ACE2: A Linkage for the Interplay Between COVID-19 and Decompensated Cirrhosis

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Am J Gastroenterol 2020;00:1. https://doi.org/10.14309/ajg.0000000000000780

We read with interest the article "Clinical Characteristics of COVID-19 Patients With Digestive Symptoms" in *The American Journal of Gastroenterology* (1). In the article, the authors reported that patients with digestive symptoms were more likely to suffer liver injury because of the upregulation of angiotensin-converting enzyme 2 (ACE-2) expression in the liver tissue. Liver cirrhosis is one of the most common digestive diseases in health care. Recent evidence indicates that cirrhosis significantly increases hepatic ACE2 expression (2). We reviewed the available literature (published in PubMed, EMBASE, and Web of Science up to April 30, 2020) and hypothesized that patients with cirrhotic may be vulnerable to the serious clinical consequences of severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2) infection.

ACE2 is a membrane-bound enzyme expressed in many organs (including the liver) that is thought to be involved in the SARS-CoV-2 infection. The mechanism of the 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 among patients with coronavirus disease 2019 (COVID-19), and ACE2-expressing liver cells are potential targets for the SARS-CoV-2 infection. Studies have demonstrated that cirrhosis significantly increases hepatic ACE2 expression (2). In normal human livers, ACE2 staining was minimal and confined to the bile duct cells, vascular endothelium, and perivenular hepatocytes (2). By contrast, in cirrhotic livers, ACE2 was detected in most hepatocytes within cirrhotic nodules, as well as bile duct cells and vascular endothelial cells (2). Upregulation 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). A recent study reported higher plasma levels of Ang II in patients with COVID-19 than in healthy controls that would be consistent with lower ACE2 activity (4). Ang II is the key effector peptide in renin-angiotensin system, which mediates vasoconstriction, sustains renal sodium retention, and promotes hepatic fibrogenesis. The important role of ACE2 is likely to balance the renin-angiotensin system 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). Therefore, in patients with cirrhotic, 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).

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

CONFLICTS OF INTEREST

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Specific author contributions: Study concept and design: F.G., M.-H.Z. Analysis and interpretation of data: F.G. and Y.-C.F. Drafting of the manuscript: F.G. and K.I.Z. Critical revision of the manuscript for important intellectual content: G.T. and C.D.B. Study supervision: M.-H.Z. All authors contributed to the manuscript for important intellectual contents and approved the submission.

Financial support: This work was supported by grants from the National Natural Science Foundation of China (81500665), High Level Creative Talents from Department of Public Health in Zhejiang Province and Project of New Century 551 Talent Nurturing in Wenzhou. GT is supported in part by grants from the School of Medicine, University of Verona, Verona, Italy. CDB is supported in part by the Southampton NIHR Biomedical Research Centre (IS-BRC-20004), UK.

Potential competing interests: None to report.

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