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EDITORIAL

COVID-19-associated cholangiopathy: What is left after the virus has gone?

While the respiratory tract represents the primary target of severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) infection, it has become evident that COVID-19 is a multisystemic infectious disease. The hepatobiliary system could be affected during infection, ranging from slightly elevated liver enzymes to liver failure or secondary sclerosing cholangitis (SSC). Whether direct cytopathic effects, host reaction, hypoxia, drugs, or a combination of all provoke liver injury in COVID-19 is still discussed controversially. In this issue of HEPATOLOGY, a large, retrospective, single-center cohort study from Vienna reports clinical features and prognostic implications of cholangiopathy after COVID-19 in patients with preexisting chronic liver diseases (CLD).[1]

Liver enzyme alterations are common in patients with or without liver disease in the setting of COVID-19. Aminotransferases were elevated in up to 50% of infected subjects. Increases are usually mild (<5 times the upper limit of normal) and occur in early stages of infection. In later states of infection, a progressive elevation of cholestasis parameters (alkaline phosphatase, gamma-glutamyl transferase) was described.[2] This biphasic pattern was also detected by Hartl and colleagues studying 496 patients hospitalized for COVID-19, with 13.1% (n = 65) of them having CLD.[1]

Cholestatic liver injury was present in about 23% of patients with CLD in their cohort. Moreover, 15% of patients with CLD developed SSC after SARS-CoV-2 infection. Cases of SSC after COVID-19 with no known CLD have been published.[3] COVID-19-associated SSC describes a cholangiopathy similar to the sclerosing cholangitis in critically ill patients (SC-CIP) and was exclusively observed in patients with COVID-19 requiring admission to an intensive care unit. Critically ill patients, regardless of the underlying disease, are susceptible to biliary damage and can develop SC-CIP after recovery from their primary illness. Ischemic injury by impaired biliary oxygen supply due to respiratory failure or hypotension seems to be the predominant underlying cause of cholangiopathy in these patients. It remains elusive if the COVID-19-associated cholangiopathy and the SC-CIP are distinct entities or the same phenomenon. To evaluate a potential unique effect of COVID-19, Hartl et al. compared patients with CLD and COVID-19 to a matched group of patients with CLD and non-COVID-19 pneumonia. In the CLD–COVID-19 group SSC occurred significantly more often (15.4% vs. 4.6%), which was shown before only for liver-healthy patients,[4] supporting the idea of an SSC entity different from SC-CIP.

Several possible underlying pathomechanisms of liver injury associated with COVID-19 have been discussed. *In vitro* data have shown that SARS-CoV-2 can infect the hepatobiliary system, potentially causing direct viral damage. Both receptors required for SARS-CoV-2 cellular entry, angiotensin-converting enzyme 2 (ACE2) as well as transmembrane serine protease 2, are expressed on cholangiocytes, underscoring the hypothesis of a potential cytopathic effect. Furthermore, it was recently shown that SARS-CoV-2 is able to infect and replicate in organoids derived from human intrahepatic biliary epithelial cells (BECs).[5] While histopathological studies have reported detection of SARS-CoV-2 RNA and/or proteins in human liver tissue and bile samples,[6] it remains elusive whether SARS-CoV-2 replicates in BECs *in vivo*. Presuming cytopathic effects on the hepatobiliary system, the route of SARS-CoV-2 infection of the liver is unknown, but it could be bloodborne because viral RNA and virions were detected in patients with severe disease.[7] Another mode of infection could be either by direct ascension through the biliary tract or through translocation of the virus through the portal vein after infection of enterocytes.[8]

Besides cytopathic effects of the virus, the host inflammatory response to viral infection could lead to damage of the hepatobiliary system. SARS-CoV-2 is known to provoke a strong proinflammatory cytokine response (TNF, IL-1, IL-6) with endothelial damage, hypercoagulation, and consecutive arterial and venous embolism, as well as secondary parenchymal damage.[2] Of note, ACE2 is also expressed in vascular

Abbreviations: CLD, chronic liver disease; OLT, orthotopic liver transplantation; SARS-CoV-2, severe acute respiratory distress syndrome coronavirus 2; SC-CIP, sclerosing cholangitis in critically ill patients; SSC, secondary sclerosing cholangitis.

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TABLE 1 Clinical features of patients with COVID-19-associated SSC based on reports of at least four patients

Case report/study	Number of patients (*n*)	Metabolic risk factor (*n*)	Preexisting chronic liver disease (*n*)	Ketamine use (*n*)	Liver transplantation performed (*n*)	Death at last follow-up (*n*)
Bütikofer et al.[4]	4	Obesity (0) Diabetes (3) Hypertension n.a. Hyperlipidemia n.a.	None	4	1 listed for OLT	2
Faruqui et al.[9]	12	Obesity (4) Diabetes (4) Hypertension (8) Hyperlipidemia (6)	1	n.a.	1 4 considered for OLT evaluation or listed for OLT	4
Hartl et al.[1]	10	Obesity (5) Diabetes (3) Hypertension (6) Hyperlipidemia (1)	10 7/10 with NAFLD/NASH	9	1 evaluated for OLT	5
Mallet et al.[11]	5	Obesity n.a. Diabetes (2) Hypertension (3) Hyperlipidemia n.a.	2 HBV infection	5	1 listed for OLT	2
Meersseman et al.[12]	4	Obesity 4 Diabetes 1 Hypertension 1 Hyperlipidemia n.a.	None	4	2	2

Abbreviations: OLT, orthotopic liver transplantation; n.a., not available.

endothelial cells, making them a potential target of SARS-CoV-2 infection.[9] Drug-related cytotoxic effects may also contribute to COVID-19-associated cholangiopathy. Various antiviral, antibiotic, immunomodulating, antipyretic, and sedative drugs have been used to treat COVID-19. Even though some of these drugs were associated with elevated liver enzymes, clear causality for liver toxicity in patients with COVID-19 is missing.[8] Recently, a prospective observational study found a dose–effect relationship between long-term infusion of ketamine, being frequently used in sedation of severe acute respiratory distress syndrome in COVID-19, and rising total bilirubin levels, as well as an increased risk of cholestatic liver injury in critically ill patients with COVID-19.[10] Nine of 10 patients with SSC in Hartl et al.'s study population were exposed to ketamine.[1]

Other risk factors for COVID-19-associated SSC in patients with liver disease identified by Hartl and colleagues are related to the metabolic syndrome including diabetes. Interestingly, diabetes was also significantly overrepresented in the COVID-19-associated severe cholestasis cohort described by Bütikofer et al. from Zurich[4] as well as in other smaller studies (Table 1). When comparing the Zurich and Vienna cohorts, the frequency of SSC in patients with COVID-19 was high, with 12% and 15% during follow-up, respectively. In the patients with SSC, mortality reached 50%, and one patient in the Zurich group required orthotopic liver transplantation (OLT). In total, 48 patients with COVID-19-associated SSC have been described in the literature to date (Table S1), 16 of whom died during follow-up. Another nine patients were considered or listed for OLT, and six patients underwent OLT. Two thirds of the patients presented at least one medical condition linked with the metabolic syndrome. At least 24 patients were treated with ketamine during the acute phase of COVID-19. Whether the need for OLT and SSC-associated mortality could possibly be reduced by ursodeoxycholic acid treatment, used in several reports on COVID-19-associated cholestasis (minimum 28 of the 48 patients), remains unclear.

Taken together, it is unlikely that the increased incidence of COVID-19-associated cholangiopathy is explained only by the necessity of intensive care treatment. Other factors including direct cytopathic effects of SARS-CoV-2 must be considered. Furthermore, preexisting CLD is another confounding factor in the study of SARS-CoV-2-associated biliary damage. Hartl et al. present data about cholangiopathy in patients with COVID-19 suffering from CLD, making their work highly insightful.

AUTHOR CONTRIBUTIONS

Niklas Heucke, Verena Keitel, Niklas Heucke: writing–original draft; writing–review & editing. Verena Keitel: writing and correction of original draft, editing of final version.

CONFLICT OF INTEREST

Verena Keitel advises AstraZeneca and is on the speakers' bureau for Albireo, Falk, AbbVie, Gilead, CSL Behring, and Intercept.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.