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## COVID-19 related biliary injury: A review of recent literature


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## COVID-19 related biliary injury: A review of recent literature

Sujani Yadlapati, Simone A. Jarrett, Daniel Baik, Adib Chaaya

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### Abstract

Since its emergence in 2019, it has become apparent that coronavirus 2019 (COVID-19) infection can result in multi systemic involvement. In addition to pulmonary symptoms, hepatobiliary involvement has been widely reported. Extent of hepatic involvement ranges from minor elevation in liver function tests (LFTs) to significant hepatocellular or cholestatic injury. In majority of cases, resolution of hepatic injury or improvement in LFTs is noted as patients recover from COVID-19 infection. However, severe biliary tract injury progressing to liver failure has been reported in patients requiring prolonged intensive care unit stay or mechanical ventilation. Due to the timing of its presentation, this form of progressive cholestatic injury has been referred to as COVID-19 cholangiopathy or post-COVID-19 cholangiopathy, and can result in devastating consequences for patients. COVID-19 cholangiopathy is recognized by dramatic elevation in serum alkaline phosphatase and bilirubin and radiologic evidence of bile duct injury. Cholangiopathy in COVID-19 occurs weeks to months after the initial infection and during the recovery phase. Imaging findings and pathology often resemble bile duct injury associated with primary or secondary sclerosing cholangitis. Etiology of COVID-19 cholangiopathy is unclear. Several mechanisms have been proposed, including direct cholangiocyte injury, vascular compromise, and cytokine release syndromes. This review summarizes existing data on COVID-19 cholangiopathy, including reported cases in the literature, proposed pathophysiology, diagnostic testing, and long-term implications.

**Key Words:** COVID-19 cholangiopathy; Post COVID-19 cholangiopathy; Cholestatic injury; Liver transplant

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**Core Tip:** Severe cholangiopathy can develop in critically ill coronavirus 2019 patients during recovery, which is reflected by significant derangements in liver function tests and imaging findings consistent with bile duct injury. This condition may progress to acute liver failure, necessitating liver transplantation, and has emerged as a novel indication for transplantation during the pandemic. There are still uncertainties regarding the long-term survival and clinical outcomes of patients who experience incomplete recovery.

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## INTRODUCTION

Coronavirus 2019 (COVID-19) infection, caused by severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), has been a major public health concern in recent years, resulting in significant mortality and morbidity worldwide. Although most patients affected by COVID-19 present with respiratory symptoms and sequelae, extra-pulmonary manifestations, including renal failure, neurological deficits, hepatic injury, and gastrointestinal symptoms, worsening coagulopathy, have been reported. Abnormal liver enzymes are seen in up to 20% of patients and are associated with poor clinical outcomes[1]. In the early stages of infection, aspartate (AST) and alanine aminotransferase levels (ALT) are elevated, followed by cholestatic markers like serum bilirubin, alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT) in later stages. Cholestatic liver injury is particularly associated with worse outcomes[2]. This biphasic pattern was described by Hart and colleagues in a study evaluating 496 hospitalized COVID-19 patients[3]. About 6%-20% of patients may have elevation in ALP and GGT at initial presentation. A rise in ALP more than three times the upper limit of normal (ULN) associated with COVID-19 induced cholestatic injury is reported among 1% of critically ill patients[3].

Cholestatic injury in patients ranges from marginal elevation in liver function tests (LFTs) to secondary sclerosing cholangitis (SSC) and liver failure[4]. SSC has been reported in critically ill patients with prolonged hospital stays, patients recovering from sepsis, burns, trauma, and major cardiothoracic surgery.

Post COVID-19 cholangiopathy is a recently described entity considered to be a secondary complication of COVID-19. Currently, there is no consensus on diagnostic criteria for this rare entity. Faruqui *et al*[5] at American Association for the Study of Liver Diseases 2020 described COVID-19 cholangiopathy as severe biliary tract injury resembling SSC seen in patients recovering from severe COVID-19 infection. Diagnosis is made weeks to months after initial admission for COVID-19 infection hence called "post COVID-19 cholangiopathy". These patients often have abnormal LFTs similar to cholestatic injury and bile duct injury on imaging. This review article highlights existing literature on COVID-19 cholangiopathy, including proposed pathophysiology, epidemiology, clinical presentation, treatment, and long-term outcomes[5].

## DEFINITION AND DIAGNOSTIC CRITERIA

Although there is no clear consensus on diagnostic criteria for post COVID-19 cholangiopathy, in most studies, patients with severe COVID-19 cholangiopathy were defined as having ALP greater than 1.5 times the ULN, serum bilirubin greater than 2 times the ULN or GGT greater than 3.0 times the ULN[6-9]. These patients often do not have active sepsis or underlying chronic liver disease that may contribute to cholestasis or liver injury. Bile duct abnormalities are noted on imaging.

Magnetic resonance cholangiopancreatography (MRCP) findings include biliary strictures, beaded appearance of intrahepatic bile ducts, biliary dilation, and irregularities of common bile duct, among others (Table 1). A liver biopsy may be needed in some patients to further corroborate the diagnosis. Biopsy findings include cholangiocyte injury, ductal fibrosis, strictures, intravascular microthrombi, *etc.* (Table 1). Endoscopic retrograde cholangiopancreatography (ERCP) may be indicated in some cases to evaluate the bile ducts further and treat biliary strictures or manage choledocholithiasis which may contribute to cholestasis.

**Table 1 Liver biopsy and Imaging findings in few previously reported cases of coronavirus disease 2019 cholangiopathy**

Ref.	Pathology findings	MRCP
Faruqi <i>et al</i> [5], 2021	Acute and chronic large duct obstruction Peri-portal fibrosis Cholestasis	Beaded appearance of intrahepatic ducts Biliary hyper-enhancement
Roth <i>et al</i> [6], 2021	Intra-hepatic ductal beading Biliary strictures and dilation Peri-portal fibrosis Cholangiocyte regeneration Endothelial swelling of hepatic arteries	Beaded appearance of bile ducts along with segments of strictures and dilation
Rojas <i>et al</i> [7], 2021	Cholestasis Peri-portal inflammation	No biliary obstruction
Daneshjoo <i>et al</i> [22], 2020	Enlarged portal tracts Bile duct epithelial changes Cholestasis, hepatocyte dropout and biliary metaplasia Focal biliary infarcts	Prominence of intra and extrahepatic bile ducts
Tafreshi <i>et al</i> [17], 2021	Bridging fibrosis Cholestasis and cholangiocyte injury Bile duct proliferation	Beaded appearance of intrahepatic bile ducts. Periductal prominence Normal liver parenchyma
Lee <i>et al</i> [16], 2021	Bridging fibrosis Onion skinning of bile ducts and cytoplasmic vacuolization of epithelium Cholestasis Bile duct loss Lymphoplasmacytic infiltration	Mild intrahepatic ductal dilation
Durazo <i>et al</i> [8], 2021	Degenerative cholangiocyte injury and cytoplasmic vacuolization Intrahepatic microangiopathy Hepatic artery endothelial swelling, portal vein phlebitis, sinusoidal obstruction	Beaded appearance of intrahepatic ducts with multiple segmental strictures
Cesar Machado <i>et al</i> [23], 2022	Cholangiocyte injury Neutrophilic infiltrate Severe cholestasis and fibrosis	Multi focal strictures and segmental dilation of intra and extra hepatic bile ducts

MRCP: Magnetic resonance cholangiopancreatography.

## PATHOPHYSIOLOGY OF COVID-19 RELATED BILIARY INJURY

Mechanisms by which COVID-19 results in biliary injury are unclear; however, several hypotheses have been put forth from review of liver biopsies and autopsy studies in COVID-19 patients with significant cholestatic injury (Table 2). One such theory highlights the possibility of bile duct ischemia resulting in cholangiocyte necrosis[10]. Intrahepatic biliary epithelium is often more susceptible to ischemia because of its single source of arterial blood supply from hepatic artery compared to common bile duct and hepatocytes supplied by the portal vein and hepatic artery. Autopsy series by Lagana *et al*[11] and Bütikofer *et al*[12] showed sinusoidal microthrombi with mild hepatic steatosis in patients with COVID-19. Some studies noted the presence of platelet aggregation in sinusoids without gross intravascular thrombi[5]. Contrarily others did not report any evidence of thrombotic injury[5,8,13].



**Table 2 Proposed mechanisms of coronavirus disease 2019 cholangiopathy**

No.	Proposed pathogenesis of COVID-19 cholangiopathy
1	Cholangiocyte necrosis because of bile duct ischemia[24,25]
2	Micro thrombosis of hepatic sinusoids and ischemic injury[6]
3	Inflammation triggered due to cytokine release (cytokine release syndrome)
4	Direct virus mediated damage[11]
5	Drug induced liver injury in setting of severe COVID-19 infection (antibiotics, Remdesivir among others)
6	Ketamine related cholangiopathy in setting of COVID-19[14]

COVID-19: Coronavirus disease 2019.

Other theories include direct viral damage to biliary epithelium and direct inflammation resulting from cytokine release syndrome. Cytokine release syndrome has been described in patients with critical illness from COVID-19. Release of pro-inflammatory cytokines and mediators results in direct cholangiocyte injury and fibrosis. Angiotensin-converting enzyme 2 (ACE2), the host receptor for SARS-CoV-2, is expressed on respiratory epithelium as well as cholangiocytes. Prior studies evaluating ACE2 expression have concluded that this receptor is more frequently expressed in cholangiocyte clusters (59.7%) compared to hepatocytes (2.6%)[11]. This explains the potential for direct cholangiocyte injury in severe cases of COVID-19. Critically ill patients are often ventilator dependent and receive anesthetics such as ketamine in addition to antibiotics and antiviral therapy. Ketamine associated cholangiopathy has been described in several case reports[14]. Drugs such as remdesivir and amoxicillin-clavulanate are implicated in liver injury, although predominantly hepatocellular damage[15].

## CASES OF COVID-19 CHOLANGIOPATHY AND LONG-TERM IMPLICATIONS

To date several authors have reported cases of post COVID-19 cholangiopathy. In the initial published case series, Roth NC and colleagues reported three such cases[6]. These patients developed severe cholestasis after prolonged hospitalization. Biochemical markers consistent with cholestatic injury, persistent jaundice, and liver biopsy findings concerning for moderate peri-portal fibrosis, cholangiocyte injury with microvascular changes were noted in these patients. These abnormalities persisted despite recovery from COVID-19 infection in all patients. No cirrhosis was seen, and none of the patients had prior history of chronic liver disease[6]. Liver transplantation was not required in any of these cases. These patients received hydroxychloroquine, tocilizumab in addition to prophylactic antibiotics during hospital course.

Similarly, Faruqi *et al*[5] reported 12 cases of COVID-19 cholangiopathy. Average time to diagnosis of cholangiopathy was over 100 d in these cases. Bilirubin levels as high as 13 mg/dL and ALP with a median around 1900 U/L was reported. All twelve patients required intubation and three patients required extracorporeal membrane oxygenation (ECMO). Abnormal MRCP findings were noted in all patients. These findings include beaded appearance of intrahepatic ducts and hyperenhancement of common bile duct. Liver biopsy findings in these patients include ductal obstruction as well as mild peri-portal fibrosis without definite duct loss. Majority of these patients were treated with ursodiol without any significant improvement. Liver transplantation was considered in five patients however only one patient received a living donor transplant. One patient in the series developed decompensated cirrhosis with liver and kidney failure at one year[5].

Keta-Cov research group[13] studied 34 patients admitted to intensive care unit (ICU) with COVID-19 pneumonia in a single center in Zurich. Four of the patients in this cohort had persistently elevated cholestatic markers and abnormal imaging. MRCP findings in this group include irregular bile ducts with stricturing. Average time to diagnosis of cholangiopathy ranged from two weeks to over nine months. All patients required mechanical ventilation and were treated with hydroxychloroquine. Ultimately, two of the four patients died. One patient was listed for liver transplant and one patient had stable but persistent disease at one year[13].

Linneweber *et al*[9] reported two patients in Germany who developed biliary injury during recovery from COVID-19 infection. Both patients developed biliary strictures and required ERCP and stent placement. MRCP findings were overall consistent with SSC. One patient remained stable but required multiple ERCPs while the other patient had progressive near complete destruction of intrahepatic bile ducts and died 8 mo after initial diagnosis[9]. Similar findings of SSC were reported in case series by Edwards *et al*[15], Bütikofer *et al*[12], Lee *et al*[16], and Rojas *et al*[7].

Rojas *et al*[7] reported described a case of COVID-19 cholangiopathy in a young female who had a prolonged hospital course for COVID-19. Patient developed jaundice and deranged LFTs 3 mo after her index admission. Peak bilirubin was close to 15 mg/dL and ALP more than 6000 U/L. Interestingly this patient did not have bile duct abnormalities on imaging or ERCP. Patient subsequently underwent a liver biopsy which showed severe obstructive cholestatic picture with periportal inflammation. This patient eventually had improvement in her liver function and did not require a transplant[7].

Durazo *et al*[8] reported a case of COVID 19 cholangiopathy in a 47-year-old obese man who required mechanical ventilation and ECMO in setting of severe COVID-19 infection. Patient developed markedly deranged liver tests two and half months after initial hospitalization. A peak bilirubin close to 20 mg/dL and ALP close to 2700 U/L was noted. Imaging in this case was concerning for diffuse intrahepatic biliary strictures and beading. Pt underwent ERCP. Pt continued to have significant involvement and destruction of intrahepatic ducts and was listed for liver transplant. This patient successfully received liver transplant and had an uncomplicated post op course. Similar cases of successful liver transplant for refractory cholangitis have been reported by Lee *et al*[16], Tafreshi *et al*[17], Blondeel *et al*[18], as well as Rela *et al*[19], among others[17-20]. Allografts in these patients have been reported to be disease free. Cases of persistent liver function abnormalities with stable disease have been reported by a few authors [16,21]. Rate of progression of disease appears to vary among cases with poor outcomes more commonly noted among men, obese patients with metabolic syndromes and more severe COVID-19 illness.

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## CONCLUSION

Post-COVID 19 cholangiopathy has been described in several case reports and case series. This entity is characterized by severe progressive cholestatic liver injury that can result in liver failure and require transplantation. Progression and onset of disease varies among patients and is not well understood. Individuals with metabolic risk factors and comorbidities who require prolonged ICU stay, mechanical ventilation are at the greatest risk of developing COVID-19 cholangiopathy. It is more commonly reported in men in published literature. At present there is no effective treatment. Hydroxychloroquine, azithromycin and ursodiol have been used in treatment of these patients. Based on follow ups reported in published cases majority of the patients have continued elevation in LFTs, while some progress to liver failure and require liver transplant. In a meta-analysis published by Daneshjoo *et al*[22], the authors concluded that 16% of 30 patients described in the study required liver transplant. Although a rare complication of COVID-19 infection, medical personnel must be aware of this clinical entity. High risk patients should be monitored closely during the recovery period particularly if they suffered a severe clinical course and prolonged recovery. Patients suspected to have COVID-19 cholangiopathy should be referred to liver transplant centers promptly. As time progresses, we will continue to learn more about long term outcomes of those patients diagnosed with cholangiopathy including post-transplant survival and clinical course of those without liver failure however with incomplete recovery.

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## FOOTNOTES

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