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Title: Liver dysfunction as a cytokine storm manifestation and prognostic factor for severe COVID-19

Manuscript Type: Mini Review

Authors: Gergana Taneva, Dimitar Dimitrov, Tsvetelina Velikova

Dear Editors,

Dear Reviewers,

Thank you for your time to review our paper. We acknowledge that our paper might have some issues in the conformity with the following comments.

We took into account all the comments and suggestions the reviewers made. We have made the respective changes in the manuscript according to the remarks. Those changes are highlighted within the manuscript (and while using track changes). Please see below, in blue, for a point-by-point response to the reviewers' comments.

Reviewer #03441022

Conclusion: Major revision

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

The manuscript by Taneva et al. reviews the existence literature on liver dysfunction in Covid19 patients. The authors try to answer the question if that might be the prognostic factor for the severe Covid19 course. Te article reads well, however some issues should be expanded and clarified.

➤ Thank you very much for the evaluation of our paper as overall good.

1. The authors should include the information on SARS-CoV-2 in the Introduction section and cite relevant papers.

- We agree with the referee that general information on SARS-CoV-2 should be included in the Introduction section.

2. In the Introduction section the authors claim "Abnormal liver function is expected during COVID-19 infection." However it is not clear why is expected. The authors should explain it.

- Thank you for the valuable note; We have added explanation why we expect abnormal liver function.

3. "Cytokine storm syndrome occurring in COVID-19 infected patients involved many organs, liver as all [4]." As well?

- Thank you for the valuable note, We have added the other organs damaged by cytokine storm.

4. "There are three important 'actors' found to be guilty of the liver damage during COVID-19 – " Actors usually are not guilty. This sentence should be rewritten. It is also not clear why these conditions were chosen? Reference(s) could help.

- We have corrected the mentioned issue. We meant factors, but made a technical mistakes of writing "actors". We extended that paragraph.

5. "SARS-CoV-2 affects the liver by binding toACE2 receptors on cholangiocytes. This caused dysfunction and inducing a systemic inflammatory response leading to severe liver injury. Indeed, the specific expression of ACE2 in bile duct cells is higher than that in the hepatocytes." It was recently published that SARS-CoV-2 Spike protein binds the asialoglycoprotein receptor of located on human hepatocytes (Hepat Med. 2021 Apr 14;13:37-44. doi: 10.2147/HMER.S301979. Please discuss this issue.

- Thank you for the valuable suggestion. We extended the paragraph to further discuss the issue.

6. “Effenberger et al. [7] discovered a clear link between systemic inflammation (as measured by IL-6, CRP, and ferritin) and liver damage. IL-6 development can be attributed to immune cells, fibroblasts, endothelial cells, and hepatocytes, which orchestrate an acute phase response in the liver. Though IL-6 signaling impacts hepatic regeneration, clinical trials (for example, testing the effect of IL-6 administration in cancer patients) have shown that this pathway is essential in hepatic injury and hepatotoxicity [7]. The authors also found a strong association between acute-phase proteins and IL-6 in the serum of COVID-19 patients with elevated AST, which is consistent with the importance of systemic inflammation and, in particular, IL-6 on liver injury.” The main sources of IL-6, which is the chief stimulator of the production of most acute phase proteins, are macrophages and monocytes at inflammatory sites. It has been shown that macrophages and monocytes produce high amounts of IL-6 in response to SARS-CoV-2 proteins (Vaccines (Basel). 2021 Jan 15;9(1):54.doi: 10.3390/vaccines9010054.) Please include this information and citation.

➤ Thank you for the important suggestion. We have included the information in our paper.

7. “Liver biopsies revealed moderate microvesicular steatosis with slight lobular and portal inflammation, indicating either direct viral or drug-induced liver damage [15]. It is proposed that a direct virus-mediated cytopathic effect exists. The latter can result after triggered immunological reactions and inflammatory cytokines, leading to liver damage [16,17].” Here the authors should expand this paragraph and write about liver infiltrating cells that may initiate the inflammation e.g. Front Immunol. 2018; 9: 2948.

➤ Thank you for the important suggestion. We have included the information in our paper.

8. “Many of the patients have been treated with antipyretic agents such as acetaminophen, which can cause significant liver damage, as well [18]. Many of the patients have been treated with antipyretic agents such as acetaminophen, which can cause significant liver damage, as well [18]. Covid19 patients are treated with many others drugs. Please expand this paragraph and check if others can also lead to liver injury.

➤ Thank you for the important suggestion. We have included the information in our paper.

9. In conclusion section the authors should clearly state if liver dysfunction is a prognostic factor for severe Covid19 patients (as suggested in the title).

➤ Thank you for the important suggestion. We have included the information in our paper.

10. All acronyms should be spelled out the first time are mentioned or the authors should include abbreviation section into the manuscript.

➤ Thank you for the valuable note. We have extended all the abbreviations when mention.