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New onset of severe and long-term hepatobiliary diseases post-COVID-19 infection: a systematic review

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Abstract

Background The COVID-19 pandemic has resulted in a surge of reports linking the virus to various systemic complications, including hepatobiliary disorders. Understanding the spectrum and severity of hepatobiliary diseases following COVID-19 infection is crucial for comprehensive patient management and long-term health outcomes.

Methods A systematic review was conducted to identify studies reporting on hepatobiliary manifestations post-COVID-19 infection. PubMed, Medline, Embase, Scopus, Web of Science, Science Direct and Cochrane Library databases were searched in October 2023, with set inclusion and exclusion criteria in place to select papers documenting new onset hepatobiliary diseases following COVID-19 infection.

Results A total of 23 studies met the inclusion criteria, covering a diverse range of hepatobiliary conditions such as acute hepatitis, cholestasis, autoimmune liver diseases, and gallbladder pathology.

Conclusion This systematic review underscores the emerging evidence of severe and long-term hepatobiliary diseases following COVID-19 infection. Healthcare providers should maintain a high index of suspicion for hepatobiliary complications in patients recovering from COVID-19, emphasizing the need for prolonged monitoring and specialized management strategies to mitigate long-term morbidity and mortality."

Keywords COVID-19, SARS-CoV-2, "post-COVID sequelae", "long-COVID", "liver injury", "hepatic injury", "biliary disease", "hepatobiliary disease", "cholangiopathy"

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive sense RNA virus that belongs to the coronaviruses family and is responsible for the coronavirus disease of 2019 (COVID-19) pandemic. Initial manifestations of the disease affected the respiratory tract, as most cases caused symptoms of a mild upper respiratory tract infection. Pneumonia and respiratory failure are the major culprits for the short-term mortality rate of COVID-19. Other short-term effects include myalgias, anosmia, ageusia, memory deficits, flu-like symptoms, weight loss, and a varicella-like dermatologic exanthem,

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among others [1, 2]. However, a wide variety of complications and long-term sequelae of COVID-19 have been reported in the last five years since the virus was initially discovered.

The most common long-term effects of COVID-19 are functional mobility impairments, pulmonary abnormalities, and mental health disorders [1]. With increasing reports of long-term sequelae of the disease, the Department of Health and Human Services (HHS) coined the term "long-COVID", which broadly refers to signs, symptoms, and conditions that persist or develop at least four weeks after initial infection with SARS-CoV-2. Patients with long-COVID may have a relapsing–remitting course of symptoms or a more progressive pattern of disease. Long-COVID encompasses a variety of conditions that may overlap, suggesting diverse risk factors and patient outcomes [3].

Liver injuries can manifest in various forms, notably classified as parenchymal or biliary in nature. Parenchymal injuries primarily affect the liver tissue itself, encompassing conditions like hepatitis and cirrhosis, where inflammation and fibrosis compromise liver function. On the other hand, biliary injuries involve the bile ducts, leading to conditions such as cholangitis and biliary obstruction [4]. Amidst this spectrum of liver ailments, COVID-19 has emerged as a significant contributor to liver injury, capable of inducing both acute and chronic complications [5]. Acute liver injury in COVID-19 patients often stems from direct viral invasion or systemic inflammation, while chronic effects may arise from prolonged inflammation and immune dysregulation, potentially culminating in liver fibrosis and cirrhosis [6]. In severe cases, COVID-19-related liver injury may necessitate liver transplants (LTs) to mitigate long-term complications and ensure patient survival [5].

The aim of this study is to compile published data reporting fatal, severe or long-term complications impacting the biliary system post-COVID-19 infection.

Methods

The preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement was used to develop the protocol of this systematic review [7].

Information sources and search strategy

This study is part of a project investigating the long term and severe complications of COVID-19. An information professional conducted a comprehensive search that prioritized sensitivity to retrieve all relevant studies. The following databases were searched in October 2023: PubMed, Medline (Ovid, 1946 – Current), Embase (Ovid, 1974 –2021), Scopus, Web of Science, Science Direct and Cochrane Library. The search was designed around keywords and controlled vocabulary that focused on "Long Covid" and variants (see Appendix I for full search details). No language or date restrictions were used. All database search results were imported into EndNote (version 19) and exported to Covidence, where duplicates were removed prior to initial screening (Appendix 1).

Eligibility criteria

No restrictions were made based on country, age or gender. Any articles that did not have primary data, such as review articles, were excluded from the study after removing the duplicates. Furthermore, studies that were not in English were excluded. Only full articles were included, while any conference abstracts were excluded. During the full text screening, any studies that reported liver injury related to the biliary system were included if a clear diagnosis was reported. Any studies reporting only liver function test (LFT) derangement were excluded. We only included severe and/or long term hepatobiliary complications. The inclusion criteria related to this point included any patients who developed a hepatobiliary injury after recovering from COVID-19. If the hepatobiliary injury was diagnosed at least a month after COVID-19 diagnosis or if the study reports that anti-SARS-CoV-2 IgG but not IgM antibodies were detected, the study was included. The studies that reported hepatobiliary injury diagnosis during the active COVID-19 infection were included only if the patient did not recover from the liver injury within 12 weeks or if the patient died before 12 weeks. Any cases with hepatobiliary injury that were diagnosed during the active infection of COVID-19 and recovered within less than 12 weeks were excluded.

Study selection and data collection

Title and abstract screening, full-text screening, and data extraction were conducted by two independent reviewers for each study using Covidence and disagreements were resolved by consensus.

Data items

Demographic and clinical data, including age, sex, comorbidities, treatments, and outcomes, was collected. Continuous variables were expressed as mean ± standard deviation or range of results. Categorical variables were expressed as percentages.

Risk of bias and quality assessment

The quality of the included studies was assessed using different methods depending on the type of study. The Newcastle–Ottawa Quality Assessment Scale (NOS) was used to assess the cohort studies [8]. The scale developed by Murad et al. was used to assess the case reports and case series [9]. Quality assessment was conducted and crosschecked by two independent reviewers.

Data analysis

The hepatobiliary disorders reported by the included studies were classified under the following categories: post-COVID-19 cholangitis, post-COVID-19 cholecystitis, post-COVID-19 hepatitis and any other post-COVID-19 hepatobiliary diseases that do not fall under the previous groups.

Results

Figure 1. shows the flow diagram of our protocol. After removing the duplicates, the titles and abstracts of 38,148 studies were screened, of which 275 were selected for full text screening. Only 23 studies met our inclusion criteria. Of the 252 excluded studies, 135 were irrelevant, 18 had no primary data, 41 were conference abstracts, 43 did not have enough data, 14 were not in English and 1 was duplicate. Supplementary Table S1 summarizes the demographic and clinical data of the included subjects as well as the quality assessment score for each study [10–32]. Furthermore, the details of the quality assessment results using Murad et al. and NOS scales [8, 9] are shown in supplementary tables S2 and S3 respectively.

Types of studies and demographic data

Of the 23 included studies, 14 were case reports, 6 were case series, 2 were cohort studies and 1 was an observational autopsy study. Among the 23 included studies, 6 were from the USA, 2 from India, 1 from both the USA and India, 2 from Germany, 2 from Colombia, 2 from Austria, 1 from Turkey, 1 from Iran, 1 from Israel, 1 from Mexico, 1 from Egypt, 1 from Poland, 1 from Brazil and 1 from Hungary.

The total number of patients reported by 21 studies (case series and case reports) was 74 in addition to 156,917 patients reported by Xu et al. and Leonhardt et al. [11, 24]. Pestri et al. reported 150 subjects who all died after COVID-19 infection [29]. Of these patients, 214 experienced post-COVID-19

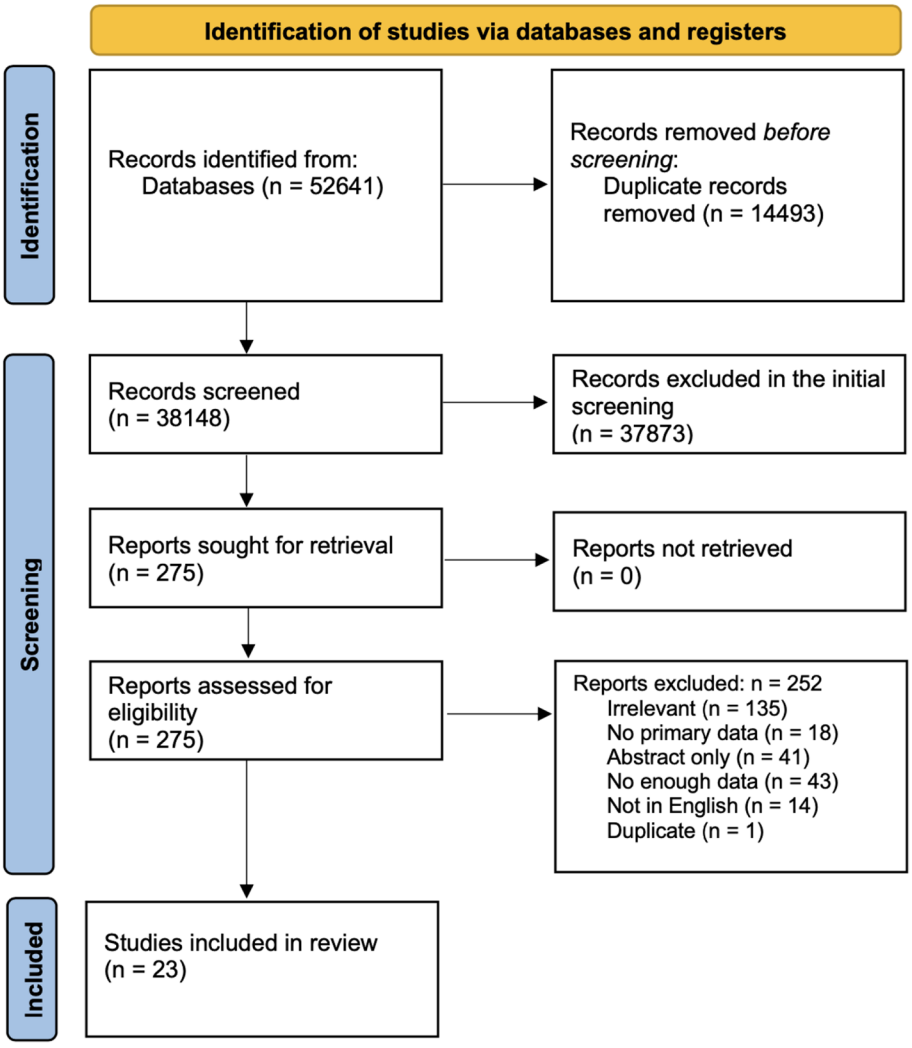

Fig. 1 Database search protocol; screening and study selection

hepatobiliary diseases. Approximately 59% of patients were males excluding Pestri et al. [29] which did not report the gender ratio for patients with hepatobiliary disease post-COVID-19 infection. Furthermore, the age of the included patients ranged from 8 to 76 years (Supplementary table S1).

Clinical data

The reported disorders related to the hepatobiliary system post-COVID-19 were categorized into post-COVID-19 cholangitis, post-COVID-19 cholecystitis, post-COVID-19 hepatitis and any other post-COVID-19 hepatobiliary diseases that do not fall under the previous groups. There was an overlap between the different categories where some studies reported different types of hepatobiliary diseases or patients with multiple disorders that may fall under different categories. Therefore, some studies were included under multiple categories and some patients were counted under different categories (Supplementary table S1). Fig. 2 summarizes the types of the reported hepatobiliary injury post-COVID-19 infection and the reported outcomes.

Post-COVID cholangitis and secondary sclerosing cholangiopathy

Post-COVID-19 cholangitis (PCC) and secondary sclerosing cholangiopathy (SSC) were reported by 17 studies in 66 patients whose age ranged from 14 to 76 years. This was excluding Xu et al. who reported that the HR 1000 persons at 12 months (95% CI) for cholangitis compared to contemporary and historical controls is 2.02 (1.55–2.63) and 1.94 (1.49–2.53) respectively (Table 1) [11].

One patient was reported to have cholangitic abscess, 1 with autoimmune sclerosing cholangitis (ASC), 10 with SSC, 23 with PCC and 31 with SSC in critically ill patients (SSC-CIP). The prevalence of SSC-CIP among COVID-19 patients was 0.88% according to Leonhardt et al. Out of the 66 patients, 64 had severe COVID-19, 16 recovered or were recovering from the liver injury, 24 had severe complications and 12 died within one year (Table 1). Fig. 3a summarizes the reported types of post-COVID-19 cholangitis/cholangiopathy.

Post-COVID cholecystitis

Post-COVID-19 Cholecystitis was reported by 2 studies in 6 patients. One patient was 25 years old in one study, while the mean age was 56.5 ± 9.2 years in the other study. Of the 6 patients, 5 patients had severe COVID-19, 1

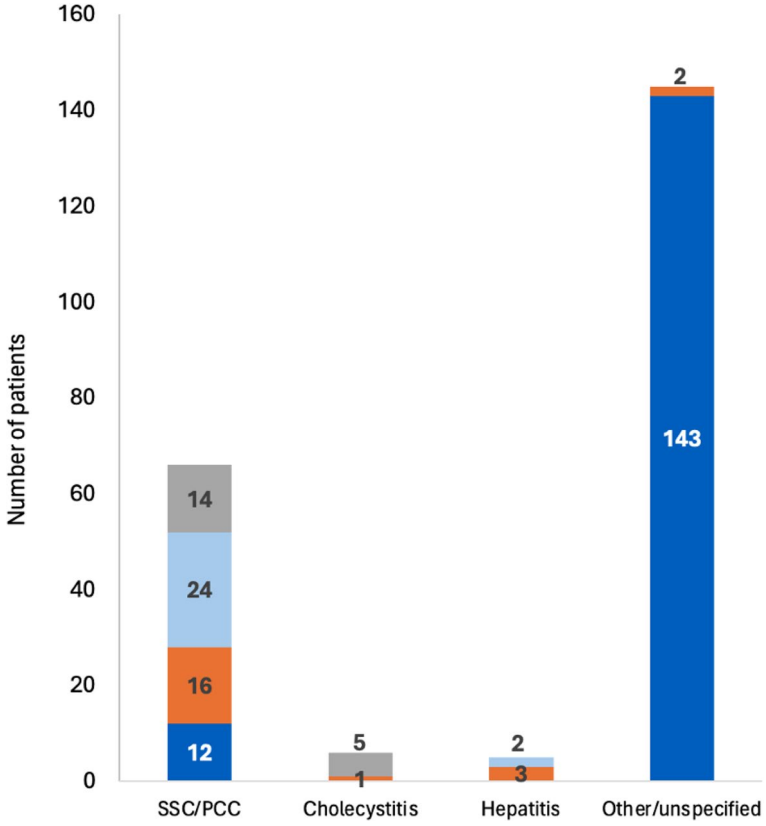

Fig. 2 Types of hepatobiliary injury reported post-COVID-19 infection and the reported outcomes. NR: Not Reported, PCC: Post-COVID cholangiopathy, SSC: Secondary sclerosing cholangitis

Table 1 Post-COVID Cholangitis including SSC aka PCC

Study	Study type/ Country	N (total)/ Gender (%M)	n/N (%)/ Type of HBD	Age Mean ± SE/ Median (IQR) (years)	Previous liver disease	COVID-19 severity	Follow up time/ Outcome
Zdanowicz et al. [23]	Case report Poland	1 M	**ASC** 1/1 (100%)	14	No	NR	Hospitalization: October & December 2021, January 2022 Follow up: March 2022 (normal lab markers)
Alhaddad et al. [22]	Case report Egypt	1 F	**Cholangitic abscess** 1/1 (100%)	62	No	Severe Pneumonia ICU	2 weeks after papillotomy and papilloplasty Stable recovery
Pena-Amaya et al. * [28]	Case series Colombia	8 (63% M)	**PCC** 8/8 (100%)	56.5 ± 9.2	No	Severe ICU Bacterial superinfection Pulmonary thromboses: 3	After 6 months: No deaths 3 in pre-hepatic transplant consultation
Shih et al. [12]	Postmortem pathology study (Case series) USA	7 (86% M)	**SSC** 7/7 (100%)	63 (56—76)	No	Severe Intubation Tracheostomies: 6	119–396 days from COVID dx 5/7: Persistent ALP elevation at follow up Many showed marked improvement
Tafreshi et al. [13]	Case report USA	1 M +	**SSC** and ischemic hepatitis 1/1 (100%)	38	No	Severe Pneumonia with ARDS MV	NR Evaluated for LT
Lee et al. [14]	Case Report USA	1 M	**SSC** 1/1 (100%)	64	No	Severe Pneumonia Intubation Acute hypoxic respiratory failure	Stable 8 months post-op Normal liver function
Durazo et al. [15]	Case report USA	1 M	**SSC** 1/1 (100%)	47	No	Severe pneumonia ARDS AKI MV	10.5 months after presentation (7 months post-OLT) Liver enzymes and bilirubin levels returning to normal
Bauer et al. ^ [25]	Case report Germany	2 (100% M)	**SSC-CIP** 2/2 (100%) Cholangitis with microabscesses 1/2 (50%)	48, 60	Mild liver impairment (< 2 × ULN): 50%	Severe Pneumonia ICU MV ECMO	P1: Discharged after 75 days with persistent elevation of ALP, GGT, LFTs P2: SSC-CIP confirmed by MRI and MRCP (after 542 days)
Leonhardt et al. [24]	Bidirectional observational cohort study Germany	2949	**SSC-CIP** 25/2949 (0.88%) (72%)	59 (49.0–63.0)	in the SSC-CIP group: Liver disease (4%)	Critically ill ARDS ICU MV	Cut off: 30 April 2022 Survival of SSC-CIP vs control group [HR 3.91 (1.53–9.98) p = 0.004] Estimated survival rate: 40.0% (21.3–58.1) vs. 76.0% (54.2–88.4) respectively after 1 year
Roth et al. [26]	Case series USA	3 (67% M)	**SSC-CIP** 3/3 (100%)	25–40	No	Critical ill ICU MV Tracheostomy	167–189 days 2 discharged 1 remained hospitalized
Xu et al. ~ [11]	Prospective cohort study USA	COVID group: 154,068 (89% M)	**Cholangitis** HR 1000 persons at 12 months (95% CI) Compared to contemporary control: HR 2.02 (1.55, 2.63) Compared to historical control: HR 1.94 (1.49, 2.53)	NR	Cholangitis (0.09%) No other liver/biliary diseases reported	NR	Roughly 400 days NR

Table 1 (continued)

Study	Study type/ Country	N (total)/ Gender (%M)	n/N (%)/ Type of HBD	Age Mean ± SE/ Median (IQR) (years)	Previous liver disease	COVID-19 severity	Follow up time/ Outcome
Kiyak et al. [10]	Case report Turkey	1 M	**PCC** 1/1 (100%)	38	NR	Severe Required intubation	3 months post-transplant 15 months since admission LFTs normalized
Rojas et al. [16]	Case report Colombia	1 F	**PCC** 1/1 (100%)	29	NR	Severe multilobar pneumonia Intubation ICU	3 months Jaundice Elevated liver enzymes and T/D Bili levels
Sambommatsu et al. [17]	Retrospective multicenter case series USA India	7 (86% M)	**PCC** 7/7 (100%)	Mean age: 61	No	6/7 cases were severe 1/7 cases were moderate	Median follow-up of 11 months (range, 3 – 18 months)
Rela et al. [20]	Case report India	1 M	**PCC** 1/1 (100%)	50	No	Severe Pneumonia MV	6 months with unremarkable LFTs following APOLT
Mayorquín-Aguilar et al. [21]	Case series Mexico	3 (67% M)	**PCC** 3/3 (100%)	45–52	No	Severe/fatal Pneumonia ICU MV Vasopressor Hemodialysis	2 patients still under follow up (8 weeks and 6 months) 1 patient died after 1 month
Kroepfl et al. [30]	Case report Austria	2 (100% M)	**PCC** 2/2 (100%)	NR	NR	Critical ICU	Death 2/2
Steiner et al. ^ [31]	Case report Austria	1 F	**SSC-CIP** 1/1 (100%) Additional cholangitic abscess formation	33	No	Severe ICU MV vvECMO Hemodialysis Polypharmacy Convalescent plasma transfusion	Death (day 154) due to multiorgan failure (lungs, liver, kidney) Due to poor prognosis and deteriorating health the option for liver and kidney transplants was discarded

AKI Acute Kidney Injury, *ALP* Alkaline Phosphatase, *APOLT* Auxiliary Partial Orthotopic Liver Transplantation, *ARDS* Acute Respiratory Distress Syndrome, *ASC* Autoimmune Sclerosing Cholangitis, *COVID* Coronavirus Disease, *DBili* Direct Bilirubin, *ECMO* Extracorporeal Membrane Oxygenation, *(vv)ECMO* (venovenous) Extracorporeal Membrane Oxygenation, *GGT* Gamma-Glutamyl Transpeptidase, *ICU* Intensive Care Unit, *LFTs* Liver Function Tests, *LT* Liver Transplant, *MRCP* Magnetic Resonance Cholangiopancreatography, *MRI* Magnetic Resonance Imaging, *MV* Mechanical Ventilation, *NR* Not Reported, *OLT* Orthotopic Liver Transplantation, *PCC* Post-COVID Cholangiopathy, *SSC* Secondary Sclerosing Cholangitis, *SSC-CIP* Secondary Sclerosing Cholangitis in Critically Ill Patients, *TBili* Total Bilirubin, *ULN* Upper Limit of Normal

*Pena-Amaya, et. al (2023) includes overlap in multiple categories

^Bauer et. al (2022) and Steiner et. al (2022) included patients that had both SSC-CIP and cholangitis complicated by abscesses

~Xu et. al (2023) will not be included in the final count of patients as the data was reported in HR and burden

+indicates that this patient was included in another table as they experienced multiple forms of liver/biliary injury

recovered or was recovering from liver injury and no deaths were reported (Table 2). Fig. 3b summarizes the reported post-COVID-19 cholecystitis as reported by 2 included studies.

Post-COVID hepatitis

Post-COVID-19 hepatitis was reported by 3 studies in 5 patients whose age ranged from 8 to 25 years. Of the 5 patients, 1 patient was reported with severe COVID-19, 3 recovered or was recovering from the liver injury and no death was reported (Table 3). Fig. 3c summarizes the reported post-COVID-19 hepatitis.

Other/unspecified post-COVID hepatobiliary disease

Khonsari et al., reported a female patient with post-COVID cholangiocarcinoma mimic (aged 54 years) [18]. Furthermore, Pesti et al., reported 143 cases of cholestasis or other unspecified hepatobiliary diseases using autopsies from 150 patients who died after COVID-19 infection [29]. cases were stratified as strongly (79%), contributive (47%), and weakly (24%) based on how much the COVID-19 infection contributed to their death (Table 4). Soldera et al. reported a case of liver injury secondary to hemophagocytic lymphohistiocytosis (HLH) in a male patient with a history of polymyalgia rheumatica (aged 57 years) [32]. Fig. 3d summarizes any other or unspecified post-COVID-19 biliary injury.

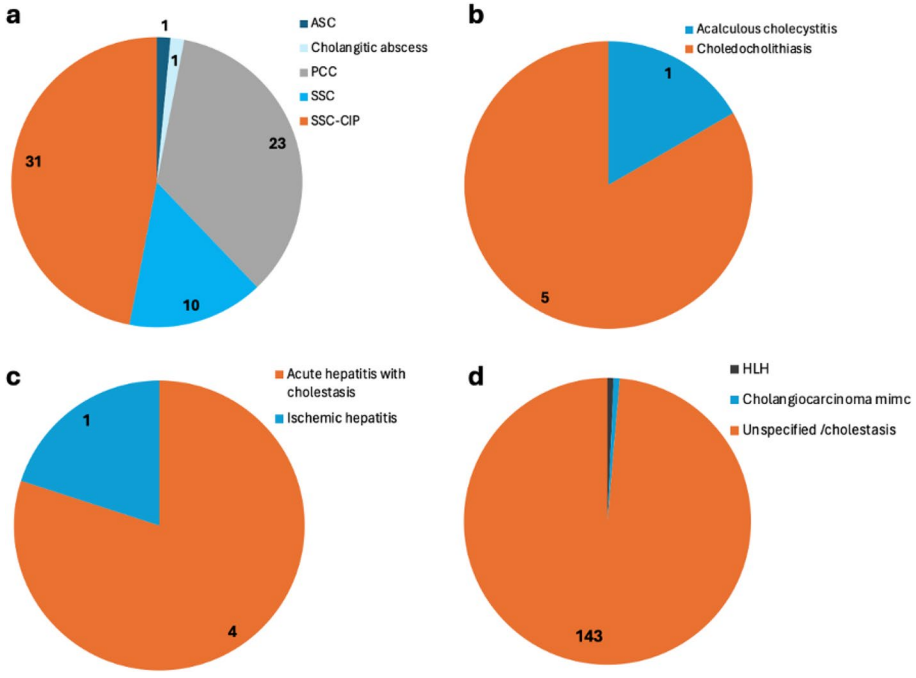

Fig. 3 Types of hepatobiliary injury post-COVID-19 infection as reported by the 23 included studies. The numbers on the figures show the reported number of patients. **a**: Types of post-COVID-19 cholangitis/cholangiopathy as reported by 17 included studies. Xu et al. reported their data as HR 1000 persons at 12 months (95% CI) for cholangitis compared to contemporary and historical controls which were 2.02 (1.55–2.63) and 1.94 (1.49–2.53) respectively. **b**: Post-COVID-19 cholecystitis as reported by 2 included studies. **c**: Post-COVID-19 hepatitis as reported by three included studies. **d**: Other or unspecified post-COVID-19 biliary injury as reported by two included studies. ASC: Autoimmune Sclerosing Cholangitis, HLH: hemophagocytic lymphohistiocytosis, PCC: Post-COVID cholangiopathy, SSC: Secondary sclerosing cholangitis, SSC-CIP: Secondary Sclerosing Cholangitis in Critically Ill Patients

Table 2 Post-COVID Cholecystitis

Study	Study type/ Country	N (total)/ Gender (%M)	n/N (%)/ Type of HBD	Age Mean ± SE/ Median (IQR) (years)	Previous liver disease	COVID-19 severity	Follow up time/ Outcome
Daga et al. [27]	Case report India	1 F **!!**	**Acalculous cholecystitis** and Acute hepatitis with features of submissive hepatic necrosis	25	NR	Mild	5 months after presentation Persistent elevation in liver enzymes (mild) ALP (moderate) DBili (moderate)
Pena-Amaya et al. * [28]	Case series Colombia	8 (63% M)	PCC 8/8 (100%) Cholangitis or liver abscesses 8/8 (100%) Recurrent cholangitis 7/8 (88%) **Cholecystitis/choledocholithiasis before diagnosis of post-COVID cholangiopathy** 5/8 (63%)	56.5 ± 9.2	No	Severe	After 6 months: No deaths 3 in pre-hepatic transplant consultation

LP Alkaline Phosphatase, *COVID* coronavirus disease, *DBili* Direct Bilirubin, *ICU* Intensive Care Unit, *NR* Not Reported, *PCC* Post-COVID cholangiopathy

*Pena-Amaya, et. al (2023) includes overlap in multiple categories

!! indicates that this patient was included in another table as they experienced multiple forms of liver/biliary injury

Discussion

Post-COVID-19 sequelae are extensive and include hepatobiliary involvement which has been documented on several occasions. This study aims to categorize such pathology to provide insight into the pathophysiology and long-term management. This systematic review includes 23 studies highlighting patients who experienced post-COVID-19 hepatobiliary diseases. The included case reports and case series reported a total of 73 patients with post-COVID-19 hepatobiliary diseases. Furthermore, Xu et al. and Leonhardt et al. [11, 24]. investigated the prevalence of hepatobiliary diseases in 156,917 patients who had COVID-19 while Pesti et al., conducted their study on 150 subjects who all died after COVID-19 infection [29].

Table 3 Post-COVID Hepatitis

Study	Study type/ Country	N (total) Gender (%M)	n/N (%)/ Type of HBD	Age Mean ± SE/ Median (IQR) (years)	Previous liver disease	COVID-19 Severity	Follow up time/Outcome
Tafreshi et al. [13]	Case report USA	1 M+	**Ischemic hepatitis** and SSC	38	No	Severe	NR Evaluated for LT
Cooper et al. [19]	Retrospective case series Israel	5 (100% M)	**Acute hepatitis with cholestasis** 3/5 (60%)		NAFLD 1/5 (20%)	3/3: Mild	
		Patient 3 M	Acute hepatitis with cholestasis	8	No	Mild	4 months LFTs normalized
		Patient 4 M	Acute hepatitis with cholestasis	8	NAFLD	Mild	4 months LFTs, GGT and bilirubin levels normalized
		Patient 5 M	Acute hepatitis with cholestasis	13	No	Mild	45 days LFTs and bilirubin normalized
Daga et al. [27]	Case report India	1 F **!!**	Acalculous cholecystitis and **Acute hepatitis with features of submissive hepatic necrosis**	25	NR	Mild	5 months after presentation Persistent elevation in liver enzymes (mild) ALP (moderate) DBili (moderate)

ALP Alkaline Phosphatase, *ARDS* Acute Respiratory Distress Syndrome, *COVID* coronavirus disease, *DBili* Direct Bilirubin, *GGT* Gamma-glutamyl Transpeptidase, *LFTs* liver function tests, *LT* Liver Transplant, *MV* mechanical ventilation, *NR* Not Reported, *NAFLD* non-alcoholic fatty liver disease, *SSC* Secondary sclerosing cholangitis

+ indicates that this patient was included in another table as they experienced multiple forms of liver/biliary injury

!! indicates that this patient was included in another table as they experienced multiple forms of liver/biliary injury

Two different symbols (+ and!) were used as they signify two different patients

We categorized incidents of post-COVID hepatobiliary diseases into four separate categories: Post-COVID-19 cholangitis including SSC and PCC, post-COVID-19 cholecystitis, post-COVID-19 hepatitis, and the last category is for any other or unspecified post-COVID-19 hepatobiliary diseases. PCC was the most prevalent reported type of hepatobiliary disease which was reported by 17 studies in 66 patients (excluding Xu et. al.) [11]. Previous studies in the literature, such as the systematic review by Rasheed et al. [33], have highlighted post-COVID-19 cholangitis, reporting on 540 patients with this condition. Our review builds upon this by expanding the discussion to include other hepatobiliary pathologies, such as cholecystitis. This broader scope provides a more comprehensive understanding of the potential post-COVID complications affecting the hepatobiliary system, emphasizing the need for continued monitoring and research in this area.

Post-COVID-19 cholangitis and secondary sclerosing cholangiopathy

Cholangitis refers to inflammation of the bile ducts, typically caused by a bacterial infection. It can lead to symptoms such as jaundice, fever, and abdominal pain. Prompt treatment is essential to prevent serious complications like septic shock. On the other hand, cholangiopathy is a broader term encompassing various diseases affecting the bile ducts, including but not limited to cholangitis. Cholangiopathy may involve structural abnormalities, strictures, or other functional impairments of the bile ducts, which can result from autoimmune disorders, genetic predispositions, or biliary obstruction. PCC refers to inflammation or dysfunction of the bile ducts occurring after a COVID-19 infection. Emerging evidence suggests that COVID-19 can lead to various gastrointestinal complications, including liver and bile duct involvement. PCC may present with symptoms such as jaundice, abdominal pain, and abnormal LFTs. On the other hand, SSC is a broader term describing bile duct damage resulting from various underlying conditions, such as infections, autoimmune diseases, or long-term biliary obstruction. While both PCC and SSC involve bile duct pathology, the key distinction lies in their etiology, with PCC specifically linked to COVID-19 infection and SSC encompassing a range of predisposing factors beyond viral illness [34]. As some studies referred to the disorder as PCC and others as SSC, we will use PCC/SSC in the context of the discussion.

PCC/SSC post-COVID-19 infection

PCC/SSC was the most reported liver pathology in the post-COVID-19 setting. It was reported by 17 studies in 66 patients excluding Xu et al. [11]. who reported the HR 1000 persons at 12 months (95% CI) for cholangitis compared to contemporary and historical controls as 2.02 (1.55–2.63) and 1.94 (1.49–2.53) respectively. Of the 66 patients, 1 had cholangitic abscess, 1 had ASC, 10 had SSC, 23 had PCC and 31 had SSC-CIP. Leonhardt et al.

Table 4 Unspecified post-COVID hepatic biliary disease/Other hepatic biliary disease

Study	Study type/ Country	N (total) Gender (%M)	n/N (%)/ Type of HBD	Age Mean ± SE/ Median (IQR) (years)	Previous liver disease	COVID-19 severity	Follow up time/ Outcome
Pesti et al. [29]	Observational study Hungary	150 (54% M)	**Possible biliary injury** observed in 143/150 (95%) Steatosis ($n=147$): F3: 15 F2: 29 F1: 49 F0: 54 Cholestasis ($n=143$): F2: 2 F1: 52 F0: 89 Chronic inflammation ($n=146$): F2: 4 F1: 59 F0: 83 Endothelial damage: ($n=119$) F3: 46 F2: 52 F1: 21 F0: 0 Sinus dilatation ($n=119$) F3: 31 F2: 52 F1: 36 F0: 0	69.61 ± 14.31	Liver disease 10 (6.67%)	Cause of death categories: Strong COVID: 79 (52.67%) Contributive COVID: 47/150 (31.33%) COVID: 24/150 (16.0%) ICU: 83/150 (55%)	NR Post-mortem study
Khonsari et al. [18]	Case report Iran	1 F	COVID induced **biliary and hepatic injury** **Cholangiocarcinoma mimic**	54	No	Severe	2 months ERCP was repeated showing signs of improvement
Soldera et al. [32]	Case report Brazil	1 M	Acute hepatobiliary injury due to HLH	57	No	Mild	NR Resolved, patient is asymptomatic

COVID coronavirus disease, *ERCP* Endoscopic Retrograde Cholangiopancreatography, *HLH* Hemophagocytic Lymphohistiocytosis, *ICU* Intensive Care Unit, *NR* Not Reported

reported the prevalence of SSC-CIP among COVID-19 patients as 0.88% [24].

Critically ill COVID-19 patients were found to be vulnerable to developing SSC-CIP as reported by Leonhardt et al. [24]. They conducted a bidirectional cohort study that involved 25 COVID-19 patients who developed SSC-CIP and 25 matched COVID-19 patients who did not develop SSC-CIP as controls. Death was almost 4 times more likely in patients with SSC-CIP than without [HR 3.91 (1.53–9.98) $p=0.004$]. The estimated survival rates were 40.0% (21.3–58.1) vs. 76.0% (54.2–88.4) respectively after 1 year. Biliary cast formation was found in 76% of cases. Similarly, Bauer et al. reported a case of SSC-CIP complicated by liver microabscesses in a 60-year-old male, where they describe a multitude of mechanisms leading to cholangitis and abscess formation, which included ischemic injury and immunological changes damaging the biliary epithelium [25]. While the cases highlighted by Roth et al. [26]. may also resemble SSC-CIP, they have unique histologic features such as bile duct paucity, cytokeratin 7 metaplasia, fibrosis patterns, and degenerative cholangiocyte injury. This may suggest a more long-term hepatic complication of COVID-19 that requires further investigation and extensive follow-up, especially when developed in three young patients.

The milder, yet equally destructive version, SSC also known as PCC is an alarming condition brought to light in patients presenting with jaundice and/or persistent cholestasis following a COVID-19 infection. Rojas et al. [16]. reported a case of a 29-year-old female who developed PCC two months after severe COVID-19 pneumonia. They described the 'characteristic' evolution of the disease as going from persistent jaundice with mixed hyperbilirubinemia that persisted 7 months later. The cholangiogram revealed no biliary obstruction and reported a cystic-appearing lesion in segment VII of the liver. The liver biopsy revealed low periportal inflammatory infiltrate without necrosis but with a severe

obstructive cholestatic pattern. This seems to be a common finding among other patients with PCC. Uniquely however, this case was complicated by post-COVID syndrome (PCS) which included memory loss, attention disorders, headache, dizziness, and chest pain. Nevertheless, cholangiopathy must also be considered as a clinical manifestation of PCS [35]. The management of this case was limited to ursodeoxycholic acid (UDCA) and cholestyramine, while the definitive treatment was often LT. A few studies led to their patients undergoing LT for persistent cholestasis refractory to medical management (Lee et al., Durazo et al., Kiyak et al., and Sambommatsu et al.). All cases that underwent LT or orthotopic liver transplantation(OLT) had complete resolution of jaundice and/or cholestasis with normalization of LFTs, bar one patient who passed away 5 months post-LT due to respiratory failure. Rela et al. reported a novel treatment of PCC in auxiliary partial orthotopic liver transplantation (APOLT). The decision for APOLT was made considering the patient's persistent cholestasis and intractable pruritus following 8 cycles of therapeutic plasma exchange without significant improvement, as well as an episode of sepsis. Explant histology revealed diffuse ductopenia with focal inflammatory infiltrate in the portal tracts with lymphocytes, histiocytes, and eosinophils [20]. Additionally, marked hepatocanalicular bilirubinostasis and patchy inflammation was seen in the lobular parenchyma. SARS-CoV-2 was confirmed to have a direct role in the injury of the liver through granular positivity seen in the hepatocytes. Six months later, the patient is well, and the study emphasizes the need for consideration of APOLT as it provides the patient with a realistic possibility of becoming immunosuppression free, given that the native liver recovers from the cholangiopathic insult. Of note, the magnetic resonance cholangiopancreatography (MRCP) findings were 'characteristic' of PCC and included: prominence of the biliary, intrahepatic, and extrahepatic ducts, as well as beading of the biliary ducts.

Zdanowicz et al. reported a case of ASC in a 14-year-old male following COVID-19 infection [23]. Diagnosis via MRCP and liver biopsy revealed advanced fibrosis, possibly accelerated by COVID-19. An anti-smooth muscle antibody (ASMA) titer was found to be positive (1:40). A liver biopsy was done revealing a morphological picture of autoimmune liver disease with advanced fibrosis (Batts and Ludwig score 3) corresponding to the autoimmune hepatitis (AIH)/PSC overlap syndrome. Immunohistochemical (IHC) staining of the portal tract for CK7 and CK19 revealed a proliferation of the biliary tree, which morphologically corresponds to small-duct sclerosing cholangitis [36]. Given all the findings a diagnosis of ASC secondary to SARS-CoV-2 infection was made utilizing the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) scoring system, confirmed by a score of 9. Steroid treatment normalized liver function, while azathioprine therapy improved enzymes, coagulation, and bilirubin levels after two months. UDCA was also given for increased markers of cholestasis. Therefore, it was recommended to monitor the liver function for children with COVID-19-associated liver pathology [23].

Cholangitis was reported by Xu et al. who conducted a large prospective cohort study involving 154,068 patients, looking at gastrointestinal sequelae post-COVID-19 infection [11]. This included analyzing the burden of cholangitis among these patients as compared to their matched contemporary and historical controls. Contemporary controls involved uninfected patients using healthcare systems during the COVID-19 era, and historical controls involved uninfected patients before the COVID-19 era. The study showed that the COVID-19 group were approximately two times as likely to develop cholangitis as compared to both control groups. Additionally, the COVID-19 group were between 1.2–1.3 times as likely to develop hepatobiliary lab marker derangements at 1 year follow-up, as compared to both control groups.

Suggested mechanisms for developing PCC/SSC post-COVID-19 infection

Tafreshi et al. suggested a mechanism of injury previously mentioned in bile acid transport and barrier disruption due to the virus binding to angiotensin converting enzyme II (ACE-II) receptors expressed on cholangiocytes cell surfaces [13]. Zdanowicz et al. suggested that liver damage in SARS-CoV-2 infection may stem from direct viral action, hepatotoxic drugs, hypoxia, and inflammation, marked by elevated enzymes and cholestasis, with ACE-II expression in liver cells implicated [23]. Similarly, Roth NC et al., 2021 suggested that direct viral damage to cholangiocytes is the proposed mechanism of injury since they too express ACE-II, the host receptor for SARS-CoV-2 [28].

Furthermore, it was reported that the persistence of viral antigens in the hepatic tissues could be contributing to the LFTs derangement in Long-COVID [37]. Therefore, it was suggested that COVID-19 led to an increased risk and burden of post-acute gastrointestinal sequelae spanning several disease categories that include hepatic and biliary disease. This necessitates post-COVID care strategies that involve attention to the overall gastrointestinal health of a patient.

Al Haddad et al. reported a peculiar case of cholangitic abscess formation in a 72-year-old female one month after a severe COVID-19 infection [22]. However, it was found that a forgotten stent was placed in her common bile duct (CBD) following a cholecystectomy she had

done many years ago. This was thought to be one of the reasons for her non-resolving liver abscess. However, the mechanism of liver injury in this case was speculated to be due to virus-mediated immunosuppression caused by SARS-COV-2, which could have allowed opportunistic bacteria to colonize and lead to the non-resolving liver abscess the patient had [38].

Leonhardt et al. suggested that post-COVID-19 SSC-CIP is primarily a hypoxic/ischemic event, potentially worsened by fibrinogen-related hyperviscosity [24]. They suggested that hyperfibrinogenemia might contribute to bile duct hypoxemia and destruction, leading to independently increasing the risk of SSC-CIP in critically ill patients.

Additionally, ketamine use; given to sedate intubated patients, is also considered as a cause for development of cholangiopathies as it has been associated with liver damage and post-COVID-19 cholangiopathies in other studies [28].

Biliary cast formation is a manifestation synonymous with PCC and may serve as an indication of disease severity. Graciolli et al. presented the case of a previous healthy 63-year-old male with choledochal casts, following a severe COVID-19 infection [39]. Following imaging findings such as a dilated CBD, an ERCP was performed, a biliary cast was then identified and removed. Other studies such as Durazo et al. and Leonhardt et al. have also reported the formation of biliary casts [15, 24], with the latter reporting in 76% of cases. The pathophysiology suggested by Durazo et al. revolves around ischemia of cholangiocytes and biliary epithelium, which then becomes necrotic and sloughs away. The necrotic tissue then accumulates in the biliary tree and develops into casts [15]. This description is further supported by a case study by Soldera et al. of a 50-year-old male patient with PCC unresponsive to medical therapy [40]. MRCP findings showed a dilated CBD with no signs of lithiasis. Months later, in suspicion of pancreatitis, an ERCP was done that identified and removed a cast in the format of the external biliary tract. Symptom improvement and resolution of laboratory abnormalities followed. These studies amplify the importance of ERCP in the diagnosis and management of PCC, especially when a dilated choledocus is observed.

Post-COVID cholecystitis

Cholecystitis is inflammation of the gallbladder, typically caused by gallstones blocking the cystic duct. This condition often manifests with symptoms like abdominal pain, nausea, and fever. Acalculous cholecystitis refers to inflammation of the gallbladder occurring without the presence of gallstones. It can be associated with conditions like trauma, critical illness, or ischemia [38]. Choledocholithiasis refers to the presence of gallstones in the CBD, causing obstruction. This obstruction can lead to symptoms like jaundice, abdominal pain, and pancreatitis [41].

Two studies reported the development of cholecystitis in post-COVID-19 patients. This included 6 patients, 5 of which developed acute calculous cholecystitis and choledocholithiasis. One patient developed acalculous cholecystitis, with acute hepatitis with features of submissive hepatic necrosis appearing only one month after COVID-19 recovery. Interestingly, Daga et al. [27]. reported the case of acalculous cholecystitis following a mild COVID-19 infection. Despite the administration of Prednisolone 40 mg/day for 2 weeks, the patient continued to have persistent cholestasis and elevation in LFTs 5 months after initial presentation. The proposed mechanism of injury centered around post-infectious impact of COVID-19 causing a viral reactivation, as the patient later tested positive for Ebstein-Barr virus (EBV) IgG and cytomegalovirus (CMV) IgG. Pena-Amaya et al. [28]. reported a case series of a multitude of post-COVID-19 hepatic biliary diseases that were seen in 8 patients who had severe COVID-19 infections requiring prolonged intensive care unit (ICU) stay. All patients suffered from superimposed sepsis by a variety of bacteria. All 8 patients developed cholangitis or liver abscesses, seven of which were cases of recurrent cholangitis. Five patients developed PCC with preceding cholecystitis/choledocholithiasis. At the 6-month follow-up no deaths were reported, 3 patients are undergoing pre-hepatic transplant consultations, and 1 patient has spontaneously recovered. Given the nature of the cases, superimposed bacterial infections have been suggested to be the primary catalyst in biliary disease development, as it has been found to be a risk factor for cholangiopathies in other studies [42]. The severity of COVID-19 infections seemed to correlate with poorer prognoses when comparing both studies. As the severity increases, the likelihood of cholestasis resolution diminishes and the likelihood of LT being the definitive treatment rises. The case of acalculous cholecystitis with acute hepatitis was limited to steroid treatment, while the remaining patients received medical management without improvement and multiple endoscopic retrograde cholangiopancreatographies (ERCPs) with stenting. Only 1 patient recovered well without complications and no deaths were reported among this patient selection. Daga et al. recommend following LFTs for at least one month following COVID-19 infections to identify and treat such cholangiopathies in a timely manner [27].

Post-COVID-19 hepatitis

Hepatitis is a broad term referring to inflammation of the liver. It can be caused by various factors, including viral infections, alcohol consumption, autoimmune diseases, or toxic substances. Ischemic hepatitis occurs when there

is insufficient blood supply to the liver, leading to liver cell damage or death. This condition often occurs in individuals experiencing severe shock or cardiovascular collapse, such as those with heart failure, severe infections, or hypotension. Ischemic hepatitis can result in elevated liver enzymes, jaundice, and may lead to liver failure if not promptly treated [43].

A total of 3 studies reported post-COVID-19 hepatitis which involved 5 patients. The hepatitis was linked to some sort of biliary pathology; 4 cases were of acute hepatitis with cholestasis and 1 case of ischemic hepatitis. Daga et al. and Tafreshi et al. [13, 27]. reported cases of two distinct patients who had two or more forms of post-COVID-19 hepatobiliary disease in addition to hepatitis. Tafreshi et al. reported a case of SSC and ischemic hepatitis due to severe COVID-19 infection requiring prolonged hospital stay in a 38-year-old male [13]. The patient suffered from many complications such as renal failure requiring renal replacement therapy, as well as an embolic stroke. The patient was treated with supportive measures and an ERCP that revealed tortuous and attenuated intrahepatic bile ducts with normal caliber extrahepatic ducts. A liver biopsy was done revealing findings most consistent with SSC/PCC; cholestatic hepatitis with cholangiocyte injury, bile ductular proliferation, a bile lake and disrupted architecture in the form of focal bridging fibrosis. Due to the patient's poor prognosis and circulatory collapse resulting in ischemic hepatitis, the patient was being evaluated for LT. The authors also believe that the patient's long hospital course could have contributed via cholestasis of critical illness and hypoxic biliary injury due to circulatory collapse. In contrast, Cooper et al. reported the cases of acute hepatitis from direct viral damage, as opposed to ischemic, with accompanying cholestasis in a pediatric population [19]. The 3 patients who developed acute hepatitis all had recent mild COVID-19 infections. Two of the three patients were 8 years old, and one was 13 years old. One of the 8-year-old patients had a history of non-alcoholic fatty liver disease (NAFLD), and his disease course was complicated by aplastic anemia, two months after initial presentation, requiring bone marrow transplant roughly five months later. Despite this, all patients made a complete recovery, with the fastest recovery time being 45 days. The longest recovery reported among all patients with post-COVID-19 hepatitis was longer than 5 months. This may support the link between COVID-19 severity and the extent of hepatic biliary injury; however, such positive recovery may also be due to stronger immune responses in the pediatric population as compared to adults and/or elderly patients. The authors conclude two possible mechanisms that may explain the pathology. The first was the post-infectious immune reaction like multisystem inflammatory syndrome in children (MIS-C). The second was a SARS-CoV-2 induced immune dysregulation causing priming to other infectious agents such as adenovirus, like the mechanism suggested by Daga et al. [27]. Viruses may induce type II and IV hypersensitivity reactions in addition to their specific cytopathic effect [19]. Among all patients who developed post-COVID-19 hepatitis, no deaths were reported, and 3 patients recovered well without complications (60%). Systemic steroids were given to the pediatric patients, who showed complete recovery, as well as the young adult described in Daga et al. who showed mild persistence of cholestasis [27]. While the remaining patient was treated with supportive measures and an ERCP. The studies conclude that secondary viral infections seem to be the leading cause of these cases of acute hepatitis, warranting further investigation. Systemic steroid use should be considered in the setting of suspected immune-mediated injury.

Unspecified post-COVID-19 hepatobiliary disease/other hepatic biliary disease

In the 3 included studies, other forms of hepatic biliary disease were reported such as cholestasis, liver injury that mimics cholangiocarcinoma, and liver injury secondary to HLH. Cholangiocarcinoma is a type of cancer that originates in the bile ducts. It can occur anywhere along the bile ducts, both inside and outside the liver [44]. Cholestasis is a condition characterized by impaired bile flow from the liver. This can occur due to various factors, including liver disease, bile duct obstruction, or certain medications. As a result, bile accumulates in the liver, leading to symptoms such as jaundice, pruritis, dark urine, and pale stools [45].

Pesti et al. reported 143 cases of possible biliary injury in an observational autopsy study of 150 patients who died after COVID-19 [29]. 52.7% of patients died of a strong COVID-19 infection, with 55% requiring ICU admission. Interestingly, cholestasis and steatosis were observed in 143 and 147 patients, respectively, while only 119 exhibited signs of endothelial damage. Most bile ducts were found to be normal, but ductular reaction was detected in cases with cirrhosis and intralobular canalicular cholestasis was seen in 54 of 143 cases. A polymerase chain reaction (PCR) test was performed on the livers of 20 patients who had rapid autopsies, revealing detectable COVID-19 RNA in 13 patients. The study could not find an association between liver fibrosis or steatosis with severity of COVID-19 infection, suggesting no direct effect of COVID-19 on the liver in this aspect, but rather a secondary effect from the patient's pre-existing conditions or treatments. The study frequently found evidence of apoptosis in the histopathology slides of livers lacking COVID-19 protein/RNA, suggesting an indirect method of liver damage (e.g. hypoxia, sepsis, circulatory disturbances, etc.) caused by COVID-19

rather than direct cytopathic mechanisms [29]. The study concluded that endothelial damage (whether primary or secondary to viral infection), leaves patients vulnerable to prolonged liver regeneration following recovery from severe COVID-19. Hence these patients should be followed accordingly during recovery, with regular checking of hepatobiliary-injury biomarkers. Following a similar pattern of COVID-19 induced biliary and hepatic injury, Khonsari et al. describes a case of a 54-year-old female who develops biliary injury mimicking a cholangiocarcinoma, two months following a severe COVID-19 infection [18]. Liver ultrasound (US) findings revealed dilated intra and extrahepatic ducts with a CBD measuring 10 mm. ERCP was done and revealed severe diffuse dilatation suggestive of cholangiocarcinoma. Sphincterotomy and balloon dilation were done, followed by stent placement and brush cytology of the stenosis site. Brush cytology revealed only moderate to no specific inflammation, ruling out cholangiocarcinoma. ERCP was repeated two months later, with stent removal, and showed signs of improvement. The whole portion of the CBD had an irregular appearance; however, the diameter was near normal. The study suggests that ischemic cholangiopathy and altered bile composition or bile duct ischemia are the two mechanisms responsible for bile duct involvement in critically ill patients [46]. Evidently, COVID-19-associated hypoxia and ischemia seem to play a major role in hepatobiliary injury. The study concludes that severe forms of COVID-19 have the propensity to produce progressive biliary injury and long-term hepatic morbidity which may mimic cholangiocarcinoma. Soldera et al. described a case of liver injury secondary to hemophagocytic lymphohistiocytosis (HLH) in a 57-year-old male with a history of polymyalgia rheumatica [32]. Despite his rheumatologic condition being well-controlled for the past 10 years on leflunomide, the patient developed jaundice, high-grade fever, and upper abdominal pain one month following COVID-19 infection. MRI findings revealed abdominal lymphadenopathy and hepatosplenomegaly, suggesting a hyperinflammatory, obstructive pathology. A bone marrow biopsy was done revealing hyperplasia and dysplasia of the megakaryocytes and histiocytosis with hemophagocytosis, suggestive of HLH. An HScore, the most appropriate diagnostic tool, was calculated to determine the probability of this case being HLH. The case scored 238 points, making the probability 98% to 99%. Treatment included etoposide, dexamethasone, and cyclosporine maintenance, resulting in resolution of the HLH episode. The study highlights the systemic nature of the syndrome and the significant overlap between it and COVID-19 infection, through immunological hyperactivation. Signs of high fever, splenomegaly, and pancytopenia in a patient with COVID-19 infection, should raise suspicion of HLH. Retamozo et al. presents an analysis of the clinical, biochemical and hematological overlap between HLH and severe COVID-19 infection [47]. The study draws a parallel between high grade fevers, high ferritin and AST levels and abnormal macrophage activation in severe COVID-19 patients to that of HLH patients. It is suggested that exaggerated monocyte/macrophage activation during COVID-19 infection can induce an overstated pro-inflammatory systemic cytokine response [47]. Thus manifesting as a high-grade fever, lymphadenopathy, symptoms of splenic sequestration, cytopenias, and hyper-elevated inflammatory markers. No deaths were reported, and both the HLH and the cholangiocarcinoma-like patient recovered well without complications, with a recovery time of 2 months following initial presentation for the latter.

Liver transplantation due to hepatobiliary injury post-COVID-19 infection

In the case of severe cholestasis and/or acute liver failure, LT is often the definitive treatment. Previous reports indicate that up to 22% of all SSC-CIP patients require transplantation [48]. Our review involves 11 patients that underwent LT, of which 10 led to complete resolution of hepatobiliary disease and one patient died due to respiratory failure 5 months after LT with a normally functioning liver graft. Of the 11 cases, 10 underwent OLT procedures while 1 underwent an APOLT procedure. The average age was approximately 55 years, and 91% of patients were male. The quickest and longest recovery times post-transplant were 3 and 18 months, respectively. Sambommatsu et al. reported a patient and graft survival is 86% at a median follow-up of 11 months, among six patients who are alive and well [17]. All patients who underwent LT were cases of PCC, also referred to as post-COVID-19 SSC. This further signifies the extent to which PCC can progress, leaving the patient with ultimately one solution, that seems to be curative in most cases. OLT should be considered in younger patients who are good surgical candidates, and APOLT may be considered as an alternative method to avoid immunosuppression in vulnerable patients.

Study limitations

This study has some limitations, including the possible overlap between the hepatobiliary categories and between the hepatobiliary and parenchymal injury. Some studies reported patients with multiple types of injury and clustered them without describing the individual cases. Because of this, some patients were counted multiple times under different categories as we were unable to specify which patient had which combination of disorders. One limitation was the small number of included studies due to including only full article journal publications. All conference abstracts were excluded to maintain

the quality of the included studies and to avoid duplication when the work is published in both conferences and journals. Furthermore, one limitation was the small number of cohort studies as most of the included studies were either case series or case reports. This did not allow enough data to calculate the rate of incidence of hepatobiliary injury post-COVID-19 infection. However, the case reports provided enough details about the individual cases which gave a better insight into the included cases with more details about prognosis and management.

Conclusion and recommendations

The included studies encompassed a diverse range of patients with varying severities of COVID-19 infections and markedly distinct outcomes. Overall, there exists a discernible correlation between the severity of COVID-19 infection and the extent of hepatobiliary injury observed. Patients classified as "critically ill" and those with "severe" infection were more frequently referred for OLT/LT and exhibited sustained elevation in liver enzymes and other abnormalities at follow-up, compared to those with less severe hospitalizations. Hence, the evidence from these studies suggests that COVID-19 severity could potentially predict the likelihood of serious, long-term hepatobiliary injuries. However, definitive conclusions are hampered by limitations within the current research. Several studies lacked sufficient detail on COVID-19 severity and long-term outcomes, which restricts our ability to make conclusive statements regarding this relationship.

Importantly, 17 out of the 22 included studies did not document the vaccination status of patients, which may have served as a confounding factor, thereby limiting the interpretability of their findings. Vaccination status could potentially influence outcomes, possibly mitigating severity in some cases while exacerbating it in others. Future investigations should explore the correlation between COVID-19 outcomes and the likelihood of hepatobiliary complications in vaccinated versus unvaccinated individuals. Given the potential for delayed onset and progression of hepatobiliary diseases post-COVID-19 infection, longitudinal monitoring of liver function and imaging studies should be integrated into follow-up care plans. This approach can facilitate early detection of complications and timely intervention, thereby improving patient outcomes and reducing long-term morbidity. Collaboration between hepatologists, infectious disease specialists, and primary care physicians is crucial in the management of COVID-19 survivors with hepatobiliary complications. Continued research efforts are warranted to elucidate the underlying pathophysiological mechanisms driving hepatobiliary diseases post-COVID-19 infection. Future studies should focus on prospective cohort designs, mechanistic investigations, and clinical trials to validate therapeutic interventions aimed at mitigating hepatobiliary complications associated with COVID-19.

In conclusion, this systematic review highlights the significant association between COVID-19 infection and the development of hepatobiliary disorders, encompassing a spectrum from acute hepatitis to more chronic conditions such as autoimmune liver diseases and gallbladder pathology. The findings underscore the importance of vigilance among healthcare providers regarding hepatobiliary complications in COVID-19 survivors, particularly given the potential for delayed onset and long-term implications. The identified studies collectively contribute to our understanding of the pathophysiological mechanisms underlying these complications, although further research is needed to elucidate precise causal relationships and optimal management strategies. Routine liver function testing in COVID-19 patients may prove beneficial in preventing more serious sequela of hepatobiliary disease in these patients. In conclusion, as the world continues to navigate the aftermath of the COVID-19 pandemic, prioritizing research, clinical vigilance, and integrated care approaches will be crucial in addressing the emerging challenge of hepatobiliary diseases in COVID-19 survivors.

Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
COVID-19	Coronavirus Disease of 2019
HHS	Health and Human Services
LT	Liver Transplant
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
LFT	Liver Function Test
NOS	Newcastle–Ottawa Quality Assessment Scale
PCC	Post-COVID Cholangiopathy
SSC	Secondary Sclerosing Cholangitis
ASC	Autoimmune Sclerosing Cholangitis
SSC-CIP	Secondary Sclerosing Cholangitis in Critically-Ill Patients
HLH	Hemophagocytic Lymphohistiocytosis
PCS	Post-COVID Syndrome
UDCA	Ursodeoxycholic Acid
OLT	Orthotopic Liver Transplantation
APOLT	Auxiliary Partial Orthotopic Liver Transplantation
MRCP	Magnetic Resonance Cholangiopancreatography
ASMA	Anti-Smooth Muscle Antibody
AIH	Autoimmune Hepatitis
IHC	Immunohistochemical
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology, and Nutrition
ACE-II	Angiotensin Converting Enzyme II
CBD	Common Bile Duct
EBV	Epstein-Barr Virus
CMV	Cytomegalovirus
ICU	Intensive Care Unit
ERCP	Endoscopic Retrograde Cholangiopancreatography
NAFLD	Non-Alcoholic Fatty Liver Disease
MIS-C	Multisystem Inflammatory Syndrome in Children
PCR	Polymerase Chain Reaction
US	Ultrasound

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

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