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Liver injury in COVID-19: management and challenges

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For WHO COVID-19 situation report 41 see https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200301-sitrep-41-covid-19.pdf?sfvrsn=6768306d_2

In December, 2019, an outbreak of a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], previously 2019-nCoV) started in Wuhan, China, and has since become a global threat to human health. The number of confirmed cases of 2019 coronavirus disease (COVID-19) has reached 87 137 worldwide as of March 1, 2020, according to WHO COVID-19 situation report 41; most of these patients are in Wuhan, China. Many cases of COVID-19 are acute and resolve quickly, but the disease can also be fatal, with a mortality rate of around 3%.¹ Onset of severe disease can result in death due to massive alveolar damage and progressive respiratory failure.²

SARS-CoV-2 shares 82% genome sequence similarity to SARS-CoV and 50% genome sequence homology to Middle East respiratory syndrome coronavirus (MERS-CoV)—all three coronaviruses are known to cause severe respiratory symptoms. Liver impairment has been reported in up to 60% of patients with SARS³ and has also been reported in patients infected with MERS-CoV.⁴

At least seven relatively large-scale case studies have reported the clinical features of patients with COVID-19.^{1,5-10} In this Comment, we assess how the liver is affected using the available case studies and data from The Fifth Medical Center of PLS General Hospital, Beijing, China. These data indicate that 2–11% of patients with COVID-19 had liver comorbidities and 14–53% cases reported abnormal levels of alanine aminotransferase and aspartate aminotransferase (AST) during disease progression (table). Patients with severe COVID-19 seem to have higher rates of liver dysfunction. In a study in *The Lancet* by Huang and colleagues,⁵ elevation of AST was observed in eight (62%) of 13 patients in the intensive care unit (ICU) compared with seven (25%) of 28 patients who did not require care in the ICU. Moreover, in a large cohort including 1099 patients from 552 hospitals in 31 provinces or provincial municipalities,

more severe patients with disease had abnormal liver aminotransferase levels than did non-severe patients with disease.¹ Furthermore, in another study,⁸ patients who had a diagnosis of COVID-19 confirmed by CT scan while in the subclinical phase (ie, before symptom onset) had significantly lower incidence of AST abnormality than did patients diagnosed after the onset of symptoms. Therefore, liver injury is more prevalent in severe cases than in mild cases of COVID-19.

Liver damage in patients with coronavirus infections might be directly caused by the viral infection of liver cells. Approximately 2–10% of patients with COVID-19 present with diarrhoea, and SARS-CoV-2 RNA has been detected in stool and blood samples.¹¹ This evidence implicates the possibility of viral exposure in the liver. Both SARS-CoV-2 and SARS-CoV bind to the angiotensin-converting enzyme 2 (ACE2) receptor to enter the target cell,⁷ where the virus replicates and subsequently infects other cells in the upper respiratory tract and lung tissue; patients then begin to have clinical symptoms and manifestations. Pathological studies in patients with SARS confirmed the presence of the virus in liver tissue, although the viral titre was relatively low because viral inclusions were not observed.³ In patients with MERS, viral particles were not detectable in liver tissue.⁴ Gamma-glutamyl transferase (GGT), a diagnostic biomarker for cholangiocyte injury, has not been reported in the existing COVID-19 case studies; we found that it was elevated in 30 (54%) of 56 patients with COVID-19 during hospitalisation in our centre (unpublished). We also found that elevated alkaline phosphatase levels were observed in one (1.8%) of 56 patients with COVID-19 during hospitalisation. A preliminary study (albeit not peer-reviewed) suggested that ACE2 receptor expression is enriched in cholangiocytes,¹² indicating that SARS-CoV-2 might directly bind to ACE2-positive cholangiocytes to dysregulate liver function. Nevertheless, pathological

	Patients with SARS-CoV-2 infection	Patients with pre-existing liver conditions	Patients with abnormal liver function	Notes
Guan et al ¹	1099	23 (2.3%)	AST abnormal (22.2%), ALT abnormal (21.3%)	Elevated levels of AST were observed in 112 (18.2%) of 615 patients with non-severe disease and 56 (39.4%) of 142 patients with severe disease. Elevated levels of ALT were observed in 120 (19.8%) of patients with non-severe disease and 38 (28.1%) of 135 patients with severe disease.
Huang et al ⁵	41	1 (2.0%)	15 (31.0%)	Patients with severe disease had increased incidence of abnormal liver function. Elevation of AST level was observed in eight (62%) of 13 patients in the ICU compared with seven (25%) 25 patients who did not require care in the ICU.
Chen et al ⁶	99	NA	43 (43.0%)	One patient with severe liver function damage.
Wang et al ⁷	138	4 (2.9%)	NA	..
Shi et al ⁸	81	7 (8.6%)	43 (53.1%)	Patients who had a diagnosis of COVID-19 confirmed by CT scan while in the subclinical phase had significantly lower incidence of AST abnormality than did patients diagnosed after the onset of symptoms.
Xu et al ⁹	62	7 (11.0%)	10 (16.1%)	..
Yang et al ¹⁰	52	NA	15 (29.0%)	No difference for the incidences of abnormal liver function between survivors (30%) and non-survivors (28%).
Our data (unpublished)	56	2 (3.6%)	16 (28.6%)	One fatal case, with evaluated liver injury. ¹³

AST= aspartate aminotransferase. ALT= alanine aminotransferase. ICU=intensive care unit.

Table: Comorbidity with liver disease and liver dysfunction in patients with SARS-CoV-2 infection

analysis of liver tissue from a patient who died from COVID-19 showed that viral inclusions were not observed in the liver.¹³

It is also possible that the liver impairment is due to drug hepatotoxicity, which might explain the large variation observed across the different cohorts. In addition, immune-mediated inflammation, such as cytokine storm and pneumonia-associated hypoxia, might also contribute to liver injury or even develop into liver failure in patients with COVID-19 who are critically ill.

Liver damage in mild cases of COVID-19 is often transient and can return to normal without any special treatment. However, when severe liver damage occurs, liver protective drugs have usually been given to such patients in our unit.

Chronic liver disease represents a major disease burden globally. Liver diseases including chronic viral hepatitis, non-alcoholic fatty liver disease, and alcohol-related liver disease affect approximately 300 million people in China. Given this high burden, how different underlying liver conditions influence liver injury in patients with COVID-19 needs to be meticulously evaluated. However, the exact cause of pre-existing liver conditions has not been outlined in the case studies of COVID-19 and the interaction between existing liver disease and COVID-19 has not been studied. Immune dysfunction—including lymphopenia, decreases of CD4+ T-cell levels, and

abnormal cytokine levels (including cytokine storm)—is a common feature in cases of COVID-19 and might be a critical factor associated with disease severity and mortality. For patients with chronic hepatitis B in immunotolerant phases or with viral suppression under long-term treatment with nucleos(t)ide analogues, evidence of persistent liver injury and active viral replication after co-infection with SARS-CoV-2 need to be further investigated. In patients with COVID-19 with autoimmune hepatitis, the effects of administration of glucocorticoids on disease prognosis is unclear. Given the expression of the ACE2 receptor in cholangiocytes, whether infection with SARS-CoV-2 aggravates cholestasis in patients with primary biliary cholangitis, or leads to an increase in alkaline phosphatase and GGT, also needs to be monitored. Moreover, patients with COVID-19 with liver cirrhosis or liver cancer might be more susceptible to SARS-CoV-2 infection because of their systemic immunocompromised status. The severity, mortality, and incidence of complications in these patients, including secondary infection, hepatic encephalopathy, upper gastrointestinal bleeding, and liver failure, need to be examined in large-cohort clinical studies.

Considering their immunocompromised status, more intensive surveillance or individually tailored therapeutic approaches is needed for severe patients

with COVID-19 with pre-existing conditions such as advanced liver disease, especially in older patients with other comorbidities. Further research should focus on the causes of liver injury in COVID-19 and the effect of existing liver-related comorbidities on treatment and outcome of COVID-19.

We declare no competing interests.

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Screening of faecal microbiota transplant donors during the COVID-19 outbreak: suggestions for urgent updates from an international expert panel

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As the outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread from China to other countries, governments and the medical community are taking steps to prevent transmission, from common sense recommendations to radical quarantine measures.¹

In that context, timely recommendations concerning the screening of donors of human cells, tissues, or cellular or tissue-based products have been released, as the potential for transmission of COVID-19 through transplant is not yet known. Several institutions have recommended interim precautions to screen new donors. The US Food and Drug Administration has suggested considering a donor's history of travel to areas of outbreak, cohabitation with infected individuals, or diagnosis or suspicion of COVID-19 within the 28 days before recovery of donor tissue.² Similar measures have been taken by the Global Alliance of Eye Bank Associations and by the Joint United Kingdom Blood Transfusion Services Professional Advisory Committee to rule out

potential donors.^{3,4} The European Society for Blood and Marrow Transplantation has recommended excluding potential donors who have been diagnosed with COVID-19, and waiting at least 21 days before donation in those with a history of high-risk travel or contact.⁵ In Italy, where the COVID-19 outbreak is spreading rapidly, the national transplant centre has taken stronger measures and has recommended testing all potential tissue and stem-cell living donors, as well as dead donors, through real-time RT-PCR assays of nasopharyngeal swab samples (or bronchoalveolar lavage in deceased individuals).⁶

Faecal microbiota transplantation is a novel treatment that has rapidly earned a major role in the management of recurrent *Clostridioides difficile* infection because of its clear advantages over antibiotics.⁷ It is becoming increasingly more widespread and standardised around the world. Last year, an international expert panel, including several authors of this Comment, released recommendations on how to screen faecal microbiota transplant donors, including a medical history and blood and stool examinations.⁸