Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
activity and markers of inflammation in cirrhosis. Hepatology 2017;65:2019–2030.

[4] Angeli P, Ginès P, Wong F, Benardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015;62:968–974.

[5] Wong RJ, Robinson A, Ginzberg D, Gomes C, Liu B, Bhuket T. Assessing the safety of beta-blocker therapy in cirrhosis patients with ascites: a meta-analysis. Liver Int 2019;39:1080–1088.

Is the increased risk for MAFLD patients to develop severe COVID-19 linked to perturbation of the gut-liver axis?

To the Editor:

Two recent studies in the Journal of Hepatology suggest that metabolic dysfunction-associated fatty liver disease (MAFLD) is a risk factor for progression to severe COVID-19. A Chinese study of 202 patients with COVID-19 found that those with indicators of MAFLD had a higher risk of respiratory disease progression than patients without MAFLD.1 A subsequent study of 327 patients, also from China, found increased risk for COVID-19 progression in younger (<60 years old) patients with MAFLD but not in older ones.2 More studies are required to confirm this, especially in cohorts of patients with COVID-19 and imaging or biopsy-proven MAFLD prior to infection. However, it potentially adds MAFLD to a list of risk factors that also includes obesity, type 2 diabetes (T2D), chronic lung disease, inflammatory bowel disease (IBD), asthma, cardiovascular disease, immunodeficiency, and renal failure.

There are likely to be several contributing (and overlapping) explanations for an increased risk for severe COVID-19 in patients with MAFLD. These include an additive strain on an already stressed immune system, hepatic functional impairment in those with clinically significant disease at baseline, infection of the liver itself, or an indirect association due to comorbidities such as obesity and insulin resistance. More studies are urgently needed to separate MAFLD from its comorbidities, and to identify the factors that causally drive COVID-19 progression in individuals with dysmetabolism. However, herein, we wish to highlight the possibility that the increased risk observed in patients with MAFLD is driven by SARS CoV-2 infection of the gut, which exacerbates an existing state of intestinal permeability and mucosal inflammation, thereby contributing to the systemic immune dysfunction characteristic of severe COVID-19. Indeed, this process may also explain the increased risk for COVID-19 progression in obesity, T2D and even IBD which are associated with similar gut microbiota, intestinal inflammation and barrier integrity disturbances.

Multiple studies have reported that gastrointestinal symptoms such as diarrhoea, vomiting, and abdominal pain are common in patients with COVID-19.3–5 The severity of digestive symptoms increases alongside respiratory symptoms and liver injury.6,7 ACE-2 is abundantly expressed on enterocytes in the small intestine,8 and the high level of virus in faeces and the intestinal lumen suggests that the organ is a site of viral infection and inflammation. It is currently unclear whether this induces high levels of cell death and/or increases the permeability of the gut barrier. However, the gut symptoms correlate with markers of liver damage,1 which supports the notion of increased transmission of pathogen-associated molecular patterns (PAMPs) to the liver.

This process could increase the severity of COVID-19 by either sequestering immune resources away from the lungs to the gut and liver, or by ‘priming’ the liver and systemic immune systems to hyperactivity (cytokine storm). The latter explanation may be supported by similarities in the range of circulating proinflammatory cytokines that are induced by non-alcoholic steatohepatitis and severe COVID-19, such as IL-1β, IL-6, and TNF-α.5,9 Furthermore, priming of toll-like receptor (TLR)-mediated proinflammatory release from circulating immune cells has been observed with an initial exposure to malarial parasites10 or respiratory syncytial virus infection,11 and a subsequent exposure to a TLR agonist (lipopolysaccharide, LPS). MAFLD has been shown to increase levels of TLRs in liver.9 so could that ‘first-hit’ prime liver immune cells to hyperactivity upon a ‘second-hit’ of PAMPs such as LPS from a SARS-CoV2-infected gut? As the liver contains the largest population (~80%) of all tissue-resident macrophages (Kupffer cells), a strong immune response from that organ would be able to cause large alterations to systemic inflammation. Research is needed to confirm whether intestinal permeability increases in COVID-19, whether the particular pro-inflammatory cytokines entering circulation from the gut and liver overlap between MAFLD, T2D, IBD, obesity and COVID-19, and whether immune

Keywords: MAFLD; COVID-19; Gut-liver axis; Intestinal permeability; Obesity; Inflammation.

Received 11 May 2020; received in revised form 15 May 2020; accepted 19 May 2020; available online 20 June 2020

https://doi.org/10.1016/j.jhep.2020.05.051
cell numbers are reduced in the lungs when the gut and liver are inflamed.

If gut-liver axis alterations due to metabolic diseases are a key contributor to progression to severe COVID-19 then this information can be used to guide treatment of a large sector of society. Global prevalence rates are estimated at 24% for MAFLD, 13% for obesity and 8.5% for T2D. These subgroups are major contributors to the overall number of patients with COVID-19 that require hospitalisation (up to 25–35% in Western countries\(^{[9]}\)). Trials of treatments that restore gut mucosal protection/regeneration, could reduce the number of patients with MAFLD/obesity/T2D that progress to severe COVID-19. Moreover, caution may have to be taken with drugs that disturb intestinal microbiota composition or abundance.

**Financial support**
The authors received no financial support to produce this manuscript.

**Conflict of interest**
The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

**Authors’ contributions**
NAY and GA wrote the letter, RW revised and approved the final version of the letter.

**Supplementary data**
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.05.051.

**References**
Author names in bold designate shared co-first authorship

[1] J D Qin E Xu J, Zhang D, Cheng G, Wang Y, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. J Hepatol 2020;73(2):451–453.
[2] Zhou YJZ, Wang KL, Yan X, Sun HD, Pan QF, Wang KH, et al. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: a multicenter preliminary analysis. J Hepatol 2020;73(3):719–721.
[3] Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020;115(5):766–773.
[4] Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020;158(6):1831–1833.e3.
[5] Giamarellos-Bourboulis EJ, Netea MG, Rosina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 2020;27(6):992–1000.e3.
[6] Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020;146(1):110–118.
[7] Franklin BS, Parroche P, Ataide MA, Lautf F, Ropert C, de Oliveira RB, et al. Malaria primes the innate immune response due to interferon-gamma induced enhancement of toll-like receptor expression and function. Proc Natl Acad Sci U S A 2009;106:5789–5794.
[8] Monick MM, Varonovsyo TO, Powers LS, Butler NS, Carter AB, Gudmundsson G, et al. Respiratory syncytial virus up-regulates TLR4 and sensitizes airway epithelial cells to endotoxin. J Biol Chem 2003;278:33035–33044.
[9] Kanuri G, Ladurner R, Skibovskaya J, Spruss A, Konigsrainer A, Bischoff SC, et al. Expression of toll-like receptors 1–5 but not TLR 6-10 is elevated in livers of patients with non-alcoholic fatty liver disease. Liver Int 2020;40(10):2562–2568.
[10] Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. MedRxiv 2020. http://dx.doi.org/10.1101/2020.04.23.20076042.

Gabriella Assante 1  
Roger Williams 1  
Neil Alexander Youngson 1,2,3,*

1The Institute of Hepatology, Foundation for Liver Research, London, UK  
2Faculty of Life Sciences and Medicine, King’s College London, London, UK  
3School of medical Sciences, UNSW Sydney, Australia  
*Corresponding author. Address: The Institute of Hepatology, 111 Coldharbour Lane, London, SE5 9NT, UK. Tel.: +44 (0)207 255 9835.  
E-mail address: n.youngson@researchinliver.org.uk (N.A. Youngson)

**Relevance of platelet-derived microvesicles in cirrhosis: The debate remains open**

*To the Editor:*
We read with great interest the review by Thietart and Rautou on extracellular microvesicles in liver diseases.\(^{[1]}\) They accurately describe the remaining challenges regarding both technical aspects and the relevance of microvesicle assessment for diagnostic and prognostic purposes. However, a couple of points deserve specific comment.

Regarding the technical aspects: According to the authors, filtration should be preferred to centrifugation as a method to measure microvesicles. Indeed, they used filtration in their own studies.\(^{[2,4]}\) However, the society of microvesicles does not recommend any one technique over another\(^{[3]}\) and this point thus remains a matter of local practice. More importantly, whatever the method used, it is crucial to verify that the labelling used to identify the cellular origin of microvesicles is actually located in the membrane. To address this question,