Cholangiopathy After Severe COVID-19: Clinical Features and Prognostic Implications

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INTRODUCTION: **Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 virus, is a predominantly respiratory tract infection with the capacity to affect multiple organ systems. Abnormal liver tests, mainly transaminase elevations, have been reported in hospitalized patients. We describe a syndrome of cholangiopathy in patients recovering from severe COVID-19 characterized by marked elevation in serum alkaline phosphatase (ALP) accompanied by evidence of bile duct injury on imaging.**

METHODS: **We conducted a retrospective study of COVID-19 patients admitted to our institution from March 1, 2020, to August 15, 2020, on whom the hepatology service was consulted for abnormal liver tests. Bile duct injury was identified by abnormal liver tests with serum ALP > 3x upper limit of normal and abnormal findings on magnetic resonance cholangiopacreatography. Clinical, laboratory, radiological, and histological findings were recorded in a Research Electronic Data Capture database.**

RESULTS: **Twelve patients were identified, 11 men and 1 woman, with a mean age of 58 years. Mean time from COVID-19 diagnosis to diagnosis of cholangiopathy was 118 days. Peak median serum alanine aminotransferase was 661 U/L and peak median serum ALP was 1855 U/L. Marked elevations of erythrocyte sedimentation rate, C-reactive protein, and D-dimers were common. Magnetic resonance cholangiopacreatography findings included beading of intrahepatic ducts (11/12, 92%), bile duct wall thickening with enhancement (7/12, 58%), and peribiliary diffusion high signal (10/12, 83%). Liver biopsy in 4 patients showed acute and/or chronic large duct obstruction without clear bile duct loss. Progressive biliary tract damage has been demonstrated radiographically. Five patients were referred for consideration of liver transplantation after experiencing persistent jaundice, hepatic insufficiency, and/or recurrent bacterial cholangitis. One patient underwent successful living donor liver transplantation.**

DISCUSSION: **Cholangiopathy is a late complication of severe COVID-19 with the potential for progressive biliary injury and liver failure. Further studies are required to understand pathogenesis, natural history, and therapeutic interventions.**

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INTRODUCTION

In December 2019, a severe viral respiratory illness known as coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China. The disease was designated a pandemic by the World Health Organization. At the time of submission, COVID-19 infection was documented to have occurred in more than 109 million people with more than 2.4 million deaths as of February 15, 2021 (1). In the United States alone, there have been more than 27.6 million cases and more than 486,000 deaths. Risk factors for death, or severe illness, from COVID-19 include older age and comorbid conditions such as obesity, diabetes, and hypertension. This dramatic spread of COVID-19 has led to successive waves of sick patients that have overwhelmed hospital and healthcare systems more broadly (2). The clinical features of COVID-19 have featured pneumonia as a defining feature of severe disease, but symptoms and complications are remarkably diverse, and the virus has proven capable to affect multiple organ systems. Hypercoagulability, with potentially severe or fatal cardiovascular, cerebrovascular, and other thrombotic complications, has been recognized as an alarmingly common feature of the disease.

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COVID-19 is frequently associated with abnormal liver tests, with no disease-specific lesions on biopsy. The incidence of elevated serum liver biochemistries in hospitalized patients ranges from 14% to 58%, with the degree of elevations ranging from mild to severe (3). In the AGA Institute's large systematic review and meta-analysis, liver abnormalities were seen more frequently in US patients as compared to patients from other parts of the world (4). The preponderance of findings has focused on serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations, with mild elevations of liver tests (1–2 × upper limit of normal [ULN]) more often seen as compared to more severe elevations (>2 × ULN) (4–6). In 1 retrospective observational cohort study, many hospitalized patients had liver function test abnormalities on admission: 66.9% AST, 41.6% ALT, 13.5% alkaline phosphatase (ALP), 4.3% total bilirubin, and 56.7% albumin (7). These liver test patterns have been presumed to reflect primarily hepatocellular injury. Of note, this study examined laboratory values during hospitalization after initial diagnosis of SARS-CoV-2 infection, and 20% of patients had abnormal liver tests before hospitalization. In many studies, abnormal liver tests during hospitalization have correlated with disease severity (3,5,7,8). One US study of more than 2000 patients focusing on ALT elevations and their correlation with disease severity highlighted the rarity of cholestasis (5).

Although abundant literature has reported on the course of severe COVID-19, there are also increasing reports on sequelae of COVID-19. The phrase "long-haulers" has been applied to individuals who have had recovery from acute illness but have persistent symptoms and complications, including long-standing respiratory, cardiac, neurologic, and psychiatric effects (9–11).

We describe a syndrome in patients recovering from severe COVID-19 characterized by elevations in liver tests, most prominently including marked elevations in serum ALP and inflammation of the biliary tract on imaging, frequently with strictures similar to secondary sclerosing cholangitis (SSC) as previously described in critically ill patients (12). This syndrome seems to have important adverse consequences for patient recovery and may lead to long-term morbidity, need for liver transplantation, or mortality after other manifestations of COVID-19 have improved.

METHODS

We included adult patients (aged 18 years and older) with severe COVID-19 admitted to NYU Langone Tisch Hospital from March 1, 2020, to August 15, 2020, on whom the hepatology service was consulted at some point in their course for cholestatic injury characterized by ALP > 3 × ULN and abnormalities of the biliary tract on magnetic resonance cholangiopancreatography (MRCP). In this period, severe COVID-19 was defined as requiring intensive care unit (ICU) admission, respiratory failure requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO), and use of vasopressors. The diagnosis of COVID-19 was confirmed with a positive result on nasopharyngeal swab polymerase-chain-reaction (PCR) assay. Bile duct injury was identified by abnormal liver tests with serum ALP > 3 × ULN, combined with abnormalities of the biliary tract on MRCP findings. This retrospective study was approved by the New York University Grossman School of Medicine Institutional Review Board.

We analyzed the demographic and clinical data on this group of patients, including medical course, laboratory data, and radiographic and histologic findings where available. A Research Electronic Data Capture database captured the data elements of interest. Demographic information included age at admission, sex of patient, race of patient, date of positive COVID-19 PCR test, duration of hospitalization, time from admission to cholangiopathy diagnosis, comorbidities of the patient, and medications before admission. We defined time of COVID cholangiopathy diagnosis as time when the hepatology service was consulted.

Clinical features of each patient's admission included medications given for treatment of COVID (including antivirals, antibiotics, anti-inflammatory medications, and monoclonal antibodies), anticoagulation (both therapeutic and prophylactic), and antiplatelet therapy. Other features recorded included respiratory and circulatory support including supplemental oxygen, mechanical ventilation, prone positioning, and ECMO. Additional details of hospital course included development of sepsis, pneumonia, thrombotic events, strokes, or cardiac events. Patients' dates of discharge or expiration were also recorded.

Four values for laboratory tests were obtained at admission; peak value, value at time of cholangiopathy diagnosis, and value at most recent follow-up. Tests included total bilirubin, AST, ALT, ALP, gamma-glutamyl transpeptidase (GGTP), white blood cell count (WBC), hemoglobin (Hb), platelet count (plt), prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), D-dimer, fibrinogen level, erythrocyte sedimentation rate, C-reactive protein, blood urea nitrogen (BUN), and creatinine level. The data were obtained by review of Epic Systems electronic health record and deidentified. Continuous variables were reported with mean (SD) or median (IQR), as appropriate. Categorical variables were reported as counts and frequencies (%). MRCP images were reported by 1 or both of 2 radiologists, and liver biopsy findings were reported by 2 pathologists.

RESULTS

During the time span covered by this study, 2,047 patients were admitted to Tisch Hospital with COVID-19 including 1,178 men (57.5%) and 869 women (42.5%). We identified 12 patients, representing 0.59% of those admitted, who were otherwise recovering from severe COVID-19 and exhibited abnormal biochemical findings indicative of cholestatic liver injury. Table 1 provides comprehensive data on each of the patients. Eleven patients were men, and 1 woman, with a mean age of 58 years. Nine of the 12 patients had a history of hypertension before admission, 5 had obesity, and 5 had history of diabetes. Only 1 patient had a diagnosis of chronic liver disease (hepatic steatosis without evidence of cirrhosis) on previous imaging. Table 2 summarizes the pooled baseline demographic features of the patients.

All patients had pneumonia and sepsis during hospitalization and required mechanical ventilation. Three of the patients (25%) received ECMO, and 8 (67%), required prone positioning in addition to mechanical ventilation to optimize oxygen exchange. Eight of 12 (67%) patients experienced a thromboembolic event and required therapeutic anticoagulation treatment. The remaining 4 patients received prophylactic anticoagulation during their hospitalization. Table 3 indicates pooled COVID-19–related features and treatments during hospitalization.

The mean time from COVID-19 diagnosis to diagnosis of cholangiopathy was 118 days. Peak median laboratory values of the patients included ALT 661 U/L, AST 498 U/L, ALP 1,945 U/L, and total bilirubin 13 mg/dL. Inflammatory markers were

Table 1. Demographics and clinical characteristics of all patients

Patient number	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Demographics												
Age (yr)	73	39	64	77	46	72	38	60	42	57	68	62
Sex	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Female
Race/ethnicity	White Non-Hispanic	Hispanic	Other	White Non-Hispanic	White Non-Hispanic	Hispanic	White Non-Hispanic	White Non-Hispanic	Hispanic	Hispanic	Other	Other
Alcohol status	None	None	None	None	Mild	None	Mild	None	None	Mild	None	None
Comorbidities												
Obesity	No	No	No	No	No	Yes	No	Yes	No	Yes	No	Yes
Diabetes	Yes	No	Yes	No	No	No	No	No	No	No	Yes	Yes
Hypertension	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No
Cardiovascular disease	No	No	Yes	Yes	No	No	No	No	No	No	Yes	No
Cerebrovascular disease	Yes	No	No	No	No	No	No	No	No	No	No	No
Hyperlipidemia	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes	No
Other	No	Yes, cocaine use	No	Yes, Parkinson's disease	No	No	No	No	No	No	Yes, Hypothyroidism	No
COVID-19 clinical characteristics and treatments												
Total length of hospitalization (d)	70	79	57	74	114	64	127	33	138	140	58	59
Total length of MICU stay (d)	55	47	44	35	107	15	120	27	138	118	36	24
Pneumonia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sepsis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gastrointestinal	Yes	Yes	No	No	No	No	Yes	Yes	No	No	No	No
Thrombosis	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Mechanical ventilation, total d	Yes, 52	Yes, 62	Yes, 39	Yes, 54	Yes, 99	Yes, 13	Yes, 114	Yes, 22	Yes, 138	Yes, 49	Yes, 35	Yes, 40
ECMO	No	No	No	No	Yes	No	Yes	No	Yes	No	No	No

Table 1. (*continued*)

Patient number	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Required proning	Yes	Yes	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Medications												
Hydroxycholoroquine	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No
Tocliuzimab	No	Yes	No	No	Yes	No	No	No	No	No	No	No
Azithromycin	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Pressors	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Antivirals	No	No	No	Remdesivir	No	No	No	No	Remdesivir Valcyclovir Foscarnet		No	No
Anticoagulants	Apixaban	Enoxaparin	Enoxaparin (DVT prophylaxis)	Apixaban (for atrial fibrillation)	Enoxiparin (DVT prophylaxis)	Heparin	Heparin	Enoxaparin (DVT prophylaxis)	Heparin Bivalirudin	Heparin IVC filter	Heparin	Heparin
Other							Sarilumab			Clazakizum-ab		
Peak laboratory values												
ALP (U/L)	1,221	2,129	2035	1855	2,366	2,200	1723	1,325	1,036	2,544	2057	965
Total bilirubin (mg/dL)	16.9	2.2	16.9	8.5	2.9	16.0	10.22	15.1	21.6	35.0	2.0	4.4
ALT (U/L)	242	726	338	792	2,171	595	929	1,553	385	260	286	5,854
AST (U/L)	336	328	323	711	2,739	1,260	409	1,123	576	332	420	7,400
CRP (mg/L)	346.6	388	338.7	277.2	360.3	360.4	315.8	378.7	476.6	413.4	382.4	324.2
ESR (mm/hr)	94	120	120	35	90	120	84	120	120	40	142	120
INR	2.1	1.6	1.4	2.6	1.5	1.3	1.3	1.6	3.8	6.6	2.7	1.5
BUN (mg/dL)	34	189	228	166	65	183	74	86	85	157	111	203
Creatinine (mg/dL)	6.4	12.8	6.6	3.4	0.4	13.0	1.4	2.6	5.7	10.9	7.7	7.2
MRCP findings												
Beading of intrahepatic ducts	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Bile duct thickening and hyperenhancement	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes
Peribiliary diffusion high signal	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Outcomes												

Table 1. (*continued*)

Patient number	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Last follow-up (months since initial COVID-19 diagnosis)	7	5	10	10	9	7	9	10	4	4	10	6
Clinical status	Alive Declined for LT evaluation	Alive No LT	Alive Had LT (living donor)	Alive No LT On ursodiol	Alive No LT Laparoscopic cholecystectomy, off ursodiol since then	Deceased No LT	Deceased Listed for LT at outside institution	Alive Listed for LT On ursodiol With extreme pruritus requring plasmapheresis	Deceased No LT	Deceased No LT	Alive Declined LT evaluation On ursodiol	Alive No LT
Most recent hepatic laboratory values												
Days since initial COVID-19 diagnosis	238	175	319	258	302	229	240	314	138	138	308	189
Total bilirubin (mg/dL)	35.0	0.5	1.9	1.4	3.5	37.6	5.0	12.4	7.5	22.6	6.7	2.1
ALT (U/L)	31	118	38	118	239	123	238	113	207	128	105	107
AST (U/L)	60	89	12	103	215	573	153	147	347	332	116	67
Alkaline phosphatase (U/L)	455	853	148	380	1,427	452	1,524	673	266	2,331	1,184	964

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; MICU, medical intensive care unit. LT, liver transplant; MRCP, magnetic resonance cholangiopancreatography.

Table 2. Demographics and baseline characteristics of patients

Variable	Total patients (N = 12)
Age (mean ± SD), yr	58.17 ± 13.82
Sex	
Female	1 (8.3%)
Male	11 (91.7%)
Race/ethnicity	
Non-Hispanic white	5 (41.7%)
Hispanic	4 (33.3%)
Other or unknown	3 (25.0%)
Smoking status	
Present	1 (8.3%)
Stopped	4 (33.3%)
Never	7 (58.3%)
Alcohol status	
Mild (<4 drinks/mo)	3 (25.0%)
None	9 (75.0%)
Comorbidities	
Obesity	4 (33.3%)
Diabetes	4 (33.3%)
Hypertension	8 (66.7%)
Cardiovascular disease	2 (16.7%)
Cerebrovascular disease	1 (8.3%)
Hyperlipidemia	6 (50.0%)
Other	3 (25.0%)
None	2 (16.7%)

Table 3. Clinical characteristics of patients

Variable	Total patients (N = 12)
COVID-19 clinical features	
Pneumonia	12 (100%)
Sepsis	12 (100%)
Gastrointestinal	4 (33.3%)
Loss of taste or smell	1 (8.3%)
Neurologic	5 (41.7%)
Thrombosis (organ)	8 (66.7%)
COVID-19 treatments in hospitalization	
Antivirals	2 (16.7%)
Anti-inflammatory agents	5 (41.7%)
Monoclonal antibodies	4 (33.3%)
Anticoagulants	8 (66.7%)
Antiplatelet therapy	3 (25.0%)
Pressors	10 (83.3%)
Length of time from COVID-19 diagnosis to cholangiopathy discovery, Mean ± SD, d	117.7 ± 18
Anticoagulant treatment in hospitalization	
Therapeutic	8 (66.7%)
Prophylaxis	5 (41.7%)
Mechanical ventilation	12 (100%)
ECMO	3 (25%)
Required proning	8 (66.7%)

COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation.

markedly elevated, with peak median C-reactive protein being 360 mg/L and erythrocyte sedimentation rate being 120 mm/hr. Median peak creatinine was 6.5 mg/dL, and 6 patients (50%) had peak levels of D-Dimers >10,000 ng/mL. Table 4 summarizes pooled median laboratory values at presentation, peak levels, and last follow-up.

In 4 patients, MRCP was ordered before hepatology consultation was called, whereas in 8, the consultant requested it. All 12 (100%) patients had abnormal MRCP findings: 11 patients had "beaded" appearance of intrahepatic ducts, 10 patients had peribiliary diffusion high signal, and 7 patients demonstrated thickening and hyperenhancement of the bile duct wall, which included the common bile duct in 4 patients (Figure 1). Two patients also had mild dilation of the common bile duct to the level of the ampulla, without a definable common bile duct stricture. Gallbladder wall thickening and enhancement was seen in 7 patients. Portal or hepatic vein thrombosis was not seen on any of the MRI studies. Of 8 patients who underwent ultrasound, Doppler studies showed normal hepatic artery flow in all.

Liver biopsies were performed in 4 patients at the discretion of the individual consultants. There were no significant differences in the presentations of cholangiopathy compared with the other 8 who did not undergo biopsy. All these specimens showed similar features of acute and/or chronic large duct obstruction (Figure 2a,b), but without definitive bile duct loss, confirmed by immunostains for keratins 7 and 19 stain. There was mild fibrosis of some portal tracts (Figure 2b). Immunostain for keratin 7 also showed prominent staining of hepatocytes in all specimens as well, typical of chronic cholestatic liver disease (Figure 2c). All these histologic findings may be seen in both primary sclerosing cholangitis (PSC) and SSC. CD61 immunostain, intended to highlight the presence of platelet fibrin thrombi, demonstrated widespread platelets/exosomes in small sinusoidal aggregates, but no intravascular thrombi were seen in any case (Figure 2d).

At the time of last follow-up, 4 of the patients in the study had died. One 57-year-old man (patient 10) died after a lengthy hospital course, ultimately having a perforated duodenal ulcer. A 42-year-old man (patient 9) died after having a massive gastrointestinal bleed, and a 72-year-old man (patient 6) presented with new-onset ascites and ultimately died in the setting of hemoperitoneum from large volume paracentesis. A 39-year-old man (patient 7), who had recurrent cholangitis at our institution and was subsequently listed for liver transplant at another institution, died after a lengthy hospital course.

Among other severely ill patients, a 73-year old man (patient 1) was referred to hospice after being deemed not a transplant candidate due to multiple comorbidities and multiorgan failure. At last follow-up, the patient had a total bilirubin of 35 mg/dL 8 months after initial admission with COVID-19. This patient's follow-up

Table 4. Median laboratory values at presentation, peak, and most recent time points

Laboratory value	Presentation (median, IQR)	Peak (median, IQR)	Most recent (median, IQR)
Alkaline phosphatase, U/L	52 (44–66)	1945 (1,299–2,147)	763 (434–1,245)
Total bilirubin, mg/dL	0.6 (0.4–0.8)	12.7 (4.0–16.9)	5.9 (2.1–15.0)
ALT, U/L	44 (27–61)	661 (325–1,085)	118 (107–148)
AST, U/L	48 (37–60)	498 (335–1,157)	132 (84–336)
Creatinine, mg/dL	1.0 (0.8–1.0)	6.5 (3.2–8.5)	0.9 (0.6–1.1)
INR	1.2 (1.2–1.2)	1.6 (1.5–2.6)	1.1 (1.0–1.2)
BUN, mg/dL	15 (12–19)	134 (82–185)	22 (16–44)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; INR, international normalized ratio.

MRCP, 7 months after initial diagnosis of COVID-19, demonstrated worsening of severe biliary tract disease (Figure 3). Another 65-year-old man with a history of diabetes mellitus and coronary artery disease has had 1 admission for cholangitis, treated medically, with a total bilirubin of 27 mg/dL and new abdominal ascites at last follow-up 10 months after admission with COVID-19. This patient's follow-up, 9 months after initial diagnosis of COVID-19, also showed worsening biliary tract disease (Figure 4). In all, 6 patients underwent repeat MRCP, 6–12 months after their initial diagnosis of COVID-19. Four of the 6 patients exhibited worsening intrahepatic dilation on follow-up, while the 2 other patients had stable findings.

Five patients were sufficiently ill to warrant referral for consideration of liver transplant. Patient 1, as described above, was deemed not a transplant candidate because of multiple comorbidities and advanced age, and was discharged to home hospice. Patient 11 had recurrent cholangitis and persistent hyperbilirubinemia, but ultimately declined formal transplant evaluation. Patient 7, who had recurrent cholangitis and persistent hyperbilirubinemia, was evaluated for transplant at our institution before ultimately being listed at an outside hospital. However, he died without receiving a transplant. Patient 8 is currently being evaluated for transplant and receiving appropriate work-up. Patient 3 underwent living donor liver transplantation in December of 2020. The patient was recovering well, with normal liver function tests, 4 weeks postoperatively.

Four patients in the cohort underwent endoscopic retrograde cholangiopancreatography (ERCP), 3 of whom were in the group considered for transplant. Patient 1 underwent ERCP with plastic CBD stent placed, sphincterotomy, with a repeat ERCP 1 month later with removal of the stent. Multiple biliary strictures were noted in the intrahepatic ducts. Patient 7 underwent 2 ERCPs at our institution, with stone removal, CBD stent placement and removal, and balloon dilation of strictures in the right and left hepatic ducts without improvement. Patient 8 underwent ERCP with dilation of the left main hepatic duct and placement of a plastic stent. Patient 5 underwent ERCP for a bile leak after a laparoscopic cholecystectomy for acalculous cholecystitis. No other patients underwent ERCP in large part because the predominance of diffuse intrahepatic biliary tract abnormalities did not seem likely to be conducive to endoscopic intervention.

Eleven patients have been started on ursodiol, without convincing evidence of therapeutic benefit. In general, the patients had some improvement in laboratory tests, particularly AST and ALT. However, total bilirubin and ALP have remained markedly elevated with median values on most recent follow-up of total bilirubin of 8.8 mg/dL, ALT of 117 U/L, AST of 128 U/L, and ALP of 799 U/L (Tables 1 and 4).

DISCUSSION

In this series, we have described a syndrome of severe biliary tract injury developing in patients who have had COVID-19. We have previously proposed (13) that this syndrome be designated as "COVID-associated cholangiopathy" to differentiate it from the more prevalent biochemical pattern of hepatocellular injury reported extensively in patients with COVID-19 (5–8). Our 12 patients, 11 men and 1 woman, had cholestatic or mixed cholestatic/hepatocellular liver enzyme patterns, hyperbilirubinemia, bile duct inflammation and/or stricturing on MRI/MRCP. Our patients' peak ALT and AST levels were elevated in some to above 10 times ULN, but the elevations in ALP still were the most striking feature of the liver enzyme profiles, as were the features of bile duct obstruction versus hepatocellular injury in those patients in whom liver histology was available. This syndrome was identified late in the patients' courses after critical illness, with a mean time from COVID-19 diagnosis through PCR to time of cholangiopathy diagnosis of 118 days. All patients had required ICU courses, mechanical ventilation, and 3 required ECMO. Eight of our patients had known thromboembolic events despite being on deep vein thrombosis prophylaxis.

There was a preponderance of male patients in this cohort to a degree disproportionate to the male:female ratio (92% male) of patients admitted for COVID-19 during the period of the study (57.5% male). Our sample size makes it difficult to draw definitive conclusions about the possibility of greater male susceptibility of men to cholangiopathy after severe COVID-19 as a result of specific pathogenetic factors over and beyond the greater general susceptibility of men to severe COVID-19. Further studies should help elucidate this question. Similarly, although this is the largest series of patients with COVID-associated cholangiopathy reported to date, the sample size is insufficient to draw conclusions about the relationships between clinical features such as thrombotic complications or therapeutic interventions and either the occurrence or course of cholangiopathy, for which larger prospective or case-control studies would be useful. Given our inclusion criteria for this analysis, we cannot preclude the possibility that some patients with levels of ALP $<$ 3 times ULN may have COVID-associated cholangiopathy, or that some patients with ALP elevations $>$ 3 times ULN may have cholangiopathy not apparent on imaging or other causes of such elevations.

Thus far, we have not seen complete resolution of signs of biliary injury. Eleven patients have been treated with ursodiol, with little or no improvement in their liver function tests or clinical status. Five patients have been considered for liver transplant evaluation as a result of various combinations of progressive jaundice, hepatic insufficiency, renal insufficiency, and/or episodes of bacterial cholangitis, with 1 patient having received a living donor liver transplant. As exemplified in Figures 3 and 4, several patients in this series have had documented worsening

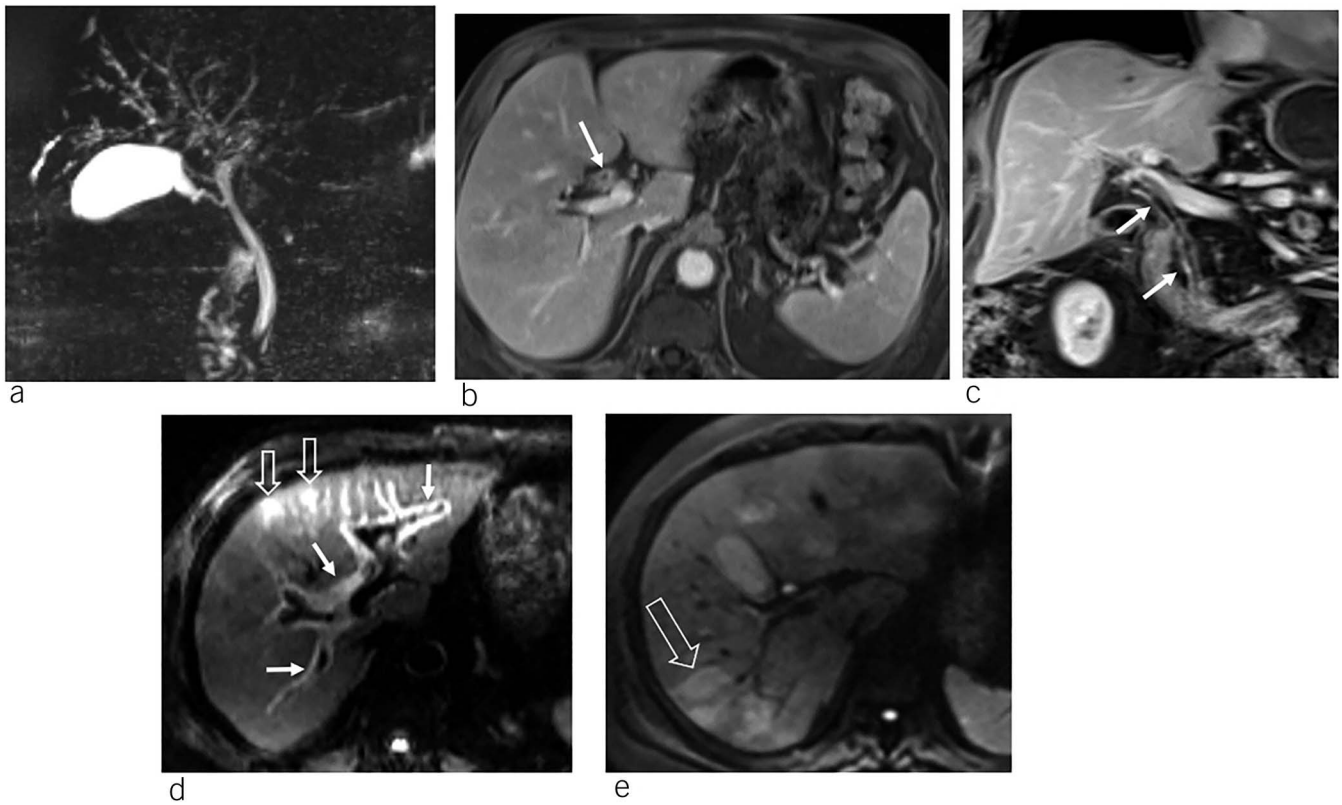

Figure 1. Spectrum of imaging findings in coronavirus disease 2019 cholangiopathy. (**a**) Coronal magnetic resonance cholangiopacreatography image demonstrates "beaded" appearance of the intrahepatic bile ducts. Axial (**b**) and coronal (**c**) gadolinium contrast-enhanced T1-weighted images demonstrate diffusely thickened wall of the common hepatic duct and common bile duct (arrows). Diffusion-weighted image (**d, e**) demonstrates periportal (white arrows) and parenchymal (black open arrows) high signal intensity.

on MRCP of severe biliary stricturing disease. During preparation of this article, we became aware of a recent case report of a patient with similar findings in which cholestasis was said to be improving slowly after discharge, but no follow-up clinical data or radiographic studies were available (14). A 3 patient series was also recently reported by Roth et al. (15) highlighting similar clinical, laboratory, and radiographic features to those described here. Liver biopsies showed hepatic fibrosis, leading the authors to speculate on the potentially severe prognostic implications of this entity. The longitudinal observations described in several patients in our series vindicate this concern in the form of progressive, severe biliary tract injury on serial MRCPs, persistent jaundice, cholestatic liver enzyme abnormalities, recurrent infection, and liver failure, with indications for liver transplantation in several patients and actual performance of a living donor transplant in 1 patient.

The hepatobiliary injury we describe may be a result of ischemic injury related to microvascular coagulopathy and/or hypotension during severe illness or sepsis. SARS-CoV-2 enters the host through the angiotensin-converting enzyme 2 (ACE2) receptor in respiratory epithelium. However, ACE2 is expressed diffusely in endothelial cells of small and large arteries and veins throughout the body (16). The ubiquitous expression of ACE2 in vascular endothelium has been proposed as the key pathogenetic factor in the widespread coagulation that contributes substantially to the morbidity and mortality of COVID-19 (3,8). A recent autopsy series showed mild hepatic steatosis with little inflammation, also described by others, but numerous platelet-fibrin microthrombi in the hepatic sinusoids (17). However, findings in livers in COVID-19 are quite variable. In a study of hepatic pathology in 40 fatal cases of COVID-19, Lagana et al. (18) reported macrovesicular steatosis in 75%, mild lobular necroinflammation and portal inflammation in 50%, and vascular pathology, including sinusoidal microthrombi, in 15%. The absence of overt vascular pathology or intravascular thrombi, other than the small sinusoidal aggregates, seen in these biopsied tissues does not preclude significant vascular injury and thrombosis elsewhere in the liver. The biliary radiographic findings are inhomogeneous in these cases, possible pathogenetic vascular lesions would likewise be so. Regarding these sinusoidal platelet/exosome aggregates, it is as yet unclear whether CD61 staining such as this is also present in PSC or SSC of other causes.

Direct virus-mediated damage to the biliary epithelium may be involved in the pathogenesis of the cholangiopathy described here. Chai et al. (17) studied specific expression of ACE2 in cholangiocytes and found ACE2 expression in 59.7% of cholangiocyte clusters and low expression in hepatocytes (2.6%). They found the expression of ACE2 in cholangiocytes to be comparable with ACE2 expression in lung alveolar type II cells. Other investigators have similarly demonstrated that biliary epithelial cells richly express ACE2 (16,19). An *in vitro* study of human liver organoids suggested that cholangiocytes may be susceptible to infection with SARS-CoV-2 (19). Ultrastructural studies have demonstrated viral particles in hepatocytes (20). These findings

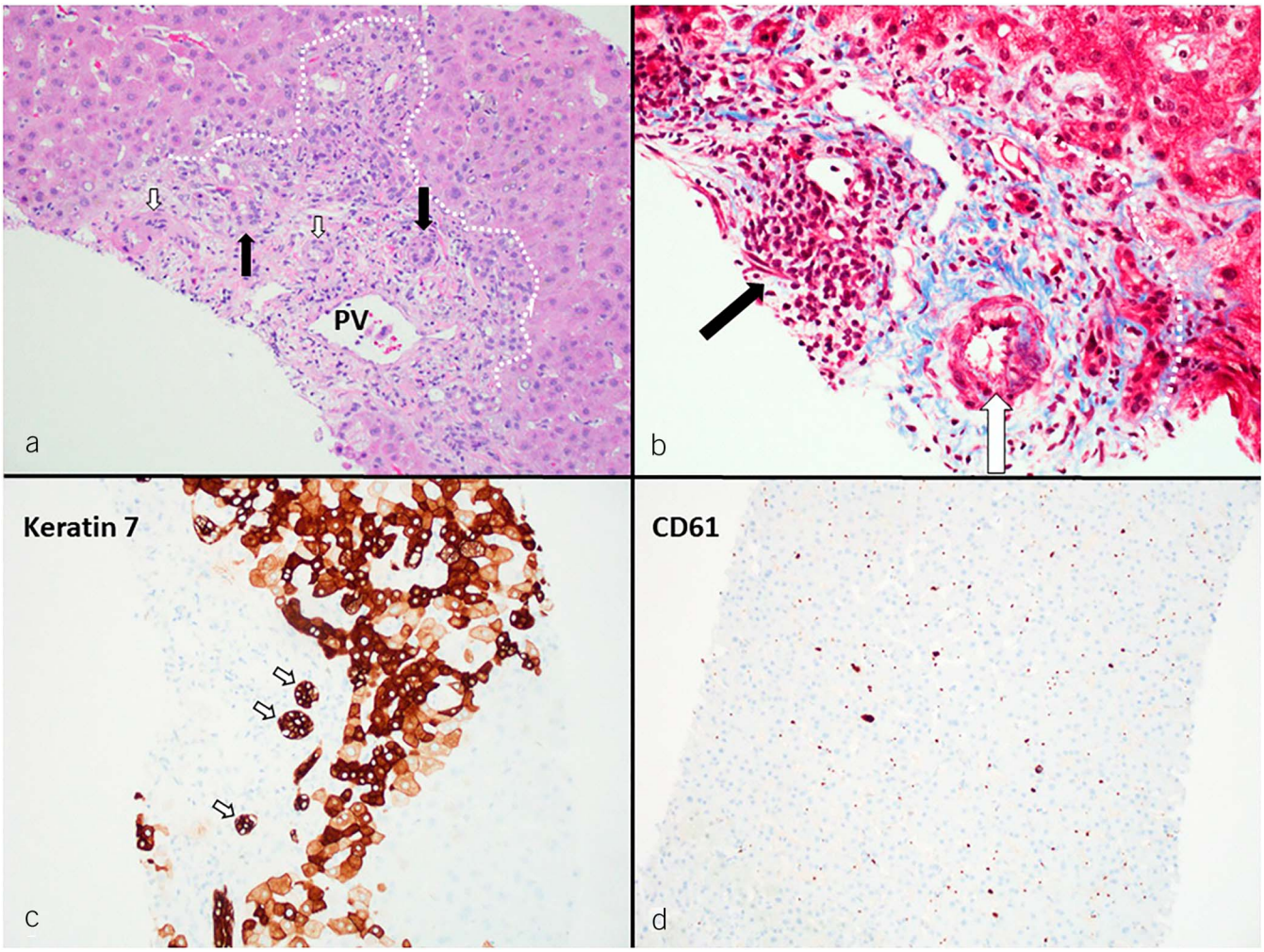

Figure 2. Histopathology of coronavirus disease 2019 cholangiopathy. (**a**) Features of acute large duct obstruction with portal expansion by edema (white spaces) and ductular reaction (dotted line) admixed with neutrophils. Bile ducts (black arrows) are present, but show mild reactive changes. White arrows: hepatic arteries, PV: portal vein. H&E ×20. (**b**) Features of chronic large duct obstruction in a patient who also shows acute duct obstructive features in other portal tracts in the same biopsy specimen. This chronic injury shows portal expansion less by edema than by fibrosis (blue collagen), chronic inflammation (black arrow), and ductular reaction with associated blue scar (dotted line). Although the bile duct is absent in this portal tract, this may be due to partial sampling. White arrows: hepatic arteries, PV: portal vein. Masson trichrome, ×40. (**c**) Immunostain (brown) for keratin 7 highlights bile ducts (arrows) and prominent hepatocellular staining indicative of ongoing cholestatic liver disease. Hematoxylin counterstain, ×20. (**d**) Immunostain (brown) for CD61 highlights finely granular sinusoidal staining of platelets or their exosomes. Larger sinusoidal aggregates may be intrasinusoidal microthrombi. Intravenous or intra-arterial thrombi were not seen in any samples. Hematoxylin counterstain, ×20.

warrant further consideration of the possibility that severe cholestatic injury may be related to direct infection of biliary epithelial cells by SARS-CoV-2.

Drug-induced liver injury is another potential hypothesis for the cholestatic liver injury seen in the patients. During the pandemic, a large assortment of medications has been subjected to trials. Among the medications that have been used in the treatment of COVID-19, remdesivir and IL-6 receptor agonists have been implicated as a cause of ALT elevations, although not with the pattern of biliary injury demonstrated in this study, nor was there any 1 medication consistently administered to all patients in this study (20–23).

The cholangiopathy described here in patients with COVID-19 bears similar features to SSC, described in patients after lengthy ICU stays (12). This entity, primarily discussed in case reports or small case series, has been seen in critically ill patients with polytrauma, infection, burn, major surgery, or respiratory failure (24–26). It has been described as a cholangiopathy similar to cases of ischemic cholangiopathy seen after liver transplantation and with radiographic features similar to those seen in PSC (24).

Many of the patients found to have SSC after critical illness have been diagnosed by ERCP and/or liver histology. Gelbmann et al. (24) described endoscopic findings of biliary casts with impairment of biliary flow and subsequent cholangitis and liver biopsy with confirmed cholangitis and hemorrhagic exudates in bile ducts. All 26 patients described in that study suffered from respiratory failure and also required mechanical ventilation, similar to our patient population. However, the findings in the studies of SSC after critical illness differed in some respects from our study. Laurent et al. (12) found increases in the ALP after a median time of only 11 days with peaking on day 15. Findings on

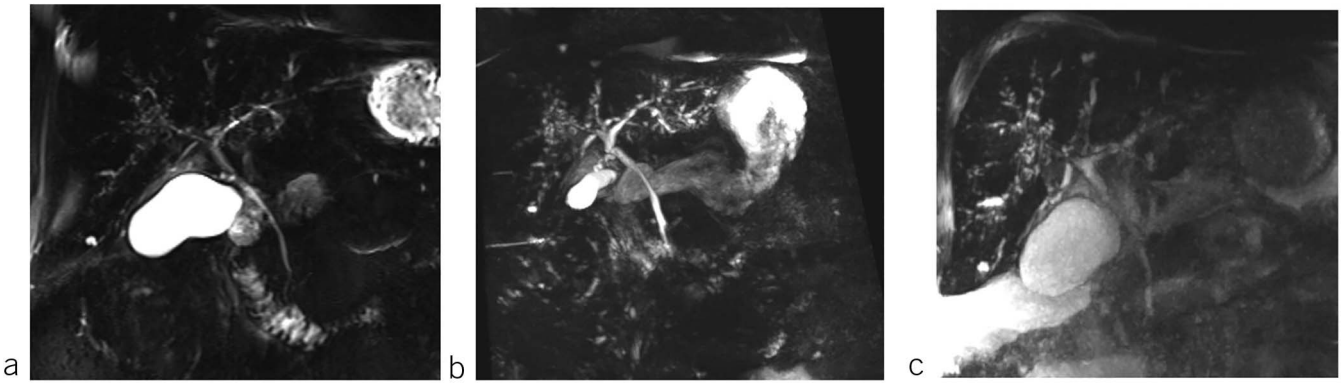

Figure 3. A 73-year-old man with progressive coronavirus disease 2019 cholangiopathy. Serial magnetic resonance cholangiopacreatography images 3 months (**a**), 4 months (**b**), and 7 months (**c**) after the initial diagnosis of coronavirus disease 2019 demonstrate worsening intrahepatic biliary dilatation with multifocal strictures.

MRCP included endoluminal defects of bile ducts corresponding to biliary casts, multiple strictures of intrahepatic bile ducts, thickening and enhancing of intrahepatic bile ducts, and biliary leakage with hyperintense collections suggestive of bilomas. On repeat MRCP, 2 patients had portal venous abnormalities, including thrombosis of branches of the portal vein. All 13 patients who continued to be followed after these findings received ursodeoxycholic acid at a dose of 10–15 mg/kg. Four patients underwent ERCP with endoscopic sphincterotomy of papilla for persistent jaundice, and 2 patients considered too ill for liver transplantation died from hepatic failure. No patient in this study received liver transplant. Nine remaining patients had persistent minor stricturing but with no significant complications, while 1 had worsening stricturing of intrahepatic ducts with no complication, and 1 had normal liver tests.

The similarities between SSC in critically ill patients and COVID cholangiopathy suggest a possible link between hypoxic liver injury or ischemic hepatopathy and cholestatic liver injury. The hepatic parenchyma, or hepatocytes, receives dual supply from the portal vein and from hepatic arteries. By contrast, the intrahepatic biliary tree is supplied exclusively by hepatic arterial branches through the peribiliary vascular plexus. This suggests that the biliary epithelium is more vulnerable to ischemic injury, given its dependence on arterial supply alone versus the hepatocytes which receive dual supply (25,27,28). This is made evident by cases of hepatic artery thrombosis, which occurs in 9% of adult recipients of liver transplant after interruption of the arterial blood supply, often resulting in biliary ischemic lesions including necrosis with biliary leakage and ischemic strictures (29,30).

An additional feature that may be pathogenetically shared by the pathogenesis of SSC related to critical illness and COVID cholangiopathy is the cytokine release syndrome (CRS) that occurs in both populations (28,31). CRS may cause immune-mediated injury to lung and liver due to excessive release of proinflammatory cytokines (27). It is possible that the biliary epithelium is particularly susceptible to the CRS-immune mediated injury, as suggested in reports that CRS can lead to severe cholestatic liver injury (31). In the recent report from the

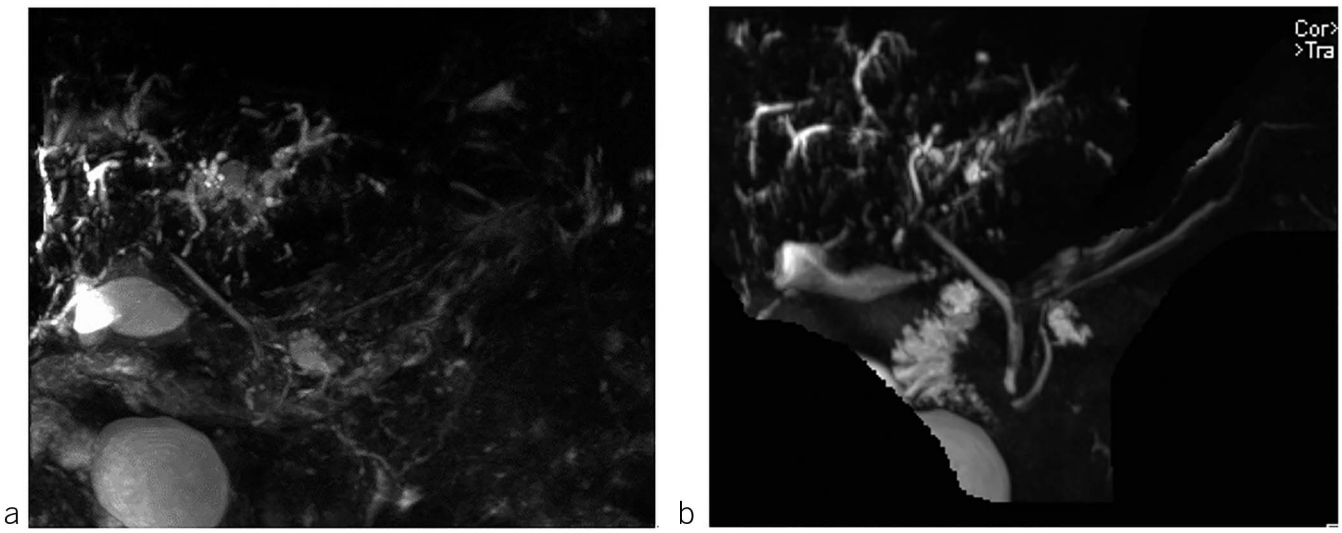

Figure 4. A 65-year-old man with progressive coronavirus disease 2019 cholangiopathy. Serial magnetic resonance cholangiopacreatography images 5 months (**a**) and 9 months (**b**) after the initial diagnosis of coronavirus disease 2019 demonstrate worsening intrahepatic biliary dilatation in the left lobe with multifocal strictures.

RECOVERY trial, the use of dexamethasone resulted in lower 28-day mortality among those with moderate to severe COVID-19 infection (32). Similarly, anticoagulant therapy seems to be associated with better prognosis in severe COVID patients meeting sepsis-induced coagulopathy criteria or with markedly elevated D-dimers (33,34). Studies on the impact of dexamethasone and anticoagulants in patients with severe COVID-19 on the incidence of emergent cholangiopathy in patients who have had severe COVID-19 would be of interest.

Should the pathogenesis of COVID cholangiopathy prove to be similar to that for SSC related to critical illness, we would speculate that the syndrome is potentiated in frequency and/or intensity by factors such as epithelial infection with SARS-CoV-2, microthrombosis. or the magnitude of the CRS peculiar to COVID-19. This could account for the frequency with which we have observed these findings in our population when SSC after critical illness is generally considered rare.

In conclusion, patients with severe COVID-19 may develop cholestatic injury associated with biliary tract inflammation and/or strictures as a late complication. This may reflect SSC after critical illness (12), but other pathogenetic mechanisms require study (e.g., ischemia related to COVID-19–associated thrombosis or direct biliary epithelial viral infection). Our observations raise important concerns about long-term morbidity and late complications, including the potential need for liver transplantation or mortality engendered by this syndrome. COVID cholangiopathy is an important complication of SARS-CoV-2 infection that requires further study on its natural history and potential preventive or therapeutic interventions.

CONFLICTS OF INTEREST

Guarantor of the article: Ira Jacobson, MD.

Specific author contributions: I.J.: conception of study, planning and conduct of study, collection and interpretation of data, drafting of manuscript, and critical revision. S.F.: collection and interpretation of data, conduct of study, drafting of manuscript, and critical revision. F.O.: collection and interpretation of data, conduct of study, drafting of manuscript, and critical revision. S.O.: collection and interpretation of data and critical revision of manuscript. D.F.: collection and interpretation of data, drafting of manuscript, and critical revision of manuscript. H.K.: collection and interpretation of data, critical revision of manuscript, and final approval. J.P.: collection and interpretation of data, drafting of manuscript, and critical revision of manuscript. C.S.: collection and interpretation of data and critical revision of manuscript. V.F.-D.: collection and interpretation of data and critical revision of manuscript. S.Y.: design of database, collection and interpretation of data, statistical support, critical review of manuscript, and final approval. N.D.: collection and interpretation of data and critical revision of manuscript. S.S.: collection and interpretation of data, drafting of manuscript, and critical revision of manuscript. N.T.: collection and interpretation of data, drafting of manuscript, and critical revision of manuscript. S.K.: collection and interpretation of data, drafting of manuscript, and critical revision of manuscript. K.S.: collection and interpretation of data, drafting of manuscript, and critical revision of manuscript.

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Study Highlights

WHAT IS KNOWN

- ✓ Patients hospitalized with coronavirus disease 2019 (COVID-19) frequently have elevations in liver enzymes.
- ✓ Most reports of hepatic involvement in COVID-19 have focused on aminotransferases.
- ✓ Biliary tract injury in severe COVID-19, similar to that seen in secondary sclerosing cholangitis after critical illness, has been reported.

WHAT IS NEW HERE

- ✓ Severe biliary tract injury resembling sclerosing cholangitis may occur during recovery after severe COVID-19.
- ✓ Patients with this syndrome have marked elevations in alkaline phosphatase and abnormal bile ducts with evidence of biliary inflammation, beading, stricturing, and dilatation.
- ✓ The mean time to recognition of this syndrome was over 3 months after admission for COVID-19.
- ✓ All patients had been critically ill and required intensive care.
- ✓ Progressive biliary tract injury with jaundice, hepatic insufficiency, and/or recurrent bacterial cholangitis has been observed.
- ✓ One patient has undergone liver transplantation, and others have been referred for transplant evaluation.

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