TGH TRANSLATIONAL GASTROENTEROLOGY AND HEPATOLOGY
A RISING JOURNAL FOR HIGH-QUALITY RESEARCH IN GASTROENTEROLOGY AND HEPATOLOGY

Peer Review File

Article Information: http://dx.doi.org/10.21037/tgh-20-243

Review Comments A:

The Authors hereby present a brief review about liver involvement during COVID-19, providing useful and reasonable advice for the management of patients with chronic liver disease in the era of the SARS-CoV-2 pandemic.

The review covers a wide range of topics and is of course timely, given the spread of the still ongoing pandemic, but a general update of the data is necessary since they seem to be freezed in May 2020 and the last two months have provided new important evidence in this ever-changing field.

We appreciate the opportunity to update this manuscript with new data after its initial submission in June. Information from additional studies is highlighted in the manuscript in yellow.

I must underline some issues I find critical before considering this paper acceptable for publication:

- Multiple times across the text (Lines 30-31, Line 62, Line 124, Lines 226-227), the Authors state that SARS-CoV-2 is able to invade gastrointestinal epithelial cells, hepatocytes, and biliary epithelial cells without providing any reference supporting this information. This is a crucial issue and deserves at least a small argumentation:

albeit a direct invasion of cholangiocytes has been demonstrated in vitro (Zhao, Protein and cell, 2020), to my knowledge it hasn't yet been proven in or ex vivo so far.

We agree that this is speculative, as direct invasion into hepatobiliary cells leading to pathogenesis by SARS-CoV-2 is not proven. We have added one more reference (ref 6) to this (reference 8 which was already present in the earlier version refers to the increased concentration of ACE-2 receptors on biliary epithelial cells

compared to GI epithelial cells). We have added another reference in the pathogenesis section (ref 29), which is a report of postmortem biopsies, in which authors report the presence of SARS-CoV-2 in 15 of 22 samples in blood clot or endothelial cells by in situ hybridization testing.

- "higher transaminase levels [...] to the intensive care unit (ICU)" (Lines 73-74) deserves at least a reference;

References are in table 1 (and are mentioned again in the text).

- "Abnormal liver associated enzymes (LAEs) are reported in 16 to 53% of cases in different series" (Lines 70-71): the highest incidence rate of LAEs across the published series is of 58% (Piano et al, Liv Int, 2020);

A more recent study has reported abnormal LAEs in 83% and we have included this reference in this revision (ref 27).

- "This pattern of abnormal LAEs is comparable to that reported with the two previous influenza pandemics" (Lines 76-77): it is not clear whether this statement came from published studies (in case, add the reference) or unpublished data from the Authors (in case, explain it in the text);
We now include this reference immediately following this sentence in this revision but qualify this with newer information that the prevalence of elevated LAEs may be higher than previously reported based on the recent study noted above (Hundt et al, *Hepatology* 2020, ref 27).

- The Authors examined only chinese and north american cohorts. I believe that adding data from italian cohorts could help in understanding the phenomenon of liver involvement during COVID-19, since Italy has a lower prevalence of HBV infection than China and a lower prevalence of MAFLD than the USA. Cite Ponziani et al, Aliment Pharmacol Therapy, 2020 (doi: 10.1111/apt.15996) and Piano et al, Liv Int, 2020 (doi: 10.1111/liv.14565);

We cited D'Antiga et al (Italy), Tschopp J et al (Swiss), Bhoori et al (Italy) and Fernández-Ruiz et al (Spain), Ponziani et al (Italy) and Piano et al (Italy). We have added another study by Sonzogni et al (Italy).

- Cite reference no. 34 in its peer-reviewed form, as recently published in Nature (doi: 10.1038/s41586-020-2521-4).

This is now reference #X and has been cited properly.

Review Comments B:

The primer by Thandassery and colleagues is an update on liver disease in the COVID-19 pandemic. This area is fast-moving and primers such as this will be useful for clinicians and researchers. The primer describes the effects of infection on liver associated enzymes, as well as the risk for patients with pre-existing liver disease including those on immunosuppression or transplant recipients. It is well written and referenced.

Minor suggestions:

The most well referenced area in liver disease and COVID-19 is the increased liver associated enzymes that are observed in a third of patients. However, these mostly normalise with the resolution of infection. It would therefore help the reader to be able to know the relative importance of this information. Could the authors comment on how valuable the LAE data are to clinicians in treating COVID? Are LAEs currently being used as markers by clinicians to grade COVID-19 severity or are they not a major consideration?

LAEs improve spontaneously in most cases. But more severe elevation of LAEs is generally seen with severe COVID-19 infection. Thus far LAEs have not been used as surrogate markers in clinical care. There are more established pulmonary and systemic indicators for monitoring severity and prognostication.

In contrast the data on chronic liver disease being a risk factor for death in COVID-19 patients deserves more attention in the primer. A section describing any explanations (even hypothetical) for this increased risk is warranted.

We have addressed this in greater detail. Any infection can cause worsening of pre-existing chronic liver disease. It stands to reason that COVID-19, just like other systemic infections, can trigger acute on chronic liver failure.

Review Comments C:

Overall a well-built and significant utility work

TGH TRANSLATIONAL GASTROENTEROLOGY AND HEPATOLOGY
A RISING JOURNAL FOR HIGH-QUALITY RESEARCH IN GASTROENTEROLOGY AND HEPATOLOGY

Thank you for this comment.

Review Comments D:

- Introduction section: please underline the recent epidemiology scenario of COVID-19 worldwide state, with regards to the Countries with high prevalence
- Pathogenesis section: recently Abenavoli et al. describe al the proposed mechanisms related to liver disease onset in COVID-19 picture (PMID: 32509818). In particular, i suggest the Author to report data about the described "cytokine storm" present in the final disease stages

Although we discussed the role of immune hyperactivation, the term cytokine storm was added to the manuscript

- Liver biopsy: limited data reported in literature, describe a histology picture like to DILI or NASH. Please report it

The report of histology resembling NASH is cited. Another recent case series of postmortem liver biopsy has been added to the manuscript.

- Microbiota: few reports indicate that during SARS-Cov-2 infection is present a dysequilibrium in gut microbiota composition. What is the idea of Author about it?

We didn't find sufficient, clinically relevant data on the role of intestinal microbiota in COVID-19 to warrant mentioning in this limited review.

- Summary section: many pivotal questions are actually open. In particular, its origin, the duration of transmission in humans, the ability to infect other animal hosts and the pathogenetic spectrum of human infections. The study of virus in successive generations of human infections will be the way to follow viral evolution and to improve diagnostic tools. Another challenge is manufacturing proteins from the virus, needed to develop fast a potential vaccine (PMID: 32116200)

We agree with this comment. So many questions are unanswered as we are just beginning to understand this complex infectious disease.

TGH TRANSLATIONAL GASTROENTEROLOGY AND HEPATOLOGY
A RISING JOURNAL FOR HIGH-QUALITY RESEARCH IN GASTROENTEROLOGY AND HEPATOLOGY

Review Comments E:
Summary of research:

Thandassery and co-authors review and summarize here the latest research regarding COVID-19 and its impact on liver related aspects of disease and treatment.

Comments to the Author:

There are some minor corrections to be done:

1) On line 51 please set a timepoint of your reference from the Johns Hopkins Coronavirus Resource Center regarding number of deaths caused by COVID-19 (is it June 8, 2020?).

Thank you for this suggestion. We have added the last date of accession.

2) On line 127 please split the two words "DILI" and "have", as well as "been" and "reported". Please do the same on line 215 ("for" and "liver").

These errors have been corrected.

3) On Table 1 please correct on Huang et al. reference with: 31% instead of 31·0% under Pattern of LAEs, and split the two words "of" and "abnormal" under Comments. Please correct with % under Pattern of LAEs on Yang et al. reference, if this is how do you mean with the number of 29. Please split the two words "AILD" and "is" under Comments on Di Giorgio et al. reference.

These errors have been corrected.
4) On summary (line 227), you talk about implications of fecal shedding of viral RNA. Unfortunately, this topic is not faced at all on any previous chapter of this review. Please consider providing just a couple of lines about it inclusive of reference(s) on a separate section of the paper, i.e. in the introduction while talking about the gastrointestinal involvement by COVID-19.

While we mentioned the finding of fecal isolation of the virus, the implications of the same in etio-pathogenesis of GI and liver disease is not clear. This has been elaborated upon in the revised manuscript.