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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

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

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Authors' contributions

J Chen 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. J Chen, QX Cai 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.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.04.042.

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Selection of MRI contrast agent and diagnostic criteria for HCC to maximize the advantages of contrast agents

To the Editor:

In the *Journal of Hepatology*, Paisant and colleagues[1] recently presented an interesting and timely study on comparisons between extracellular contrast agents (ECA) and hepatobiliary contrast agents (HBA) for the diagnosis of small hepatocellular carcinomas (HCCs), applying imaging criteria from different parts of the world. The authors should be congratulated for their results, especially as they performed this multicenter prospective study before the introduction of HBA into France. Even 10 years after the worldwide use of HBA and the active incorporation of HBA into the major clinical guidelines,[2–4] there remains a surprising paucity of studies comparing ECA and HBA in a head-to-head manner. The study of Paisant *et al.* took a step in the right direction by exploring the impacts of the choice of MRI contrast agent and diagnostic criteria. However, we would like to highlight some aspects requiring further consideration.

As this study found, restricting the timing of the "washout" appearance to the portal venous phase (PVP) on HBA-enhanced MRI significantly reduces the sensitivity of HCC diagnosis. This restriction seems unreasonable for HBA, as even with ECA, the washout appearance is more frequently depicted during the delayed phase than during the PVP.[5] Challenges in acquiring optimal arterial-phase gadoxetic acid-enhanced MRI could worsen the sensitivity further, although this can be mitigated by using multiple arterial phases or subtraction images. However, we find the authors' conclusion, claiming the superior performance of ECA over HBA, regardless of the applied criteria, to be concerning. Rather, it would be better to interpret the results as evidence that strict confinement of washout timing to the PVP on HBA-MRI, as endorsed by the western criteria, is not legitimate, given that the purpose of HBA-MRI is enhanced sensitivity. If hepatobiliary phase (HBP) hypointensity is not considered a major imaging feature, the main purpose of using HBA-MRI cannot be fully attained. In actual fact, in their study, the sensitivity of HBA-MRI (75.2%) considering HBP hypointensity as washout was higher than that of ECA-MRI (71.2%), although the difference was not statistically significant.

Considering HBP hypointensity as a major imaging feature can cost the specificity of HBA-MRI, in line with previous work.[6] Nevertheless, studies taking ancillary imaging features such as marked T2 hyperintensity or a targetoid appearance into account showed higher specificity (84.2–87.4%)[7,8] than a study not considering them (48.4%)[6] when washout timing

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