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It is our pleasure to resubmit a revised version of our manuscript (Manuscript NO: **65829**), now entitled "**Liver dysfunction and severe acute respiratory syndrome-coronavirus 2 infection**" for publication in the World Journal of Gastroenterology.

On behalf of the co-authors and mine, I would like to thank you for providing us the opportunity to revise and resubmit this manuscript. We appreciate the detailed comments from each reviewer and have incorporated the suggested changes into the manuscript to the best of our ability. The manuscript has certainly benefited from these insightful suggestions, and we look forward to working with you and the reviewers to move this manuscript toward publication in your journal.

The following pages include responses to each reviewers´ comments. Revisions to the text are highlighted in the revised manuscript as instructed in the decision letter.

We appreciate your time and consideration and hope our responses are satisfactory. Thank you again for your thorough review of our paper, as your suggestions and comments have helped us improve it greatly.

Please let us know if you require any additional information. We look forward to your decision.

Respecftully,

Abraham Edgar Gracia-Ramos MD, MSc

The corresponding author of this paper

RESPONSE TO REVIEWER

We wish to express our appreciation to the Reviewer for the insightful comments, which helped us significantly improve our paper.

Reviewer #1:

1. SARS-CoV-2 infection and liver dysfunction in patients with no previous liver disease-Epidemiology section (page 6-8) Some indicators such as ALT and AST are not specific indicators of liver dysfunction. Myositis is one of the common complications of COVID-19 (Tsivgoulis G, Palaiodimou L, et al. Neurological manifestations and implications of COVID-19 pandemic. Ther Adv Neurol Disord.2020 Jun 9; T Berth SH, Lloyd TE. Secondary Causes of Myositis. Curr Treat Options Neurol. 2020;22(11):38.), and some studies suggested that elevated aminotransferases in COVID-19 could also originate from myositis rather than liver injury (Bangash MN, et al. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol. 2020 Jun;5(6):529-530). Therefore, how to accurately determine whether patients have COVID-19-associated liver injury needs further discussion.

Response: Following the Reviewer's comment, we have added the following information on the manuscript (Pathophysiology section, page 10, line 21 – 25, references 46, 55 – 54):

"Transaminitis could originate from myositis rather than liver damage[52]. Muscular injury (defined as the presence of myalgias and creatinine kinase

[CK]>200 U/L) has been documented in 10% of hospitalized patients by COVID-19 and some studies have reported increased levels of myoglobin of CK in association with COVID-19 severity[46,53,54].”

46 Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. *Lancet Gastroenterol Hepatol* 2020; **5**: 529–530. [PMID: 32203680 PMCID: PMC7270582 DOI: 10.1016/S2468-1253(20)30084-4]

52 Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, Liu L, Shan H, Lei C, Hui DSC, Du B, Li L, Zeng G, Yuen K-Y, Chen R, Tang C, Wang T, Chen P, Xiang J, Li S, Wang J, Liang Z, Peng Y, Wei L, Liu Y, Hu Y, Peng P, Wang J, Liu J, Chen Z, Li G, Zheng Z, Qiu S, Luo J, Ye C, Zhu S, Zhong N. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382: 1708–1720. [PMID: 32109013 PMCID: PMC7092819 DOI: 10.1056/NEJMoa2002032]

53 Tsivgoulis G, Palaiodimou L, Katsanos AH, Caso V, Köhrmann M, Molina C, Cordonnier C, Fischer U, Kelly P, Sharma VK, Chan AC, Zand R, Sarraj A, Schellinger PD, Voumvourakis KI, Grigoriadis N, Alexandrov A V., Tsiodras S. Neurological manifestations and implications of COVID-19 pandemic. Ther Adv Neurol Disord 2020; 13: 175628642093203. [PMID: 32565914 PMCID: PMC7284455 DOI: 10.1177/1756286420932036]

54 Berth SH, Lloyd TE. Secondary Causes of Myositis. Curr Treat Options Neurol 2020; 22: 38. [PMID: 33041620 PMCID: PMC7538050 DOI: 10.1007/s11940-020-00646-0]

2. Epidemiology section - It may be better to list and compare similar study in tables.

Response: Following the Reviewer's comment, we have added the following information on the manuscript (Epidemiology section, page 6, line 15 – 16 and Table 1):

“A summary of the principal studies about liver damage in COVID-19 patients is showed in Table 1”.

Table 1 Principal studies about liver damage in COVID-19 patients.

First author [Ref]	Study	Findings
Mao R [15]	SR (35 studies, *N*=6,686)	The prevalence of abnormal liver functions was 19% (CI: 9-32). Patients with severe COVID-19 had higher rates of abnormal liver function including increased ALT (OR: 1.89, CI: 1·30-2·76) and increased AST (OR: 3.08, CI: 2.14-4.42) compared with those with non-severe disease.
Wijarnpreecha K [16]	SR (64 studies, *N*=11,245)	The prevalence of elevated AST, ALT, total bilirubin, GGT, and alkaline phosphatase was 23.2%, 21.2%, 9.7%, 15.0%, and 4.0%, respectively. The prevalence of elevated AST was higher among those with severe cases (45.5%) compared to non-severe cases (15.0%). Co-existing CLD presented up to 37.6% of patients with COVID-19.
Wang Q [17]	Single-center retrospective study (*N*=105)	Fifty-six percent of the patients had abnormal ALT, AST, or total bilirubin during the illness (91.4% cases were ≤3 fold of the ULN). The percentage of patients with elevated both ALT and AST was 12.7% in mild cases vs. 46.2% in severe cases. One third of patients with severe disease started to have abnormal ALT after admission, and 73.3% of all patients had normal ALT before

		discharge.
Lei F [18]	Multicenter retrospective cohort study (*N*=5,771)	The distributional and temporal patterns of liver injury indicators were following: AST elevated first, followed by ALT, in severe patients. Alkaline phosphatase modestly increased during hospitalization and largely remained in the normal range. The fluctuation in total bilirubin levels was mild in the non-severe and severe groups.
Xie H [19]	Retrospective study (*N*=79)	Logistic regression analyses suggested that the extent of pulmonary lesions on CT was a predictor of liver function damage.
Wu Y [20]	SR (45 studies, *N*=7,228)	The incidence of any abnormal liver biochemical indicator at admission and during hospitalization was 27.2% and 36%, respectively.
Kulkarni AV [21]	SR (107 studies, *N*=20,874)	The prevalence of CLD was 3.6% (CI: 2.5-5.1). The incidence of elevated liver chemistries was 23.1% (CI: 19.3-27.3) at initial presentation and 24.4% (CI: 13.5-40) during the illness. The incidence of DILI was 25.4% (CI: 14.2-41.4). The prevalence of CLD among 1,587 severely infected patients was 3.9% (3%-5.2%). CLD was no associated with the developing severe COVID-19 (OR: 0.81, CI: 0.31-2.09) compared to non-CLD

		patients. COVID-19 patients with elevated liver chemistries had an increased risk of mortality (OR: 3.46 CI: 2.42-4.95) and severe disease (OR: 2.87, CI: 2.29-3.6) compared to patients without elevated liver chemistries.
Mendizabal M [22]	Multicenter prospective cohort study (*N*=1,611)	Abnormal liver tests on admission were present on 45.2% and were independently associated with death (OR: 1.5, CI: 1.1-2.0), and severe COVID-19 (OR: 2.6, CI: 2.0-3.3). The prevalence of CLD was 8.5%.
Wong YJ [23]	SR (24 studies, *N*=5,961)	In subjects with critical COVID-19, the OR of hypoalbuminemia was 7.1 (CI: CI: 2.1-24.1), of AST elevation was 3.4 (CI: 2.3-5.0), of ALT elevation was 2.5 (CI: 1.6-3.7), and of hyperbilirubinemia was 1.7 (CI: 1.2-2.5).
Zhu J [24]	SR (34 studies, *N*= 6,492)	Patients with severe COVID-19 showed significantly longer PT, and a longer PT was associated with a higher risk to die.
Elshazli RM [25]	SR (52 studies, *N*=6,320)	Prolonged PT was associated with a higher risk of progression to severe COVID-19 (OR: 1.82) and ICU admission (OR: 2.18).
Wu ZH [26]	SR (13 studies, *N*=3,722)	The comparison between survivors and non-survivors with severe COVID-19 patients showed an OR of 1.98 (CI: 1.39-2.82) for liver dysfunction and mortality.

Richardson S [29]	Multicenter prospective cohort study (*N*=5,700)	In hospitalized COVID-19 patients, AST and ALT were both commonly increased (58.4% and 39.0% of patients, respectively). Fifty-six subjects (2.1%) developed a severe acute liver injury with a mortality of 95%.
Shi H [30]	Two-center retrospective study (*N*=81)	Abnormal liver function test was found in patients with subclinical disease (elevated AST in 8.7% and elevated ALT in 8.9%.
Sultan S [58]	SR (47 studies, *N*=10,980)	The prevalence estimates of elevated liver abnormalities were as follows: AST 15.0% (CI: 13.6%–16.5%), ALT 15.0% (CI: 13.6%–16.4%), abnormal bilirubin 16.7% (CI: 15.0%–18.5%).

Abbreviations: *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *CI*, confidence interval; *CLD*, chronic liver disease; *COVID-19*, coronavirus disease-2019; *CT*, computed tomography; *DILI*, drug-induced liver injury; *GGT*, gamma-glutamyltransferase; *ICU*, Intensive Care Unit; *PT*, prothrombin time; *OR*, odds ratio; *Ref*, reference; *SR*, systematic review; *ULN*, upper limit of normal.

3. The "kg/m2" word should be corrected as "kg/m2 (superscript)" (page 12).
Response: Following this comment, we rechecked the manuscript and have corrected the mistake.

4. The "P<0•0001" should be corrected as "P<0.0001" (page 17).
Response: Following this comment, we rechecked the manuscript and have corrected the mistake.

5. The “COVI-19” word should be corrected as “COVID-19” (page 21).

Response: By this comment, we rechecked the manuscript and have corrected the mistake.

6. I suggest adding these references: One world, one pandemic, many guidelines: management of liver diseases during COVID-19. Gut. 2020 Aug;69(8):1369-1372. The COVID-19 pandemic will have a long-lasting impact on the quality of cirrhosis care. J Hepatol. 2020 Aug;73(2):441-445.

Response: Following the Reviewer's comment, we have added the following references:

112 Bollipo S, Kapuria D, Rabiee A, Ben-Yakov G, Lui RN, Lee HW, Kumar G, Siau K, Turnes J, Dhanasekaran R. One world, one pandemic, many guidelines: management of liver diseases during COVID-19. Gut 2020; 69: 1369–1372. [PMID: 32499304 PMCID: PMC7398477 DOI: 10.1136/gutjnl-2020-321553]

113 Tapper EB, Asrani SK. The COVID-19 pandemic will have a long-lasting impact on the quality of cirrhosis care. J Hepatol 2020; 73: 441–445. [PMID: 32298769 PMCID: PMC7194911 DOI: 10.1016/j.jhep.2020.04.005]

Reviewer #2:

At present, coronavirus disease 2019 (COVID-2019) caused by 2019 novel coronavirus (2019-nCoV) infection has spread rapidly in over 70 countries around the world and thus become a public health event of international concern. In addition to fever and respiratory symptoms, varying degrees of liver injure is also observed after 2019-nCoV infection. This manuscript reviews the epidemiology, clinical features, pathophysiology, and therapeutic strategies of liver injury associated with COVID-2019 in in both patients with or without the pre-existing liver diseases including metabolic related fatty liver disease, liver cirrhosis, liver transplantation, viral hepatitis, autoimmune liver disease and drug-induced liver damage, facilitating clinicians’ access to updated information and patient care, so

as to provide a reference for clinical decision-making on the prevention and treatment of COVID-2019. The abstract of the manuscript summarize the work of the full text, and the references cited are the latest and important. The manuscript is well, concisely and coherently organized and presented, in which the style, language and grammar is accurate and appropriate. Thus, We recommend that this manuscript be published in full.

Response: We thank the Reviewer for this comment.

Reviewer #3:

Manuscript NO: 65829 Title: Liver dysfunction and SARS-CoV-2 infection Manuscript Type: Frontier Correspondence to: Abraham Edgar Gracia-Ramos, MD, MSc. This is a comprehensive review about COVID-19. Minor: There were several case reports about portal thrombosis in COVID-19. If possible, authors had better introduce this pathogenesis.

Response: Following the Reviewer's comment, we have added the following information on the manuscript (Pathophysiology section, page 9, line 9 – 11, references 42 and 43):

"In addition, transaminitis has been reported in some cases of portal thrombosis due to SARS-CoV-2 infection[42,43]."

42 Singh B, Kaur P, Maroules M. Splanchnic vein thrombosis in COVID-19: A review of literature. Dig Liver Dis 2020; 52: 1407–1409. [PMID: 32654359 PMCID: PMC7404964 DOI: 10.1016/j.dld.2020.09.025]

43 Hassan W, Ramadan HK-A. COVID-19 as a novel etiology of portal vein thrombosis: change in the current management concepts. Infect Dis (Auckl) 2021; 53: 148–150. [PMID: 33090034 DOI: 10.1080/23744235.2020.1837943]

Science editor:

1 Scientific quality: The manuscript describes a frontier of the liver dysfunction and SARS-CoV-2 infection. The topic is within the scope of the WJG. (1) Classification: Grade A, Grade C and Grade A; (2) Summary of the Peer-Review Report: The authors summarized the current evidence about COVID-19-associated liver injury, including epidemiology, pathophysiology and management, in both patients with or without the pre-existing liver disease. It is comprehensive. However, some concerns have to be dealt with. The questions raised by the reviewers should be answered; and (3) Format: There is 1 table. (4) References: A total of 130 references are cited, including 130 references published in the last 3 years; (5) Self-cited references: There is 1 self-cited reference. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade A, Grade C and Grade A. 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: (1) The language classification is Grade C. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240; and (2) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation

numbers to the reference list and list all authors of the references. Please revise throughout. 6 Recommendation: Conditional acceptance.

Response: We thank the Reviewer for these pertinent comments. Regarding language editing, we have obtained a professional English language editing certificate by Filipodia publishing which we send along with the rest of the documentation.

Concerning the PMID and DOI numbers, we have added these numbers to the references accordingly.