Reviewer #1:

Specific Comments to Authors: As the author comments, further studies are needed to determine the causes of liver injury in COVID-19 and the effect of existing liver-related comorbidities on the treatment and outcome of COVID-19.

Added :

Although, the SARS-CoV-2 viral particles have not yet been identified in hepatocytes, the autopsy of COVID-19 patients have demonstrated microvesicular steatosis and portal inflammation[13], pointing towards hepatic involvement in SARS-CoV-2 infection as well.

13. **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory medicine*. 2020;8(4):420-2.PMID: 32085846.DOI: 10.1016/s2213-2600(20)30076-x.

Both the innate and adaptive immune pathways have been implicated in the pathogenesis of SAR-CoV-2 infection. Innate immune cells of the pulmonary system include antigen presenting cells which make the first contact with the virus[15]. They activate the adaptive CD4+ and CD8+ T-cells, which in turn activates the humoral and cytotoxic immune responses, respectively[15]. This causes T-cell mediated destruction of viral infected cells which in turn leads to further inflammation creating a vicious inflammatory cascade[16]. In severe cases, this leads to an overwhelming release of inflammatory cytokines, such as IL-6, IL-10, TNFα and T- Cell exhaustion[15, 16]. This aberrant systemic inflammatory response also called cytokine storm is not only implicated in ARDS and respiratory failure, but also in shock and multi-organ failure seen in severe cases[16, 17]. Severe hypotension and hypoxemia that follows can lead to hepatic ischemia and hypoxia-reperfusion injury resulting in hepatocellular injury and death[16]

15. **Yuki K**, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. *Clinical immunology (Orlando, Fla)*. 2020;215:108427.PMID: 32325252.DOI: 10.1016/j.clim.2020.108427.

Exacerbation of chronic liver diseases (CLD), either from the overall inflammatory stress or consequence of experimental pharmacotherapies is also a possibility. Furthermore, therapeutic interruptions due to fear of contracting the infection is also

common which can cause a relapse of these conditions. Due to these reasons, some have suggested that liver damage seen in SARS-CoV-2 infection can be partially attributed to presence of an underlying CLD[19].

19. **Li Y**, Xiao SY. Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical implications. *Journal of medical virology*. 2020.PMID: 32369204.DOI: 10.1002/jmv.25973

Many of the currently approved or experimental therapeutic agents including antivirals, antibiotics, immunomodulators and steroids have a well-known adverse effect of hepatotoxicity[14].

Medications as common as acetaminophen, that may be used for its antipyretic and analgesic can inadvertently contribute to liver injury especially in those with chronic liver disease. Other experimental medications such as antivirals (eg. Remdesivir, Lopinavir/Ritonavir, Oseltamavir etc), imunomodulators (Tocilizumab) and antibiotics commonly prescribed (eg. Azithromycin) are also hepatotoxic[14, 17].

14. **Barlow A**, Landolf KM, Barlow B, Yeung SYA, Heavner JJ, Claassen CW, Heavner MS. Review of Emerging Pharmacotherapy for the Treatment of Coronavirus Disease 2019. *Pharmacotherapy*. 2020;40(5):416-37.PMID: 32259313.DOI: 10.1002/phar.2398

Some reports have indicated a higher disease severity in patients with chronic hepatitis B[22]

22. **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England journal of medicine*. 2020;382(18):1708-20.PMID: 32109013.DOI: 10.1056/NEJMoa2002032.

NAFLD patients, not only demonstrate a significantly higher disease severity but due to poorly understood mechanisms also show a prolonged shedding of SARS-CoV-2 virus[27]

27. **Ji D**, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *Journal of hepatology*. 2020.PMID: 32278005.DOI: 10.1016/j.jhep.2020.03.044

A case series from an area with a high SARS-CoV-2 infection rates from Northern Italy, reported good outcome for majority of AILD cases and suggested against the tapering of immunosuppressive therapies as previously thought[28]

28. **Di Giorgio A**, Nicastro E, Speziani C, De Giorgio M, Pasulo L, Magro B, Fagiuoli S, L DA. Health status of patients with autoimmune liver disease during SARS-CoV-2

outbreak in northern Italy. *Journal of hepatology*. 2020.PMID: 32413378.DOI: 10.1016/j.jhep.2020.05.008

Withholding immunosuppressants may cause graft rejection while continuation may increase susceptible to infection. Even the etiology of liver function derangements in such patients may be difficult to accurately determine. This dilemma has recently been addressed by multiple liver disease societies (AASLD, APASL and EASL), who have recommended against the reduction of immunosuppressive therapy in patients with mild COVID-19[30].

30. **Lau G**, Ward JW. Synthesis of Liver Associations Recommendations for Hepatology and Liver Transplant Care During the COVID-19 Pandemic. *Clinical liver disease*. 2020;15(5):204-9.PMID: 32489655.DOI: 10.1002/cld.972.

(1) Science Editor: Issues raised:

(1) The "Author Contributions" section is missing.

Added the author contribution section:

AUTHOR CONTRIBUTIONS

CONCEPTION OF IDEA and CRITICAL REVISIONS: Veysel Tahan

WRITING OF MANUSCRIPT: Harleen Kaur Chela

WRITING OF MANUSCRIPT: Syed Bilal Pasha

REVIEWING AND EDITING OF MANUSCRIPT: Omer Basar

REVIEWING AND EDITING OF MANUSCRIPT: Ebubekir Siddik Daglilar

(2) PMID and DOI numbers are missing in the reference list.

Added PMID and DOI numbers in the reference list for all except:

PMID and DOI N/A for ref #1 because it is a book article

PMID N/A for ref#11 (DOI is added though)

(2) Editorial Office Director: I have checked the comments written by the science editor. I suggest that the manuscript type should be changed as Minireviews.

Changed Manuscript type as Minireview

Overall changed polished the language as asked by the reviewers. All the changes are tracked.