

Response Reviewers

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: please check in the reference 43. make a correction

Response: In the manuscript in section SARS-COV-2 AND THE PANCREAS- 2nd paragraph the sentence “In a retrospective pooled analysis, the pooled prevalence of hyperlipasemia was 12% and the pooled odds ratio for severe COVID-19 was 3.143^[43]” was change to “In a retrospective pooled analysis, the pooled prevalence of hyperlipasemia was 11.7% and the pooled odds ratio for severe COVID-19 was 3.143^[43]”

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Authors tried to summarize the main mechanisms associated with gut damage during infection by SARS-CoV-2. I recommend this work for publication after authors provide the following justifications. 1. It is mentioned in the MS “The viral nucleocapsid protein of SARS-CoV-2 has been found in the GI lumen in the esophagus, stomach, duodenum, and the rectal glandular epithelial cells, suggesting this receptor as the entry point of the SARS-CoV-2 virus in the intestinal tract”. This statement seems contradictory with the previously published studies. Justify.

Response: Recently, a highly cited manuscript demonstrated the expression of ACE2 protein on glandular cells of gastric, duodenal, rectal epithelia (abundantly expressed), and esophageal mucosa (less expression), supporting the entry of SARS-CoV-2 into the host cells by immunofluorescent technique. *Gastroenterology*.2020 May; 158(6): 1831–1833.e3. doi: 10.1053/j.gastro.2020.02.055. Evidence for Gastrointestinal Infection of SARS-CoV-2

In general, all coronaviruses encode a surface glycoprotein and spike protein that binds to host cell receptors ACE2 and allows virus entry. The spike (S) protein of SARS-CoV-2 has a high affinity for human angiotensin-converting enzyme 2 (ACE2), which is the main entrance into the cell^[10]. Furin is an enzyme found in the small bowel, acting as a serine-protease that can divide the viral S-protein into two fragments: S1 and S2, allowing them to interact with ACE2. The separation of the S-spike into S1 and S2 is essential for the attachment of the virion to both the ACE receptor and the cell membrane. *Hamming I, Timens W, Bulthuis ML, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203:631-7. DOI: 10.1002/path.1570* S-protein proteases, such as cathepsins, expose the fusion domain to the endosome by acid-dependent proteolytic cleavage. Successful virus entry also requires a cellular serine protease, transmembrane protease serine 2 (TMPRSS2)^[12]. TMPRSS2 cleaves the S protein of SARS-CoV-2 on the cell membrane; this is critical for the fusion of the viral and cell membranes. Importantly, both ACE2 and TMPRSS2 become highly expressed in the ileum and colon^[12–14]. Hoffmann et al. demonstrated recently that inhibition of the TMPSSR (the serine protease responsible for splitting the S-spike) blocks the infection of cells by SARS-CoV-2 (21). *Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020. DOI: 10.1016/j.cell.2020.02.052.*

2. Also add these published paper to literature review: Nazari, A., Jafari, M., Rezaei, N., Taghizadeh-Hesary, F., & Taghizadeh-Hesary, F. (2021). Jet fans in the underground car

parking areas and virus transmission. *Physics of Fluids*, 33(1), 013603. Rezaei, N., Jafari, M., Nazari, A., Salehi, S., Talati, F., Torab, R., & Nejad-Rahim, R. (2020). A novel methodology and new concept of SARS-CoV-2 elimination in heating and ventilating air conditioning systems using waste heat recovery. *AIP advances*, 10(8), 085308. Kalso, M. A., Piette, J. H., Hanna, J. A., & Giacomini, A. J. (2020). Coronavirus rotational diffusivity. *Physics of Fluids*, 32(11), 113101. Kalso, M. A., Chaurasia, V., Fried, E., & Giacomini, A. J. (2021). Peplomer bulb shape and coronavirus rotational diffusivity. *Physics of Fluids*, 33(3), 033115.

We added the following sentences in the manuscript with the reference that were suggested:

-The respiratory tract is the main entry route reported, and the transmission mechanism is via large droplets containing a high enough viral load. The virus is not motile by itself and depends on its rotational diffusivity to align its proteins (organized in hollow spikes called "peplomers") to its targets during the infection process. *Dbouk and D. Drikakis, "On coughing and airborne droplet transmission to humans," Phys. Fluids 32(5), 053310 (2020). Kalso, M. A., Piette, J. H., Hanna, J. A., & Giacomini, A. J. (2020). Coronavirus rotational diffusivity. Physics of Fluids, 32(11), 113101. Kalso, M. A., Chaurasia, V., Fried, E., & Giacomini, A. J. (2021). Peplomer bulb shape and coronavirus rotational diffusivity. Physics of Fluids, 33(3), 033115.*

"It has been reported that the survival time of SARS-CoV-2 in aerosol form is 4 hours, as the virus becomes inactive at 60°C. Propagation of the droplets in the air depends on the ventilation systems of the area where an infected person is spreading the virus while breathing without using personal protection equipment." *Rezaei, N., Jafari, M., Nazari, A., Salehi, S., Talati, F., Torab, R., & Nejad-Rahim, R. (2020). A novel methodology and new concept of SARS-CoV-2 elimination in heating and ventilating air conditioning systems using waste heat recovery. AIP advances, 10(8), 085308. Nazari, A., Jafari, M., Rezaei, N., Taghizadeh-Hesary, F., & Taghizadeh-Hesary, F. (2021). Jet fans in the underground car parking areas and virus transmission. Physics of Fluids, 33(1), 013603.*

EDITORIAL OFFICE'S COMMENTS

Science editor: 1 Scientific quality: The manuscript describes a minireview of the inflammatory effect on the gastrointestinal system associated with COVID-19. The topic is within the scope of the WJG. (1) Classification: Two Grades B; (2) Summary of the Peer-Review Report: In this review the author confirms summarize several mechanisms that probably responsible by covid in gastrointestinal system that can give us knowledge and reference. Author mention about the use of heparin can induce heparin thrombocytopenia but almost all covid patient have coagulation problem and treated with low molecular weight heparin. The questions raised by the reviewers should be answered; (3) Format: There is 1 table and 2 figures; (4) References: A total of 68 references are cited, including 64 references published in the last 3 years; (5) Self-cited references: There is no self-cited reference; and (6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade A and Grade B. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJG. 5 Issues raised: (2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (2) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese

herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 6 Recommendation: Conditional acceptance.

Response: , Heparin is usually administered to patients to prevent clot formation [2]. However, heparin-induced-thrombocytopenia (HIT) can be caused by heparin treatment and by a direct interaction between heparin and platelets, thus inducing platelet clumping or sequestration. This event occurs within the first 48-72 h after starting treatment and generates mild and transient thrombocytopenia [1]. In some cases, thrombosis could be associated with HIT after heparin cessation [3].

COVID-19 patients can also present a hyper-inflammatory state with a systemic response and cytokine storm mediated by IL-6, IL-8, and TNF- α , inducing platelet activation and thrombosis and endothelial dysfunction due to direct viral damage and inflammation [5]. Heparin is used in COVID-19 patients as a prophylactic to prevent thrombosis. However, low doses may not be enough to counteract the hypercoagulable state, leading to coagulation problems in these patients [4].