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Conflict of interest

The authors declare no conflict of interest.

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

Authors' contributions

L.B. performed the bioinformatic analysis; L.B. and P.E.R. wrote the manuscript; D.V. provided guidance and proof-read the manuscript; all authors revised and approved the final version.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.04.035.

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Reply to: 'No evidence for an increased liver uptake of SARS-CoV-2 in metabolic-associated fatty liver disease'

To the Editor:

We read with interest the letter by Biquard *et al.*[1] In their study, mRNA expression of SARS-CoV-2 infection critical genes, such as angiotensin-converting enzyme 2 (ACE2), transmembrane protease serine 2 (TMPRSS2), phosphatidylinositol 3-phosphate 5-kinase (PIKFYVE) and cathepsin L were found not to be enhanced in patients with metabolic-associated fatty liver disease (MAFLD, previously called non-alcoholic fatty liver disease [NAFLD]) or obesity. This finding is of potential added value to our observation that patients with COVID-19 had worse outcomes if they had underlying MAFLD. Firstly, persistent liver injury observed in our patients was unlikely to be related to the direct cytopathic effects of the virus. Though ideally, one should compare hepatocyte expression of these 4 genes in patients with/without MAFLD that do not have COVID-19. Secondly, this is in keeping with our hypothesis that dysregulated hepatic innate immunity in patients with MAFLD contributes to the pathogenesis of COVID-19. Apart from lung alveolar epithelial cells, the enterocytes of the small intestine also have abundant expression of ACE2 receptors and thus could be another portal of entry for SARS-CoV-2. In keeping with this, gastrointestinal manifestations, such as diarrhoea and abdominal pain occurred in up to one-quarter of patients with COVID-19, without cough. Overall about half of the patients with COVID-19 tested positive for SARS-CoV-2 RNA in faecal and respiratory specimens concomitantly.[2] The liver is enriched with innate immune cells (such as macrophages, natural killer, natural killer T, and γδ T cells)[3] and due to its rich blood supply from the small bowel, circulation of the virus via the hepatic reticular system is expected. Hepatic innate immunity populations are potent cytokine producers and there are reports that obesity and NAFLD were associated with increased production of pro-inflammatory cytokines like tumour necrosis factor-α by adipose cells and Kupffer cells.[4,5] This may lead to an increased likelihood of symptomatic SARS-CoV-2 infections and the high prevalence of NAFLD in our study populations. Further studies are required to enhance our understanding of the link between the dysregulated hepatic innate immunity and COVID-19. This could be the missing link between the well-recognized risk factors of diabetes mellitus,

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obesity, chronic liver diseases and age and the outcome of COVID-19 in humans.[6]

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Conflict of interest
We declare no competing interests.

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Authors' contributions
DJ, EQ, JX, and DZ treated the patients. DJ, GC, YW and GL processed statistical data and drafted the manuscript. DJ and GL had the idea for and designed the study.

Acknowledgments
We acknowledge all patients and health-care workers involved in the diagnosis and treatment of patients with COVID-19 in our hospitals.

Supplementary data
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Younger patients with MAFLD are at increased risk of severe COVID-19 illness: A multicenter preliminary analysis

To the Editor:

We read with great interest the article by Ji *et al.* on liver injury patterns and the clinical implications of metabolic-associated fatty liver disease (MAFLD) in patients with COVID-19.[1] Metabolic and cardiovascular comorbidities like diabetes and hypertension aggravate the severity of COVID-19.[2] Another comorbidity, MAFLD, also affects COVID-19 severity, as pointed out by Ji *et al.*[1] Since excess liver fat is seen in up to a quarter of people,[3] we hypothesized that its impact on severity might be modulated by age. We considered that disease severity of older patients with a greater burden of cardiac and respiratory illness would more likely be impacted by their comorbid conditions, than the presence of liver fat. In this study, we investigated the effects of MAFLD on COVID-19 severity in older *vs.* younger patients.

We consecutively recruited 327 adult patients (≥18 years old) with COVID-19 from 4 centers (the First Affiliated Hospital of Wenzhou Medical University, Wenzhou Central Hospital, Ningbo No.2 Hospital, and Ruian People's Hospital) in China, from 17th January 2020 to 11th February 2020. COVID-19 was diagnosed by high-throughput sequencing or reverse-transcription PCR assays of oropharyngeal swab specimens. Some of these patients were the subject of a previous report.[4] All patients underwent screening for fatty liver by CT. MAFLD was diagnosed based on the recent consensus criteria.[5,6] Overweight was defined as body mass index (BMI) ≥23 kg/m^2, and obesity was defined as BMI ≥25 kg/m^2 in Asians.[7] Diabetes mellitus was diagnosed based on the history or hemoglobin A1c ≥6.5%.[8] Hypertension

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