

Peer Review File

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Reviewer A

Methodologically well conducted and useful in clinical practice

Reply: The authors appreciate the positive comment from this reviewer.

Reviewer B

Then current pandemic COVID-19 is a significant health threat over the world. The understanding of SARS-CoV-2 infection continues to expand. In this context, this article attempts to analyze the effect of liver injury as a part of COVID-19 in affecting the prognosis and treatment of COVID-19. I just recommend that the authors to include in their analysis, 1)How many patients admitted with non-severe disease progressed to severe disease during the course of hospital stay.

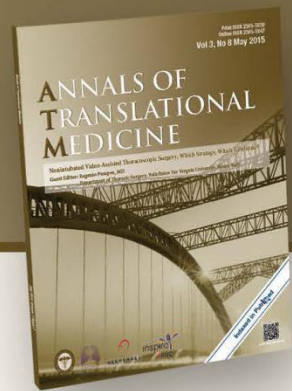
Reply 1: We appreciate that the reviewer pointed this out. As we mentioned in Page 13, line 234-241, among patients with non-severe disease, 5 individuals with liver injury and 9 individuals without liver injury were treated with glucocorticoids, and 2 individuals with liver injury and 1 individual without liver injury underwent noninvasive ventilation during hospitalization. Thus, three patients admitted with non-severe disease progressed to severe disease during the course of hospital stay.

2) The effect of liver injury in progression of non-severe disease to severe disease when compared to non-severe disease patients with normal liver function.

Reply 2: As mentioned in Page 13, line 234-241, among patients with non-severe disease, there was no difference in the use and dosage of glucocorticoids and hospital stay between individuals presenting with and without liver injury. Additionally, 2 individuals with liver injury and 1 individual without liver injury underwent noninvasive ventilation, and there was no significant difference ($p = 0.145$), and there was no individual undergoing invasive ventilation or death in the two groups. So we think that liver injury at admission did not cause negative impact on the progression of the disease in patients with COVID-19 pneumonia.

3) The role of liver injury in deciding antiviral therapy.

Reply 3: As mentioned in Discussion (in Page 16, line 293-295), there is no specific medications available to treat COVID-19 infection, and comprehensive treatments including antiviral



treatment, use of antibiotics, nutritional support, etc., are recommended. In the study, every admitted patient was administered Abidor, a kind of antiviral medications, according to the guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection by the National Health Commission (Trial Version 7). So, there was no impact of liver injury on deciding antiviral therapy in our study.

Reviewer C

Summary of research:

Guo-guang, Ya-Xing, Ling and co-authors reported here the results of a retrospective analysis of 109 patients admitted to People's Hospital of Wuhan University with confirmed COVID-19 pneumonia, in order to evaluate impact of liver injury on COVID-19 prognosis and treatment. They split the population into two groups (n=56 with severe vs n=53 with non-severe disease), and they found 39 patients (35.8% of entire population) with liver injury, as arbitrarily defined by authors by any abnormality of ALT, AST or γ -glutamyl transferase (GGT). Liver injury was more prevalent in those with severe disease (46.4% vs. 24.5%, $P = 0.017$) but wasn't a risk factor for mechanical ventilation or death in these patients ($P > 0.05$), both primary composite end-point events of this study. Based on these findings in their group of patients, authors conclude assuming that liver injury has no negative effect on the progression and treatment of COVID-19 pneumonia in hospitalized patients, which is anyway an interesting conclusion.

Comments to the Author:

1) Line 53: “diagnosed as severe disease” – should be “diagnosed with severe disease”.

Reply: We appreciate this suggestion and changed the text accordingly.

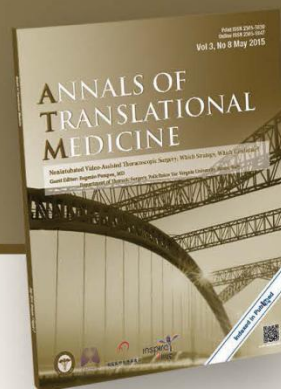
Changes in the text: We have modified our text as advised (see Page 3, line 53).

Line 60, line 61: “significant difference in the use of mechanical ventilation, the mortality, the hospital duration or the use and dosage of glucocorticoids” – it's not correctly formulated, please change with “significant difference in the use of mechanical ventilation, mortality, hospital stay or use and dosage of glucocorticoids”.

Reply: We appreciate this suggestion and changed the text accordingly.

Changes in the text: We have modified our text as advised (see Page 3, line 60-61) and corresponding changes have been made throughout the manuscript.

Line 105: please insert full bibliographic reference for STROBE from von Elm E et al. 2007.



Reply: We appreciate this suggestion and changed the text accordingly.

Changes in the text: We have modified our text as advised (see Page 6, line 110-111).

Line 174, line 281: here again, “hospital duration” should not be used, please change with “hospital stay” or “length of stay (LOS)”.

Reply: We appreciate this suggestion and changed the text accordingly.

Changes in the text: We have modified our text as advised (see Page 10, line 186 and Page 17, line 307) and corresponding changes have been made throughout the manuscript.

Line 183: concerning age analysis, here p-value is missing. Please add.

Reply: We appreciate this suggestion and changed the text accordingly.

Changes in the text: We have modified our text as advised (see Page 11, line 195).

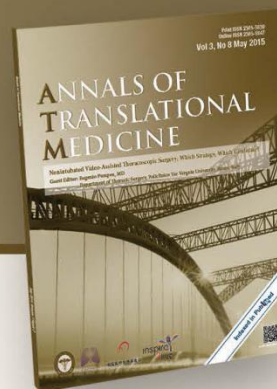
Line 188: please change “indicators” with “markers”.

Reply: We appreciate this suggestion and changed the text accordingly.

Changes in the text: We have modified our text as advised (see Page 11, line 201) and corresponding changes have been made throughout the manuscript.

2) A definition of liver injury by authors can be found in Methods on line 136 and 137: “Liver injury was defined as the levels of ALT, AST or γ -glutamyl transferase (GGT) above the upper limit of normal laboratory reference.” In my opinion this is the weaker aspect of the analysis by Guo-guang et al. This definition of liver injury sounds arbitrary, not precise enough, and at the end it can invalidate the entire study. First, concerning liver injury there are several historical references to adapt to, including i.e. Dufour et al. in Clinical chemistry 2000, Benichou et al. in J Hepatology 1990. In addition, Cai et al. (J Hepatol 2020) already described patterns of liver test abnormalities in COVID-19, classifying also the liver injury by COVID-19 in hepatocellular, cholestatic or mixed. This kind of approach is missing in this study by Guo-guang et al. I suggest the authors to change the entire architecture of the study by analyzing only patients with hepatic injury as previously defined in literature. The other only possible and credible scientific approach would be to maintain the number of patients they included in the analysis as patients with liver test abnormality and not labeling them directly with liver injury, because those are two different entities.

Reply 2: We appreciate that the reviewer provides this expert comment. There are many parameters in liver biochemical test, and some of these parameters such as albumin, globulin and lactate dehydrogenase etc., are affected by other etiological factors besides the liver. And liver enzymes are the most commonly used parameters to indicate liver injury including the injury to hepatocytes and to cholangiocytes. However, there is no uniform normal laboratory reference of liver enzymes test among different hospitals. Thus, it is difficult to define how



much the value of liver enzymes exceed to indicate liver injury. Clinically, when liver enzymes exceed the upper limit unit of normal (ULN), physicians should be alert to the occurrence of liver injury. In the study, we aimed to evaluate the potential impact of liver injury at admission on the progression and treatment of COVID-19 pneumonia. So when the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) or γ -glutamyl transferase (GGT) were above ULN, the patients were defined as with liver injury, not as with liver test abnormality.

In our study, 61.5% of the patients with liver injury were manifested by an elevated level of ALT or AST accompanied simultaneously by an increase in the level of GGT, and an elevated level of ALT or AST alone was observed in 10 patients (25.6%), and mono-elevated levels of GGT alone were in 5 patients (12.8%) (mentioned in Page 10, line 179-183). We admit that it may be more helpful to assess the potential impact of liver injury on the progression and treatment of COVID-19 pneumonia by classifying further liver injury in hepatocellular, cholestatic or mixed. However, in our study, there were hardly any patients with ALT or AST more than $3\times$ ULN (indicating hepatocellular liver injury) or with GGT more than $2\times$ ULN (indicating cholestatic liver injury) at admission (see Table 1 and 2). Additionally, the kind of classification criteria is usually used to classify drug-induced liver injury. In our study, the occurrence of liver injury showed a positive correlation with the severity of COVID-19 infection and inflammatory indicators, which indicated that hypoxia and systemic inflammatory response were might be two major causes of liver injury at admission.

3) Extensive data regarding medications and coexisting illness should have been collected, but unfortunately authors provide them only partially. It would be convenient to integrate them in order to better describe the characteristic of patients, especially in respect to patients with or without severe disease. This information should be included in the manuscript.

Reply 3: We appreciate that the reviewer provides this expert comment and have added the data regarding medications and coexisting illness in the revised manuscript and tables.

Changes in the text: We have modified our text as advised (see Page 11-12, line 206-213 and Table1, 2).