



Cholangitis in three critically ill patients after a severe CoVID-19 infection

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ABSTRACT

Coronavirus disease 2019 (CoVID-19) is a viral disease. Although the predominant presentation is respiratory disease, other manifestations such as gastrointestinal manifestations are commonly reported. Nevertheless, it has not been associated with chronic cholangitis or hepatic injury. In this study, we report three cases of severe CoVID-19 infection that required ICU admission, intubation, and sedation with ketamine. All three patients had abnormal liver function despite recovery and were diagnosed with cholangitis in the context of CoVID-19.

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Introduction

The CoVID-19 pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in Wuhan China, in December 2019, then spread throughout other continents since January 2020 [1,2]. The main presentation of CoVID-19 is respiratory symptoms such as cough, fever, and dyspnea. Many studies show an impact of Sars-CoV-2 on other organs. Gastrointestinal manifestations such as diarrhea, vomiting, and hepatobiliary abnormalities are recently noted in CoVID-19 patients [3].

During the first epidemic wave in France, from the late of February to mid-June 2020, 1271 patients with CoVID-19 infection were admitted to Bichat University Hospital in Paris. Four hundred and seventy-five patients developed severe respiratory manifestations, and 96 of them had critical manifestations with acute

respiratory distress syndrome (ARDS) requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO). We noted that 3 male patients without medical history of liver injury developed chronic cholangitis. Here we report these 3 cases and discuss the hypotheses for the underlying etiology.

Case reports

The demographics and clinical characteristics of patients were collected from the electronic medical record of our hospital (Table 1). All three patients were followed up as a part of their routine clinical care.

Patient 1

A previously healthy 55-year-old obese patient presented with dyspnea, fever, and cough for four days. He was diagnosed with SARS-CoV-2 infection on nasopharyngeal swab test. His initial assessment showed high inflammatory markers (CRP 251 mg/L) with normal renal and hepatic function tests. On day two, he had sudden ARDS with pulmonary embolism. He was transferred to the intensive

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Table 1
Main characteristics of patients presenting with cholangitis post Covid-19 infection.

	Patient 1	Patient 2	Patient 3
Patient demographics			
Sex	Male	Male	Male
Age (years)	55	45	30
Body Mass Index (Kg/m²)	33	32	23
Comorbidities	None	None	None
Characteristics at initial admission			
Symptoms at admission	Fever, dyspnea, cough	Fever, dyspnea, cough	Fever, dyspnea
White-blood cells (/mm³)	15 000	7 200	10 680
Neutrophils (/mm³)	13 000	5 440	9 010
Lymphocytes (/mm³)	1 400	1 500	1 470
Eosinophils (/mm³)	0	0	0
CRP (mg/L)	251	65	141
Creatinine (μmol/L)	81	87	125
ASAT (UI/L)	55	58	118
ALAT (UI/L)	23	44	39
GGT (UI/L)	48	62	25
ALP (UI/L)	80	41	31
Bilirubin (μmol/L)	18	10	21
LDH (UI/L)	630	695	5 260
ICU stay			
Period (days)	23	52	74
Infectious complications	Proteus vulgaris pneumonia.	Staphylococcus aureus pulmonary infection.	Staphylococcus aureus and Klebsiella aerogenes pneumonia, Neisseria subflava pneumonia
Medications received	Dexamethasone, lopinavir /ritonavir, Anakinra	Dexamethasone, lopinavir /ritonavir, Tocilizumab	Dexamethasone, lopinavir /ritonavir, Anakinra, Tocilizumab
Antibiotics	Cefotaxime, amoxicillin	Cefazoline	Cefotaxime Spiramycin, Piperacillin /Tazobactam, Meropenem, Amikacin
Intubation (days)	20	26	12
Vasopressor support	Yes (4 days)	Yes (2 days)	Yes (9 days)
Ketamine (grams)	25	27	6
ECMO	No	18 days	29 days
Prone positioning	4	2	6
Curative anticoagulation	Yes	Yes	Yes
Haemodialysis	No	15 sessions	30 sessions
Complications on follow up			
Secondary infections	Cholangitis and Enterococcus faecalis bacteremia	EBV reactivation	CMV viremia EBV reactivation
Anti-microbial medications	Piperacillin /tazobactam, Amoxicillin	None	Ganciclovir
Other complications	Peripheral neuropathy	Persistent chronic kidney disease (Stage 3)	Acute hepatic injury, Neuropathy

CRP: C reactive protein; ASAT: Aspartate aminotransferase; ALAT: Alanine aminotransferase; GGT: Gamma glutamyl transferase; ALP: Alkaline phosphatase; ICU: Intensive care unit; ECMO: Extracorporeal membrane oxygenation

care unit (ICU), intubated for 20 days, and sedated with ketamine (total 25 g). Four sessions of prone positioning were done. He was treated with dexamethasone, lopinavir /ritonavir, anakinra, and therapeutic anticoagulation.

During his stay, the patient had disturbed liver function tests that worsened gradually (Fig. 1). On day 25, he was diagnosed with cholangitis and *Enterococcus faecalis* bacteremia treated with a course of piperacillin /tazobactam. A liver ultrasound showed no biliary dilatation. He had neither active HIV, viral hepatitis (A, B, C, and E), EBV, nor CMV infection. Also, the autoimmune workup was negative. Hepatic MRI on day 66 showed a periportal hypersignal without hepatic biliary dilatation. A liver biopsy performed on day 74 showed interlobular biliary lesions with cholestasis, without evidence for infection. He was discharged home the day after.

On day 84, he was readmitted with recurrent cholangitis and *Enterococcus faecalis* bacteremia treated with amoxicillin for seven days. On day 88, endoscopic retrograde cholangiopancreatography showed irregular intrahepatic bile ducts suggesting ischemic cholangitis. He had sphincterotomy and removal of an uncalcified semi-solid stone. On 10 months follow-up, he still had persistent obstructive jaundice with prolonged prothrombin time. Follow up liver MRI after ten months of his illness showed findings suggestive of portal hypertension. He is currently in the pre-liver transplant evaluation process.

Patient 2

A previously healthy 45-year-old obese patient presented with 4-day history of fever, cough and dyspnea. SARS-CoV-2 infection was diagnosed on nasopharyngeal swab. Admission laboratory profile showed significant inflammatory state (CRP 65 mg/L) with normal renal and liver function tests. Due to severe hypoxia on day 4, he was transferred to the ICU, intubated for 26 days, and sedated with ketamine (total 27 g) for 24 days. Two sessions of prone positioning were performed. Also, he was placed on ECMO for 18 days. He was treated with dexamethasone, lopinavir /ritonavir, and tocilizumab. His ICU stay was complicated by diffuse venous thrombosis post ECMO treated with therapeutic anticoagulation. Besides, he had acute kidney injury that required 15 sessions of haemodialysis.

Throughout his stay, he had gradual worsening of his liver function tests (Fig. 1). Workup showed neither active HIV nor viral hepatitis (A, B, and C) infections, but previous EBV and CMV immunity with reactivation of EBV that resolved spontaneously. No autoimmune antibodies were detectable. Abdominal ultrasound on day 96 showed hepatic steatosis without hepatomegaly or biliary dilatation. Hepatic MRI on day 130 showed diffuse intra-hepatic dilatation and liver steatosis without any focal obstructing lesion. Transaminases resumed to normal values, but cholestasis persisted. Repeat liver MRI on day 200 showed unchanged aspect of

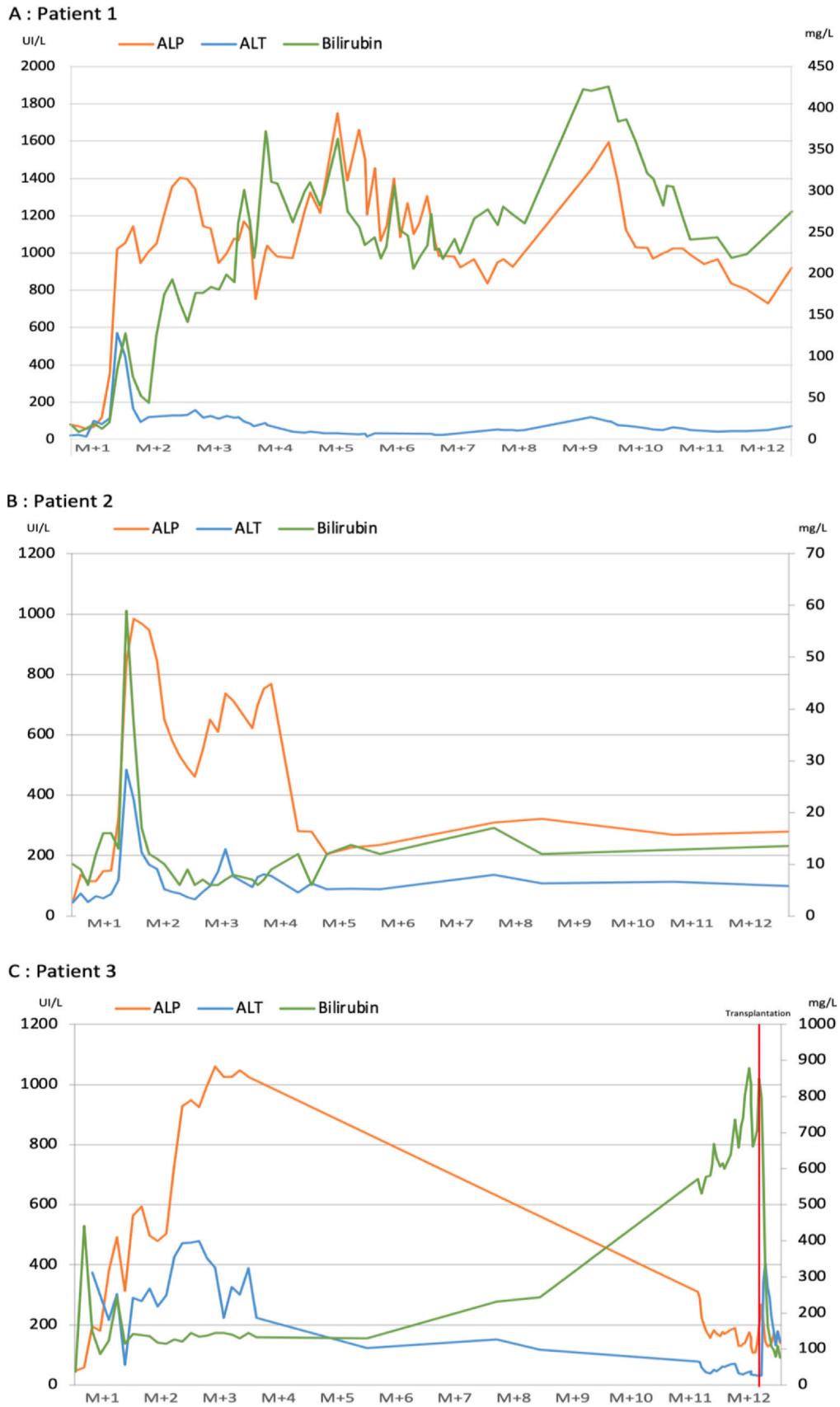


Fig. 1. Trends of liver function test of patients with cholangitis since their Day one of admission to one year of follow up. ALT: alanine transaminase (normal 16–63 U/L), ALP: alkalin phosphatase (normal 50–136 U/L), Bilirubin (normal < 17 $\mu\text{mol/L}$). Line in panel C indicate the date of transplantation.

intrahepatic bile duct wall irregularities in keeping with cholangitis along with partial resolution of bile ducts wall enhancement and hepatic perfusion disorders. On 1-year follow up after his illness, the patient had significant clinical and biochemical improvement.

Patient 3

A previously healthy 30-year-old patient presented with 2 days history of fever and dyspnea. His initial assessment showed high inflammatory markers (CRP 141 mg/L) accompanied with mild disturbance in his hepatic profile. He was diagnosed with SARS-CoV-2 infection on nasopharyngeal swab. On day two, he was admitted to the ICU for severe hypoxia and acute hepatic cytolysis. In the setting of severe ARDS, he was intubated for 12 days, placed on ECMO for 29 days, and sedated with ketamine (total 6 g) for 8 days. Six sessions of prone positioning were performed. His hospitalization was complicated by venous thrombosis and acute kidney injury that required 30 sessions of haemodialysis. He was treated with dexamethasone, lopinavir /ritonavir, tocilizumab, anakinra, and therapeutic anticoagulation.

During his stay, the patient had abnormal liver function tests (Fig. 1). He had neither active HIV nor viral hepatitis (A, B, C, and E) infections. He had EBV reactivation with spontaneous resolution and CMV reactivation with viremia (3.3Log) treated with ganciclovir for 14 days. Plasma CMV viral load was undetectable on day 60. No autoimmune antibodies were detectable.

Hepatic ultrasound was normal. Histology of liver biopsy done on day 62 showed cholestatic hepatitis lesions and bile ducts dystrophy suggesting a viral cytopathic effect. Viral panel performed on liver biopsy was negative (SARS-CoV-2, CMV, EBV, HSV-1, HSV-2, VZV, adenovirus and enterovirus). Throughout his hospital stay, his hepatic profile showed only persistent cholestatic disturbance. After nine months from his CoVID-19 illness, he developed liver failure with ascites and prolonged prothrombin time (54 s). On a follow up hepatic MRI, findings of progressive irregular intrahepatic ductal dilatation with narrowing were highly suggestive of diffuse cholangitis. He ended up having a liver transplant 11 months after his admission for CoVID-19. Histology report of hepatic explant showed extensive portal fibrosis, biliary infarction, and cholangitic lesions. Also, there was atrophy of central areas suggesting an ischemic etiology.

Discussion

Mildly elevated liver function tests are frequently observed in CoVID-19 patients. In general, this usually spontaneously resolved, and does not lead to liver failure nor specific treatment [4]. Remdesivir can aggravate the perturbation in liver tests [5]. This was not the case the reported patients, none of them had received remdesivir and all of them developed a chronic liver failure and did not have spontaneous resolution of abnormal liver tests.

Chronic cholangitis is an infrequent entity in critically ill patients and occurs in 1 per 2000 ICU patients [6]. Recently, it has been reported in CoVID-19 patients after ICU stay [7,8]. In our study, 3 out of 475 ICU patients had cholangitis which is around 10 times more frequent than what has been previously reported in the literature. In addition, post-CoVID-19 cholangitis may lead to severe hepatic injury and consequently liver transplantation as reported in the third patient of our study.

ARDS occurs in 15–31% of CoVID-19 patients [2], particularly obese patients. Obesity is thought to promote ischemia-hypoxemia through the use of small volumes during protective ventilation, high PEEP and multiple prone sessions [9]. In our study, all three patients shared these conditions. Obesity might have been, through hypoxemia, a contributing factor to ischemic cholangitis.

A second contributing factor could be direct viral injury on cholangiocytes. ACE2, which facilitates SARS-CoV-2 infection, is expressed by cholangiocytes as by lung alveolar cells [10]. However, detection of SARS-CoV-2 in cholangiocytes on liver biopsy has not been reported before. In our third case report (patient 3), dystrophic intrahepatic bile ducts in liver biopsy could suggest a viral cytopathic effect on cholangiocytes. In fact, CMV hepatitis in this patient was ruled out by the absence of hepatocellular abnormalities (viral inclusion) and negative CMV PCR on biopsy.

Thirdly, cholangiocytes play an important role in liver regeneration and immune regulation [11]. The release of pro-inflammatory cytokines TNF- α , IL-1, or IL-6, which is common in patients with SARS-CoV-2 infection, especially ICU patients, induce hyperviscosity, hyper-coagulopathy, thromboembolic event which may worsen the hypoxic phenomenon [12]. Pro-inflammatory cytokines alter the hepato-biliary transporters function, pAE2 anion exchangers which allow protective micelles in bile ducts. The defect of protective micelles leads to bile toxicity [13] and may be a risk factor of chronic cholangitis.

The fourth and crucial cause might be the use of ketamine in these three patients, known to induce sclerosing cholangitis associated with high doses or prolonged use [14]. We cannot exclude that our patients had genetic predisposition such as MDR3 polymorphism promoting drug-induced cholangitis [15]. Getting the result of this genetic testing needs around one-year duration which was not feasible to perform in our institution. These three patients received two to three grams of ketamine per day during the first week of management (between 0.6 and 1.2 mg/kg/h) with cumulative doses ranging from 10 to 25 g, which is consistent with Leonhart's study, reporting cholangitis [16].

In conclusion, Patients with severe SARS-CoV-2 infection are prone to develop chronic cholangitis, which may result from cumulative events: thrombotic events, hypoxemia, direct viral injury, and use of ketamine in patients with genetic promoting factors. However, none of the three patients reported here underwent MDR3 genetic analysis. Further studies are in progress to address this question.

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Ethics approval

Our three patients were a part of a research study entitled "Sociodemographic characteristics and transmission risk factors in patients hospitalized for CoVID-19 before and during the lockdown in France". This study was approved by the local ethics committee, IRB number 00006477.

Consent

All patients involved in this research study have declared voluntary participation without any opposition.

CRediT authorship contribution statement

All authors attest that they meet the current ICMJE criteria for Authorship. All authors treated and followed patients. CG, HT, AA, DLP and AG collected the data and performed the literature search. CG, HT, MR, CR and MP drafted the initial manuscript. MT prepared the figure. SI prepare the table. VP, JG, YY, FXL and AG edited and supervised the manuscript. All authors had access to the underlying data, which they verified. All authors revised the manuscript before approving its final version.

Declaration of Competing Interest

None of the authors has any financial/competing interests to disclose.

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