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Column: Opinion Review

Title: Mechanisms and consequences of COVID-19 associated liver injury: what can we affirm?

Dear Editor,

We thank you for the opportunity to revise our manuscripts

We have read thoroughly all the reviewer comments with the constructive criticism which I do respect for the perfection of the manuscript.

We have taken all comments into consideration and we answered the questions and revised the text accordingly (all changes are highlighted in yellow).

I am here with attaching the revised manuscript and the point to point replies to the reviewers.

I always do appreciate very much your support.

With my best regards,

Sincerely,

Carlos Brito

Reply to reviewer

1. R: Carlos et al. reported a nice mini-review on "Mechanisms and consequences of COVID-19 associated liver injury" Overall, it is a nice study, however, there is several drawbacks the first limitation of the study is the presentation of table 1 - which discuss and summarize the rate of liver abnormalities among different studies, however, this table lacks a lot of data - given what the authors stated in their review that liver injury in COVID-19 is multifactorial (COVID-19 itself ? medications to target COVID-19 used ?

hemodynamic instability ? shock ? ), all studies in table 1 should include all of these data,

A: Thanks for this very interesting suggestion.

We considered to draw a table with information suggested by the reviewer, but because the available trials are essentially retrospective and observational, such information as shock or hemodynamic instability are not recorded. For an indirect point of view of that general information about severity and complication rates of the disease, we included a table (Table 1) where the reader would have an overview of patients' severity and overall complications. Although further details may be missing. As discussed in the text, the more severe patients presented a higher rise in liver enzymes, though even in these extremely sick patients the liver enzymes are not very elevated, after all. Most of them present liver enzymes increment below twice the ULN.

In that new Table 1 were also included information such as the frequency of use of antivirals and antimicrobials *per* severity of disease, as suggested by the Reviewer.

In OTHER CAUSES OF LIVER INJURY IN SARS-COV-2 section, page 8 (shown in yellow color) we introduce an explanation (text below) about the difficult to establish a causality relationship between a specific drug and liver injury during COVID-19 infection

In the reviewed papers, antivirals and antimicrobials were often prescribed to COVID-19 patients, ranging from 21% to 93% and 58% to 100%, respectively and many times they were used simultaneously.[5-11,13,17] Liver enzymes abnormalities were often seen, even in the trials that less frequently used antiviral treatment[6,8,11]. In Zhou et al trial, lopinavir/ritonavir was used in around 20% of the patients either they survive or not, and ALT abnormalities was observed in 24 and 48% respectively [8]. There is also a wide variability in antivirals prescribed to patients, such as oseltamivir, remdesivir, lopinavir/ritonavir and ganciclovir. The same is also observed with the use of antimicrobials, either alone or in combination with antivirals and other drugs. This does not allow us to establish a clear causality relationship or even the amount of importance to the use of this drugs and the liver injury. Besides it the histopathological findings do not suggest a DILI pattern [23].

In our mini-review, we also discuss DILI mainly related to azithromycin and hydroxychloroquine due to the rise in the volume of those prescribed drugs in some countries. This would come as a note of caution for the doctors. However, the amount of scientific information regarding those drugs and DILI are not too robust as expected, being mainly case reports. When we draw a table, as suggested by the reviewer, we observed that those drugs were not as much prescribed in most part of the trials. Therefore, a straightforward relationship between them and DIL may not be clear-cut. But we think this note of caution should be kept to clinicians in the COVID-19 frontline.

2. R: Furthermore, the authors should provide another table comparing liver indices data among COVID-19 patients without treatment and with COVID-19 who were treated with anti-virals and antibiotics.

A: Thanks for this suggestion.

In the new table inserted in manuscript, information regarding frequency of antivirals and antimicrobials use and stratification by severity of the disease were also noted. However, as stated above, the so far published and revised trials do not describe such findings separately, therefore, not allowing to a clear-cut analysis in this subject.

3. R: Moreover, another important issue in this paper is the issue of DILI, as it is known that one of the most difficult issues in the diagnosis of DILI is the determination of causality, in this setting the authors should provide data regarding the ways and approaches used to assess causality, mainly discussing the Roussel Uclaf Causality Assessment Method (RUCAM) scale.

Finally, regarding the histopathological findings, the authors should add a table describing the histopathological liver findings in pure patients with COVID-19 with and without anti-viral/antibiotics therapy, as well including liver finding among non-COVID-19 patients who were treated with lopinavir/ritonavir and remdesivir, chloroquine and hydroxychloroquine antimalarials, antibiotics including azithromycin, or immune-modulators such as tocilizumab and who developed DILI - this table is needed to summarize the histopathological findings and to ease it for the readers.

A: Ok, we agree. Thanks !

We introduced a sentence stressing that so far the main histopathological findings in the liver parenchyma during COVID-19 are due to vascular phenomena, at page 7, shown in yellow color.

Therefore, the largest study describing liver histopathological findings is from Milan. This trial performed post-mortem liver biopsy in 48 individuals, but most of these patients were on medical treatment with drugs, but they did not name them. Possibly all of them were on drugs, once the median time of hospitalization before death was 7 days, ranging from 1 to 21 days. Trials cited in this mini review emphasize the wide use of drugs in this population of patients.

Besides all of that, the main histopathological findings are suggestive of vascular abnormalities, possibly due to the rise in arterial blood flow to the liver related to cardiac injury and thrombotic events in the portal tract and sinusoids. These thrombotic events may be triggered by the coagulation cascade induced by the inflammation/infections or by endothelial injury seen in COVID-19. Furthermore, some cases of risen serum liver enzymes may be explained by vascular thrombi within the liver that might trigger parenchymal focal necrosis. And most of the histopathological findings observed in COVID-19 are not suggestive of DILI.

Additionally, as stated by the reviewer, it is highly difficult to establish a causality relationship between a specific drug and liver injury during COVID-19 infection, because most of the times they are used as combination of antimalarials, antivirals, antimicrobials, anticoagulants and sometimes vasoactive drugs. This comment was introduced at page 9, before the CONCLUSION, shown in yellow color.

Thanks

Authors