Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical characteristics of COVID-19 patients with abnormal liver tests

To the Editor:

We read with great interest the research article "COVID-19: Abnormal liver function tests" by Cai *et al.* published recently in *Journal of Hepatology*.[1] The authors assessed the clinical characteristics of COVID-19 in patients with abnormal liver tests and found that patients with abnormal liver tests, especially in hepatocyte type or mixed type, were at higher risk of progressing to severe disease. They found that liver impairment in patients with COVID-19 was mainly related to certain medications used during hospitalization. This study is important and interesting; however, there are still some concerns about it.

First, selection bias cannot be entirely excluded, although it is likely to be minimal as all patients with COVID-19 (severe group and not-severe group) during the study period were included and matched for age, sex, body mass index, illness severity, some biochemistry indicators and the admission time point. However, whether the included patients had taken medications before admission was still completely unclear in this study. It is noteworthy that mild liver test derangement would also be present at baseline in confirmed cases of COVID-19 who had received medications such as antipyretics (acetaminophen), antibiotics (macrolides, quinolones) or steroids before admission to hospital.[2]

Furthermore, it has been reported that another possible contributing factor for hepatic injury in COVID-19 patients may be the high levels of positive end expiratory pressure that can cause hepatic congestion by increasing right atrial pressure and impeding venous return.[3] However, whether the patients with COVID-19 received mechanical ventilation remained unclear in the current study. Additionally, it has been found that remdesivir treatment during COVID-19 can also induce liver impairment. In a paper describing the first 12 patients with COVID-19 in the United States, the 3 hospitalized patients who received remdesivir at the time of clinical worsening reported elevated liver enzymes.[4] However, this issue has not been mentioned in the current study, and the authors should give some interpretation and explanation of these data in the text.

Another issue is that the authors have found that patients also tended to have underlying liver diseases, including non-alcoholic fatty liver disease, alcohol-related liver disease, and chronic hepatitis B, and had cough as an initial symptom; however, the specific ratio of COVID-19 patients with liver comorbidities was still unknown in this study. Preliminary data reported by Zhang C *et al.* indicate that 2–11% of patients with COVID-19 had liver comorbidities, and whether the results in this study contradict the data of Zhang C *et al.* is not clear.[5] If these results are contradictory, we would presume that this is caused by differences in the study populations; the patients in the current study were mainly aged less than 50 years old and more than half of the patients were from Hubei. Furthermore, the exact cause of pre-existing liver conditions has not yet been outlined in this study.

In a study of 1,099 patients with laboratory confirmed COVID-19, 23 (2.1%) patients had hepatitis B infection. Severe cases were more likely to have hepatitis B infection (2.4% *vs.* 0.6%) than non-severe cases.[6] SARS patients with HBV/HCV infection were more prone to develop severe hepatitis.[7] These data suggest more intensive immunotherapy may be required to minimize COVID-19, an issue that warrants further study. However, in patients with COVID-19 with autoimmune hepatitis, the effects of administration of glucocorticoids on disease prognosis is unclear. Given the expression of the ACE2 receptor in cholangiocytes, whether infection with SARS-CoV-2 aggravates cholestasis in patients with primary biliary cholangitis, also needs to be studied.

Finally, as a cohort study, this research can reflect the "real-world" findings and further support the conclusion, but the cohort data may be influenced by bias due to the patient selection process. Therefore, a large-scale study should be conducted in the future.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

CP and BH Zhou had the idea for and designed the study, received the grant supports and had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CP contributed to the writing and statistical analysis of the report. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.04.028.

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Reply to: "Clinical characteristics of COVID-19 patients with abnormal liver tests"

To the Editor:

We thank Chen P. and Zhou B. for their interest in our manuscript and for their thoughtful comments.

Concerning selection bias, as our study was not a multicenter, randomized controlled clinical trial with a large, real-world sample, we aimed to minimize it. The Third People's Hospital of Shenzhen is the only government mandated referral hospital in Shenzhen, China for the treatment of patients with COVID-19. Thus all infected patients in the region would present to our hospital and would generally be representative of patients with COVID-19 in the city. Bias in the estimated association of an exposure on an outcome that arises from the procedures used to select individuals into the study was avoided.

We agree that pre-hospital medication could influence liver tests. However, as described in the paper, because the accessibility of medical resources in our city are quite different from that in Hubei and other epidemic regions, over-the-counter medicines are rarely used to self-treat. Additionally, during this unique pandemic period, all medical staff and the general population were well aware of the disease. Once individuals presented any COVID-19-related symptoms, they would receive confirmatory testing. Once the diagnosis was confirmed, the patient would be referred to our hospital for further treatment as soon as possible. Patients were very unlikely to have taken antipyretics (acetaminophen), antibiotics (macrolides, quinolones), or steroids before admission; thus, any effect of these drugs on the results would not be substantial.

We agree that ischemia, hypoxia, and reperfusion are important factors related to liver injury. As we have reported, severe cases of COVID-19 are defined by the official clinical practice guidelines of the American Thoracic Society and Infectious Diseases Society, and respiratory abnormalities are a key diagnostic criterion.[1,2] Mechanical ventilation was usually needed in severe cases, which has been reported in a recent study. Furthermore, in ours and other studies,[1,3–5] severe cases consistently showed a higher percentage of severe liver abnormality than non-severe cases. As remdesivir was not used in our hospital, we could not assess its effects on liver function.

In addition, our data showed that 5.04% of patients with COVID-19 had liver comorbidities, which was consistent with the prevalence of 2–11% reported by Zhang C *et al.*[6] We agree that the question of whether intensive immunotherapy may minimize the COVID-19-related inflammatory response may be relevant. Actually, some related experimental studies in our hospital are ongoing and hope to give answers to these questions. Inspired by the current study, we will conduct more in-depth studies in the future to improve our understanding of this disease.

Last, but not least, angiotensin-converting enzyme 2 (ACE2) expression was reported in various human organs but the results were controversial. For example, a recent study failed to replicate the expression of ACE2 in the alveolar type II (AT2) cells or in the AT2 lung carcinoma cell line A549.[7] Similarly, our study showed that patients treated with ACE-inhibitors/angiotensin II receptor blockers were not at increased odds of progressing to severe disease compared to patients taking other antihypertensive drugs. These results indicate that the expression of ACE2 in the human respiratory system may be limited, and thus the expression of the receptor in lung or respiratory epithelia on the protein level is yet to be confirmed. Most concerns above have been discussed in our discussion section.

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Conflict of interest

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