Dear professor Subrata Ghosh and Tarnawski,

Thank you very much for your comments and suggestions.

We have revised the manuscript, according to the comments and suggestions of reviewers and editor, and responded, point by point to, the comments as listed below.

The revised manuscript has been edited and polished by Austin Yang who is a native English speaker from USA.

It is with excitement that I resubmit to you a revised version of manuscript (NO.63416) "**Interplay Between NRF2 and Inflammatory Mediators in COVID-19-Related Liver Injury**" for the "World Journal of Gastroenterology (WJG)"., and hope it is acceptable for publication in the journal.

Looking forward to hearing from you soon.

Thank you and best regards.
Yours sincerely,
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Reviewer #1：

Authors review the potential role of NRF2 and inflammatory mediators in the context of COVID19 infection and the associated liver injury. The review is well organized in terms of the different components involved in viral-dependent liver injury. I suggest to introduce a classification of the severity of liver injury in terms of the adverse outcome of COVID19 infection. This is important since the

virus has individualized responses and several data from cohorts around the World are available. In this regard, authors should provide additional evidence from the literature in support of their reciprocal mechanisms of injury associated to NRF2/COVID19 interplay.

We thank the reviewer for careful reading and positive comments about our work.

Question1: I suggest to introduce a classification of the severity of liver injury in terms of the adverse outcome of COVID19 infection. This is important since the virus has individualized responses and several data from cohorts around the World are available.

Reply: As per the reviewer's suggestion, we include parts about a classification of the severity of liver injury in terms of the adverse outcome of COVID19 infection before summary .

Alanine aminotransferase (ALT) was selected to represent liver injury rather than aspartate aminotransferase (AST), because the sources of extrahepatic AST are very common, including the breakdown of the heart and skeletal muscle. Therefore, among patients infected with COVID-19, we classified liver damage into

normal/mild (<2 times ULN), moderate (2-5 times ULN), and severe (>5 times ULN) according to the degree of ALT elevation (Table 2)[129].

Normal and mild liver injury account for the largest proportion (60-90%) among COVID-19 infected patients. Severe liver injury accounts for less than 20%. In addition, moderate to severe liver injury is more common in patients requiring ICU care. But in general, the most common is mild liver injury, and the degree of liver injury is related to the occurrence of end events (ICU admission, death, mechanical injury) rate independently [129-131]. Only 5% of COVID-19 patients had severe liver damage [132]. From Cai et al. study, the incidence of liver injury in hospital is higher than at the time of admission. For these patients, few other factors affected liver test abnormalities, such as potential liver disease and drug use[133]. Therefore, it can be speculated that occurrence of liver damage is caused by COVID-19. Zhao et al. compared mild COVID-19 infected patients with non-COVID-19. The absolute value of lymphocytes between the two groups decreased, and there was no difference in C-reactive protein and IL-6[134]. ALT was not elevated in patients with non-COVID-19 pneumonia when they are admitted to the hospital, but it was elevated in 28% of COVID-19 patients. Compared with the general inflammation caused by other

pathogens, the specific inflammation caused by COVID19 is more likely to cause abnormal liver function. Also, severe liver damage from COVID-19 infection is associated with serum inflammatory markers (white blood cell count and neutrophil to lymphocyte ratio are significantly higher). Age, hypertension, and the presence of diabetes is negatively correlated with the severe liver damage of COVID-19 patient[129]. It can be speculated that young patients may have a stronger immune and inflammatory response to infection, which will lead to more severe liver damage. In other words, the inflammatory response will cause liver damage and determine the degree of liver damage. Therefore, inflammation plays an important role in the development of liver injury induced by Covid-19. Because of the individual response of virus, different patients may have different degrees of liver injury so that it is necessary to grade the degree of liver injury. We have described the anti-inflammatory effect of NRF2 above, which is of great benefit to the prevention or treatment of COVID-19-mediated liver injury, and it is also crucial for improving the prognosis of the patients.

Table2. Classification of the severity of liver injury in terms of the adverse outcome of COVID19

infection

Reference	Date	Cohort	The severity of liver injury			How the ULN was defined
			normal/mild (<2 times ULN)	moderate (2 - 5 times ULN)	severe (>5 times ULN)	
Phipps, et al[129]	2020.3.8-2020.4.14	2273	1,784(78.5)	344(15.1)	145（6.4）	ALT=50 U / L
Mendizabal, et al[130]	2020.4.15-2020.7.31	1611	322(84.7)	185(11.5)	61(3.8)	ALT (the reference value of different institutions)
Hundt, et al[131]	2020.3.14-2020.4	1753	1123 (64.1)	408 (23.3)	222 (12.7)	ALT=34 U / L
Yip, et al[132]	2020.1.23-2020.5.1	816	635(77.8）	141(17.3)	40(4.9)	ALT=40 U / L

Data were expressed as n (%). ALT, alanine aminotransferase; ULN, the upper limit of normal.

RE:

129 **Phipps MM,** Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, Fox AN, Zucker J, Verna EC. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. Hepatology 2020; 72(3): 807-817 [PMID: 32473607 PMCID: PMC7300739 DOI: 10.1002/hep.31404]

130 **Mendizabal M,** Piñero F, Ridruejo E, Anders M, Silveyra MD, Torre A, Montes P, Urzúa A, Pages J, Toro LG, Díaz J, Gonzalez Ballerga E, Miranda-Zazueta G, Peralta M, Gutiérrez I, Michelato D, Venturelli MG, Varón A, Vera-Pozo E, Tagle M, García M, Tassara A, Brutti J, Ruiz García S, Bustios C, Escajadillo N, Macias Y, Higuera-de la Tijera F, Gómez AJ, Dominguez A, Castillo-Barradas M, Contreras F, Scarpin A, Schinoni MI, Toledo C, Girala M, Mainardi V, Sanchez A, Bessone F, Rubinstein F, Silva MO. Prospective Latin American cohort evaluating outcomes of patients with COVID-19 and abnormal liver tests on admission. *Ann Hepatol* 2021; **21**: 100298 [PMID: 33359234 PMCID: PMC7832153 DOI: 10.1016/j.aohep.2020.100298]

131 **Hundt MA,** Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal Liver Tests in COVID-19: A Retrospective Observational Cohort Study of 1,827 Patients in a Major U.S. Hospital Network. *Hepatology* 2020; **72**(4): 1169-1176 [PMID: 32725890 DOI: 10.1002/hep.31487]

132 **Yip TC,** Lui GC, Wong VW, Chow VC, Ho TH, Li TC, Tse YK, Hui DS, Chan HL, Wong GL. Liver injury is independently associated with adverse clinical

outcomes in patients with COVID-19. *Gut* 2020 [PMID: 32641471 PMCID: PMC7371491 DOI: 10.1136/gutjnl-2020-321726]

133 **Cai Q,** Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J, Sun Y, Liu Y, He Q, Chen J, Liu L, Xu L. COVID-19: Abnormal liver function tests. *J Hepatol* 2020; **73**(3): 566-574 [PMID: 32298767 PMCID: PMC7194951 DOI: 10.1016/j.jhep.2020.04.006]

134 **Zhao D,** Yao F, Wang L, Zheng L, Gao Y, Ye J, Guo F, Zhao H, Gao R. A Comparative Study on the Clinical Features of Coronavirus 2019 (COVID-19) Pneumonia With Other Pneumonias. *Clin Infect Dis* 2020; **71**(15): 756-761 [PMID: 32161968 PMCID: PMC7108162 DOI: 10.1093/cid/ciaa247]

Question2: Language Quality: Grade B (Minor language polishing)

Reply: Thanks for your suggestion. We feel sorry for our poor writings. Now, we do invite Austin Yang who is a native English speaker from USA help polish our article. These changes will not influence the content and framework of the paper. And here we did not list the changes but have changed in revised paper. And we hope the revised manuscript could be acceptable for you.