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Letter: intestinal inflammation, COVID-19 and gastrointestinal ACE2—exploring RAS inhibitors. Authors' reply

EDITORS,

We thank Garg et al for their comments and interest in our case series study reporting the incidence and clinical characteristics of laboratory-confirmed COVID-19 cases among IBD patients.[1,2] A relevant finding of our study was the high rate of diarrhoea as a presenting symptom among IBD patients with COVID-19. This in theory could be explained by the high affinity of the SARS-CoV-2 spike (S) protein for the angiotensin-converting enzyme 2 (ACE2), which is overexpressed in the inflamed gastrointestinal (GI) tract of IBD patients and considered to be essential for viral entry into human cells.

Garg et al exhaustively analysed the potential influence of all major components of the renin-angiotensin system (RAS), including ACE2, on GI symptoms in patients with COVID-19.[1] The authors postulated that intestinal inflammation leading to symptoms may occur due to SARS-CoV-2-mediated reduction of mucosal ACE2 following entry, resulting in elevated angiotensin II, reduced angiotensin 1-7, increased tumour necrosis factor (TNF) and tryptophan deficiency.[3] Since reduced ACE2 expression in the lungs has also been associated with acute respiratory distress syndrome, it has been suggested that drugs targeting RAS may be useful for the treatment of COVID-19.[4] However, in view of additional data showing no effect of ACE inhibitors and angiotensin receptor blockers on ACE2 GI expression, it is unlikely that these drugs could influence SARS-CoV-2 infection of the GI tract.[2]

The reported evidence, however, suggests other potential therapeutic targets for COVID-19. In severely ill COVID-19 patients, biologics may be beneficial through control of the cytokine release storm, which bears some resemblance to the process in IBD flares. IL-6 levels are significantly elevated in COVID-19, and treatment with the anti-IL-6 antibody tocilizumab dramatically decreases CRP levels, suggesting an improvement in this hyper-inflammatory state.[5] Interestingly, a recent study of patients included in the SECURE-IBD registry reported that TNF antagonist monotherapy was not associated with and even may have a protective effect against severe COVID-19.[6] Evidence that mucosal or plasma ACE2 expression or activity was not associated with the use of anti-TNF therapies[3] reinforces the need for trials evaluating these drugs for COVID-19.[7]

We agree with the authors' comment about interest in the relationship between GI symptoms and faecal calprotectin (FC). FC levels seem especially useful in symptomatic IBD patients to confirm an active flare, but elevated FC also occurs in acute bacterial and viral gastroenteritis.[8] For example, a study reported high FC levels in COVID-19 non-IBD patients with resolved or ongoing diarrhoea.[9] Therefore, we believe that FC levels in a COVID-19 IBD patient with diarrhoea may not be helpful in discriminating between an IBD flare and diarrhoea associated with intestinal cell colonisation by SARS-CoV-2. As no relationship was observed between FC and faecal ARS-CoV-2-RNA, FC levels did not seem useful in evaluating the elimination of virus from the faeces. However, FC levels <100 μg/g in patients with GI symptoms could be useful in differentiating between organic and non-organic gastrointestinal disease, thus avoiding the need for unnecessary endoscopic evaluation during pandemic.

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The authors' declarations of personal and financial interests are unchanged from those in the original article.[1]

LINKED CONTENT

This article is linked to Taxonera et al an Garg et al papers. To view these articles, visit https://doi.org/10.1111/apt.15804 and https://doi.org/10.1111/apt.15814.

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Letter: liver disease and COVID-19—not the perfect storm

EDITORS,

We read with great interest the article by Garrido et al on COVID-19 and liver disease.[1] We agree that COVID-19 is associated with elevated liver enzymes, but its significance needs to be further elucidated as well as the impact of underlying liver disease on COVID-19. From 535 patients SARS-CoV-2 patients admitted at Imperial College Healthcare NHS Trust, London, from 25 February to 5 of April 2020,[2] we found 27.7% (148/535) had elevated liver transaminases. Median ALT and AST levels were 48 IU/L (IQR 17-49) and 88 IU/L (52-172) respectively. Only 1.7% (9/535) had an ALT five times the upper limit of normal and no patients developed synthetic liver dysfunction nor acute liver failure suggesting COVID-19 is not associated with significant acute liver injury. Patients with elevated liver transaminases had similar mortality rates than patients with normal transaminases at admission (29.4% vs 23.3%; $P = 0.462$), although a greater proportion with abnormal liver transaminases were admitted to intensive care (29.8% vs 10.7%; $P < 0.001$), in line with previous findings.[3] We also did not find a correlation between the degree of transaminitis and hypoxaemia on admission defined by a blood oxygen saturation level < 94% ($r = 0.06$, $P = 0.42$) suggesting no direct link between COVID-19-induced initial hypoxemia and liver damage.

In addition, we have explored the impact of pre-existing liver disease—including cirrhosis, on the outcomes of COVID-19, which we feel is of great importance. Immune dysfunction has been well described in cirrhotic patients resulting in a high risk of infection and cirrhotic patients have poor outcomes with acute respiratory distress syndrome (ARDS).[4] In our cohort, 89/535 (16.6%) had suspected pre-existing liver disease based on radiological and laboratory results, including 21/535 (3.9%) with cirrhosis, supporting previously reported rates,[1] and 13/21 (61.9%) had decompensated cirrhosis (Child-Pugh B/C) (Table 1). The main aetiology of cirrhosis was alcohol (47.6%). COVID-19 symptoms at admission, in cirrhotic patients, were mainly cough (71.4%), fever (57.1%) and shortness of breath (23.8%), rather than worsening features of hepatic decompensation. Following admission, 6/21 (28.6%) with compensated cirrhosis developed hepatic decompensation (ie new onset encephalopathy, ascites, variceal haemorrhage or jaundice). This hepatic decompensation rate was not higher than that observed in historical in-hospital pre-COVID cirrhosis data (28.6% vs. 37%).[5]

The overall mortality of COVID-19 patients with cirrhosis was similar to those COVID-19 patients without liver disease (38.1% vs. 34.1%, $P = 0.689$). Median duration of admission was longer in cirrhotic patients compared to those without pre-existing liver disease (10 days vs. 7 days, $P = 0.016$), but development of ARDS requiring admission to ICU for intubation and ventilation was not statistically significant (5.3% vs. 13.7%, $P = 0.280$). At 14 days after diagnosis, hospital readmission rates for those with cirrhosis were comparable with those without liver disease (14.3% vs 11.8%, $P = 0.78$) and only one patient re-presented to hospital with bacterial superinfection.

To summarise, our findings suggest that: i. one third of COVID-19 patients have mild transaminitis, which may be associated with more severe disease but not increased mortality; ii. liver cirrhosis does not predispose to increase mortality but does increase length of stay. Further outcome data from large registries of COVID-19 patients with cirrhosis are awaited to confirm this.

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