is written ‘*Despite not being among the most frequent comorbidities, liver injury is common in COVID-19-infected patients*’, “Is it more common than non-infected?”

**Response:** Thank you for your comment. According to the latest studies, an abnormal liver function has been reported in almost 50% of SARS-CoV-2 positive individuals (<https://doi.org/10.1016/j.gtc.2022.09.001>), and the risk of COVID-19 severity and death is higher among chronic liver disease patients than among non-chronic liver disease patients (DOI: <http://dx.doi.org/10.5888/pcd19.210228>).

**Comment 4:** Where it is written ‘*To identify and discuss the incidence of preexisting liver-associated diseases and liver injuries induced by COVID-19 in Portuguese patients infected with SARS-CoV-2.*’ “Community or hospital patients?”

**Response:** Thank you for pointing this out. We refer to the community of COVID-19-positive individuals. However, according to the first commentary, we altered the manuscript to use the word ‘patient’.

**Comment 5:** Where it is written ‘*Portugal was one of the many countries affected by the COVID-19 pandemic. All elective and non-urgent health care were suspended, and the primary health services were also affected, which caused an impact on the waiting lists for hospital medical specialties, an increase in telemedicine, and a reduction in medical observations.*’ “Are these the results of the review or a simple observation? This is applicable to any other country in Europe.”

**Response:** Thank you for your comment. These results refer to an observation (a fact) in the Portuguese population published by Vieira et al., 2021 (DOI:10.32385/rpmgf.v37i5.13135). Alterations in the normal access and response to primary health care were also observed in other countries in Europe (for example, in Spain or the Netherlands), and in other non-European countries from America, Asia-Pacific, and Africa (doi: 10.1080/13814788.2020.1820479). On the other hand, the response of primary health care to COVID-19 was also variable and different depending on the world region. For example, in Europe (Portugal, Spain, Germany, United Kingdom, Italy, and France) teleconsultations, and digital technology to control vital signals were used to monitor the people infected with COVID-19 (doi: 10.1590/0102-311X00183820).

**Comment 6:** Where it is written '*COVID-19 combined with liver injury is common, and liver damage represents a risk factor that worsens in patients with COVID-19,*' "Again, community vs hospitalized. Liver injury is a risk factor for what? And what worsens? COVID's prognosis?"

**Response:** Thank you for pointing this out. We refer to the community, individuals that were COVID-19-positive. We have altered the text following the first recommendation concerning the use of the word 'patient'.

The presence of liver disease is considered a risk factor in the predisposition to SARS-CoV-2 infection and worsening of the COVID-19 prognosis. Depending on each type of illness, individuals with liver disease have an increased risk of developing severe or critical disease and even dying after infected with SARS-CoV-2 (DOI: 10.1016/j.biopha.2022.113568).

**Comment 7:** Where it is written '*In addition, despite not being among the most frequent comorbidities, the pathologies associated with the liver are hardly ever missing from the list of preexisting health conditions in COVID-19-infected patients,*' "Patients as hospitalized?"

**Response:** Thank you for your comment. We refer to the community, individuals that were COVID-19-positive. We have altered the text following the first recommendation concerning the use of the word 'patient'.

**Comment 8:** '*First, the authors discussed the keywords to be used in the search, agreeing upon the following string and operators: ["Portugal" or "Portuguese patients" AND "COVID" OR "SARSCoV-2" OR "coronavirus" AND "liver" or "hepatic condition" OR "chronic hepatitis" AND "clinical manifestations" OR "outcomes" AND "COVID-19 treatment"] to be found either in the titles, abstracts, or keywords of the articles,*' "It is unclear if these were the search terms of the engine or the screening criteria."

**Response:** Thank you for your comment. These were the search terms. The screening criteria are listed in the section Eligibility criteria.

**Comment 9:** Where it is written '*A two-stage approach was used to assess the retrieved studies. First, only the titles and abstracts were scanned to determine eligibility according to the research objective and criteria. Second, the full texts of the selected papers were read and thoroughly analyzed,*' "State whether it was done by one reviewer or two".

**Response:** Thank you for your comment. We agree that we should have clarified who participated in these analyses. All authors took part in these activities and we have stated that in the text.

**Comment 10:** "The '*COVID-19, HEALTH CARE AND CLINICAL PRACTICE IN PORTUGAL*' section is not related to the aim of this study, again, consider broadening the aim of the study or delete it."

**Response:** We appreciate your comment and agree with your judgment. For this reason, we have added the aim of "*studying COVID-19 pandemic and healthcare*".

**Comment 11:** "The '*COVID-19 AND LIVER DISEASE*' section is not related to the aim of this study, consider broadening the aim of the study or delete it"

**Response:** We appreciate your comment and agree with your judgment. For this reason, we have added the aim of "*studying the relationship between COVID-19 and liver diseases*".

**Comment 12:** "Some of the citations in the discussion are in a different format."

**Response:** Thank you for pointing this out. We have revised and corrected the citations that were in a different format.

**Comment 13:** "A limitations section should be included."

**Response:** Thank you for your comment. We agree and therefore have included a section stating the limitations of the study.

## COMMENTS FROM REVIEWER 2

**Comment 1:** In the 'Results' section within the abstract, "There is no information regarding liver injury and covid."

**Response:** Thank you for pointing this out. We agree with this and therefore, we have made the necessary changes in this section.

**Comment 2:** In the abstract, "The author mentioned liver damage represents a risk factor that worsens in patients with COVID-19. However, it is not completely proved by the report the author provided, therefore, I suggest to make it a hypothesis."

**Response:** Thank you for your comment. We have made the appropriate alterations in the abstract.

**Comment 3:** In the introduction, "*These symptoms may be aggravated by preexisting health conditions or comorbidities, which have been addressed in studies on the clinical characteristics and outcomes of COVID-19-infected patients [2-4] published since the official declaration of the pandemic outbreak of COVID-19 on March 11, 2020 [5]*", "The authors cited references 2-4, please cite other papers published in 2022."

**Response:** Thank you for your comment. We have cited other articles from 2022 in the introduction.

**Comment 4:** In the introduction, where it is written '*However, to date and to the best of our knowledge, only one study has been published with a review of the impact of COVID-19 on the liver in the Portuguese population since 2020 [14]. Therefore, in this study, by reviewing the available research, we aimed to identify.....*', "You performed this study only because of one study available? Justify your study with another statement like .....what are their findings? What's the gap that you intend to fill up in the present study? I recommend to revise it."

**Response:** Thank you for your comment. We performed this review because, information on COVID-19-positive individuals and liver diseases, implications and outcomes is scarce for the Portuguese population. On the other hand, we believe that the alterations in the healthcare system due to the pandemic are an important topic to explore and elucidate as it helps to reflect on how societies should prepare for the others pandemic crisis in the future.

**Comment 6:** "What is the application of your work? And/or mention who will be benefitted from this study? You must mention that at the end of the introduction."

**Response:** Thank you for this comment. As mentioned before, we think it is important to know if individuals with liver diseases may be at an increased predisposition of infection by COVID-19 and if these persons may have a worse prognosis due to the liver diseases they suffer from. Concerning the implications in health care, we believe that the alterations in the health care system due to the pandemic are an important topic to explore and elucidate because it may help to reflect on how societies should prepare for other pandemic crises in the future.

**Comment 7:** "Overall, very weak story making in the introduction. Please rewrite it. Please mention what was obtained by other authors or researchers (at least two), what's the gap? Why you have performed this review and who will be benefitted from your study."

**Response:** Thank you for your comment. We have altered the introduction to correct the weaknesses pointed out and explain better our rationale for this article.

**Comment 8:** In the Eligibility criteria, where it is written '*All the studies assessed in this review comply with the following inclusion criteria established beforehand by the authors: (a) studies reporting original research published in Portuguese or English, (b) targeting the Portuguese adult population (Please mention age??) (c) from any period since the official diagnosis of the first case of COVID-19 in Portugal, on March 2, 2020 [15] (d) reporting any liver-associated clinical manifestation or outcome.*', "The authors target the Portuguese adult population, how about their age?"

**Response:** Thank you for your comment. We have added the following sentence: "i.e., 18 years old or older" to clarify the information concerning the age of the population analyzed.

**Comment 9:** In the Eligibility criteria, "there are many unnecessary sections all throughout the manuscripts. This should be eliminated and should present in a concise way."

**Response:** Thank you for your comment. We have joined some of the sections and restructure that part of the manuscript.

**Comment 10:** In the section '*COVID-19, HEALTH CARE AND CLINICAL PRACTICE IN PORTUGAL*' where it is written "*COVID-19 has greatly affected the Portuguese population's life, modifying*

*consumption habits [21] and lifestyle*". Consumption habits are also related to lifestyle, so revise it.

**Response:** Thank you for your comment. We have altered the text to "*COVID-19 has greatly affected the Portuguese population's life, modifying lifestyle, especially consumption habits*". We believe it is clearer now.

**Comment 11:** In the section '*COVID-19, HEALTH CARE AND CLINICAL PRACTICE IN PORTUGAL*', where it is written '*In Portugal, the National Health Service also enforced the suspension of all elective and non-urgent healthcare*'. "Provide a reference for it".

**Response:** Thank you for this comment. The reference (*Order of the Minister of Health, March 16, 2020*) will be provided in the revised manuscript.

**Comment 12:** In the section '*COVID-19, HEALTH CARE AND CLINICAL PRACTICE IN PORTUGAL*', where it is written '*A Portuguese study by [22] investigated*', "Revise it and use the proper way of telling that..... "*A Portuguese study by [22] investigated*" I think better if you mention the author name."

**Response:** Thank you for your comment. We have included the names of the authors in the text "*A Portuguese study by Vieira and collaborators investigated...*".

**Comment 13:** In the section '*COVID-19 AND LIVER DISEASES*', where it is written '*Data have suggested that preexisting liver disease was associated with worse outcomes in patients with COVID-19. In a study of 2780 patients with COVID-19, patients with CLD (n = 250) had higher rates of mortality as compared with those without liver disease (12 versus 4 percent; risk ratio [RR] 2.8, 95% CI 1.9-4.0) [39, 40].*' "There are some other studies from other parts of the world. Please cite the following article and a few others which also reported hepatic disorder-induced covid severity and hospitalization (<https://ijhs.org.sa/index.php/journal/article/view/6290>).

**Response:** Thank you for your observation. The reference that you suggest is interesting, we did not find it in our search because we focused on the Portuguese population, but we have added your suggestion.

**Comment 14:** In the section '*COVID-19 AND LIVER DISEASES*', "you must prepare a scheme of how covid affected if patients had preexisting liver disease and/or the possible mechanism how covid can/may harm liver, without any scheme, this work will not impacted."

**Response:** Thank you for pointing this out. We agree with your comment. We have added a scheme about the possible mechanism for the harm of the liver due to COVID-19 (please see Figure 2).

**Comment 15:** In the Discussion, where it is written '*We aimed to review the clinical manifestations and outcomes of Portuguese patients with COVID-19 and liver injury. We began with a search using the software Publish or Perish [16] to survey the databases PubMed, Scopus, CrooRef, Google Scholar, and Web of Science, using previously established keywords. Several papers were found and screened according to the inclusion criteria. However, only 6 studies reported original observational and retrospective research on the Portuguese adult population concerning liver-associated clinical manifestations or outcomes and COVID-19,*' "This section Repeated. Make it short."

**Response:** Thank you for pointing this out. We agree and have altered the text to: “We surveyed a number of databases and screened several papers to review the clinical manifestations and outcomes of Portuguese individuals with COVID-19 and liver injury.”

**Comment 16:** In the Conclusions "What is the future perspective of this review? How and what the other researcher will address regarding your findings in future, after synthesizing your results, you must mention that in the conclusion."

**Response:** Thank you for your comment concerning this section. We performed this review because, information on COVID-19-positive individuals and liver diseases, implications and outcomes is scarce for the Portuguese population. On the other hand, we believe that the alterations in the healthcare system due the pandemic are an important topic to explore and elucidate as it helps to reflect on how societies should prepare for the others pandemic crisis in the future.

**Comment 17:** "I think this work has few limitations. I suggest to mention the limitation of this study such as very few literature reviewed, not much clinical data available, not much data on recovery duration related to liver diseases if infected by covid, sometimes geographical and/or specific community population with different underlying medical condition may affect differently. Therefore, future study is warranted."

**Response:** Thank you for pointing this out. We agree and therefore have added a section stating the limitation of this research.