The gut–liver axis in chronic liver disease associated with severe COVID-19

Jiezhong Chen[a] and **Luis Vitetta**[a,b], [a]Research Department, Medlab Clinical, Sydney 2015 and [b]Faculty of Medicine and Health, The University of Sydney, Sydney 2006, Australia

Correspondence to Jiezhong Chen, Research Department, Medlab Clinical, Alexandria, 66 McCauley St, NSW 2015, Australia
Tel: +61 2 81880311; email: jiezhong_chen@medlab.co

Received 26 August 2021 **Accepted** 27 August 2021

Severe COVID-19 has been associated with many risk factors including aging and underlying chronic diseases such as obesity, diabetes, hypertension, chronic lung disease and chronic liver disease [1]. Satapathy *et al*. demonstrated that liver chemistry abnormalities (LCA) including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and bilirubin were associated with the severity of COVID-19 [2]. Furthermore, LCA were linked to chronic liver disease but not with other risk factors of severe COVID-19, indicating chronic liver disease is an independent indicator of severe COVID-19. However, the mechanisms could be complex as hepatocytes do not express ACE2, suggesting direct hepatic injury by the virus is minor. We posit that the gut–liver axis could play a key role in LCA/chronic liver disease-associated severe COVID-19.

The gut–liver axis represents bidirectional interactions between gut microbiota and liver physiology. Whilst chronic liver disease can affect gut microbiota composition, dysregulation of gut microbiota (gut dysbiosis) can cause liver inflammation through biliary tract, portal vein and systemic circulation [3]. Gut dysbiosis has been associated with chronic liver disease through promoting inflammation and reducing anti-inflammatory mechanisms [1,3]. LCA, an indicator of the extent of hepatic pathogenic changes, have been associated with inflammatory status, particularly with the cytokine storm in COVID-19 [4].

In COVID-19 patients with chronic liver disease, gut microbiota could be highly disturbed. The infections of the intestines by SARS-CoV-2 viruses, which are common in COVID-19, can directly aggravate pre-existing gut dysbiosis in chronic liver disease [1]. Gut dysbiosis can result in intestinal and hepatic inflammation through translocation of endotoxins and bacteria due to increased intestinal permeability. Endotoxin and bacteria in the liver can activate Kuffer cells, macrophages and dendritic cells to produce high levels of proinflammatory cytokines. Recently, several studies reported that gut dysbiosis also caused proinflammatory types of T cells and B cells in the liver [3,5]. In addition, gut dysbiosis reduces the production of commensal bacterial metabolites, which have anti-inflammatory effects such as butyrate, indole and bile acid derivatives [1].

The gut dysbiosis-caused hepatic inflammation together with other pathogenic changes caused by SARS-CoV-2 such as inflammatory cytokines from the lung and local blood vessel endothelial cell infections by SARS-CoV-2 viruses lead to severe COVID-19 and increased mortality. Incorporation of the gut–liver axis could better elucidate the pathogenesis of chronic liver disease-associated severe COVID-19 and have therapeutic implications.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

References

1 Chen J, Hall S, Vitetta L. Altered gut microbial metabolites could mediate the effects of risk factors in Covid-19. *Rev Med Virol* 2021. [Epub ahead of print]
2 Satapathy S, Kuntzen C, Qiu H, Jiang Y, Bodenheimer HC, Roth NC, *et al*. Severity of liver test abnormalities in coronavirus disease 2019 depends on comorbidities and predicts early in-hospital mortality. *Eur J Gastroenterol Hepatol* 2021. [Epub ahead of print]
3 Tripathi A, Debelius J, Brenner DA, Karin M, Loomba R, Schnabl B, Knight R. The gut-liver axis and the intersection with the microbiome. *Nat Rev Gastroenterol Hepatol* 2018; 15:397–411.
4 Phipps MM, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, *et al.* Acute liver injury in COVID-19: prevalence and association with clinical outcomes in a large U.S. Cohort. *Hepatology* 2020; 72:807–817.
5 Barrow F, Khan S, Fredrickson G, Wang H, Dietsche K, Parthiban P, *et al*. Microbiota-driven activation of intrahepatic B cells aggravates Nonalcoholic Steatohepatitis through innate and adaptive signaling. *Hepatology* 2021; 74:704–722.

DOI: 10.1097/MEG.0000000000002290