

Clinical and Histopathological Discoveries in Patients with Hepatic Injury and Cholangiopathy Who Have Died of COVID-19: Insights and Opportunities for Intervention

Joseph K Lim, Basile Njei

Yale Liver Center and Section of Digestive Diseases, Yale University School of Medicine, New Haven, CT, USA

Correspondence: Joseph K Lim, Yale Liver Center and Section of Digestive Diseases, Yale University School of Medicine, 333 Cedar Street, LMP 1080, New Haven, CT, 06520, USA, Email joseph.lim@yale.edu

Abstract: The COVID-19 pandemic has had a profound impact on global health, necessitating a comprehensive understanding of its diverse manifestations. Cholangiopathy, a condition characterized by biliary dysfunction, has emerged as a significant complication in COVID-19 patients. In this review, we report the epidemiology of COVID-19, describe the hepatotropism of SARS-CoV-2, and present the histopathology of acute liver injury (ALI) in COVID-19. Additionally, we explore the relationship between pre-existing chronic liver disease and COVID-19, shedding light on the increased susceptibility of these individuals to develop cholangiopathy. Through an in-depth analysis of cholangiopathy in COVID-19 patients, we elucidate its clinical manifestations, diagnostic criteria, and underlying pathogenesis involving inflammation, immune dysregulation, and vascular changes. Furthermore, we provide a summary of studies investigating post-COVID-19 cholangiopathy, highlighting the long-term effects and potential management strategies for this condition, and discussing opportunities for intervention, including therapeutic targets, diagnostic advancements, supportive care, and future research needs.

Keywords: cholangiopathy, COVID-19, long-COVID-19, histopathology, interventions

Introduction

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global health crisis since its emergence in December 2019. It has affected millions of individuals worldwide, and its impact extends beyond respiratory manifestations, involving various organ systems, including the liver.¹⁻³ The incidence and implications of COVID-19-associated liver dysfunction, particularly cholangiopathy, have gained significant attention in emerging research. While the respiratory aspects of COVID-19 have been the primary focus of research and clinical management, mounting evidence suggests that the disease can also lead to liver dysfunction and cholangiopathy.⁴⁻⁶ The liver, being vital to the body's immune response and susceptible to viral infections, including SARS-CoV-2, plays a crucial role in understanding the disease's pathophysiology and potential interventions. Exploring the relationship between COVID-19 and cholangiopathy holds promise for uncovering new intervention strategies and improving clinical outcomes for patients with COVID-19-associated liver dysfunction.

This comprehensive review aims to address several key aspects. Firstly, understanding the epidemiology, hepatotropism, and histopathology of COVID-19-related liver dysfunction is crucial. By examining the prevalence, incidence, and associated risk factors, we can gain insights into the epidemiological aspects of COVID-19 liver dysfunction. Exploring the hepatotropism of SARS-CoV-2 provides a deeper understanding of the involvement of the liver in COVID-19. Furthermore, investigating the histopathology of acute liver injury (ALI) helps elucidate specific changes in liver tissue. Additionally, it is important to recognize the interaction between pre-existing chronic liver disease and COVID-19, as it impacts disease severity and outcomes. By

summarizing the emerging literature on COVID-19 cholangiopathy and discussing opportunities for managing cholangiopathy in subjects who have died of COVID-19, this review aims to contribute to existing knowledge and facilitate the development of targeted strategies to improve patient care and outcomes.

Epidemiology of COVID-19

In December 2019, the first occurrence of SARS-CoV-2, an RNA virus, was documented in humans in Wuhan, China.⁷ This viral infection, known as COVID-19, continues to pose a significant global public health crisis. The World Health Organization (WHO) reports that COVID-19 has impacted over 750 million individuals worldwide and has resulted in more than 6 million deaths.⁸ Within the United States, the number of diagnosed COVID-19 cases has exceeded 100 million, with over 1 million cumulative deaths attributed to complications from the disease.⁹ When discussing the epidemiology of COVID-19, it is important to note that certain individuals may be at a higher risk of experiencing severe illness or complications from COVID-19.¹⁰ This includes older adults, particularly those over the age of 65, as well as individuals with underlying health conditions such as heart disease, lung disease, diabetes, obesity, and weakened immune systems.^{10,11} Other factors that may increase the risk include living in congregate settings such as nursing homes or crowded households, working in high-risk settings with close contact to others, and belonging to certain racial or ethnic groups that have been disproportionately affected by the virus.¹² Initially regarded as primarily affecting the respiratory system, COVID-19 is now acknowledged to impact various organs, including the lungs, heart, brain, endothelium, kidneys, and liver.^{2,3}

Hepatotropism of SARS-CoV-2

Emerging evidence suggests that SARS-CoV-2 enters host cells through the ACE2 receptor,¹³ with TMPRSS2 playing a crucial role in viral entry.^{14,15} The spike protein (S) of SARS-CoV-2 interacts with ACE2 and TMPRSS2 receptors,¹⁶ and there is increasing recognition of the involvement of additional accessory receptors, such as SR-B1, in viral attachment.¹³ Notably, SR-B1 expression facilitates SARS-CoV-2 entry into ACE2-expressing cells, including cholangiocytes in the liver.¹⁷

In the liver, SARS-CoV-2 can induce local inflammation by activating liver-resident immune cells or directly infecting cholangiocytes and hepatocytes that express ACE2 receptors.^{18–20} The virus promotes intracellular cytotoxic actions in hepatocytes, resulting in cell membrane destruction and cellular structure edema.^{21,22} While cholangiocytes predominantly experience biliary injury due to higher ACE2 expression, hepatocyte injury can be more predominant in cases of re-infection or liver damage, where ACE2 expression increases during hepatocyte regeneration.^{19,20,23} Additionally, SARS-CoV-2 infection affects mitochondrial activity and induces oxidative stress,^{24–26} leading to potential complications such as steatohepatitis and exacerbation of comorbidities like non-alcoholic fatty liver disease (NAFLD).²⁷ Furthermore, severe infection can trigger a cytokine storm, involving the release of proinflammatory cytokines and chemokines, which can damage multiple organs, including the liver.^{28–43}

Histopathology of COVID-19 in the Liver

Histological examination of liver tissue from COVID-19 patients reveals various vascular abnormalities, steatosis (accumulation of fat in liver cells), and mitochondrial abnormalities, suggesting a multifactorial pathogenesis of liver injury. These changes can be attributed to multiple factors, including direct viral damage to hepatocytes/cholangiocytes, immune-mediated liver damage, systemic inflammation, hypoxia, and drug-induced liver injury.^{19,27,31,35,40,44–58} Proteomic studies have further revealed dysregulation of liver proteins associated with hepatic steatosis, sinusoidal congestion, necrosis, vascular thrombosis, hepatic fibrosis, Kupffer cell proliferation, and portal inflammation.⁵⁹

Liver histopathological changes observed in COVID-19 patients range from moderate micro-vesicular steatosis with mild lobular and portal inflammation to focal necrosis.^{25,60–62} One of the earliest pieces of evidence came from liver biopsy of a 50-year-old man who was diagnosed with COVID-19. Histopathology of his liver tissue showed moderate microvesicular steatosis and mild lobular activity.⁴² Furthermore, macrovesicular hepatic steatosis, characterized by the accumulation of larger fat droplets, is commonly observed in COVID-19 patients.^{25,49,60,63–65} Additionally, mild lobular and portal inflammation, as well as infrequent vascular pathology like sinusoidal microthrombi, have been reported.⁶² Studies involving proteomic

analysis have detected SARS-CoV-2 RNA in liver tissue and identified the presence of the virus within hepatocytes using electron microscopy.^{38,54}

Pre-Existing Chronic Liver Disease and COVID-19

Pre-existing chronic liver disease (CLD), particularly cirrhosis, is associated with impaired immune function and increased vulnerability to infections, including COVID-19.^{21,33,52,66} Cirrhosis-associated immune dysfunction (CAID) leads to alterations in innate and adaptive immunity, dysfunctional macrophage activation, impaired neutrophil and lymphocyte function, Toll-like receptor dysfunction, and increased gut permeability with changes in the gut microbiome.^{67,68} COVID-19 patients with pre-existing chronic liver disease, especially cirrhosis, have higher rates of hospitalization, mortality, thromboembolism, and severe disease course compared to those without liver disease.^{69,70} Alcohol-associated liver disease (AALD) and decompensated cirrhosis, in particular, pose the highest risk for all-cause mortality from COVID-19.^{33,69–71}

Patients with chronic hepatitis B or hepatitis C infection without advanced fibrosis or cirrhosis do not appear to have a greater risk of acquiring or experiencing worse outcomes with COVID-19.^{72–74} While HCV-infected individuals may have a higher likelihood of hospitalization, no independent association with death has been observed for HBV or HCV.^{70,72,75} Direct-acting antiviral therapy for HCV may be delayed in patients with COVID-19, although there is some evidence suggesting potential benefits of these antivirals in treating COVID-19.^{40,76–78} NAFLD, the most common chronic liver disease, may impact the course of COVID-19, with higher mortality and need for mechanical ventilation observed in NAFLD patients.^{25,50,64,65,79,80} The impact of COVID-19 on individuals with autoimmune hepatitis (AIH) is comparable to that of non-immunosuppressed persons, contrary to initial speculations that AIH patients may be protected due to immunosuppression.^{22,81,82} Finally, the impact of COVID-19 on liver transplant recipients is controversial, with some studies reporting increased risk of COVID-19-related death and others suggesting increased risk of hospitalization but not higher mortality, thrombosis, or ICU requirement compared to non-transplanted COVID-19 patients. Medications used by liver transplant recipients may influence outcomes, with tacrolimus potentially associated with better outcomes and mycophenolate mofetil identified as an independent predictor of severe COVID-19.^{40,83}

Cholangiopathy in COVID-19

Cholangiopathy, a term encompassing diseases affecting the bile ducts, has emerged as a noteworthy aspect of COVID-19 pathology. Cholangiopathy is a rare but severe complication of COVID-19 infection. The pathophysiology of COVID-19 cholangiopathy is not yet fully understood, but it is believed to be related to the virus's direct or indirect effects on the liver and bile ducts. COVID-19 cholangiopathy can present as liver infarction, severe cholangiopathy, biliary cast syndrome, and progressive cholangiopathy. The intricate pathophysiology underpinning COVID-19 cholangiopathy remains a subject of ongoing investigation. Current understanding suggests a complex interplay of the virus's direct or indirect impact on both the liver and bile ducts. Sequential synergies between Systemic Inflammatory Response (SIR) triggered by the viral infection, Non-Alcoholic Steatohepatitis (NASH), and hypoxemia may initiate a cascade of events. This cascade culminates in oxidative stress, which could subsequently prompt mitochondrial biogenesis while diminishing oxidative capacity. The resultant imbalance may ultimately foster the development of ischemic cholangiopathy. This proposed model offers a glimpse into the intricate connections underlying hepatic health in the context of COVID-19, although further research to establish this is necessary.

Furthermore, several studies have investigated the risk factors associated with the development of cholangiopathy in COVID-19 patients. Risk factors identified include signs of systemic reduced blood oxygen supply, multi-organ failure, high fibrinogen levels, and intravenous ketamine use.⁸⁴ Additionally, disease severity and the need for ICU admission have been linked to an increased risk of cholangiopathy.⁸⁵ These findings suggest that certain demographic and clinical factors contribute to the development of cholangiopathy in individuals affected by COVID-19.

While a universally agreed-upon diagnostic criteria for post COVID-19 cholangiopathy is yet to be established, several studies have provided insights into its clinical manifestations and diagnostic approaches. Typically, severe COVID-19 cholangiopathy is characterized by elevated levels of alkaline phosphatase (ALP) greater than 1.5 times the upper limit of normal (ULN), serum bilirubin greater than 2 times the ULN, or gamma-glutamyl transferase (GGT)

greater than 3.0 times the ULN.^{86–89} Notably, these patients often lack active sepsis or underlying chronic liver disease, which suggests a direct association between COVID-19 and cholestasis or liver injury. Imaging studies such as magnetic resonance cholangiopancreatography (MRCP) have revealed various bile duct abnormalities, including biliary strictures, beaded appearance of intrahepatic bile ducts,^{86,90} biliary dilation,^{5,91} and irregularities of the common bile duct. Additionally, endoscopic retrograde cholangiopancreatography (ERCP) may be employed to assess the bile ducts more extensively, manage biliary strictures, or address choledocholithiasis, which can contribute to cholestasis.⁸⁹

Summary of Studies on Post-COVID-19 Cholangiopathy

Emerging research in the literature has investigated cholangiopathy in post-COVID-19 patients. Post-COVID-19 cholangiopathy is a novel entity that has been increasingly reported in the literature.^{85–94} upon those basis, we conducted a scoping review of the literature, and Table 1 presents the findings as a summary of study characteristics for reports on cholangiopathy in COVID-19, with additional summaries for histopathological findings (Table 2) and MRCP/ERCP findings (Table 3). These investigations have documented various manifestations of biliary system involvement, including persistent liver dysfunction, cholestasis, and biliary abnormalities. For instance, Zhang et al identified biliary dilatation and sludge formation in the gallbladder as common findings in post-COVID-19 patients.⁴³ Similarly, among COVID-19 pneumonia patients in an ICU in Zurich, four cases with persistent elevated cholestatic markers and abnormal imaging were reported. MRCP showed irregular bile ducts with stricturing. Diagnosis of cholangiopathy ranged from two weeks to over nine months. Mechanical ventilation and hydroxychloroquine treatment were required. Two patients died, one underwent liver transplant evaluation, and one had persistent disease after one year.⁹⁵

Numerous studies have also reported secondary sclerosing cholangitis (SSC) in post-covid-19 patients. Leonhardt et al, conducted an observational study to investigate the occurrence and outcomes of SSC as a long-term complication of COVID-19.⁸⁴ Their findings revealed that SSC occurred exclusively in critically ill patients who required invasive ventilation, with a clustering effect observed among them. The occurrence rate of SSC in invasively ventilated COVID-19 patients was approximately 1 in 43. Risk factors associated with SSC development included signs of reduced blood oxygen supply, multi-organ failure, high fibrinogen levels, and intravenous ketamine use. The study highlighted severe tissue hypoxia and fibrinogen-associated circulatory disturbances as potential mechanisms underlying SSC in COVID-19 patients. The 1-year transplant-free survival rate for COVID-19-associated SSC was reported to be 40%, and an increase in SSC cases is anticipated in the post-COVID era. Moreover, Linneweber et al documented two cases in Germany where biliary injury emerged during the recuperation phase from COVID-19.⁸⁹ Both patients experienced the development of biliary strictures, necessitating ERCP and stent insertion. MRCP results exhibited a general conformity with SSC. While one patient remained stable but needed multiple ERCP procedures, the other patient exhibited progressive intrahepatic bile duct destruction and succumbed to the condition eight months after the initial diagnosis. Similar studies reporting SSC after COVID-19 infections are becoming increasingly prevalent in the literature, including cases in the United Kingdom,⁹⁶ Switzerland,⁹⁸ United States,⁵ and Colombia.⁸⁷ It is important to note that all reported cases of cholangiopathy in COVID-19, identified since May 2021, have been in individuals who had experienced severe COVID-19. Severe cases are characterized by factors such as ICU admission, the need for intubation or ECMO due to respiratory or circulatory failure or requiring vasopressor support. However, Onuiri et al, reported three cases of post-COVID-19 cholangiopathy arising in patients who recovered from severe COVID-19.⁹⁴ In a retrospective review, six cases of COVID-19-related cholangiopathy were identified, including three cases in patients who did not develop critical COVID-19. Histological analysis of these cases revealed features consistent with secondary sclerosing cholangitis.⁹⁴

Finally, Hunyady et al presented a pioneering retrospective cohort study that marks a significant step forward in the investigation of COVID-related SSC within ICU settings, distinct from the isolated case reports dominating prior research.⁹⁹ Encompassing 127 patients across 9 German tertiary care centers, the study comprehensively contrasts COVID-SSC with SSC-CIP, shedding light on transplant-free survival determinants. Notably, COVID-SSC's median onset occurred 91 days post-COVID-19 diagnosis, following extensive ICU care, including a median 48-day ventilation period.

Of particular interest, the comparison between COVID-SSC and SSC-CIP highlights striking similarities in clinical aspects and disease progression. Furthermore, valuable therapeutic insights emerge, with Ursodeoxycholic acid (UDCA) use and heightened serum albumin levels correlating independently with improved transplant-free survival. This is in line

Table 1 Summary of Study Characteristics for Case Reports and Case-Control Studies on Cholangiopathy in COVID-19

Study	Patient Characteristics (Age, Gender, Ethnicity)	Country	CLD	ICU, Mechanical Ventilation	Time Peak of ALP Since COVID-19 Diagnosis	Diagnosis	Treatment	Outcome
Edwards et al, 2020 ⁹⁶	59-year-old male	UK	No	Yes	79 days	MRCP, ERCP, Liver biopsy	UDCA	Alive, no LT
Roth et al, 2021 ⁸⁶	35-year-old male	USA	No	Yes	139 days	MRCP, ERCP, Liver biopsy	Hydroxychloroquine Azithromycin Tocilizumab Ampicillin Cefepime Ertapenem Vancomycin No UDC	Alive, no LT
	25-year-old male	USA	No	Yes	103 days	MRCP, ERCP, Liver biopsy	Hydroxychloroquine Azithromycin Ivermectin Corticosteroids Tocilizumab Anakinra Convalescent plasma Remdesivir Meropenem Piperacillin-tazobactam Vancomycin no UDCA	Alive, no LT
	40-year-old female	USA	No	Yes	172 days	MRCP, Liver biopsy	Hydroxychloroquine Azithromycin Corticosteroids Anakinra Aztreonam Cefepime Ertapenem Meropenem Nitrofurantoin Piperacillin-tazobactam Vancomycin no UDCA	Remained hospitalized
Durazo et al, 2021 ⁸⁸	47-year-old male	USA	No	Yes	Not known	MRCP, Liver biopsy	Hydroxychloroquine Azithromycin High dose Vitamin C no UDCA	Alive, had LT
Lee et al, 2021 ⁵	64-year-old male		No	Yes	60 days	MRCP, ERCP, Liver biopsy	Hydroxychloroquine, Azithromycin, Tocilizumab, Convalescent plasma, No UDCA	Alive, had LT
Faruqi et al, 2021 ⁹⁷	12 patients, mean age 58 years old (11 males 1 females)	USA	No	Yes	118 days	MRCP only (N = 8), ERCP (N = 4) and liver biopsy (N = 4)	Hydroxychloroquine (N=7), Azithromycin (N=10), UDCA (N=11)	
Rojas et al, 2021 ⁸⁷	29-year-old female, Hispanic/multiracial	Colombia	No	Yes	69 days	MRCP, ERCP, Liver biopsy	Antibiotics (unspecified) Colchicine Dexamethasone Furosemide UDCA	Lost to follow up

(Continued)

Table 1 (Continued).

Study	Patient Characteristics (Age, Gender, Ethnicity)	Country	CLD	ICU, Mechanical Ventilation	Time Peak of ALP Since COVID-19 Diagnosis	Diagnosis	Treatment	Outcome
Bütikofer et al, 2021 ⁹⁸	11 patients with mild cholestasis (9 males 2 females). Mean age 59 years old (range 52–70)	Switzerland	No	Yes	1.7 days	MRCP	Hydroxychloroquine	
	9 patients with severe cholestasis (7 males, 2 females). Mean age 59 years old (range 53–68)	Switzerland	No	Yes	5.4 days	MRCP	Hydroxychloroquine	
Machado et al, 2022 ⁹¹	66-year-old, male	Brazil	Yes	Not known	Not known	MRCP, Liver biopsy	N/A	Alive, no LT
Tafreshi et al, 2021 ⁹⁰	38-year-old male	USA	No	Yes	Not known	MRCP, ERCP, Liver biopsy	Hydroxychloroquine Azithromycin Tocilizumab no UDCA	Alive, no LT
Leonhardt et al, 2023 ⁸⁴	25 patients, with mean age of 59 years old (range 26– 71)	Germany	Not known	Yes	Not known	MRCP (N=1), ERCP (N=23), Autopsy (N=1)	Corticosteroids Antiviral agents/remdesivir Cytosorb Hydrochloroquin Anakinra Tocilizumab Anticoagulants (prior to cholestasis) Antibiotics Anaesthetics (Ketamine prior to cholestasis)	Only 40% of patients were alive 1 year after diagnosis
Linneweber et al, 2022 ⁸⁹	64-year-old, male	Germany	Not known	Yes	Not known	ERCP	Standard COVID treatment (unspecified), UDCA	Alive, no LT
Onuiri et al, 2022 ⁹⁴	47-year-old, male	USA	Yes	No	Not known	Liver biopsy	Not known	Alive, LT
	41-year-old, female	USA	Yes	No	Not know	Liver biopsy	Not known	Alive, LT
	51-year-old, male	USA	Yes	No	Not known	Liver biopsy	Not known	Alive, LT
Hunyady et al, 2023 ⁹⁹	24 patients with mean age 57	Germany	Yes	Yes	91 days (median)	Not known	Dexamethasone (N=16), Hydroxychloroquine (N=1), Tocilizumab (N=3), Remdesivir (N=1), Plasma therapy (N=2), UDCA (N=16)	Not known

Table 2 Summary of Histopathological Findings

Reference	N	Histopathological Findings
Machado et al, 2022 ⁹¹	1	• Extensive ductular reaction and degenerative cholangiocyte injury with biliary ductular proliferation accompanied by neutrophils and portal fibrosis.
Lee et al, 2021 ⁵	1	• Diffuse hepatic injury and bridging fibrosis. • Bile ducts showed onion skinning with nuclear disarray and cytoplasmic vacuolization of the epithelium. • A lymphoplasmacytic infiltrate was present in, and adjacent to, some bile ducts. • Bile duct loss was noted in scattered portal tracts with associated ductular reaction. • There was also evidence of intrahepatocellular cholestasis.
Faruqi et al, 2021 ⁹⁷	12	• Features of acute large duct obstruction with portal expansion by edema • Features of chronic large duct obstruction • Mild fibrosis of some portal tracts • Immunostaining for keratin 7 also showed prominent staining of hepatocytes in all specimens as well, typical of chronic cholestatic liver disease
Durazo et al, 2021 ⁸⁸	1	• Severe degenerative cholangiocyte injury with severe cholangiocyte cytoplasmic vacuolization and regenerative change • Hepatic artery endothelial swelling, portal vein phlebitis, and sinusoidal obstruction syndrome • Intrahepatic microangiopathy affecting all three microvascular compartments
Tafreshi et al, 2021 ⁹⁰	1	• Cholestatic hepatitis with cholangiocyte injury, bile ductular proliferation, canalicular cholestasis • A bile lake and disrupted architecture in the form of focal bridging fibrosis
Onuiri et al, 2022 ⁹⁴	3	• Bile infarcts, severe hepatocytic and canalicular cholestasis, ductular reaction, organizing portal vein thrombi, and necrotic bile ducts accompanied by bile lakes.

with other preliminary findings reported by Brevini et al, which demonstrated a correlation between UDCA treatment and positive clinical outcomes after SARS-CoV-2 infection using retrospective registry data and confirm these findings in an independent validation cohort of recipients of liver transplants.¹⁰⁰ Additionally, they have shown that UDCA reduces farnesoid X receptor (FXR) signaling and downregulate ACE2 in human lung, cholangiocyte and intestinal organoids and in the corresponding tissues in mice and hamsters. In turn, UDCA-mediated downregulation of ACE2 reduces susceptibility to SARS-CoV-2 infection in vitro, in vivo and in human lungs and livers perfused ex situ.¹⁰⁰

Opportunities for Intervention

Despite the growing knowledge about cholangiopathy in COVID-19, there remains an urgent need for effective interventions to address this complex condition. With the epidemiology, hepatotropism, and histopathology of COVID-19-associated cholangiopathy established, it is crucial to explore potential opportunities for intervention that could improve patient outcomes. In this section, we discuss the current gaps in our understanding and present potential strategies for intervention in cholangiopathy associated with COVID-19, aiming to pave the way for targeted approaches that can optimize patient care and improve overall outcomes.

Therapeutic Targets

COVID-19-related cholangiopathy poses a significant clinical challenge, necessitating the exploration of therapeutic targets to mitigate liver injury and promote regeneration. One potential avenue for intervention lies in targeting key pathways involved in cholangiocyte injury and inflammation. Consequently, establishing the pathway(s) in which cholangiopathy occurs within the context of COVID-19 is detrimental. We reviewed the article by Hartl et al regarding progressive cholestasis and sclerosing cholangitis in COVID-19 patients with chronic liver disease and found their findings to be highly relevant.¹⁰¹ It has been observed that patients with pre-existing chronic liver diseases, such as NAFLD, have an increased susceptibility to cholestatic liver failure following COVID-19. The underlying mechanism for this remains unclear but may involve the toxic effects of the virus on cholangiocytes and sepsis-induced cholestasis. Studies have indicated that SARS-CoV-2 can induce mitochondrial dysfunction, oxidative stress, and interfere with hepatic

Table 3 Summary of MRCP and ERCP Findings

Reference	MRCP Findings	ERCP Findings
Edwards et al, 2020 ⁹⁶	Beading effect of intrahepatic bile ducts. Few hypointense filling defects within the common bile duct (CBD) suspicious of choledocholithiasis.	"Bizarre appearances" with a large column of sludge within the whole CBD and a sclerosing cholangitis type picture within the intrahepatic ducts
Roth et al, 2021 ⁸⁶	Intrahepatic bile ducts beading with multiple short segmental strictures and intervening dilatation	Extraction of stones and sludge.
Durazo et al, 2021 ⁸⁸	Cystic-appearing lesion in segment VII of the liver with no biliary obstruction	Negative for Choledocholithiasis.
Lee et al, 2021 ⁵	Mild intrahepatic biliary ductal dilatation and mild patchy T2 hyper intensity within the right hemi liver	• Irregular intrahepatic radicals consistent with cholangiopathy. • Loose stone material was removed from the CBD • Biliary stent placed in bile duct • Repeat ERCP on day 150 showed ductopenia and subtle ductal beading consistent with secondary sclerosing cholangitis
Faruqi et al, 2021 ⁹⁷	• Intrahepatic duct beading • Bile duct thickening and hyper enhancement • Peribiliary diffusion high signal	1. 1 Plastic CBD stent placed, Multiple biliary strictures were noted in the intrahepatic ducts, Stones removal, repeat ERCP in 1 month with removal of the stent. 2. 2 ERCPs done, stone removal, CBD stent placement and removal, and balloon dilation of strictures in the right and left hepatic ducts without improvement. 3. Dilation of left main hepatic duct and placement of a plastic stent. 4. ERCP done after a bile leak after a laparoscopic cholecystectomy. Other eight patients did not undergo ERCP due to predominance of diffuse intra-hepatic biliary tract abnormalities did not seem likely to be conducive to endoscopic intervention
Machado et al, 2022 ⁹¹	Diffuse irregularity of the intra-and extrahepatic bile ducts, with multiple focal strictures alternating with mild focal dilations of the biliary tree	–
Linneweber et al, 2022 ⁸⁹	Did not show intrahepatic cholestasis opting against SSC Showed dilatation of the common bile duct	Inflammation, stricture formation and rarefication of the peripheral bile duct system consistent with SSC Choledocholithiasis Repeat ERCP three times with ductal dilation and stent implantation
Tafreshi et al, 2021 ⁹⁰	Normal liver morphology with diffuse mild intrahepatic biliary distension, marked beading and irregularity, as well as mild irregularity of extra hepatic common bile duct, diffuse periductal enhancement	Tortuous and attenuated intrahepatic bile ducts with normal caliber extrahepatic ducts

lipogenesis, potentially exacerbating comorbidities like NAFLD. In liver pathology studies of fatal COVID-19 cases, increased expression of inositol 1,4,5-trisphosphate receptors (ITPR3) was observed alongside inflammation and hepatic steatosis, suggesting a potential role of ITPR3 in COVID-19 cholangiopathy.¹⁰⁰ These findings highlight the potential for therapeutic intervention in COVID-19 cholangiopathy by targeting the identified mechanisms, such as mitochondrial dysfunction, oxidative stress, and altered calcium signaling through ITPR3 receptors. A deeper understanding of these mechanisms can pave the way for the development of targeted interventions to mitigate cholangiopathy progression and improve patient outcomes.

Patients with AALD and NAFLD are particularly vulnerable to hepatic dysfunction and decompensation following COVID-19 infection. The mechanisms underlying this association are not fully elucidated, but previous research has shown increased expression of inositol 1,4,5-trisphosphate receptors (ITPR3) and hepatic steatosis in lethal COVID-19 cases.¹⁰² Chronic alcohol consumption influences calcium (Ca²⁺) signaling, leading to sustained elevation in Ca²⁺ levels, and enhanced phospholipase C (PLC) activity, resulting in inositol 1,4,5-trisphosphate (IP3) production.¹⁰³ Perturbations in Ca²⁺ signaling can affect mitochondrial function and contribute to mitochondrial reactive oxygen species formation and opening of the permeability transition pore (PTP).¹⁰⁴ The combination of AALD and the pathological stress induced by COVID-19 infection may exacerbate hepatic dysfunction and worsen clinical outcomes, as demonstrated in our study. Targeting these mechanisms associated with chronic liver diseases, such as modulating Ca²⁺ signaling pathways and mitochondrial function, holds potential for therapeutic interventions to mitigate the impact of COVID-19-related cholangiopathy in susceptible populations. Further research is needed to explore the precise mechanisms and develop targeted interventions for this high-risk population.

Diagnostic Advancements

In the quest for improved diagnostic methods for COVID-19-related cholangiopathy, there is a pressing need for standardized diagnostic criteria. The utilization of advanced imaging techniques holds promise in enhancing diagnostic accuracy and facilitating the characterization of biliary abnormalities. Advanced magnetic resonance imaging (MRI) sequences, including MRCP, can provide detailed visualization of the biliary system, enabling the identification of strictures, dilation, and other pathological changes. Additionally, elastography techniques can assess liver stiffness and provide valuable insights into the presence of fibrosis and cholestasis. Finally, cholangioscopy has been shown to be a promising in establishing early diagnosis.¹⁰⁵

In parallel, identifying specific biomarkers associated with cholangiopathy could revolutionize the diagnostic process. Biomarkers, such as liver enzymes, cytokines, and molecular markers, may serve as early indicators of biliary dysfunction and help differentiate COVID-19-related cholangiopathy from other liver diseases. Early detection through biomarker analysis can enable timely intervention and risk stratification, allowing for targeted therapeutic approaches. By harnessing the potential of advanced imaging techniques and identifying reliable biomarkers, clinicians can improve the accuracy and efficiency of diagnosing COVID-19-related cholangiopathy. These diagnostic advancements will not only aid in the early detection and risk assessment but also contribute to a better understanding of the pathogenesis and natural history of the disease, ultimately guiding the development of effective interventions and improving patient outcomes.

Supportive and Tailored Care

Supportive care plays a vital role in the management of patients with COVID-19-related cholangiopathy, focusing on optimizing patient outcomes and alleviating associated complications. Continuous monitoring of liver function tests, including ALP, bilirubin, and GGT is essential for the early detection of cholestasis, allowing for timely intervention and treatment adjustment. Serial measurements of these biomarkers can aid in risk stratification, tracking disease progression, and assessing the response to therapeutic interventions.

In the presence of complications such as choledocholithiasis or biliary strictures, endoscopic interventions can offer significant benefits. ERCP enables both diagnostic and therapeutic interventions, allowing for the identification and removal of biliary stones, as well as the placement of stents to relieve biliary obstruction. By addressing these underlying factors, ERCP not only improves biliary flow but also mitigates the risk of complications such as ascending cholangitis and liver abscesses. Regular monitoring and intervention in cases of biliary obstruction can contribute to improved outcomes and enhance the overall management of COVID-19-related cholangiopathy. In addition to specific interventions, supportive care strategies

should encompass general measures aimed at optimizing the patient's overall well-being. This includes close monitoring of fluid and electrolyte balance, nutritional support, and appropriate pain management. Multidisciplinary collaboration among hepatologists, gastroenterologists, infectious disease specialists, and intensivists is crucial to tailor the supportive care approach to the individual patient's needs, ensuring comprehensive management and improved clinical outcomes.

Future Research

Future research in the field of COVID-19-related cholangiopathy should aim to investigate the long-term effects of the disease and expand our understanding of its implications, considering the significant impact of COVID-19 on the population at large. Further studies employing chart review methodologies are needed to identify and validate risk factors associated with COVID-19-induced liver injury. This will facilitate risk stratification of COVID-19 patients, leading to improved long-term outcomes. Additionally, there is a need to delve into the pathobiology of patients exhibiting a mixed pattern of ALI, and longitudinal data on COVID-19 patients are crucial in determining whether hepato-cholangiopathy resolves or persists as a chronic condition. To gain further insights, future research can explore the role of ACE2, ITPR3 receptors, mitochondrial Ca²⁺ signals, as well as the influence of AALD and NAFLD in enhancing COVID-19 hepato-cholangiopathy. Complementary investigations using cell cultures, animal models, or liver biopsy specimens can shed light on whether SARS-CoV-2 directly affects cholangiocytes, resulting in liver injury with cytopathic effects. These research avenues hold promise in uncovering underlying mechanisms and guiding potential interventions for COVID-19-related cholangiopathy. Finally, future research endeavors should also delve into the intricate dynamics between COVID-19 infection and the increased prevalence of autoimmune disorders observed during the pandemic, such as Type 1 Diabetes (T1D), Sjogren's syndrome, Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis, and autoimmune thyroid disease. Understanding the multifaceted interactions and potential implications for disease severity, distinct from the clear association observed in secondary sclerosing cholangitis (SSC), could illuminate novel avenues for intervention and contribute to a more comprehensive understanding of the evolving landscape of COVID-19-related hepatic complications.

Ethics Approval and Informed Consent

This manuscript is a review article and does not involve any primary research or data collection from human subjects. As such, it does not require ethics approval. Additionally, this review does not involve the collection of personal data or the inclusion of individual patient information. Therefore, informed consent from human subjects is not applicable.

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