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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Correspondence

Post COVID-19 cholangiopathy – A deep dive

Dear Editor,

Enteric symptoms are significant in COVID-19 and are sometimes the only symptoms presented by the patient [1]. The common gastrointestinal symptom reported among COVID-19 patients is lack of appetite, nausea, vomiting, diarrhea and abdominal pain/discomfort [1]. Alteration in respiratory tract microbial flora can damage the gastrointestinal tract through immune activation, also known as the 'gut-lung-axis' [2]. When the infection is directly through the gastrointestinal tract, it can spread to the respiratory tract through blood [2]. In such cases, gastrointestinal symptoms precede the respiratory symptoms causing misconception of mild gastrointestinal infections and lethal outcomes.

Post-COVID-19 cholangiopathy is a special entity of liver injury that has been suggested as a variant of secondary sclerosing cholangitis in critically ill patients. It usually involves damage to the liver and gallbladder. It might be secondary to infection by the SARS-CoV-2 virus or by drug-induced damage that causes deterioration of the parenchymal cells causing loss of function. Nevertheless, the diagnosis and treatment for this condition are continuously revised as per available information. Cholangiopathy can be caused in multiple other associated diseases like AIDS, cholangiolithiasis, diffuse intrahepatic metastasis, histiocytosis C and many more. The symptoms in cholangiopathy following COVID-19 are not much different from other etiological types [3].

The molecular explanation could be due to the predominance of the Angiotensin-converting enzyme 2 (ACE2) receptor in the gut and is further confirmed by the presence of SARS-CoV-2 in faecal samples of COVID-19 patient. The presence of viral receptors on the host cell surface in a particular tissue is a major determinant of viral tropism. SARS-CoV-2 cell entry is mediated by the S protein of the virus, which specifically interacts with host ACE2 and transmembrane serine protease 2 (TMPRSS2) [3]. The presence of ACE2 is relatively low in hepatocytes and mainly located in higher levels in cholangiocytes, while the presence of TMPRSS2 is relatively higher in hepatocytes. These findings may be important considering recent reports on endotheliitis of large intrahepatic vessels caused by SARS-CoV-2 and high ACE2 expression in other endothelial, including central and portal veins, which also can become infected by the virus [3,4].

Diagnosis mostly depends on the history presented beside the doctor's clinical evaluation, blood tests and imaging studies. Ultrasonography helps clinicians to visualize the ducts but does not helps in clinching the diagnosis firmly. For more clear conclusive reports, magnetic resonance imaging of the bile ducts or endoscopic retrograde cholangiopancreatography is required [4,5].

Disruption of intestinal wall mucosa can lead to disseminating the virus from the gastrointestinal tract to blood and liver by the portal tract system. It is then excreted in bile, causing more widespread circulatory spread in the gut besides multiplying in the hepatic (hepatocytes) and gallbladder parenchymal cells [2]. In that scenario, Liver function tests could show elevated liver enzymes, i.e., aspartate transferase, alanine transferase, and total bilirubin [6]. Cai Q et al. reported that gamma-glutamyl transferase in serum is increased to thrice the normal levels [7]. This implies that cholangiocyte injury occurs as well. Though the elevation of liver enzymes could be caused by the concurrent drugs administered for treatment of COVID-19, cholangiopathy is more likely due to the SARS-CoV2 infection itself. Recognition of the occurrence of post-COVID cholangiopathy by the treating physician is important for deciding the appropriate course of action [8].

Till date, very few studies were reported on post-covid-19 cholangiopathy. Roth NC et al. reported 3 cases who developed severe cholestasis post-COVID-19, as revealed during liver biopsy, which showed moderate portal to peri-portal fibrosis [9]. The 3 patients had prolonged hospitalization due to acute respiratory failure, and liver enzymes were slightly elevated during the hospital stay. Persistent cholestasis and jaundice were noticed even after cardiopulmonary and renal recovery. No cirrhosis was found, and intrahepatic microangiopathy suggests the direct hepatic injury due to COVID-19. None of the 3 patients have chronic liver disease in the past [9]. Alkaline phosphatase, Aspartate aminotransferase, Alanine aminotransferase and total bilirubin levels were found normal at the time of admission time, but peaks reaching 10-100 times of initial values were found later reducing to baseline after covid-19 recovery.

Durazo FA et al. reported a case of post–COVID-19 cholangiopathy, which required liver transplantation. The patient had no history of any liver disease, and during his hospitalization, he developed acute respiratory distress syndrome and acute kidney injury and required mechanical ventilation and dialysis. Elevated Levels of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) were found during hospitalization. The liver size was normal, and abdominal ultrasound revealed fatty liver, gall stones without showing any biliary dilation or gallbladder wall thickening. After 81 days of the first presentation, endoscopic retrograde cholangiopancreatography (ERCP) revealed secondary sclerosing cholangitis with no pathological findings in bile ducts. The expert's team suggested both renal and liver transplantation, but liver transplantation was conducted first due to an end-stage liver disease score of 37. The patients finally underwent orthotopic liver transplantation (OLT). After 7 months, liver function and enzyme levels were normal, and the patient was under further valuation for the suitability of renal transplantation [10].

In many patients, cholangiopathy was developing during COVID-19 infection or after recovery of COVID-19 infection, but the clinical presentation is after COVID-19 recovery in almost all cases – so leading to the term post COVID-19 cholangiopathy. It is a

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