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.

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Luis Téllez[1]
Rafael Bañares[2]
Agustín Albillos[1,*]

[1]*Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), CIBEREHD, Universidad de Alcalá, Madrid, Spain*
[2]*Department of Digestive Diseases, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (iISGM), CIBEREHD, and Facultad de Medicina, Universidad Complutense de Madrid, Spain*
[*]Corresponding author. Address: Servicio de Gastroenterología y Hepatología, Hospital Universitario Ramón y Cajal, Ctra Colmenar Viejo Km 9.100, 28034, Madrid, Spain. Tel.: +34 91368000.
E-mail address: agustin.albillos@uah.es (A. Albillos)

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] The severity of digestive symptoms increases alongside respiratory symptoms and liver injury.[3,4] ACE-2 is abundantly expressed on enterocytes in the small intestine,[4] 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,[3] 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*.[5,6] Furthermore, priming of toll-like receptor (TLR)-mediated proinflammatory release from circulating immune cells has been observed with an initial exposure to malarial parasites[7] or respiratory syncytial virus infection,[8] 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

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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[10]). Trials of treatments that restore gut barrier integrity are also supported by this disease mechanism. For instance, therapeutics that have been developed for IBD, including probiotics and modulators of 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.

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Author names in bold designate shared co-first authorship

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Gabriella Assante[1]
Roger Williams[1]
Neil Alexander Youngson[1,2,3,*]
[1]*The Institute of Hepatology, Foundation for Liver Research, London, UK*
[2]*Faculty of Life Sciences and Medicine, King's College London, London, UK*
[3]*School 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.

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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.[2,3] However, the society of microvesicles does not recommend any one technique over another[4] 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,