Secondary sclerosing cholangitis: an emerging complication in critically ill COVID-19 patients

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The hallmark pneumonia of SARS-CoV-2 infection (coronavirus disease 2019, COVID-19) is often accompanied by important extra-pulmonary manifestations. Liver dysfunction occurs in up to 45% of patients and manifests predominantly as moderate transaminitis. Although the hepatic expression of angiotensin-converting-enzyme-2 (ACE2) receptor is largely restricted to cholangiocytes, reports of cholestatic injury have been rare [1].

In the first 12 weeks of the pandemic, 3/114 COVID-19 patients admitted to our tertiary intensive care unit (ICU) developed a rapidly progressive cholestatic liver injury that persisted after the acute respiratory distress syndrome (ARDS) had resolved, and evolved to a condition reminiscent of secondary sclerosing cholangitis in critically ill patients (SSC-CIP), a rare but often fatal complication in patients receiving prolonged critical care [2]. During the same time period, a fourth patient with this condition was referred to our center (Fig. 1).

The patients were male, aged 48–68, and required prolonged mechanical ventilation, renal support, and veno-venous extracorporeal membrane oxygenation (VV-ECMO, supplementary Table 1). Magnetic resonance cholangiopancreatography (MRCP) showed focal strictures in intrahepatic bile ducts with intraluminal sludge and casts, the radiological hallmark of SSC-CIP. Liver biopsies showed findings consistent with biliary obstruction, typical for SSC (supplementary Fig. 2). Patients 1 and 2 ultimately required liver transplantation because of refractory cholangitis with irreversible biliary damage: patient 1 is currently doing well but patient 2 died of post-transplant pneumonia and septic shock. Patient 3 experienced a milder form of SSC-CIP and is currently doing well, while patient 4 died as a result of a lethal hepatic haemorrhage.

With an estimated prevalence of 1/2000 (0.05%) ICU admissions, SSC-CIP was remarkably frequent with 3/114 ICU patients (2.6%) over 3 months and represented 3/74 (4.1%) of mechanically ventilated and 3/13 (23.1%) of VV-ECMO-treated patients [3]. COVID-19-specific disease and treatment factors may have precipitated biliary ischemia and cholangiopathy, including varying degrees of hemodynamic instability, high positive end-expiratory pressures reducing hepatosplanchnic blood flow, drug-induced bile duct injury by sedatives such as ketamine, parenteral nutrition, and the exaggerated pro-inflammatory cytokine storm that interferes with the biliary epithelium’s physiological defense against hydrophobic bile salts [2, 4].

Importantly, SARS-CoV-2 RNA and nucleo-capsid protein have been detected in the cholangiocytes and bile of patients with fatal COVID-19 pneumonia, suggesting that a direct cytopathic effect may occur [5]. Moreover, endothelialitis resulting in hypercoagulability and microthrombi deposition in the peribiliary vascular plexus may aggravate ischemia of the biliary epithelium.

This report aims to raise awareness about the risk for COVID-19 patients to develop severe cholestatic liver dysfunction.
Fig. 1 (See legend on next page.)
dysfunction reminiscent of SSC-CIP. As COVID-19 becomes better understood, more patients may recover from ARDS and require prolonged critical care with its associated risks. Our data—although from a small cohort—indicate a spectrum of severity, ranging from asymptomatic bile duct abnormalities to cholangiosepsis. Infamous for its bleak prognosis, early diagnosis with MRCP is critical. Whether mild forms confer a risk for secondary biliary cirrhosis is unknown. The outcome of liver transplantation for COVID-19-cholangiopathy remains to be determined, but a timely multidisciplinary evaluation is warranted. A direct causal role of SARS-CoV-2 in COVID-19-associated SSC-CIP is the subject of ongoing investigations.

Supplementary Information
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