***Title:***

***ACE2: a linkage for the interplay between COVID-19 and decompensated cirrhosis***

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**List of Abbreviations**

ACE2, Angiotensin-converting enzyme 2; Ang, angiotensin; COVID-19, coronavirus disease-2019; SARS-CoV-2, severe acute respiratory syndrome-associated coronavirus 2.

**Authors Contributions**

Study concept and design: Feng Gao, Ming-Hua Zheng

Analysis and interpretation of data: Fen Gao and Yu-Chen Fan

Drafting of the manuscript: Feng Gao and Kenneth I. Zheng

Critical revision of the manuscript for important intellectual content: Giovanni Targher and Christopher D. Byrne

Study supervision: Ming-Hua Zheng

All authors contributed to the manuscript for important intellectual contents and approved the submission.

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**Conflict of Interest Statement**

All authors: nothing to declare.

**To the Editor,**

We read with interest the paper “Clinical Characteristics of COVID-19 Patients With Digestive Symptoms” in *The American Journal of Gastroenterology*.([1](#_ENREF_1)) In the article, the authors report patients with digestive symptoms were more likely to suffer liver injury because of the upregulation of ACE-2 expression in liver tissue. Liver cirrhosis is one of the most common digestive diseases in healthcare. Recent evidence indicates that cirrhosis significantly increases hepatic ACE2 expression.([2](#_ENREF_2)) We reviewed the available literature (published in PubMed, EMBASE, and Web of Science up to April 30, 2020) and hypothesized cirrhotic patients may be vulnerable to the serious clinical consequences of SARS-CoV-2 infection.

Angiotensin-converting enzyme 2 (ACE2) is a membrane-bound enzyme expressed in many organs (including the liver) that is thought to be involved in SARS-CoV-2 infection. The mechanism of SARS-CoV-2 infection involves a viral coat protein termed SPIKE (S protein) acting as a receptor-binding region that binds to the extracellular domain of ACE2 to gain cell entry. Liver impairment is relatively common amongst COVID-19 patients and ACE2-expressing liver cells are potential targets for SARS-CoV-2 infection. Studies have demonstrated that cirrhosis significantly increases hepatic ACE2 expression.([2](#_ENREF_2)) In normal human livers, ACE2 staining was minimal and confined to bile duct cells, vascular endothelium, and perivenular hepatocytes.([2](#_ENREF_2)) In contrast, in cirrhotic livers, ACE2 was detected in most hepatocytes within cirrhotic nodules, as well as bile duct cells and vascular endothelial cells.([2](#_ENREF_2)) Up-regulation of hepatic ACE2 allows more SARS-CoV-2 entry into cells and may cause greater virulence of SARS-CoV-2 in the liver. Therefore, compared with healthy individuals, patients with cirrhosis and COVID-19 may have a greater severity of hepatic dysfunction and even a higher risk of progression to liver failure.

ACE2 internalization by SARS-CoV-2 potentially results in the loss of ACE2 activity at the cell surface and voids a key pathway of angiotensin (Ang)-II metabolism and Ang-(1-7) generation.([3](#_ENREF_3)) A recent study reported higher plasma levels of Ang II in COVID-19 patients than in healthy controls that would be consistent with lower ACE2 activity.([4](#_ENREF_4)) Ang II is the key effector peptide in renin-angiotensin system (RAS), which mediates vasoconstriction, sustains renal sodium retention and promotes hepatic fibrogenesis. The important role of ACE2 is likely to balance the RAS status by degrading Ang II and generating Ang-(1–7). Experimentally, Ang-(1–7) inhibits liver fibrogenesis and exerts natriuretic and portal hypotensive effects.([5](#_ENREF_5)) Therefore, in cirrhotic patients, the reduction in ACE2 by SARS-CoV-2-induced internalization would be predicted to aggravate liver fibrosis and portal hypertension, and exacerbate disease severity acutely and, perhaps, even in the long-term. Besides, cell surface reduction of ACE2 contributes to widespread inflammation associated with COVID-19.([3](#_ENREF_3))

In summary, we speculate that COVID-19 infection may specifically affect patients with decompensated cirrhosis, since these patients may over-express the ACE2 enzyme leading to higher levels of SARS-COV-2 infection in a group of patients who are already at greater risk of microbial infection.

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