

# Potential implications of COVID-19 in non-alcoholic fatty liver disease

Dear Editor-in-chief,

COVID-19 burdens all areas of healthcare, and the relationship between COVID-19 and liver injury is being examined. The recently published papers by Xu et al and Xie et al nicely describe liver injury resulting from COVID-19.<sup>1,2</sup> As with many papers the focus lies on patients without pre-existing liver disease, even though it has been suggested that pre-existing conditions affect COVID-19.

The relation between metabolic syndrome, such as diabetes and hypertension, and mortality rate of COVID-19 is becoming increasingly clear. These diseases are often treated with ACE inhibitors, which might upregulate angiotensin-converting enzyme 2 (ACE2) expression.<sup>3</sup> Non-alcoholic fatty liver disease (NAFLD) is linked to extra-hepatic manifestations of metabolic syndrome and is one of the most common liver disorders. ACE2 is normally expressed in low amounts in cholangiocytes and hepatocytes, but was shown to increase in chronic liver damage and in experimental set-ups of diet-induced NAFLD.<sup>4</sup>



While under normal conditions, ACE2 may exert anti-obesity and anti-inflammatory effects, it is also the way of entry for SARS-CoV-2.<sup>1</sup> Therefore, liver injury, treatment with ACE inhibitors and possibly metabolic syndrome itself could lead to increased viral load and worsened effects of COVID-19.

Increased rates of liver dysfunction were observed in patients with severe COVID-19, regardless of pre-existing conditions.<sup>1,5</sup> As the liver is host to the majority of macrophages, and NAFLD patients often already present with elevated cytokine levels, these patients may also be more vulnerable to increased cytokine production associated with COVID-19. This means the NAFLD progression could be expedited by COVID-19.

The link between NAFLD and COVID-19 has not been described as of 8 April 2020. Investigation into this topic is limited by a lack of knowledge about prior history of liver disease in general in COVID-19 patients.<sup>5</sup> For NAFLD this is even more complicated as many NAFLD patients go unnoticed because early stages of the disease are not accompanied by symptoms.

In short, patients suffering from NAFLD might be especially vulnerable to SARS-CoV-2 infection and COVID-19 complications,

where the latter may also increase NAFLD progression to non-alcoholic steatohepatitis in the long-term. These observations underline the importance of identification and monitoring of patients with pre-existing liver disease, especially those with metabolic disorder, during and after the COVID-19 crisis. It would be beneficial to examine these patients in more detail in future meta-analyses and retrospective studies.

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## REFERENCES

- Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int.* 2020;1-7. <https://doi.org/10.1111/liv.14435>
- Xie H, Zhao J, Lian N, et al. Clinical characteristics of Non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: a Retrospective study. *Liver Int.* 2020. <https://doi.org/10.1111/liv.14449>
- Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med.* 2020;8:e21. [https://doi.org/10.1016/S2213-2600\(20\)30116-8](https://doi.org/10.1016/S2213-2600(20)30116-8)
- Paizis G, Tikellis C, Cooper ME, et al. Chronic liver injury in rats and humans upregulates the novel enzyme angiotensin converting enzyme 2. *Gut.* 2005;54:1790-1796. <https://doi.org/10.1136/gut.2004.062398>
- Mantovani A, Beatrice G, Dalbeni A. Coronavirus disease 2019 (COVID-19) and prevalence of chronic liver disease: a meta-analysis. *Liver Int.* 2020. <https://doi.org/10.1111/liv.14465>