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Dear Journal Editor and Reviewers,

Thank you for your promptness, care and speed in reviewing my manuscript. Below is the response to reviewers:

1. **Reviewer 1:** (...) *you may need to read more about the proposed hypotheses of liver damage and check if the information provided doesn't exist already.*
2. **Science Editor 1:** (...) *All hypotheses need further explanation. In addition, the use of abbreviations is not standard. Furthermore, there are many details need to be corrected. The questions raised by the reviewers should be answered.*

Answer:

1. All acronyms were preceded in their literal form in the text;
2. The text was reviewed by a second and different reviewer (native English speaker);
- 3.1. To support the first hypothesis, the following studies were added:

Tseng H-S, Xiong W, Badeti S, Yang Y, Ma M, et al. Efficacy of anti-CD147 chimeric antigen receptors targeting hepatocellular carcinoma. *Nat Comm*; 2020; **11**: 4810. <https://doi.org/10.1038/s41467-020-18444-2>.

Zhang Q, Xiang R, Hou S, Zhou Y, Jiang S, Wang Q, et al. Molecular mechanism of interaction between SARS-CoV-2 and host cells and interventional therapy. *Signal Transduct Target Ther*. 2021; **6**, 23: doi.org/10.1038/s41392-021-00653-w

Wang K, Chen W, Zhang Z, Deng Y, Lian J-Q, Du P, et al. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. *Signal Transduct Target Ther.* 2020; 5: **283**. doi: 10.1038/s41392-020-00426-x.

Léger P, Tetard M, Youness B, Cordes N, Rouxel RN, Flamand M et al. Differential Use of the C-Type Lectins L-SIGN and DC-SIGN for Phlebovirus Endocytosis. *Traffic.* 2016; **17**, 6, 639-56. doi.org/10.1111/tra.12393

Kondo Y, Larabee JL, Gao L, Shi H, Shao B, Hoover CM, et al. L-SIGN is a receptor on liver sinusoidal endothelial cells for SARS-CoV-2 virus. *JCI Insight.* 2021; **6**,14, e148999. doi:10.1172/jci.insight.148999.

Gadanec LK, McSweeney KR, Qaradakhi T, Ali B, Zulii A, Apostolopoulos V. Can SARS-CoV-2 Virus Use Multiple Receptors to Enter Host Cells? *Int J Mol Sci.* 2021 Feb; 22(3): 992. doi: 10.3390/ijms22030992.

Gao C, Zeng J, Jia N, Stavenhagen K, Matsumoto Y, Zhang H et al. SARS-CoV-2 Spike protein interacts with multiple innate immune receptors. bioRxiv. 2020. doi: 10.1101/2020.07.29.227462.

Frayne J, Ingram C, Love S, Hall L. Localisation of phosphatidylethanolamine-binding protein in the brain and other tissues of the rat. *Cell Tissue Res* 1999; 298(3): 415-23.

These Papers demonstrate that since 1999 L-SIGN and CD147 receptors have been studied in the pathogenesis of liver infections. As much for its hepatic expression, as for its correction with immunity. This is true for several diseases (Hepatitis C, HIV, SARS) and, more recently, we discuss this hypothesis for SARS-CoV-2.

3.2. To support the second hypothesis, the following studies were added:

Zuo T, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H et al. Alterations in Gut Microbiota of Patients With COVID-19 During Time of

Hospitalization. *Gastroenterology* 2020; **159**: 944–955.
10.1053/j.gastro.2020.05.048

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497–506. 10.1016/S0140-6736(20)30183-5.

Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod Pathol.* 2020; **14**: 1-8. doi: 10.1038/s41379-020-0536-x

Cheng VC, Lau SK, Woo PC, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. *Clin. Microbiol. Rev.* 2007; **20**: 660–694. 10.1128/CMR.00023-07.

Vodnar D-C, Mitrea L, Teleky B-E, Szabo K, Calinoiu L-F, Nemes S-A, et al. Coronavirus Disease (COVID-19) Caused by (SARS-CoV-2) Infections: A Real Challenge for Human Gut Microbiota. *Front Cell Infect Microbiol.* 2020; 10: 575559. doi: 10.3389/fcimb.2020.575559

Parasa S, Desai M, Thoguluva Chandrasekar V. Prevalence of gastrointestinal symptoms and fecal viral shedding in patients with Coronavirus disease 2019: a systematic review and meta-analysis. *JAMA Netw Open.* 2020;**3**. doi: 10.1001/jamanetworkopen.2020.11335.

Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang Y-M et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut.* 2020; **69**:1002–1009. doi: 10.1136/gutjnl-2020-320926

Xie C, Jiang L, Huang G. Comparison of different samples for 2019 novel coronavirus detection by nucleic acid amplification tests. *Int J Infect Dis.* 2020;**93**:264–267. Doi: 10.1016/j.ijid.2020.02.050.

Mazza S, Sorce A, Peyvandi F, Vecchi M, Caprioli F. A fatal case of COVID-19 pneumonia occurring in a patient with severe acute ulcerative colitis. *Gut*. 2020;**69**:1148–1149. doi: 10.1136/gutjnl-2020-321183.

These papers discuss how - direct damage to the gastric mucosa; and the overgrowth of opportunistic bacteria can lead to dybiosis / worsening of the inflammatory response and organ ischemia (eg liver) and, consequently, worse prognosis and aggression in patients with COVID-19. Inclusive, it is noteworthy that this discussion comes from the involvement of SARS (2002) and is also present in other viruses transmitted by droplets of saliva such as H1N1.

3.3. To support the third hypothesis, the following studies were added:

Riera M, Anguiano L, Clotet S. et al. Paricalcitol modulates ACE2 shedding and renal ADAM17 in NOD mice beyond proteinuria. *Am J Physiol Renal Physiol* 2016; 310: F534–F546. doi: 10.1152/ajprenal.00082.2015

Zipeto D, Palmeira JF, Argañaraz GA, Argañaraz ER. ACE2/ADAM17/TMPRSS2 Interplay May Be the Main Risk Factor for COVID-19. *Front. Immunol.* 2020. doi.org/10.3389/fimmu.2020.576745.

Sama IE, Ravera A, Santema BT, van Goor H, ter Maaten JM, Cleland JGF, et al. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin–angiotensin–aldosterone inhibitors. *Eur Heart J* (2020) **41**:1810–7. doi: 10.1093/eurheartj/ehaa373.

Saheb Sharif-Askari N, Saheb Sharif-Askari F, Alabed M, Temsah MH, Al Heialy S, Hamid Q, et al. Airways Expression of SARS-CoV-2 Receptor, ACE2, and TMPRSS2 Is Lower in Children Than Adults and Increases with Smoking and COPD. *Mol Ther Methods Clin Dev* (2020) **18**:1–6. doi: 10.1016/j.omtm.2020.05.013

Fiorentino L, Vivanti A, Cavalera M, Marzano V, Ronci M, Fabrizi M, et al. Increased tumor necrosis factor α -converting enzyme activity induces insulin resistance and hepatosteatosis in mice. *Hepatology* (2010) **51**:103–10. doi: 10.1002/hep.23250.

Salem ESB, Grobe N, Elased KM. Insulin treatment attenuates renal ADAM17 and ACE2 shedding in diabetic Akita mice. *Am J Physiol Physiol* (2014) **306**:F629–39. doi: 10.1152/ajprenal.00516.2013

Al-Salihi M, Bornikoel A, Zhuang Y, Stachura P, Schelle J, Lang KS, Lang PA. The role of ADAM17 during liver damage. *Biol Chem.* 2021;402(9):1115-1128. doi: 10.1515/hsz-2021-0149.

In this case, studies presented as ADAM17 - the enzyme responsible for increasing the entry of SARS-CoV-2 into the cell is also responsible for liver damage. Thus, COVID-19 and liver damage from other causes may have a common genesis.

We hope that with this References, we can prove that the hypotheses demonstrated are feasible and are being discussed in the most renowned Journals in Hepatology and Gastroenterology. So there are. Although, they still need more robust studies to be proved.

Finally, it is noteworthy that, as an editorial, the authors aim to promote debate, instigate questions and foster possibilities on the subject.

Regards,