

PEER-REVIEW REPORT

Name of journal: *World Journal of Hepatology*

Manuscript NO: 67387

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

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03441022

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Poland

Author's Country/Territory: Bulgaria

Manuscript submission date: 2021-04-22

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-04-23 09:19

Reviewer performed review: 2021-04-28 09:27

Review time: 5 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

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. The article reads well, however some issues should be expanded and clarified.

1. The authors should include the information on SARS-CoV-2 in the Introduction section and cite relevant papers.
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.
3. "Cytokine storm syndrome occurring in COVID-19 infected patients involved many organs, liver as all [4]." As well?
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.
5. "SARS-CoV-2 affects the liver by binding to ACE2 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.
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. 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. 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. 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). 10. All acronyms should be spelled out the first time are mentioned or the authors should include abbreviation section into the manuscript.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Professional title: Associate Professor

Reviewer's Country/Territory: Poland

Author's Country/Territory: Bulgaria

Manuscript submission date: 2021-04-22

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-07-29 02:11

Reviewer performed review: 2021-07-29 02:20

Review time: 1 Hour

Scientific quality	<input checked="" type="radio"/> Grade A: Excellent <input type="radio"/> Grade B: Very good <input type="radio"/> Grade C: Good <input type="radio"/> Grade D: Fair <input type="radio"/> Grade E: Do not publish
Language quality	<input checked="" type="radio"/> Grade A: Priority publishing <input type="radio"/> Grade B: Minor language polishing <input type="radio"/> Grade C: A great deal of language polishing <input type="radio"/> Grade D: Rejection
Conclusion	<input type="radio"/> Accept (High priority) <input checked="" type="radio"/> Accept (General priority) <input type="radio"/> Minor revision <input type="radio"/> Major revision <input type="radio"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="radio"/> Anonymous <input type="radio"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors improved the manuscript significantly, thus I have no further comments.