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.

Reply. We thank Mr Ng for his insightful remarks related to COVID-19, liver injury, and regeneration in our recent article.[1] These additional comments will help to open up commentary on the possible long-term consequences with COVID-19 in liver transplant (LT) recipients, particularly in the setting of severe disease and/or reinfection. However, it is hoped that widespread and early use of COVD-19 vaccines in these patients may preclude some of these concerns.[2,3]

In our own work, we investigated patterns of liver injury, vascular involvement, and regeneration in 60 patients who died of COVID-19 pneumonia, along with 13 patients who died of non-COVID fatal pneumonia (serving as disease control subjects). There are other autopsy studies where COVID-19 has been likewise significantly associated with liver involvement and thromboembolic complications.[4] Additional recent publications indicate that the presence of underlying liver disease can provoke worse outcomes in COVID-19 disease.[5]

COVID-19 in LT recipients results in higher numbers of intensive care unit admission and rates of mechanical ventilation.[6,7] LT patients with COVID-19 do exhibit a higher risk of acute liver injury, which may mirror the histopathologic findings we have noted in nontransplant patients. We might postulate, that direct damage of liver cells by SARS-CoV-2 and changes of immunometabolic responses might provoke severe liver injury especially in immunosuppressed LT recipients with coexistent metabolic syndrome, as noted previously.

Our data on regenerative responses in fatal COVID-19 revealed increased frequency of hepatic stem/progenitor cells. The relevance of such histopathologic changes of hepatic repair for patients in the course of LT or other concomitant pathophysiological scenarios of the liver in COVID-19 remains unclear.

We agree that adverse possibilities may be afforded by SARS-CoV-2 "long-haul" outcomes, reinfection, and emergence of variant viruses. These do raise the spectra of irreversible graft disease, which might increase risks of retransplantation. This area of clinical endeavor requires further research with elucidation of pathogenic mechanisms and better determination of risk to help answer the provocative questions raised by Mr. Ng.

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References

1. Kaltschmidt B, et al. Clin Gastroenterol Hepatol 2021 Jan 29;S1542-3565(21)00094-X. https://doi.org/10.1016/j.cgh.2021.01.044. Online ahead of print.
2. Fix OK, et al. Hepatology 2021 Feb 12;10.1002/hep.31751. https://doi.org/10.1002/hep.31751. Online ahead of print.
3. Cornberg M, et al. J Hepatol 2021;74:944–951.
4. Wichmann D, et al. Ann Intern Med 2020;173:268–277.
5. Kim D, et al. Clin Gastroenterol Hepatol 2021;19:1469–1479.
6. Rabiee A, et al. Hepatology 2020;72:1900–1911.
7. Jayant K, et al. Clin Transplant 2021;e14246.

Conflicts of interest
The authors disclose no conflicts

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Reply. We thank the authors for their interest in our article about relative adrenal insufficiency (RAI) in patients admitted for acute decompensation of cirrhosis.[1] The authors correctly pointed out that we highlighted the role of the deficiency of substrates of steroidogenesis and inflammation as relevant mechanisms involved in the pathophysiology of RAI. However, we stated the pathogenesis of RAI is much more complex in patients with cirrhosis, and we fully agree with the authors that abnormalities of hypothalamic-pituitary-adrenal axis can be relevant in the pathogenesis of RAI. Unfortunately, we were unable to perform an insulin-induced hypoglycemia test, which is not routinely used nowadays, because of safety concerns in very sick patients. Indeed, hypoglycemia is associated with poor outcomes in patients with acute decompensation of cirrhosis.[2] However, in our cohort we measured levels of adrenocorticotropic hormone (ACTH), which were higher in patients with RAI than in those without (19 vs 15 ng/L; $P = .051$); this is more suggestive of a lower response of adrenal glands to ACTH instead of a lower ACTH production by pituitary gland. Nevertheless, we cannot completely rule out the concomitant role of a secondary relative adrenal insufficiency due to abnormalities of hypothalamic-pituitary-adrenal axis.