

Reviewer's Comments	Authors Response
Reviewer #1 Scientific Quality: Grade A (Excellent) Language Quality: Grade A (Priority publishing) Conclusion: Accept (General priority) The author reviewed the origin of corona virus detailly as well as its transmission and mutation. Five SARS-CoV-2 strains were listed in Table 1. The liver is one of the favorite proliferation spots for coronaviruses. It has been evaluated in many studies that around 1/3rd of the Covid-19 patients complained about liver dysfunction. The article deduced mechanism of corona virus inducing liver dysfunction, that included hepatocyte ballooning	The authors are highly grateful to the reviewer for their appreciating and humble comments. Thanks for your kind consideration. We have supported the facts with relevant references cited in the revised manuscript. References have been increased from 52 (unrevised) to 129 in the revised manuscript.

majorly, eosinophilic action creating a cytokine storm, hypoxia, and ischemia leading to liver necrosis. Actually ACE-2 aided viral invasion and damage mediating immune response was the key factor. The article elaborated the molecular features after coronaviruses invaded liver cells, as well as the latest confirmed signal path. The author expounded the newest pharmacologic therapies specific to corona-associated hepatic injure, including immunomodulators and anti-inflammatory agents, anti-viral drugs and neutralizing antibodies. The article is very novel and contains many cutting-edge knowledge, which can be

helpful for future basic and clinical research.	
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Reviewer #2 Scientific Quality: Grade C (Good) Language Quality: Grade B (Minor language polishing) Conclusion: Major revision The idea of the review itself is innovative and will be useful for researchers planning experimental work. The authors were particularly successful in their comparative analysis of viruses. However, when authors reviewing the association of SARS-CoV-2 infection with the liver, they present numerous controversial claims that require more rigorous confirmation. Some of examples are presented below: 1. "cytokine upsurge owing to multiorgan failure" 'Since liver is the primary	The authors appreciate the astute and valuable comments of the reviewer. We have attempted to provide sufficient justifying references to resolve the controversial claims (all highlighted in yellow in the article). References have been increased from 52 (unrevised) to 129 in the revised manuscript. We inserted appropriate references to justify the claims as Racanelli V, Rehermann B. The liver as an immunological organ. <i>Hepatology</i>. 2006 Feb;43(2 Suppl 1):S54-62. doi: 10.1002/hep.21060. PMID: 16447271. 'Hepatic involvement in COVID-19 could be related to the direct cytopathic effect of the virus, an uncontrolled immune reaction' 'viruses may enter the portal circulation, and reach the liver' Thus is a shared gateway Wu J, Song S, Cao HC, Li LJ. Liver diseases in COVID-19: Etiology, treatment and prognosis. <i>World J Gastroenterol</i>. 2020 May 21;26(19):2286-2293. doi: 10.3748/wjg.v26.i19.2286. PMID: 32476793; PMCID: PMC7243650. Lei HY, Ding YH, Nie K, Dong YM, Xu JH, Yang ML, Liu MQ, Wei L, Nasser MI, Xu LY, Zhu P, Zhao MY. Potential effects of SARS-CoV-2 on the gastrointestinal tract and liver. <i>Biomed Pharmacother</i>. 2021 Jan;133:111064. doi: 10.1016/j.biopha.2020.111064. Epub 2020 Nov 28. PMID: 33378966; PMCID: PMC7700011.
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site of synthesis of proteins associated with immunity” “After almost three years of corona panic, it is still disquietude as to what makes these viruses jump onto a human host and invade hepatocytes as a shared gateway-detection of the SARS-CoV-2 in the liver does not confirm virus enters the hepatocytes. It can be detected in the liver because of its presence in the bloodstream. Please, provide the journal readers with evidence that hepatocytes are SARS-CoV-2 gateway. 2.“the liver serves as one of the favorite proliferation spots for coronaviruses since it is a common gateway for viruses entering the blood”- please provide a reference to the	Zhong P, Xu J, Yang D, Shen Y, Wang L, Feng Y, Du C, Song Y, Wu C, Hu X, Sun Y. COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms. <i>Signal Transduct Target Ther.</i> 2020 Nov 2;5(1):256. doi: 10.1038/s41392-020-00373-7. PMID: 33139693; PMCID: PMC7605138. Reference to the study in which viral proliferation in hepatocytes was confirmed. doi: https://doi.org/10.1038/d41586-020-01864-x <i>We have revised the text and References and quotes from research papers justifying those viruses replicate in liver cells are provided in the revised manuscript and highlighted</i> Wu J, Song S, Cao HC, Li LJ. Liver diseases in COVID-19: Etiology, treatment and prognosis. <i>World J Gastroenterol.</i> 2020 May 21;26(19):2286-2293 Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. <i>JAMA.</i> 2020 Mar 17;323(11):1061-1069. doi: 10.1001/jama.2020.1585. Erratum in: <i>JAMA.</i> 2021 Mar 16;325(11):1113. PMID: 32031570; PMCID: PMC7042881.
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study in which viral proliferation in hepatocytes was confirmed. "Even autopsies and biopsies performed post-mortem on the liver reflected that corona virus-2 inflicted cholangiocytes, hepatocytes, and endothelial cells, causing severe liver damage." – infliction does not mean replication. 3. reference on the study with 11 deceased patients's autopsies is not sufficient to make conclusion about mechanisms of liver injury by SARS-CoV-2 virus. Ischemic hepatitis is characterized by an extremely high elevation of transaminases, but that is not the case in SARS-CoV-2 patients. Drawing on our experience and that of other	These are experimental results: We are supporting these claims with references to the corresponding experiments rather than relying on reviews This is also attested by many other studies: Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061-1069. doi: 10.1001/jama.2020.1585. Erratum in: JAMA. 2021 Mar 16;325(11):1113. PMID: 32031570; PMCID: PMC7042881. Tay SW, Teh KKJ, Wang LM, Ang TL. Impact of COVID-19: perspectives from gastroenterology. Singapore Med J. 2020 Sep;61(9):460-462. doi: 10.11622/smedj.2020051. Epub 2020 Apr 13. PMID: 32279480; PMCID: PMC7927171. All the claims have been supported by suitable references as per the suggestion. We have thoroughly checked the references and edited wherever wrong doi were mentioned.
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clinicians, most SARS-CoV-2 infected patients with elevated liver enzymes (including those with underlying liver disease) do not experience a cytokine storm either.

Please reconsider the liver involvement in the review. In conclusion, as the authors make many controversial claims concerning mechanisms of liver injury in SARS-CoV-2 infected patients, it would be preferable to support these claims with references to the corresponding experiments rather than relying on reviews.

4. Please check the reference for the proper PMID and DOI (11 reference - wrong DOI).	
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Reviewer #3 Scientific Quality: Grade E (Do not publish) Language Quality: Grade C (A great deal of language polishing) Conclusion: Rejection 1. Authors mentioned in the abstract section that "The epicenter of this disease, China alone, carries a burden of 300 million chronic liver patients, which could deluge the death toll owing to Covid". The above description of defining China as the epicenter of Covid-19 is contrary to the current international data on Covid-19 and lacks essential scientific spirit, so please excuse the rejection of this manuscript.	We respect the reviewer's sentiments (concerning the description of China as the epicenter of COVID-19) but with no bias or any intentional content, we have cited sufficient references to buttress the fact which has been repeatedly quoted in many research papers (international data) published in some of the most reputed journals like Nature, Science etc. (highlighted in yellow). The reviewer may kindly go through any of the mentioned articles for confirmation as doi: https://doi.org/10.1038/d41586-022-00584-8 doi: 0.1126/science.abp8715 https://www.science.org/doi/10.1126/science.abp8715 doi: 10.1016/j.socscimed.2021.114371 doi: 10.1016/j.psychres.2020.112998 https://doi.org/10.1159/000508448 DOI: 10.1126/science.abp8715 https://doi.org/10.1148/radiol.2020200274 DOI:https://doi.org/10.1016/j.lanwpc.2021.100094 2.The references supporting the facts are incorporated for the kind appraisal of the reviewer. Hopefully these sufficiently justify and attest the author's description. We have incorporated the sources of these data (highlighted in yellow).
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2. Some currently used vaccines are listed in Table 2. However, the descriptions of the efficacy of some vaccines are quite different from each other and not specific enough, for example, "efficacy of 70.4%", "73.1% efficacy", and "95% protection against COVID-19", and the sources of these data is not apparent in this manuscript. 3. Furthermore, the descriptions of doses in Table 2 are also confusing, which include "2 doses", "2 dose", "two doses", and a missing item.	3. Description of doses have also been corrected as per the suggestion.
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Revision reviewer's Comments:

Query 1: Thanks for the author's reply, but I still can't accept the author's response and inaction to the first question. The authors mentioned in the abstract that "the epicenter of this disease, China alone, carries a burden of 300 million chronic liver patients, which could deluge the death toll owing to Covid". 1. Since the original manuscript was pointed out to be easily misunderstood and the authors mentioned "with no bias or any intentional content" in their response, why didn't the author adjust this sentence?

Author's Response: As per the reviewer's suggestions, we have removed the sentence mentioned in the abstract that "the epicenter of this disease, China alone, carries a burden of 300 million chronic liver patients, which could deluge the death toll owing to Covid".

Query 2. Could you please add references in the main text to the data mentioned in this sentence, and to deaths due to COVID-19 in patients with liver diseases?

Author's Response: A reference number 7 is already there in the introduction part of R1 as "Kovalic AJ, Huang G, Thuluvath PJ, Satapathy SK. Elevated Liver Biochemistries in Hospitalized Chinese Patients with Severe COVID-19: Systematic Review and Meta-analysis. Hepatology 2021; 73(4): 1521-1530 [PMID: 32692464 PMCID: PMC7405102 DOI: 10.1002/hep.31472]"

Query 3. The author highlighted the fully vaccinated data in the conclusion part. Could you please add some references?

Author's Response: WHO Report Reference included in the conclusion part as (<https://www.who.int/publications/m/item/covid-19-vaccine-implementation-analysis-insights-2-september-2022>)