Post-COVID-19 Cholangiopathy: A Systematic Review

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Objectives: **Post-COVID-19 cholangiopathy (PCC) is a rare but poorly understood and serious complication of COVID-19 infection. We sought to better understand the epidemiology, mechanism of action, histology, imaging findings, and outcomes of PCC.** ***Methods:*** **We searched PubMed, Cochrane Library, Embase, and Web of Science from December 2019 to December 2021. Mesh words used "post-Covid-19 cholangiopathy," "COVID-19 liver injury," "Covid-19 and cholangiopathy," and "COVID-19 liver disease." The data on epidemiology, mechanism of action, histology, imaging findings, and outcomes were collected.** ***Results:*** **PCC was reported in 30 cases during the study period. The mean (standard deviation [SD]) age was 53.7 (5). Men accounted for cases (83.3%). All patients had required intensive level of care and mechanical ventilation. Mean (SD) number of days from COVID infection to severe disease or liver disease was 63.5 (38). Peak mean (SD) alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and total bilirubin were 2014 (831.8) U/L, 1555 (2432.8) U/L, 899.72 (1238.6) U/L, and 10.32 (9.32) mg/dl, respectively. Four patients successfully underwent liver transplantation.** ***Conclusion:*** **PCC is a severe and progressive complication of COVID-19 infection. More research is needed to better understand the pathophysiology and best treatment approach. Clinicians should suspect PCC in patients with cholestatic liver injury following COVID-19 infection. (J Clin Exp Hepatol 2023;13:489–499)**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus) is a major public health concern and has been associated with substantial morbidity and mortality across the globe.[1] According to the World Health Organization, SARS-CoV-2 has led to over 5 million deaths worldwide as of January 20, 2022.[3] Although the most reported complications after SARS-CoV-2 are related to the cardiopulmonary system, the virus has been implicated in causing multiorgan failure and multiple postrecovery complications.[2–4] Extrapulmonary complications include liver injury, kidney failure, coagulopathy, and neurological defects.[5]

Elevated liver enzymes are reported in approximately 20% of COVID-infected patients and can be a harbinger of outcomes.[6,7] Elevated aminotransferases are associated with greater severity of COVID-19 infection, likelihood of admission, respiratory failure, and death.[7] COVID-19 can also lead to cholestatic pattern of liver injury, which is especially associated with worse outcome.[8] One manifestation of this cholestatic presentation is post-COVID-19 cholangiopathy (PCC).[4,9,10] However, there is no consensus in diagnostic criteria for this rare secondary cholangiopathic complication of COVID-19.

The epidemiology and pathophysiology of PCC are not very well understood. In this systematic literature review, we discuss the epidemiology, clinical and laboratory presentation, evaluation, treatment, and outcomes of PCC. In this review, we also discuss proposed mechanisms of action that may contribute to the development of COVID cholangiopathy.

METHODS

We conducted a systematic search of literature using PubMed, Cochrane Library, Embase, Web of Science, Google Scholar, and Google Search from December 1, 2019, to June 30, 2022. A combination of keywords was used in the medical subjects headings, including: "COVID-19," "Cholangiopathy," "Hepatopathy," "Post-COVID-19 Cholangiopathy." We screened the bibliographies and manuscripts of all the primary articles that contained all the cases. Our research was limited to articles written in English. We limited our research to case reports, case series, and letters to the editor.

Keywords: COVID-19, cholangiopathy, hepatopathy, sclerosing cholangitis

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Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ERCP: endoscopic retrograde cholangiography; LT: liver transplant; MRCP: magnetic retrograde cholangiography; PCC: Post-COVID-19 cholangiopathy; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SD: standard of deviation; SE: standard error; TB: total bilirubin; UDSA: ursodeoxycholic acid; ULN: upper limit of normal

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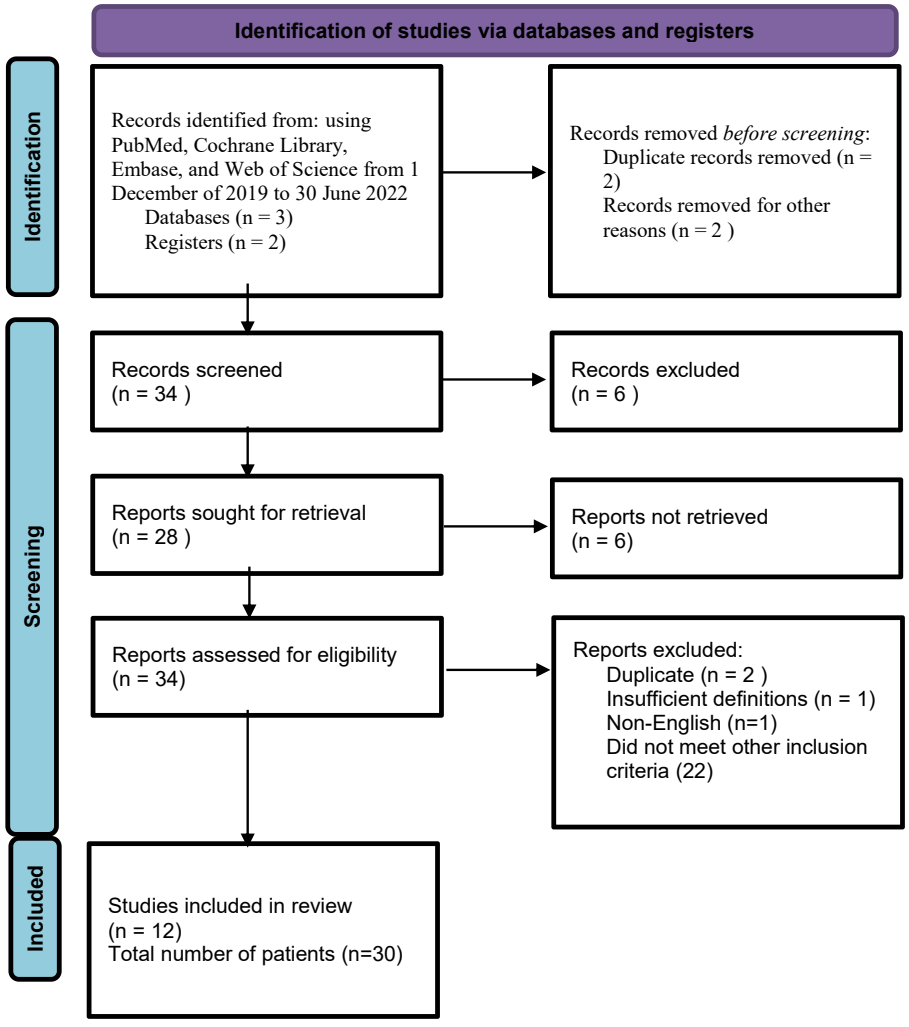

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart.

Inclusion Criteria/Exclusion

Our inclusion criteria incorporated only studies published in English. Non-English studies were excluded. Studies without clear COVID-19 polymerase chain reaction diagnosis were excluded. Our research was in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Figure 1). Patients with other etiologies of liver disease and possible drug-induced liver injury from a known hepatotoxic drug were excluded. Papers that did not include diagnostic modality to confirm cholangiopathy were excluded. Diagnostic modalities for PCC were defined as liver biopsy, magnetic retrograde cholangiopancreatography (MRCP), and/or endoscopic retrograde cholangiopancreatography (ERCP). A total of 106 cases were identified by our literature search. We extracted information from 28 articles (Table 1).[4,9,11–21] We collected data on patients' demographics, symptom onset, liver associated values including initial values and peak values, diagnostic modalities, pathology findings, modes of treatments, and overall disease course. Simple statistics were utilized, and the data were reported.

Operational Definitions

The definitions of COVID-19 cholangiopathy and severe COVID-19 were characterized by the authors of the included studies. In regard to the definition of COVID-19 cholangiopathy, all studies demonstrated injury to the biliary system determined by endoscopy, imaging, or liver biopsy. The most frequent laboratory definition used for a diagnosis of COVID-19 cholangiopathy included: COVID-19-induced cholestasis was defined as a rise in alkaline phosphatase (ALP) by ≥ 1.5 times the upper limit of normal (ULN) with serum bilirubin (≥2 ULN); gamma glutamyl transferase (≥3 ULN); absence of active sepsis; and exclusion of other underlying causes of chronic liver disease.[8–13] The most common features of severe pulmonary COVID-19 were respiratory rate >30/minute; dyspnea and/or SpO2 < 90% on room air; need for mechanical

Table 1 Summary of Articles/Cases of COVID-19-Related Cholangiopathy Published.

Author (reference)	Country	Gender	Age (years)	Ethnicity	Presenting labs	Peak labs	Diagnosis	Treatment	Outcome	Months since (COVID-19 diagnosis)	Hospitalization status/Mechanical ventilation status
Roth *et al.*[4]	USA	Male	38	Non-Hispanic/ White	AP - 81 AST- 30 ALT- 34 TB- 0.3	AP- 3665; AST- 539; ALT- 456 TB- 9.8	MRCP, ERCP, Liver biopsy	Hydroxychloroquine Azithromycin Tocilizumab Ampicillin Cefepime Ertapenem Vancomycin No UDCA	Alive, no LT	6 months	Hospitalized/Required mechanical ventilation
Roth *et al.*[4]	USA	Male	25	Hispanic/ Multiracial	AP- 80 AST- 55 ALT- 52 TB- 0.5	AP- 2892; AST- 4491; ALT-1573 TB- 23.9	MRCP, ERCP, Liver biopsy	Hydroxychloroquine Azithromycin Ivermectin Corticosteroids Tocilizumab Anakinra Convalescent plasma Remdesivir Meropenem Piperacillin-tazobactam Vancomycin no UDCA	Alive, no LT	5 months	Hospitalized/Required mechanical ventilation
Roth *et al.*[4]	USA	Female	40	Hispanic/ Multiracial	AP- 163 AST- 24 ALT- 20 TB-0.3	AP- 2784; AST- 8860; ALT- 2546 TB- 12.7	MRCP, Liver biopsy	Hydroxychloroquine Azithromycin Corticosteroids Anakinra Aztreonam Cefepime Ertapenem Meropenem Nitrofurantoin Piperacillin-tazobactam Vancomycin no UDCA	Remained hospitalized	6 months	Hospitalized/Required mechanical ventilation
Durazo *et al.*[9]	USA	Male	47	Non-hispanic/ White	AP- 90 AST- 79 ALT- 52 TB 0.3	AP- 1644; AST- 384; ALT- 175 TB- 19	MRCP, ERCP, Liver biopsy	Hydroxychloroquine Azithromycin High dose Vitamin C no UDCA	Alive, had LT	2 months	Hospitalized/Required mechanical ventilation
Rojas *et al.*[11]	Colombia	Female	29	Hispanic/ Multiracial	AP- 180 AST- 60 ALT-50 TB- 0.4	AP- 470; AST- 410 ALT- 410; TB- 19	MRCP, ERCP, Liver biopsy	Antibiotics (unspecified) Colchicine Dexamethasone Furosemide UDCA	Alive, no LT	Lost to follow-up	Hospitalized/Required mechanical ventilation
Linnewebber *et al.*[12]	Germany	Male	64	Not reported	Elevated liver enzymes	TB – 17; Others not described	ERCP	Supportive standard COVID treatment (Not specified), UDCA.	Alive, no LT	Lost to follow-up	Hospitalized/Required mechanical ventilation

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Table 1 (*Continued*)

Author (reference)	Country	Gender	Age (years)	Ethnicity	Presenting labs	Peak labs	Diagnosis	Treatment	Outcome	Months since (COVID-19 diagnosis)	Hospitalization status/Mechanical ventilation status
Linnewebber *et al.*[12]	Germany	Male	72	Not reported	Elevated liver enzymes	TB – 7.5; Others not described	MRCP, ERCP	Supportive standard COVID treatment (Not specified), UDCA.	Deceased, no LT		Hospitalized/Required mechanical ventilation
Faraqui *et al.*[13]	USA	Male	73	Non-hispanic/ White	Elevated liver enzymes	AP- 1221; AST-336; ALT- 242 TB 16.9	MRCP, ERCP, Liver biopsy	Azithromycin UDCA	Alive, declined LT evaluation	7 months	Hospitalized/Required mechanical ventilation
Faraqui *et al.*[13]	USA	Male	39	Hispanic	Elevated liver enzymes	AP- 2129; AST- 328; ALT- 242 TB 2.2	MRCP, ERCP, Liver biopsy	Tocilizumab Azithromycin UDCA	Alive, no LT	5 months	Hospitalized/Required mechanical ventilation
Faraqui *et al.*[13]	USA	Male	64	Other	Elevated liver enzymes	AP- 2035; AST- 323; ALT- 338 TB- 16.9	MRCP, ERCP, Liver biopsy	Hydroxychloroquine Azithromycin UDCA	Alive, had LT	10 months	Hospitalized/Required mechanical ventilation
Faraqui *et al.*[13]	USA	Male	77	Non-hispanic/ White	Elevated liver enzymes	AP- 1855; AST- 711; ALT- 792 TB- 8.5	MRCP, ERCP, Liver biopsy	Hydroxychloroquine Azithromycin Remdesivir UDCA	Alive, no LT	10 months	Hospitalized/Required mechanical ventilation
Faraqui *et al.*[13]	USA	Male	46	Non-hispanic/ White	Elevated liver enzymes	AP-2366; AST-2739; ALT- 2171 TB- 2.9	MRCP	Hydroxychloroquine Azithromycin Tocilizumab UDCA	Alive, no LT	9 months	Hospitalized/Required mechanical ventilation
Faraqui *et al.*[13]	USA	Male	72	Hispanic	Elevated liver enzymes	AP-2200; AST-1260; ALT-595 TB-16.0	MRCP	Hydroxychloroquine Azithromycin UDCA	Deceased, no LT	7 months	Hospitalized/Required mechanical ventilation
Faraqui *et al.*[13]	USA	Male	38	Non-hispanic/ White	Elevated liver enzymes	AP-1723; AST-409 ALT- 929; TB- 10.22	MRCP	Hydroxychloroquine Azithromycin UDCA	Deceased, listed for LT	9 months	Hospitalized/Required mechanical ventilation
Faraqui *et al.*[13]	USA	Male	60	Non-hispanic/ White	Elevated liver enzymes	AP -1325; AST- 30 ALT- 34; TB- 0.3	MRCP	Hydroxychloroquine Azithromycin UDCA	Alive, listed for LT	10 months	Hospitalized/Required mechanical ventilation
Faraqui *et al.*[13]	USA	Male	42	Hispanic	Elevated liver enzymes	AP-1036; AST-576 ALT-385; TB-21.6	MRCP	Remdesivir Valacyclovir Foscarnet UDCA	Deceased, no LT	4 months	Hospitalized/Required mechanical ventilation

Table 1 (*Continued*)

Author (reference)	Country	Gender	Age (years)	Ethnicity	Presenting labs	Peak labs	Diagnosis	Treatment	Outcome	Months since (COVID-19 diagnosis)	Hospitalization status/Mechanical ventilation status
Faraqui *et al.*[13]	USA	Male	57	Hispanic	Elevated liver enzymes	AP-2544; AST-332 ALT-260; TB-35	MRCP	Azithromycin UDCA	Deceased, no LT	4 months	Hospitalized/Required mechanical ventilation
Faraqui *et al.*[13]	USA	Male	68	Other	Elevated liver enzymes	AP- 2057; AST- 420; ALT- 286 TB-2.0	MRCP	Hydroxychloroquine UDCA	Alive, declined LT	10 months	Hospitalized/Required mechanical ventilation
Faraqui *et al.*[13]	USA	Female	62	Other	Elevated liver enzymes	AP- 965; AST-7400; LT-5854 TB- 4.4	MRCP	Azithromycin no UDCA	Alive, no LT	6 months	Hospitalized/Required mechanical ventilation
Lee *et al.*[14]	USA	Male	64	Not reported	Normal Liver enzymes initially	Elevated but not reported	MRCP, ERCP, Liver biopsy	Hydroxychloroquine Azithromycin Tocilizumab Convalescent plasma No UDCA	Alive, had LT	8 months	Hospitalized/Required mechanical ventilation
Tafreshi S *et al.*[15]	USA	Male	38	Not reported	AP- 81 AST- 30 ALT- 34 TB-0.3	AP- 3665 AST- 539 ALT- 456 TB- 9.8	MRCP, ERCP, Liver biopsy	Hydroxychloroquine Azithromycin Tocilizumab no UDCA	Alive, no LT	Lost to follow up	Hospitalized/Required mechanical ventilation
Klindt *et al.*[16]	Germany	Male	47	Not reported	AP-203 AST-83 ALT- 91 TB- 0.4	AP- 1700 AST- 470 ALT- 754 TB- 18	MRCP, Liver biopsy	Lopinvir – ritonavir Remdesivir Piperacillin-tazobactam Meropenem no UDCA	Alive, had LT	5 months	Hospitalized/Required mechanical ventilation
Kate *et al.*[17]	UK	Male	59	Not reported	Reportedly normal	ALP 130 AST 83 ALT 102 Bili T 12	MRCP	Corticosteroids	Alive, persistent disease	6 months	Required mechanical ventilation
Butikofer *et al.*[18]	Switzerland	Male	59	Not reported	Normal	ALP 18	MRCP	Hydroxychloroquine	On transplant waitlist	7 months	Required mechanical ventilation
Butikofer *et al.*[18]	Switzerland	Male	67	Not reported	Unknown	Peak ALP 21 x ULN	MRCP	Hydroxychloroquine	Exitus letalis	55 days	Required mechanical ventilation
Butikofer *et al.*[18]	Switzerland	Female	54	Note reported	Unknown	Peak ALP 18.8 ULN	MRCP	Hydroxychloroquine	Alive with persistent disease	9 months 2 weeks	Required mechanical ventilation
Butikofer *et al.*[18]	Switzerland	Male	64	Not reported	Unknown	Peak ALP 12.85 ULN	MRCP	Hydroxychloroquine	Exitus letalis	14 days	Required mechanical ventilation

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Table 1 (*Continued*)

Author (reference)	Country	Gender	Age (years)	Ethnicity	Presenting labs	Peak labs	Diagnosis	Treatment	Outcome	Months since (COVID-19 diagnosis)	Hospitalization status/Mechanical ventilation status
Rela *et al.*[19]	India	Male	50	Not reported	Normal	Peak ALP 420 IU	Liver biopsy post OLT	Hydroxychloroquine	Status post OLT with normal liver tests	6 months	Required mechanical ventilation
Franzini *et al.*[20]	Brazil	Male	65	No reported	Not reported	Peak ALP 807 IU	MRCP and ERCP	Corticosteroids	Continued elevation in liver tests	1 month	Required mechanical ventilation
Rojas *et al.*[21]	Columbia	Female	29	Not reported	Not reported	Peak ALP 400 IU	Liver biopsy	Corticosteroids	Improvement	3 months	Required mechanical ventilation

AP (U/L), alkaline phosphatase, ALT (U/L), alanine aminotransferase, AST (U/L), aspartate aminotransferase, TB (mg/dl), total bilirubin, LT, liver transplant. MRCP, magnetic resonance cholangiopancreatography, ERCP, endoscopic retrograde cholangiopancreatography, UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

ventilation related to COVID-19 illness; and detectable COVID-19 by polymerase chain reaction.[4,9,11–21]

RESULTS

Demographics and Patient Information

We identified 30 cases of patients with PCC that matched our inclusion criteria.[4,9,11–21] (Table 1). Most cases described were from the United States.[4,9,13–15] The mean (SD) age was 53.7 (5). Men accounted for cases (83.3%). Seven patients were non-Hispanic whites, and there were seven patients of Hispanic ethnicity. In the cohort, the most common metabolic disorders including hypertension (53.3%) and obesity (40.9%). The mean (SD) time from diagnosis of COVID-19 infection to diagnosis of PCC was 66 (36.0) days. Demographic data can be found in (Table 2). All patients required hospitalization and mechanical ventilator support. Nine patients were evaluated for liver transplant (Table 1). Four of those patients were successfully transplanted,[9,14,16,19] and one expired while on the list.[13]

Table 2 Demographics and Baseline Characteristics of Patients Identified in This Review.

Variable	Total patients (N = 30)
Age (mean), Years	53.7 ± 5
Gender	
Female	5 (16.7%)
Male	25 (83.3%)
Race/ethnicity	
Non-Hispanic White	7 (31.8%)
Hispanic	7 (31.8%)
Other or unknown	8 (36.4%)
Alcohol status	
Mild (<4 drinks/mo)	3 (13.6%)
Moderate	1 (4.55%)
Not reported	1 (4.55%)
Comorbidities	
Obesity	9 (40.9%)
Diabetes	7 (31.8%)
Hypertension	14 (53.3%)
Chronic liver disease	0 (0%)
Cardiovascular disease	2 (9%)
Cerebrovascular disease	1 (4.5%)
Hyperlipidemia	8 (36.4%)
Other	5 (22.7%)
None	7 (31.81%)

LABORATORY FEATURES

Pertinent liver associated test results are shown in Table 1. Initial presenting labs were not reported in over half of the patients.[12,13,15,16] The labs were described as normal in three patients.[14] Of the seven patients with reported presenting labs, the AST, alanine aminotransferase (ALT), and ALP were elevated in three, four, and three patients of the cohort, respectively. Presenting total bilirubin was normal in the seven patients. Peak mean (SD) ALP, aspartate aminotransferase, ALT, and total bilirubin were 2014 (831.8) U/L, 1555 (2432.8) U/L, 899.72 (1238.6) U/L, and 10.32 (9.32) mg/dl, respectively (Table 3).

LIVER BIOPSY FEATURES

Of the 30 cases identified in this review, 14 underwent a liver biopsy as part of their evaluation.[4,9,11,13–16,19,21] The results are summarized in Table 4. The common histological finding was moderate portal and periportal fibrosis in eight patients.[4,9,11,13,15,16] The next common histological finding in six patients was degenerative cholangiocyte injury, with prominent cholangiocyte vacuolization, regenerative change, apoptosis, and necrosis of the cholangiocyte epithelial layer of terminal bile ducts and marginal ductules.[4,9,13,14] Histologic evidence of both small and large duct obstruction was described in one and three patients, respectively.[13] Bile duct paucity or absence was described in four patients.[13,16,19]

CHOLANGIOGRAPHY FEATURES

Twenty-nine of the thirty patients in our cohort underwent MRCP.[4,9,11–21] The results of the MRCP examinations are shown in Table 5. The most common finding reported in 23 patients was intrahepatic bile ducts beading with multiple short segmental strictures and intervening dilatation.[4,9,13–15,17–21] Bile duct thickening and hyper

Table 3 Peak Relevant Laboratory Values and Scores.[4–21]

Numbers of cases	N = 30
Mean peak AP (U/L), SD	2014 ± 831.8
Mean peak AST (U/L), SD	1555 ± 2432.8
Mean peak ALT (U/L), SD	899.72 ± 1238.6
Mean peak bilirubin (mg/dl), SD	10.32 ± 9.32
Mean number of days (time) from COVID infection to severe disease or liver disease	63.5 ± 38

AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase, SD, standard of deviation, SE, standard error.

Table 4 Summary of Histopathological Findings.

Authors (reference)	N	Histopathology findings
Roth *et al.*[4]	3	• Intrahepatic bile ducts beading, with multiple segmental strictures and intervening dilatation • Mild bile duct paucity (63%) • Moderate ductal reaction and focally moderate cholangiocytes regenerative changes • Mild-moderate portal tract inflammation. Hepatic arteries endothelial swelling
Rojas *et al.*[11]	1	• Low peri-portal inflammatory infiltrates without fibrosis with severe cholestatic pattern
Durazo *et al.*[9]	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
Faraqui *et al.*[13]	12	• Features of acute large duct obstruction with portal expansion by edema • Features of chronic large duct obstruction • Mild fibrosis of some portal tracts • Immunostain for keratin 7 also showed prominent staining of hepatocytes in all specimens as well, typical of chronic cholestatic liver disease
Lee *et al.*[14]	1	• Diffuse hepatic injury and bridging fibrosis • Bile ducts showed onion skinning with nuclear disarray and cytoplasmic vacuolisation 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
Tafreshi *et al.*[15]	1	• Cholestatic hepatitis with cholangiocyte injury, bile ductular proliferation, canalicular cholestasis • A bile lake and disrupted architecture in the form of focal bridging fibrosis
Klindt *et al.*[16]	1	• Slight to moderately enlarged portal tracts with a mixed inflammatory infiltrate, degenerative changes of the bile duct epithelium, and ductular reaction. • Focal biliary metaplasia of the periportal hepatocytes. In addition, perivenular canalicular cholestasis, beginning hepatocyte dropout. • A few bile infarcts could be seen. Immunohistochemistry for Ki67 shows the high rate of proliferation of the bile duct epithelia (arrow) and the hepatocytes

Table 5 Summary of Imaging Findings (MRCP) (N = 21).

Authors (reference)	Number	MRCP findings
Roth *et al.*[4]	3	Intrahepatic bile ducts beading with multiple short segmental strictures and intervening dilatation
Rojas *et al.*[11]	1	Cystic-appearing lesion in segment VII of the liver with no biliary obstruction
Durazo *et al.*[9]	1	Mild intrahepatic biliary ductal dilatation with multifocal strictures or beading without extrahepatic biliary dilatation
Faraqui *et al.*[13]	12	Intrahepatic duct beading Bile duct thickening and hyper enhancement Peribiliary diffusion high signal
Lee *et al.*[14]	1	Mild intrahepatic biliary ductal dilatation and mild patchy T2 hyper intensity within the right hemiliver
Tafreshi *et al.*[15]	1	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
Klindt *et al.*[16]	1	Aggravated accentuation of intra- and extrahepatic biliary ducts
Linneweber *et al.*[12]	1	Did not show intrahepatic cholestasis opting against SSC Showed dilatation of the common bile duct

MRCP, magnetic retrograde cholangiography.

enhancement were reported in 14 patients and peribiliary diffusion high signal reported in 13 patients.[13–16] Twelve patients underwent ERCP. The summary of ERCP findings are listed in Table 6. Briefly, eight patients had evidence of diffuse intrahepatic biliary strictures or cholangiopathy.[9,12–14] Ten patients required extraction of stones

Table 6 Summary of ERCP Findings (N = 12).

Authors (reference)	Number	ERCP findings and interventions
Roth *et al.*[4]	2	Extraction of stones and sludge.
Rojas *et al.*[11]	1	Negative for Choledocholithiasis.
Durazo *et al.*[9]	1	A small pigment stone retrieved Diffuse intrahepatic biliary strictures or cholangiopathy
Faraqui *et al.*[13]	4	Case 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. Case 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. Case 3: dilation of left main hepatic duct and placement of a plastic stent. Case 4: ERCP done after a bile leak after a laparoscopic cholecystectomy. Other eight patients did not undergo ERCP due to predominance of diffuse intrahepatic biliary tract abnormalities did not seem likely to be conductive to endoscopic intervention
Lee *et al.*[14]	1	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
Tafreshi *et al.*[15]	1	Tortuous and attenuated intrahepatic bile ducts with normal caliber extrahepatic ducts
Linnewever *et al.*[12]	2	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

ERCP, endoscopic retrograde cholangiography.

and sludge.[9,12–14] Six patients required common bile duct stent placement.[12–14]

TREATMENT

There was no consensus pharmacologic therapy used by all the 30 patients in our review. Thirteen patients received hydroxychloroquine and 10 remdesivir. Three patients received corticosteroids. Ursodiol was prescribed to most patients (14 of 30 patients received ursodiol). It was noted to be of low benefit.[11–13] Endoscopic interventions to help with biliary drainages such as sphincterotomy, balloon dilatation, and stenting of the bile ducts relieved the cholestasis and improved liver associated laboratory values in five patients.[13,14] However, endoscopic interventions did not impact LT free prognosis in patients who were evaluated for LT.[9,14,16,19] Four patients underwent liver transplantation.[9,14,16,19] One study did not report follow-up after liver transplantation.[16] Follow-up in the remaining three patients was 1, 7, and 8 months[9,14,16] reported patient continued to have normal transaminases post-transplant.

DISCUSSION

PCC is serious progressive cholestatic liver complication that can result in liver failure requiring transplantation. This rare complication has been reported in the context of case reports across the globe. The severity and progression of the disease vary and are not very well understood. The exact mechanism for the development of PCC is not completely known. In this systematic review, we describe the clinical presentation and natural history of PCC.

Our study shows that men with comorbid conditions who require mechanical ventilation are at the highest risk of developing PCC. Specifically, most patients with PCC were men (87%), and most patients had a diagnosis of hypertension (53.3%). Table 2 lists patient demographics. The biochemical presentation varied substantially in our cohort, with few patients having normal liver tests. Peak mean (SD) ALP, aspartate aminotransferase, ALT, total bilirubin were 2014 (831.8) U/L, 1555 (2432.8) U/L, 899.72 (1238.6) U/L, and 10.32 (9.32) mg/dl, in our cohort, respectively. All patients required intensive unit level of care reflecting the severity of COVID-19 infection. There was no uniform pharmacologic treatment in our cohort. The most common therapies used for COVID-19 being hydroxychloroquine, azithromycin, and ursodeoxycholic acid. Unfortunately, no treatment has been consistently effective. Mortality occurred in 7 out of 30 patients (23.3%).[12,13,18] Liver transplant evaluation and listing were completed in 27.2% in our series, but LT was performed in 16% at the time of publication (refs). Sixty-eight percent of the patients previously reported had continued elevation in transaminases and ALP post-COVID-19 recovery. Studies published after our review suggest a possible role of plasmaphereses as a bridge to transplant.[21,24,26] The proposed beneficial mechanism of action for plasmaphereses is the removal of antibodies from that can be contributing to liver injury. In the study, plasma exchange was done in five patients, and two were successfully bridged to living donor liver transplantation in the unvaccinated group of the study.[24] A number of studies have emerged discussing liver disease and PCC describing up to 250 cases; however, these studies did not meet our search criteria therefore are not included, which shows the elevance of the diseases by replication of the publications.[21–26]

There are a number of proposed mechanisms for the development of PCC. One of mechanisms revolves around the role of ACE2 receptors in the pathogenesis of COVID-related cholangiopathy.[27–35] Direct damage to the cholangiocytes may be related to direct viral entry because of concentration of ACE-2 receptors found on the cholangiocytes. Another proposed mechanism include ischemic injury since the liver biliary system is particularly at risk of ischemia because of its single hepatic artery blood supply. As a result, cholangiocytes are easily damaged in situations of prolonged ischemia.[34,37,46] Prolonged mechanical ventilation, sepsis, and hypotension during prolonged mechanical ventilation result in decreased blood supply to the cholangiocytes causing cell death, scaring, and stricture of the bile ducts.[38,39] Furthermore, another proposed mechanism is direct cholangiopathy toxic metabolic injury from viral particles and medications associated with ICU stay.[4,14,43] Finally, immune-mediated cholangiocyte damage due to cytokine and immune cell storm has also been proposed for the development of PCC.[40,47] It is likely that the exact mechanism of action is multifactorial, which includes ischemia, receptor-mediated ACE-2 selective viral entry to cholangiocytes, toxic metabolic due to medications and viral particles, and immune-mediated effects. Several studies have suggested that COVID-19 cholangiopathy is a result of progressive paucity of bile ducts the exact pathophysiology to explain the histologic finding of bile duct paucity is not well known.[16,27,30,31] A number of mechanisms have been proposed and include ischemia, direct viral insult, drug-induced injury, autoimmune mediated, or a combination of all.[11–16,36,41,42,44,45,47]

There are a number of important limitations to our review. One limitation is that changing variants of Covid-19 infection. COVID infection in the current studies likely reflects the original variant. Subsequent variants may not share the same risk of PCC as the original one. Another limitation is the evolving literature available after our inclusion study dates. Updated reviews will be necessary to assess differences in risk factors, management, and outcomes of patients with PCC. For instance, studies included in our review were published largely before immunization against

COVID-19 was available. The results of recent case series by Anand et al describe a potential lower risk of liver failure in COVID-19-immunized individuals.[24] Plasma exchange was done in five patients, and two were successfully bridged to living donor liver transplantation in unvaccinated group.[24]

PCC is a rare complication to viral infection. Men who suffered severe disease requiring intubation and mechanical ventilation with history of chronic disease including diabetes, hypertension, obesity and dyslipidemia are at the higher risk. High-risk population should be closely monitored post disease recovery for evidence of PCC.[40] There appears to be a strong correlation between age, gender, mechanical ventilation, lack of immunization against COVID-19, and COVID-19 cholangiopathy; however, this correlation does not necessarily suggest causation. Unfortunately, no treatment has been consistently effective, and patient with worsening liver function should be referred to a liver transplant center and considered for liver transplantation if condition permits. Clinicians should be vigilant to identify patients with PCC. More studies are needed to determine the true prevalence and long-term outcomes of those who undergo liver transplantation and who exhibit incomplete recovery.

CREDIT AUTHOR STATEMENT

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CONFLICTS OF INTEREST

The authors have none to declare.

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SUPPLEMENTARY DATA

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