

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Needs minor language polishing. example; Univariate analysis was used to analyzed clinical and laboratory; Univariate analysis was used to analyze clinical and laboratory It is a research documenting the effects of COVID-19 infection on the liver. It has been shown that liver injury is more common in patients with more severe disease. It was found that male sex, high D-dimer levels and neutrophil precentages might be important predictors of liver injury with COVID-19. The discussion on possible mechanisms is satisfactory. However, it would be more infromative if the effect of oxygen saturation (may be low in patients with lung involvement) was also evaluated.

Answer:

At the same time, patients with hypoxic saturation have extensive pulmonary inflammation, which leads to tissue ischemia and hypoxia, resulting in the internal environment disorder and multiple organ dysfunction [???].

17 Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang F. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020, **08**: 420-422. [PMID:32085846 DOI:10.1016/S2213-2600(20)30076-X]

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The manuscript details the liver injury markers of a short cohort of COVID-19 patients form the Wuhan region. The

number of patients is reduced (218), but the analysis is well presented. The data support the view of a link between worse liver function and hematologic alterations. The panel of markers is sufficient; however, if a time course of the evolution could be obtained, this would benefit a better follow-up and a more direct correlation between liver injury and disease progression. Also, it is remarkable that the liver injury markers, although elevated, are not associated to a serious liver injury. The analysis of sex distribution fits into what is known on COVID-19 aggravation and is probably reflecting a link between the viremia outcome and liver injury. It remains to be established the mechanisms by which SARS-CoV2 is promoting this liver injury and how it correlates with other serum markers (kidney, heart, etc.)

Answer:

We had focused on the liver injury in COVID-19 patients on admission, but not included other serological markers (kidney, heart, etc.). Therefore, it is necessary to further analyze the correlation between the dynamic evolution of liver injury and disease progression, and the relationship between these serological markers (kidney, heart, etc.) and liver injury in COVID-19.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The present study by Zhang et al is aimed to analyze clinical variables regarding liver injury in COVID-19 patients. The manuscript has been clearly written, easy to follow and present valuable evidences that are worth to be shared with the community. However, the study has important limitations as have been well identified and indicated in the text. It would be interesting to assess whether these patients had any liver complication before SARS-CoV-2 infection. Besides, since liver disease patients are significantly older, it should be discussed whether the increased

incidence of, for instance, coexisting diseases, could result from the different age range among groups.

Answer:

Furthermore, it is noteworthy that the older patients often with comorbidities, such as chronic obstructive pulmonary disease (COPD), may also result in the liver injury. With aging degenerative changes, the older patients, especially with underlying diseases, were more susceptible to the attack of SARS-CoV-2. It may be related to the low immunity of the body. Yu et al. [17] studied the age-related rhesus macaque models of COVID-19 and found that viral replication of nasopharyngeal swabs, anal swabs and lung was more active in old monkeys after infection, and SARS-CoV-2 caused more severe pneumonia in old monkeys.

17 Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang F. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020, **08**: 420-422. [PMID:32085846 DOI:10.1016/S2213-2600(20)30076-X]

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Overall Comments: In spite of drawbacks including the retrospective study design, the limited spectrum of assessed parameters and the lack of data on pre-medication, this evaluation provides interesting information on liver injury in COVID-19 patients in Wuhan. Of course, the temporal course of the values would also be of interest. Specific Comments: The "Core Tip" should be improved. (已修改) "Statistical Analysis": "Univariate analysis was used to analyzed clinical and laboratory variances between patients with normal liver function and liver injury" -> Univariate

analysis was used to analyze clinical and laboratory variances between patients with normal liver function and liver injury. (已修改) "Results": "The median age (已修改mean age) for all patients was 50.1 (range 22-91) years old" -> The median age for all patients was 50.1 (range 22-91) years. Table 2: "PTA: prothrombin active"? (已修改prothrombin activity). Reference list: The format of some references is not consistent with the guidelines of the journal. (已修改)

Univariate analysis was used to analyze clinical and laboratory

Answer:

Core tip: Coronavirus disease 2019 (COVID-19) has become a worldwide pandemic.

The study analyzed the clinical characteristics and risk factors of liver injury in Wuhan region COVID-19 patients. The early stage of COVID-19 may be associated with mildly elevated aminotransferase levels. We believed male sex and high D-dimer levels and neutrophil percentages may be important predictors of liver injury in patients with COVID-19.

REFERENCES

- 1 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS. Clinical characteristics of 2019 will be coronavirus infection in China. *N Engl J Med* 2020; [PMID:32109013 DOI:10.1056/NEJMoa2002032]
- 2 **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 will be coronavirus - infected root in Wuhan, China. *JAMA* 2020; [PMID:32031570 DOI:10.1001/jama.2020.1585]
- 3 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu, Y, Wang J, Liu Y, Wei

Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID:32007143 DOI:10.1016/S0140-6736(20)30211-7]

4 **Li W**, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; **426**: 450-454. [PMID:14647384 DOI:10.1038/nature02145]

5 **Chai X**, Hu L, Zhang Y, Han W, Lu Z, Ke A, Zhou J, Shi G, Fang N, Fan J, Cai J, Fan J, Lan F. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. Available from: bioRxiv:2020.02.03.931766 [DOI: 10.1101/2020.02.03.931766]

6 **National Health Committee of the People's Republic of China**. Diagnosis and treatment plan for pneumonitis caused by new coronavirus (trial version 7). [2020-03-03]. Available from: <http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989/files/ce3e6945832a438eaae415350a8ce964.pdf>

7 **Xu L**, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020; **40**: 998-1004. [PMID:32170806 DOI:10.1111/liv.14435]

8 **Fang D**, Ma JD, Guan JL, Wang MR, Song Y, Tian DA, Li PY. Manifestations of digestive system in hospitalized patients with novel coronavirus pneumonia in Wuhan, China: a single-center, descriptive study. *Chin J Dig* 2020; **40**. [DOI:10.3760/cma.j.issn.0254-1432.2020.03.000.]

9 **Li J**, Zhang Y, Wang F, Liu B, Li H, Tang G, Chang Z, Liu A, Fu C, Gao J, Li J. Sex differences in clinical findings among patients with coronavirus disease 2019 (COVID-19) and severe condition. Available from: Medrxiv:2020.02.27.20027524 [DOI: 10.1101/2020.02.27.20027524]

10 **Karlberg J**, Chong DS, Lai WY. Do men have a higher case fatality rate of

severe acute respiratory syndrome than women do? *Am J Epidemiol* 2004; 159: 229-31. [PMID:14742282

DOI:10.1093/aje/kwh056]

11 **Klein SL** and Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol* 2016; **16**: 626-38. [PMID:27546235 DOI:10.1038/nri.2016.90]

12 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020, **395**: 497-506. [PMID:31986264

DOI:10.1016/S0140-6736(20)30183-5]

13 **Yu P**, Qi FF, Xu YF, Li FD, Liu P, Liu J, Bao L, Deng W, Gao H, Xiang Z, Xiao C, Lv Q, Gong S, Liu J, Song Z, Qu Y, Xue J, Wei Q, Liu M, Wang G, Wang S, Yu H, Liu X, Huang B, Wang W, Zhao L, Wang H, Ye F, Zhou W, Zhen W, Han J, Wu G, Jin Q, Wang J, Tan W, Qin C. Age-related rhesus macaque models of COVID-19. *Animal Model Exp Med* 2020; 00:1-5 [PMID:32318665 DOI:10.1002/ame2.12108]

14 **Hoffmann M**, Kleine-Weber H, Krüger N, Marcel M, Christian D, Stefan P. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. Available from: bioRxiv:2020.01.31.929042 [DOI: 10.1101/2020.01.31.929042]

15 **Banales JM**, Huebert RC, Karlsen T, Strazzabosco M, LaRusso NF, Gores GJ. Cholangiocyte pathobiology. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 269-281. [PMID:30850822 DOI:10.1038/s41575-019-0125-y]

16 **Tisoncik JR**, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. *Microbiol Mol Biol Rev* 2012, **76**: 16-32. [PMID:22390970 DOI:10.1128/MMBR.05015-11]

17 Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang F. Pathological findings of COVID-19 associated with acute respiratory distress

syndrome. *Lancet Respir Med* 2020, **08**: 420-422. [PMID:32085846

DOI:10.1016/S2213-2600(20)30076-X]

18 **Duan Z**, Chen Y, Zhang J, Zhao J, Lang Z, Meng F, Bao X. Clinical characteristics and mechanism of liver injury in patients with severe acute respiratory syndrome. *Chin J Hepatol* 2003; **11**: 493-496. [DOI: 10.3760/j.issn:1007-3418.2003.08.014]