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.

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Reply to: "NAFLD is a predictor of liver injury in COVID-19 hospitalized patients but not of mortality, disease severity on the presentation or progression – The debate continues"

To the Editor:

We read with interest the article by Mushtaq *et al.*[1] Both their study and ours[1,2] used similar inclusion criteria and the hepatic steatosis index as a surrogate marker for the presence of NAFLD. We found that NAFLD is an independent predictor of disease progression. However, their study showed that when controlled for covariates in multivariate analysis, NAFLD was not a predictor of mortality, disease severity, or markers of disease progression. Mushtaq *et al.* correctly pointed out the different conclusions may be due to the different criteria used to define COVID-19 disease progression, development of tachypnea and requirement of oxygen supplements in our study as opposed to development of acute respiratory distress syndrome, intensive care unit (ICU) admission, and the need for mechanical ventilation in their study. We chose a less stringent criteria for disease progression because our main purpose was to identify those patients who were absolutely safe to be managed at home or community facilities (no need for supplementary oxygen) as opposed to identifying patients that may require mechanical ventilation or ICU requirement. Zhou *et al.*, using a definition of severe COVID-19 similar to ours, also showed that metabolic dysfunction-associated fatty liver disease (MAFLD) was associated with severe COVID-19 in patients age <60.[3] Also, the prevalence of diabetes and hypertension in their NAFLD population were 50% and 42%, respectively, compared with 17.1% and 26.3%, respectively, in our and Zhou *et al.*'s studies. This may affect the impact of NAFLD in multivariate analysis. We agreed with the authors' suggestion that there is a need to study the outcomes in large scale studies with histologically confirmed cases of NAFLD and COVID-19 disease. Recently, Lax *et al.* reported hepatic steatosis, involving 50% to 60% of hepatocytes, in all 12 COVID-19 patients with pulmonary embolism on autopsy.[4] NAFLD patients had elevated plasma levels of von Willebrand factor and circulating plasminogen activator inhibitor type 1.[5] The liver is a frontline immune organ and increased production of pro-inflammatory cytokines by adipose cells and Kupffer cells has been reported in patients with NAFLD.[6] We had also observed that the mean admission and peak D-dimer levels were also significantly higher in COVID-19 patients with NAFLD than in those without NAFLD, 0.72 ± 1.10 ug/ml *vs.* 0.38 ± 0.46 ug/ml, p = 0.003 and 1.81 ± 4.1 mg/ml *vs.* 0.63 ± 0.41 mg/ml, p = 0.003 respectively. Therefore, the likelihood of activation of the coagulation cascade by pro-inflammatory cytokines, and subsequent thrombosis, may be higher in COVID-19 patients with underlying NAFLD. This NAFLD-associated hypercoagulable state may contribute to disease progression in COVID-19.

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

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Authors' contributions
DJ and GC wrote the manuscript; GL provided guidance and proof-read the manuscript; all authors revised and approved the final version.

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Supplementary data
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Open or closed window: That is the question

To the Editor:

We read with great interest the recently published article by Téllez *et al.*, which approaches the controversial issue of the use of beta-blockers in patients with refractory ascites.[1] The authors are to be praised for the use of load-independent gold-standard-validated parameters to evaluate systolic function.[2] This is particularly important in patients with cirrhosis, which is characterized by increased central hypovolemia along the disease course.[3] The authors showed very elegantly that initiation of beta-blockers reduces the cardiac output and lowers the renal perfusion pressure, impairing renal function in these patients. Despite this, we have several comments on their results.

One confusing factor which can influence the results is the use of albumin in patients with refractory ascites. A previous study has shown that administration of albumin in the acute setting leads to an improvement in EIPVD (ejection intraventricular pressure difference: load independent parameter to evaluate systolic function).[4] This effect was considered to be due to the scavenger effect of albumin.[5] Patients with refractory ascites will often receive albumin on a regular basis, which could have influenced the results.

Secondly, the effect of initiation of beta-blockers was not homogenous in all patients with refractory ascites. Indeed, while some patients had a marked decrease in the EIPVD, other patients had almost no change and some patients even had an increase in the ejection fraction. Similarly, only some patients developed acute kidney injury. According to the present hypothesis, which is supported by the results of this study, patients who have a worsening of renal function should be the ones who had a decrease in their systolic function. Furthermore, despite the initial study which was published over a decade ago suggesting that beta-blockers increased mortality in patients with refractory ascites,[6] many studies have since shown a survival benefit.[7,8] In our opinion these facts suggest that patients with refractory ascites are a heterogeneous group and that further studies are necessary to identify patients for whom the window is closed and those for whom the window remains open.

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CR wrote the letter. AZ provided valuable intellectual input.

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