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 amino-transferase, 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)

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.
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
| 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, ERCP, 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. \(^5\) | 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 |
| Linneweber \(^12\) et al. | Germany | Male   | 64          | Not reported Elevated liver enzymes | Elevated liver enzymes | Elevated liver enzymes | ERCP | Supportive standard COVID treatment (Not specified), UDCA | Alive, no LT | Lost to follow-up | Hospitalized/Required mechanical ventilation |

(Continued on next page)
| 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. | 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 | 7 months | Hospitalized/Required mechanical ventilation |
| Faraqui et al.     | 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.     | 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.     | 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.     | USA     | Male   | 77          | Non-hispanic/White | Elevated liver enzymes | AP - 1855; AST- 711; ALT- 792 TB 16.9 | MRCP, ERCP, Liver biopsy | Hydroxychloroquine Azithromycin Remdesivir UDCA | Alive, no LT | 10 months | Hospitalized/Required mechanical ventilation |
| Faraqui et al.     | 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.     | 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.     | 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.     | 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.     | 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 |
| 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. | 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. | 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. | USA | Female | 62 | Other | Elevated liver enzymes | AP-965; AST-7400; ALT-5854 TB-4.4 | MRCP | Azithromycin no UDCA | Alive, no LT | 6 months | Hospitalized/Required mechanical ventilation |
| Lee et al. | 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. | 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. | 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 | Lopinavir – ritonavir Remdesivir Piperacillin-tazobactam Meropenem no UDCA | Alive, had LT | 5 months | Hospitalized/Required mechanical ventilation |
| Kate et al. | 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. | Switzerland | Male | 59 | Not reported | Normal ALP 18 | MRCP | Hydroxychloroquine | On transplant waitlist | 7 months | Required mechanical ventilation |
| Butikofer et al. | Switzerland | Male | 67 | Not reported | Unknown Peak ALP 21 x ULN | MRCP | Hydroxychloroquine | Exitus letalis | 55 days | Required mechanical ventilation |
| Butikofer et al. | 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. | Switzerland | Male | 64 | Not reported | Unknown Peak ALP 12.85 ULN | MRCP | Hydroxychloroquine | Exitus letalis | 14 days | Required mechanical ventilation |
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.3,9,11–21 (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,5,14,16,19 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. The labs were described as normal in three patients. 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. The labs were described as normal in three patients. 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).

CHOLANGIOGRAPHY FEATURES

Twenty-nine of the thirty patients in our cohort underwent MRCP. 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.

Table 3 Peak Relevant Laboratory Values and Scores.

| 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 cholangioctyes 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 microangioopathy 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 intrahepato cellular 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 |
| Klinkert 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 |
enhancement were reported in 14 patients and peribiliary diffusion high signal reported in 13 patients.\textsuperscript{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.\textsuperscript{5,12-14} Ten patients required extraction of stones

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

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

MRCP, magnetic retrograde cholangiography.

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

| Authors (reference) | Number | ERCP findings and interventions |
|---------------------|--------|---------------------------------|
| Roth et al.\textsuperscript{1} | 2 | Extraction of stones and sludge. |
| Rojas et al.\textsuperscript{11} | 1 | Negative for Choledocholithiasis. |
| Durazo et al.\textsuperscript{9} | 1 | A small pigment stone retrieved Diffuse intrahepatic biliary strictures or cholangiopathy |
| Faraqui et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{15} | 1 | Tortuous and attenuated intrahepatic bile ducts with normal caliber extrahepatic ducts |
| Linneweber et al.\textsuperscript{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. Six patients required common bile duct stent placement.

**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. 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. However, endoscopic interventions did not impact LT free prognosis in patients who were evaluated for LT. Four patients underwent liver transplantation. One study did not report follow-up after liver transplantation. Follow-up in the remaining three patients was 1, 7, and 8 months 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%). 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 plasmapheresis as a bridge to transplant. The proposed beneficial mechanism of action for plasmapheresis 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. 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 elevation of the diseases by replication of the publications.

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. 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. 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. Furthermore, another proposed mechanism is direct cholangiopathy toxic metabolic injury from viral particles and medications associated with ICU stay. Finally, immune-mediated cholangiocyte damage due to cytokine and immune cell storm has also been proposed for the development of PCC. 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. A number of mechanisms have been proposed and include ischemia, direct viral insult, drug-induced injury, autoimmune mediated, or a combination of all.

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. Plasma exchange was done in five patients, and two were successfully bridged to living donor liver transplantation in unvaccinated group.

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. 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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2022.10.009.