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LETTER TO THE EDITOR

Proposed mechanism for increased COVID-19 mortality in patients with decompensated cirrhosis

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We read with interest the article by Qi et al. on the clinical course of COVID-19 in patients with pre-existing decompensated cirrhosis [1]. We wish to draw attention to a possible contribution of increased hepatic expression of angiotensin converting enzyme 2 (ACE2) and ACE to explain the poor outcomes in these patients.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the closely related SARS-CoV bind to the ACE2 receptor to enter the target cell. ACE2 is expressed in the liver and it has been postulated that SARS-CoV-2 may bind to ACE2 to directly infect the liver. This is supported by the finding that 14–53% of patients with COVID-19 have evidence of liver dysfunction, which is more marked in patients with severe illness [2]. SARS-CoV-2 has been identified in the liver of patients with SARS and may induce liver cell apoptosis via a caspase-dependent pathway [3]. It is possible that SARS-CoV-2 produces liver injury via a similar mechanism. In addition, while ACE and its product angiotensin II promote vasoconstriction, inflammation and fibrosis, the so-called "alternate arm" of the renin angiotensin system (RAS), consisting of ACE2 and angiotensin-(1–7), has vasodilatory and antifibrotic effects [4]. In respiratory failure due to SARS-CoV-2, receptor binding results in shedding of the ACE2 ectodomain and downregulation of ACE2 activity [5]. Binding of SARS-CoV-2 to ACE2 may lead to unopposed ACE activity and angiotensin II mediated tissue injury [6]. This is supported by the observation that angiotensin II levels are increased in otherwise healthy patients with COVID-19 and correlate with viral load [7].

Our work has demonstrated that expression of the "alternate" arm of the RAS is increased in cirrhosis [4]. In healthy livers, ACE2 is predominantly found in cholangiocytes, but in both experimental and human cirrhosis ACE2 gene expression in markedly upregulated and there is widespread parenchymal expression of ACE2 protein. Moreover, we have previously reported that patients with decompensated cirrhosis have increased circulatory ACE2 enzyme (and Ang-(1–7) levels) compared to compensated cirrhotics [8]. We have also shown that ACE activity and angiotensin II levels are increased in cirrhosis [9].

We propose that increased liver parenchymal expression of ACE2 in patients with cirrhosis, and particularly those with decompensated cirrhosis, facilitates entry of virus into the host. Furthermore, upregulated ACE activity in the cirrhotic liver may make it subsequently more vulnerable to angiotensin II-mediated injury.

This hypothesis raises interesting questions regarding possible therapeutic interventions. Emerging observational data suggest that ACE inhibitors and angiotensin-receptor blockers do not increase risk in COVID-19 [10], and we await with interest data forthcoming from therapeutic trials. These drugs, however, are poorly tolerated in patients with advanced liver disease associated with a hyperdynamic circulation, where they commonly cause renal compromise. Further studies elucidating the role the RAS plays in liver injury due to SARS-CoV-2 and the excess mortality in patients with cirrhosis may lead to novel therapeutic targets.

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