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ORIGINAL ARTICLE

Progressive cholestasis and associated sclerosing cholangitis are frequent complications of COVID-19 in patients with chronic liver disease

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Abstract

Background and Aims: Cholestasis is associated with disease severity and worse outcome in COVID-19. Cases of secondary sclerosing cholangitis (SSC) after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been described.

Approach and Results: Hospitalized patients with COVID-19 between 03/2020 and 07/2021 were included. Patients were stratified as having (i) no chronic liver disease (CLD), (ii) non-advanced CLD (non-ACLD), or (iii) advanced CLD (ACLD). Patients with CLD and non–COVID-19 pneumonia were matched to patients with CLD and COVID-19 as a control cohort. Liver chemistries before (Pre) and at first, second, and third blood withdrawal after SARS-CoV-2 infection (T1–T3) and at last available time point (last) were recorded. A total of 496 patients were included. In total, 13.1% (n = 65) had CLD (non-ACLD: 70.8%; ACLD: 29.2%); the predominant etiology was NAFLD/NASH (60.0%). COVID-19–related liver injury was more common among patients with CLD (24.6% vs. 10.6%; p = 0.001). After SARS-CoV-2 infection, patients with CLD exhibited progressive cholestasis with persistently increasing levels of alkaline phosphatase (Pre: 91.0 vs. T1: 121.0 vs. last: 175.0 U/L; p < 0.001) and gamma-glutamyl transferase (Pre: 95.0 vs. T1: 135.0 vs. last: 202.0 U/L; p = 0.001). A total of 23.1% of patients

Abbreviations: 95% CI, 95% confidence interval; ACLD, advanced chronic liver disease; aHR, adjusted hazard ratio; ALD, alcohol-associated liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; ECMO, extracorporeal membrane oxygenation; GGT, gamma-glutamyl transferase; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory distress syndrome coronavirus 2; SSC, secondary sclerosing cholangitis; ULN, upper limit of normal.

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with CLD (n = 15/65) developed cholestatic liver failure (cholestasis plus bilirubin ≥6 mg/dl) during COVID-19, and 15.4% of patients (n = 10/65) developed SSC. SSC was significantly more frequent among patients with CLD and COVID-19 than in patients with CLD and non–COVID-19 pneumonia (p = 0.040). COVID-19–associated SSC occurred predominantly in patients with NAFLD/NASH and metabolic risk factors. A total of 26.3% (n = 5/19) of patients with ACLD experienced hepatic decompensation after SARS-CoV-2 infection.

Conclusions: About 20% of patients with CLD develop progressive cholestasis after SARS-CoV-2 infection. Patients with NAFLD/NASH and metabolic risk factors are at particular risk for developing cholestatic liver failure and/or SSC after COVID-19.

INTRODUCTION

Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), causes considerable morbidity and mortality globally.[1] COVID-19 is an infectious disease affecting the respiratory, hepatic, neuronal and intestinal system, oftentimes leading to multiorgan failure and acute respiratory distress syndrome (ARDS).[2,3] Among others, old age, obesity, male sex, and preexisting comorbidities are known to be risk factors for mortality due to COVID-19.[4–6]

Viral particles were detected in the cytoplasm of hepatocytes in liver biopsies of patients with SARS-CoV-2 infection, directly linking COVID-19–associated liver injury with hepatocellular infection.[7] Moreover, SARS-CoV-2 is capable of infecting cholangiocytes in vitro.[3,8,9] Apart from SARS-CoV-2-mediated cytotoxicity, other factors that may contribute to COVID-19–associated liver injury are the excessive proinflammatory state, coagulopathy-associated vascular dysfunction, drug-induced liver injury, hypoxemia and cardiac congestion likely all contribute to COVID-19–associated liver injury.[3,10]

Liver chemistry abnormalities are known to occur in a substantial number of patients with COVID-19.[11–18] Importantly, liver enzyme elevations were observed more frequently in patients who were critically ill and patients with severe courses of COVID-19.[10,19–21] Initially, elevated levels of aspartate aminotransferase (AST) and bilirubin were established as independent predictors of COVID-19–associated mortality,[18,22] indicating the clinical relevance of elevated liver chemistries in patients with SARS-CoV-2 infection. Although aminotransferase elevation is common early during COVID-19, cholestatic liver injury parameters increase in later stages of the disease.[8,23,24] Cholestatic enzyme patterns and even progressive cholestatic liver failure with development of secondary sclerosing cholangitis (SSC) after severe SARS-CoV-2 infection have been reported, in some cases even requiring liver transplantation.[3,25–28]

In patients with chronic liver disease (CLD), COVID-19–related liver injury has been reported, as well.[29] Notably, patients with preexisting CLD have increased risk for severe COVID-19 and mortality, with particularly high rates of mortality among patients infected with SARS-CoV-2 with advanced CLD (ACLD).[29–33] Moreover, patients with ACLD and COVID-19 exhibit high rates of hepatic decompensation and acute-on-chronic liver failure.[33] However, data on cholestatic liver injury and SSC in patients with CLD and COVID-19 are still scarce.

This study aimed to investigate (i) the prevalence of abnormal liver chemistries of patients with CLD at the initial blood withdrawal after first positive SARS-CoV-2 polymerase chain reaction (PCR) test and (ii) the trajectories of parameters of hepatocellular and cholestatic liver injury in these patients. Furthermore, our objective was to assess (iii) clinical outcomes of patients with COVID-19 and preexisting CLD and (iv) the impact of liver abnormalities on clinical outcomes in this cohort.

PATIENTS AND METHODS

Study Population

This retrospective study included adult patients hospitalized for COVID-19 with positive SARS-CoV-2 test at the Vienna General Hospital between 03/2020 and 07/2021. Clinical and laboratory parameters, including preexisting CLD or ACLD, age, body mass index (BMI), comorbidities (i.e., preexisting diabetes mellitus, arterial hypertension, hyperlipidemia, as well as lung, cardiovascular, chronic kidney and malignant disease), hepatic decompensation events (portal hypertensive bleeding, paracentesis, hepatic encephalopathy), liver chemistries (AST, alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], and total

bilirubin), hemoglobin, white blood cell count, platelet count, D-dimer, international normalized ratio, creatinine, serum sodium, albumin and C-reactive protein, hospital and intensive care unit (ICU) admission, as well as intubation, death, COVID-19–related death and liver-related death were assessed by chart review. Definitions for (A)CLD, liver-related death and COVID-19–related death are provided in the supplementary material. Patients without hospital admission or available data on the presence of CLD were excluded from the study (Figure S1). Notably, due to the retrospective design of the study, not all parameters were available for every patient. Patients were stratified for presence of CLD and presence of ACLD.

Control cohort of patients with CLD and non–COVID-19 pneumonia

In order assess a potential distinct effect of COVID-19 in patients with CLD, the clinical outcomes of these patients were compared to a control cohort of patients with CLD and non–COVID-19 pneumonia. The cohorts were matched for liver disease severity (i.e., non-ACLD, compensated ACLD [cACLD], and decompensated ACLD [dACLD]) and other key characteristics (see Supporting Material).

Laboratory parameters

All parameters were assessed by standard laboratory assays. The last available value prior to first positive SARS-CoV-2 PCR test (Pre), the first three available values after first positive SARS-CoV-2 PCR test (T1, T2 and T3, respectively) and the last available value (last) were recorded for each patient.

Local laboratory thresholds for men and women were implemented as upper limit of normal (ULN) for parameters of hepatocellular (AST and ALT) and cholestatic liver injury (ALP, GGT, and bilirubin). The definition of COVID-19–related liver injury is provided in the supplementary methods.

Severe cholestasis, cholestatic liver failure, and SSC

Severe cholestasis was defined as ALP/GGT >5× ULN and cholestatic liver failure was defined as presence of severe cholestasis and BIL ≥6 mg/dl. SSC was defined as presence of SSC-specific bile duct alterations or liver abnormalities (see Supporting Methods) in cross-sectional imaging or in endoscopic retrograde cholangiopancreaticography (ERCP).

Statistical analysis

For categorical variables, the number (*n*) and proportion (%) of patients displaying the parameter of interest were reported. The total number of available values (*n* total) was added where appropriate. Continuous data was reported as median with interquartile range (IQR). Shapiro–Wilk and D'Agostino & Pearson normality tests were used to test for normal distribution. Mann–Whitney U test was implemented for comparison of non-normally distributed continuous variables between two groups. Kruskal-Wallis test was computed for comparison of non-normally distributed continuous variables in three or more groups. Dunn's multiple comparisons test was used as post-hoc test. Fisher's exact test or Pearson's Chi-squared were used for group comparisons of categorical variables. Differences in survival between groups of elevated versus nonelevated levels of the parameters of interest were depicted by Kaplan–Meier curves. Log-rank test was used to determine differences in survival between these groups. Cox proportional hazard models were computed to assess the impact of the parameters of interest on (liver-related) mortality. Further information on the Cox proportional hazard models is provided in the supplementary methods. GraphPad Prism 8 (Graphpad Software, La Jolla, CA, USA) and IBM SPSS 22.0 statistic software (IBM, Armonk, NY) were used for statistical analysis. A two-sided p value of < 0.05 was considered statistically significant.

RESULTS

Patient characteristics of patients with CLD and COVID-19 (Table 1)

In total, 496 patients with COVID-19 and associated hospital admission (normal bed ward: 59.1% [*n* = 293]; ICU: 40.9% [*n* = 203]) were included in this study. A total of 58.9% of patients were male. The median age was 67.4 (IQR 27.5) years. In total, 13.1% (*n* = 65) of included patients had preexisting CLD, including 19 (29.2%) patients with ACLD, 7 (36.8%) of whom were decompensated before the SARS-CoV-2 infection. The main etiology was NAFLD/NASH (60.0% of patients with CLD), followed by alcohol-associated liver disease (ALD; 15.4% of patients with CLD) and viral hepatitis (7.7% of patients with CLD). The frequency of specific CLD etiologies did not differ significantly between patients with and without ACLD. Further information on patient characteristics of patients with and without CLD with COVID-19 as well as of patients with CLD and non–COVID-19 pneumonia are provided in the supplementary results.

TABLE 1 Patient characteristics at the time of severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) infection and outcomes with and without advanced chronic liver disease (ACLD)

Patient characteristics	Patients with liver disease (*n* = 65)	Patients without ACLD (*n* = 46)	Patients with ACLD (*n* = 19)	*p* value
Sex, male/female (% male)	39/26 (60.0%)	26/20 (56.5%)	13/6 (68.4%)	0.373
Age, years (IQR)	67.7 (19.6)	70.3 (20.4)	67.6 (19.8)	0.641
Etiology				0.172
NAFLD/NASH, *n* (%)	39 (60.0%)	31 (67.4%)	8 (42.1%)	
ALD, *n* (%)	10 (15.4%)	4 (8.7%)	6 (31.6%)	
Viral hepatitis, *n* (%)	5 (7.7%)	3 (6.5%)	2 (10.5%)	
Cryptogenic, *n* (%)	3 (4.6%)	2 (4.3%)	1 (5.3%)	
Other, *n* (%)	8 (12.3%)	6 (13.0%)	2 (10.5%)	
Decompensated ACLD, *n* (%)	7 (10.8%)	0 (−)	7 (36.8%)	
MELD, points (IQR)	9.0 (7.0)	8.5 (10.0)	10.0 (6.0)	0.432
COVID-19–related liver injury, *n* (%)[a]	14 (21.5%)	9 (19.6%)	5 (26.3%)	0.547
Median hospital stay, days (IQR)	25.0 (40.0)	27.0 (41.0)	21.0 (39.0)	0.641
ICU admission, *n* (%)	28 (43.1%)	21 (45.7%)	7 (36.8%)	0.514
Median ICU stay, days (IQR)	24.5 (52.0)	28.0 (60.0)	20.0 (32.0)	0.385
Intubation, *n* (%)	25 (38.5%)	19 (41.3%)	6 (31.6%)	0.464
Median duration of intubation, days (IQR)	24.0 (50.0)	28.0 (58.0)	20.0 (28.0)	0.645
Severe cholestasis, *n* (%)	31 (47.7%)	22 (47.8%)	9 (47.4%)	0.973
Cholestatic liver failure, *n* (%)	15 (23.1%)	11 (23.9%)	4 (21.1%)	0.803
Secondary sclerosing cholangitis, *n* (%)	10 (15.4%)	8 (17.4%)	2 (11.1%)	0.485
Decompensation/further decompensation, *n* (%)	5 (7.7%)	0 (−)	5 (26.3%)	
Death, *n* (%)	27 (41.5%)	16 (34.8%)	11 (57.9%)	0.085
COVID-19–related death, *n* (%)	21 (32.3%)	14 (30.4%)	7 (36.8%)	0.615
Liver-related death, *n* (%)	11 (16.9%)	8 (17.4%)	3 (15.8%)	0.876

Abbreviations: ALD, alcohol-associated liver disease; ICU, intensive care unit; IQR, interquartile range; PCR, polymerase chain reaction.
[a]After first positive SARS-CoV-2 PCR test.

Trajectory of liver chemistries in patients with CLD who tested positive for SARS-CoV-2 (Figure 1, Table S2)

Over the course of the SARS-CoV-2 infection in patients with CLD, there was an elevation of aminotransferases (AST: Pre: 26.5 U/L vs. T1: 46.5 U/L vs. last: 37.0 U/L, $p < 0.001$; ALT: Pre: 25.0 U/L vs. T1: 30.0 U/L vs. last: 36.0 U/L, $p = 0.080$), followed by a progressive increase of parameters of cholestatic liver injury (ALP: Pre: 91.0 U/L vs. T1: 119.0 U/L vs. last: 175.0 U/L, $p < 0.001$; GGT: $p < 0.001$). Although plasma levels of AST declined at the last available time point, GGT and especially ALP levels showed a steady increase during SARS-CoV-2 infection, which continued until the last available value, indicating a progressive state of cholestasis. Of note, this sustained ALP elevation in patients with CLD was visible even after excluding the patients, who developed SSC (Pre: 92.0 U/L vs. T1: 121 U/L vs. last: 138 U/L; $p = 0.047$). Although there was no significant difference in median levels of bilirubin during SARS-CoV-2 infection ($p = 0.813$), the rate of patients with bilirubin >2× ULN doubled over time (BIL >2× ULN: Pre: 9.2% vs. T1: 10.8% vs. last: 21.5%, $p = 0.086$).

In patients without CLD, the same pattern of liver enzyme elevation was present with significant AST/ALT elevation during early stages of COVID-19 (T1 to T3) and subsequently decrease to normal levels (last), whereas there was a steady increase of parameters of cholestatic liver injury with significant elevation of ALP at the time of last available values (Table S3).

Information on prevalence of COVID-19–related liver injury in patients with and without CLD is provided in the Supporting Material.

Clinical outcomes of patients with liver disease compared with patients without liver disease with COVID-19 (Table S1)

Median follow-up time was 34.5 (IQR 107.0) days. The rate of ICU admissions ($p = 0.886$), intubation

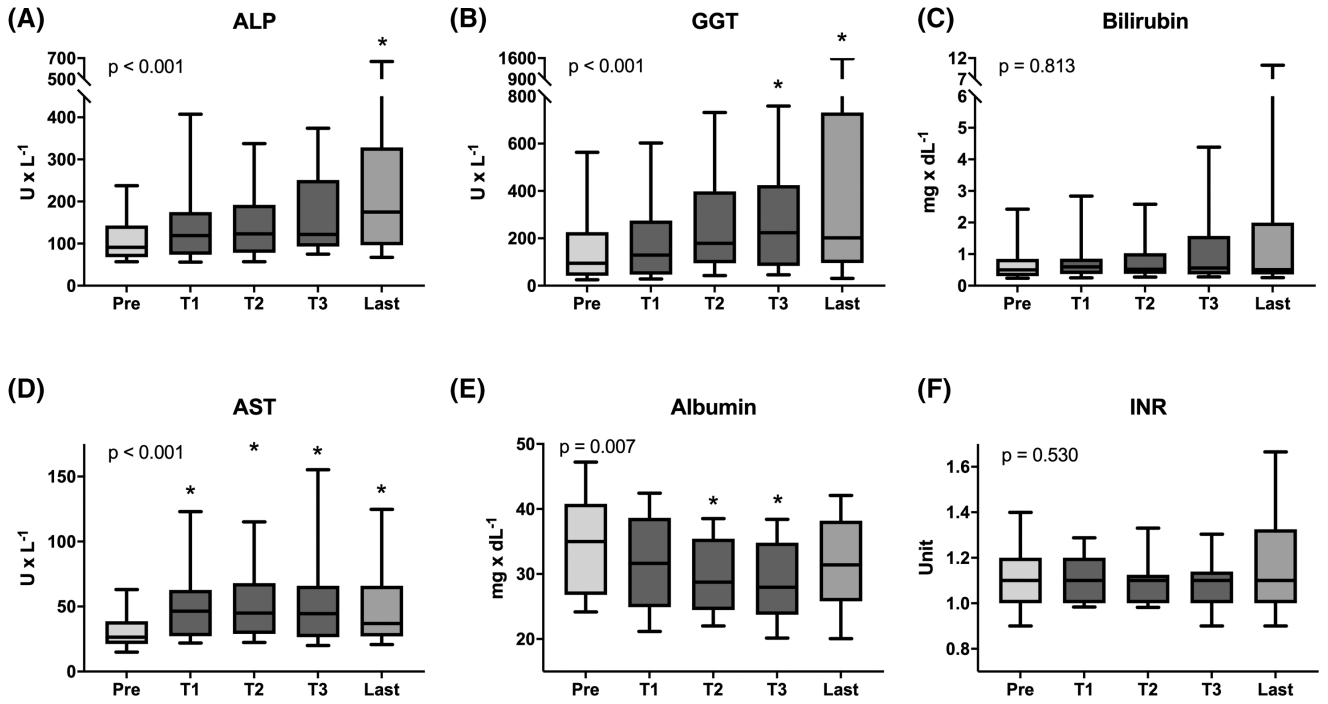

FIGURE 1 Blood levels of hepatic aminotransferases and liver function parameters prior and during COVID-19 infection. (A) Alkaline phosphatase (ALP), (B) gamma-glutamyl transferase (GGT), (C) bilirubin, (D) aspartate aminotransferase (AST), (E) albumin and international normalized ratio (INR) in patients with liver disease and COVID-19. The borders of the whiskers are the 10th and the 90th percentile. Pre, last available value before severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) infection; T1/T2/T3, first/second/third available value after SARS-CoV-2 infection; Last, last available value; *$p < 0.050$ compared to Pre.

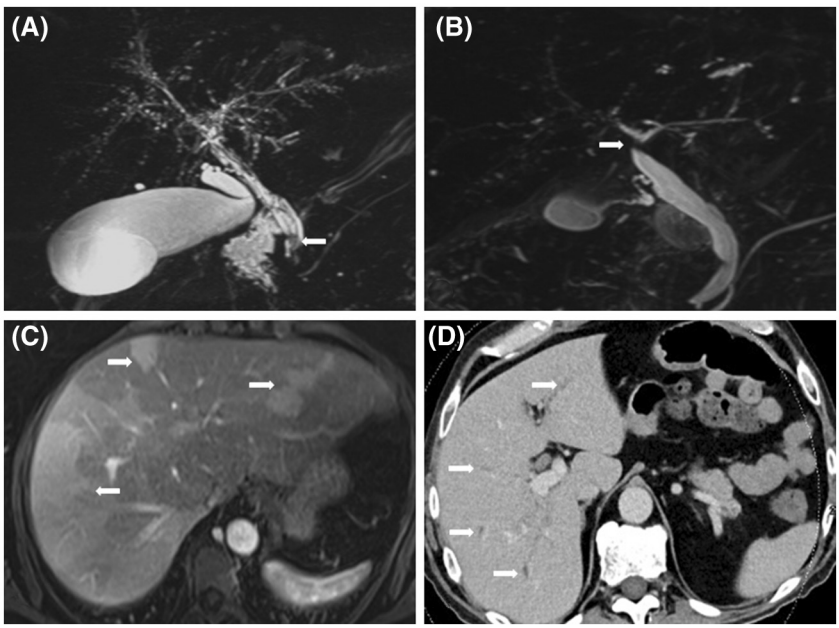

FIGURE 2 Imaging features of secondary sclerosing cholangitis (SSC). (A) Coronal MIP MRCP image shows the "beaded" appearance of intrahepatic bile ducts due to alternating strictures and dilatation. A filling defect can be seen in the distal common bile duct due to stones (white arrow). (B) Coronal MIP MRCP image shows a more advanced form with poor visualization of intrahepatic bile ducts due to obliteration of peripheral ducts resulting in a "pruned tree" appearance. Stenosis at the proximal common hepatic duct is also seen (white arrow). (C) Hepatic arterial phase MRI shows inhomogeneous and wedge-shaped parenchymal enhancement (white arrows) representing edema and an increased perfusion due to focal inflammation. (D) Portal venous phase imaging on CT shows focal, intrahepatic cholangiectasis (white arrows; same patient as in A). CT, computed tomography; MIP, maximum intensity projection; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging.

(p = 0.455), as well as median duration of hospital stay (p = 0.417), ICU stay (p = 0.679) and intubation (p = 0.487) did not differ between patients with and without CLD. However, prevalence of death (41.5% vs. 28.8%; p = 0.037) and liver-related death (15.4% vs. 3.5%; p < 0.001) were significantly higher in patients with CLD. The impact of liver function (as assessed by MELD) and comorbidities on ICU admission rate is depicted in Table S4.

Assessed by log-rank test (p = 0.308) and Cox regression analysis (hazard ratio [HR]: 1.24; 95% confidence interval [95% CI]: 0.82–1.89; Table S5), preexisting CLD was not associated with mortality. Independent predictors of mortality in the overall cohort included older age, lower albumin, higher D-dimer and preexisting lung disease.

Clinical outcomes of patients with liver disease with and without ACLD (Table 1, Figure 2)

Importantly, 47.7% (n = 31/65) of patients with CLD exhibited severe cholestasis (ALP/GGT >5× ULN) during follow-up, and 15 patients (23.1%) with preexisting liver disease developed laboratory signs of cholestatic liver failure (severe cholestasis and BIL ≥6 mg/dl) during COVID-19. Moreover, 10 patients (15.4% of patients with CLD) were diagnosed with SSC during follow-up and one patient with preexisting primary sclerosing cholangitis showed radiological and laboratory signs of disease progression after COVID-19. Figure 2 depicts SSC-specific bile duct alterations and liver abnormalities in patients with CLD and COVID-19. Notably, there was no significant difference in frequency of cholestatic liver failure and SSC between patients with and without ACLD.

Moreover, 26.3% (n = 5/19) of patients with ACLD had a decompensation event during follow-up (ascites: n = 1, hepatic encephalopathy: n = 1 and acute-on-chronic liver failure: n = 3). Mortality was generally high among patients with CLD and COVID-19 (41.5%), but even higher in patients with ACLD (57.9%; n = 11/19; p = 0.085). There was no difference in frequency of COVID-19–related and liver-related death between patients with CLD with and without ACLD.

Comparison of clinical outcomes between patients with CLD and COVID-19 and patients with CLD and non–COVID-19 pneumonia (Table 2)

Follow-up duration (COVID-19: 59.0 days vs. non–COVID-19: 43.0 days; p = 0.166) and need for extracorporeal membrane oxygenation (ECMO; COVID-19: 20.0% vs. non–COVID-19: 18.5%; p = 0.823) did not differ between patients with CLD and COVID-19 and patients with CLD and non–COVID-19 pneumonia.

Importantly, patients with CLD and COVID-19 developed SSC more often (COVID-19: 15.4% vs. non–COVID-19: 4.6%; p = 0.040), whereas the prevalence of severe cholestasis (COVID-19: 47.7% vs. non–COVID-19: 40.0%; p = 0.376) and cholestatic liver failure (COVID-19: 23.1% vs. non–COVID-19: 21.5%; p = 0.833) did not differ compared to patients with CLD and non–COVID-19 pneumonia.

Patient characteristics and outcomes of patients with liver disease and development of SSC after SARS-CoV-2 infection (Table 3, Figure 3)

Among all 10 patients with liver disease developing SSC, five (50.0%) were male. In total, 70.0% (n = 7/10) had CLD due to NAFLD/NASH, whereas one patient had ALD, viral liver disease, and polycystic liver disease, respectively. Three patients developing SSC were 18–39 years old, whereas six patients were aged 40–69 years and one patient ≥70 years. SSC was diagnosed in two patients via ERCP and in eight patients using cross-sectional imaging. Median time from first positive SARS-CoV-2 PCR test to SSC diagnosis was 48.5 days. Median time of patients with CLD to develop cholestatic liver failure without SSC diagnosis was 43.0 (IQR 234) days, indicating that not all patients with cholestatic liver failure will progress to SSC.

Median BMI was 29.0 kg/m^2, and five patients (50.0%) were obese. In total, 60.0% (n = 6/10) had a history of arterial hypertension. All 10 patients had severe courses of COVID-19, as all of them were admitted to the ICU, nine (90.0%) required mechanical ventilation. ECMO was required in 80.0% (n = 8/10) of patients with CLD developing SSC, and 90.0% (n = 9/10) received ketamine. The lowest (median) arterial pO2 measured in patients with CLD developing SSC was clearly in the hypoxemic range with 57.6 mmHg. Most patients with SSC (9/10) were treated with ursodesoxycholic acid. Figure 2 depicts the trajectory of ALP, AST, and bilirubin in patients with CLD who developed SSC.

Median ICU stay was 69.0 days, and median duration of intubation was 75.0 days. In total, 50.0% (5/10) of patients with SSC died during follow-up and one patient was evaluated for liver transplantation.

Elevated total bilirubin after first positive SARS-CoV-2 PCR test and clinical outcomes among patients with liver disease (Table 4)

Patients with CLD with elevated bilirubin after first positive SARS-CoV-2 PCR test were more frequently

TABLE 2 Patient characteristics at the time of SARS-CoV-2 infection/pneumonia onset and outcomes of patients with chronic liver disease and COVID-19 versus non–COVID-19 pneumonia

Patient characteristics	COVID-19 (*n* = 65)	Non–COVID-19 pneumonia (*n* = 65)	*p* value
Sex, male/female (% male)	39/26 (60.0%)	40/25 (61.5%)	0.857
Age, years (IQR)	67.7 (19.6)	58.6 (25.5)	**0.002**
Chronic liver disease severity			0.999
non-ACLD	46 (70.8%)	46 (70.8%)	
cACLD	12 (18.4%)	12 (18.4%)	
dACLD	7 (10.8%)	7 (10.8%)	
Etiology			0.446
NAFLD/NASH, *n* (%)	39 (60.0%)	31 (47.7%)	
ALD, *n* (%)	10 (15.4%)	14 (21.5%)	
Viral hepatitis, *n* (%)	5 (7.7%)	7 (10.8%)	
Cryptogenic, *n* (%)	3 (4.6%)	1 (1.5%)	
Other, *n* (%)	8 (12.3%)	12 (18.5%)	
Follow-up duration, days (IQR)	59.0 (170.0)	43.0 (763.0)	0.166
Intubation, *n* (%)	25 (38.5%)	56 (86.2%)	**<0.001**
Extracorporeal membrane oxygenation, *n* (%)	13 (20.0%)	12 (18.5%)	0.823
Severe cholestasis, *n* (%)	31 (47.7%)	26 (40.0%)	0.376
Cholestatic liver failure, *n* (%)	15 (23.1%)	14 (21.5%)	0.833
Secondary sclerosing cholangitis, *n* (%)	10 (15.4%)	3 (4.6%)	**0.040**
Death, *n* (%)	27 (41.5%)	39 (60.0%)	**0.003**
COVID-19/pneumonia-related death, *n* (%)	21 (32.3%)	30 (46.2%)	0.106
Liver-related death, *n* (%)	11 (16.9%)	18 (27.7%)	0.140

Abbreviations: ACLD, advanced chronic liver disease; ALD, alcohol-associated liver disease; cACLD, compensated advanced chronic liver disease; dACLD, decompensated advanced chronic liver disease; IQR, interquartile range; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory distress syndrome coronavirus 2. DACLD is defined as ACLD with a previous decompensation event (portal hypertensive bleeding, ascites or hepatic encephalopathy). Bold *p* values denote statistically significant difference.

admitted to the ICU (91.7% vs. 32.1%; $p < 0.001$) and intubated (91.7% vs. 26.4%; $p < 0.001$), had longer median hospital stay (58.0 days vs. 21.0 days; $p = 0.022$), ICU stay (47.0 days vs. 21.0 days; $p = 0.120$) and intubation duration (41.0 days vs. 19.5 days; $p = 0.047$). Moreover, they exhibited higher mortality (75.0% vs. 34.0%; $p = 0.009$), more COVID-19–related deaths (75.0% vs. 22.6%; $p < 0.001$) and more liver-related deaths (75.0% vs. 3.8%; $p < 0.001$) (Figure 4).

Association of liver-related mortality and elevated liver enzymes after first positive SARS-CoV-2 PCR test in patients with liver disease (Table S6)

Assessed by log-rank test, elevated levels of bilirubin ($n = 12/65$; $p < 0.001$) after first positive SARS-CoV-2 PCR test were associated with shorter time to liver-related death. There was no link between liver-related mortality and elevated ALP ($n = 31/57$; $p = 0.794$), GGT ($n = 47/59$; $p = 0.126$), AST ($n = 38/63$; $p = 0.106$) or ALT ($n = 23/64$; $p = 0.884$).

Correspondingly, elevated bilirubin (HR: 18.25; 95% CI: 3.94–84.52) and tendentially elevated AST (HR: 3.86; 95% CI: 0.83–17.90) after first positive SARS-CoV-2 PCR test were associated with increased liver-related mortality among patients with CLD in univariate Cox regression analysis. After adjustment for potentially confounding factors, elevated bilirubin (adjusted HR [aHR]: 8.81; 95% CI: 1.84–42.31), but not elevated AST (aHR: 1.62; 95% CI: 0.31–8.35) independently predicted liver-related mortality in patients with CLD and COVID-19. Higher MELD after first positive SARS-CoV-2 PCR test also independently predicted liver-related related mortality among patients with CLD and COVID-19 (aHR: 1.15; 95% CI: 1.03–1.29).

DISCUSSION

In this study, we thoroughly characterized the patterns of liver injury and clinical outcomes of Austrian patients with CLD hospitalized for COVID-19. Importantly, we identified a biphasic pattern of liver injury in patients with CLD over the course of COVID-19, characterized by initial mild elevations of parameters of hepatocellular liver injury (AST/ALT) elevation followed by prolonged and progressive cholestasis. Almost one quarter of patients

TABLE 3 Patient characteristics at the time of severe acute respiratory distress syndrome coronavirus 2 infection and outcomes of patients with chronic liver disease and COVID-19, who developed secondary sclerosing cholangitis (SSC)

Patient characteristics	Patients with liver disease developing SSC (*n* = 10)
Sex, male/female (% male)	5/5 (50.0%)
Age	
18–39 years, *n* (%)	3 (30.0%)
40–69 years, *n* (%)	6 (60.0%)
≥70 years, *n* (%)	1 (10.0%)
Body mass index, kg × m^{-2}, median (IQR)	29.0 (8.5)
Etiology	
NAFLD/NASH, *n* (%)	7 (70.0%)
ALD, *n* (%)	1 (10.0%)
Viral hepatitis, *n* (%)	1 (10.0%)
Polycystic liver, *n* (%)	1 (10.0%)
ACLD, *n* (%)	2 (20.0%)
Obesity, *n* (%)	5 (50.0%)
Arterial hypertension, *n* (%)	6 (60.0%)
Diabetes mellitus, *n* (%)	3 (30.0%)
Dyslipidemia, *n* (%)	1 (10.0%)
Cardiovascular disease, *n* (%)	1 (10.0%)
Chronic renal insufficiency, *n* (%)	1 (10.0%)
Lung disease, *n* (%)	2 (20.0%)
Median duration to SSC diagnosis, days (IQR)	48.5 (63.0)
ICU admission, *n* (%)	10 (100.0%)
ICU stay, days, median (IQR)	69.0 (94.0)
Mechanical ventilation, *n* (%)	9 (90.0%)
Duration of mechanical ventilation, days, median (IQR)	75.0 (66.0)
Extracorporeal membrane oxygenation, *n* (%)	8 (80.0%)
Exposure to ketamine, *n* (%)	9 (90.0%)
UDCA treatment, *n* (%)	9 (90.0%)
Minimal arterial pO2, mmHg (IQR)	57.6 (5.1)
Death, *n* (%)	5 (50.0%)

Abbreviations: ACLD, advanced chronic liver disease; ALD, alcohol-associated liver disease; ICU, intensive care unit; IQR, interquartile range.

with CLD and COVID-19 developed laboratory signs of cholestatic liver failure, and 15.4% of patients with CLD were diagnosed with SSC. SSC development occurred almost exclusively in patients with CLD with severe courses of COVID-19 and was more frequent than in the control cohort of patients who were chronically ill with CLD with non–COVID-19 pneumonia. Moreover, patients with NAFLD/NASH and metabolic risk factors were at particular risk for SSC after COVID-19.

Overall, COVID-19–related liver injury occurred in about one quarter of patients with CLD. This is in line with previous studies reporting elevated aminotransferases (AST/ALT) in patients with liver disease and COVID-19.[10,29,34] Although, indeed, AST/ALT elevations occurred in 60.0% of patients with CLD in our study, aminotransferase elevation was usually mild with less than 10% of patients with CLD exhibiting AST/ALT levels >3× ULN. This is in accordance with previous studies.[3,10,18]

Furthermore, a pronounced cholestatic pattern of liver injury was common in our patients with CLD and COVID-19, particularly in later stages of the disease: although approximately 20% of patients with CLD had ALP >2× ULN already after the first positive SARS-CoV-2 PCR test, suggesting relevant cholestasis, this number almost doubled over time, which indicates sustained cholestatic alterations. Moreover, our longitudinal observation shows that ALP, as well as GGT increases over the course of COVID-19 in patients with CLD and COVID-19, whereas AST/ALT decrease following an initial peak after SARS-CoV-2 infection. This conforms to the established view of a biphasic pattern of liver injury after SARS-CoV-2 infection.[8,23,24] Previous studies have reported elevated parameters of cholestasis in patients with CLD and COVID-19, particularly in patients with NAFLD[29,34]; however, this biphasic pattern has previously not been investigated in detail in patients with CLD. Importantly, the sustained elevation of ALP in patients with CLD was still present after exclusion of patients developing SSC, indicating progressive cholestasis in patients with CLD after COVID-19.

Furthermore, laboratory signs of cholestatic liver failure were observed in 23.1% of patients with CLD, and 15.4% developed SSC. Although there are few case reports of SSC after COVID-19,[3,25–27] the high prevalence of persistent cholestasis and SSC in patients with liver disease after COVID-19 has not yet been described. Importantly, the prevalence of SSC was significantly higher among patients with CLD and COVID-19 compared to the non-COVID pneumonia control group. This suggests that progressive cholestasis and bile duct alterations are indeed distinct for COVID-19 in patients who are critically ill with CLD, as these occur more frequently than in patients with CLD with non–COVID-19 pneumonia.

Of note, the development of progressive cholestasis in the context of SARS-CoV-2 infection was independent of preexisting liver disease severity, as there was no difference between patients with and without ACLD. However, among the patients with COVID-19–associated SSC, there was a high prevalence of patients with obesity and/or patients with NAFLD/NASH. All patients developing SSC had severe courses of COVID-19. Notably, these patients were relatively young patients, with one third being 18–39 years old and only one patient being 70 years old or older. Seven of 10 patients with CLD developing SSC had NAFLD/

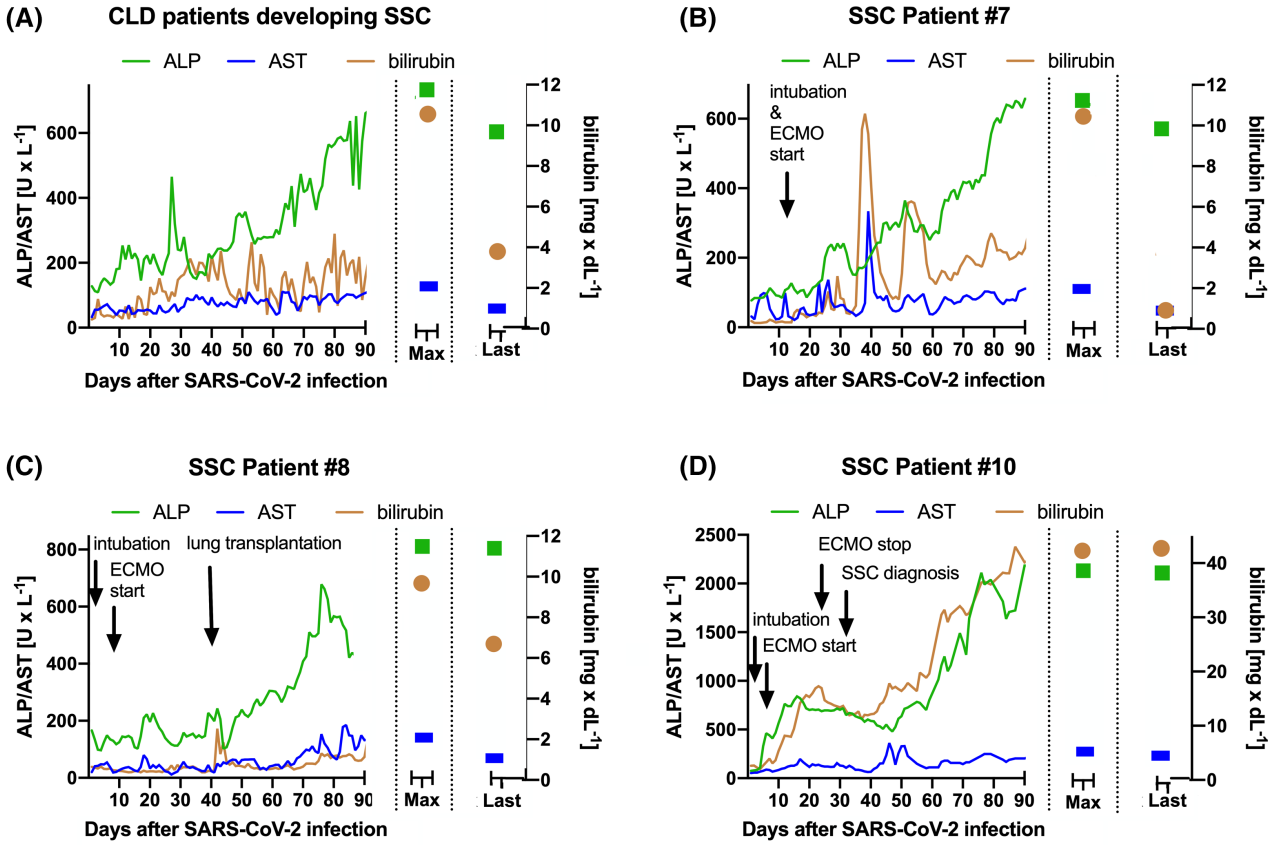

FIGURE 3 Trajectory of blood levels of liver chemistries in patients with chronic liver disease (CLD) and COVID-19, who developed secondary sclerosing cholangitis (SSC). Panel (A) represents the median levels of ALP, AST, and bilirubin of all patients with CLD, who developed SSC, whereas panels (B–D) show the trajectory of ALP, AST, and bilirubin in exemplary patients with CLD developing SSC. Next to the course over the first 90 days after severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) infection, the maximum value (Max), as well as the last available value (Last) are depicted. ALP, alkaline phosphatase; AST, aspartate aminotransferase; ECMO, extracorporeal membrane oxygenation; Last, last available value; Max, maximum value.

TABLE 4 Clinical outcomes of patients with chronic liver disease with and without elevated total bilirubin at COVID-19 diagnosis

Follow-up and clinical outcomes	Bilirubin > ULN (>1.2 mg/dl) (*n* = 12)	Bilirubin ≤ ULN (≤1.2 mg/dl) (*n* = 53)	*p* value
Median hospital stay, days (IQR)	58.0 (66.0)	21.0 (35.0)	**0.022**
ICU admission, *n* (%)	11 (91.7%)	17 (32.1%)	**<0.001**
Median ICU stay, days (IQR)	47.0 (59.0)	21.0 (24.0)	0.120
Intubation, *n* (%)	11 (91.7%)	14 (26.4%)	**<0.001**
Median duration of intubation, days (IQR)	41.0 (53.0)	19.5 (25.0)	**0.047**
Death, *n* (%)	9 (75.0%)	18 (34.0%)	**0.009**
COVID-19–related death, *n* (%)	9 (75.0%)	12 (22.6%)	**<0.001**
Liver-related death, *n* (%)	9 (75.0%)	2 (3.8%)	**<0.001**

Abbreviations: ICU, intensive care unit; IQR, interquartile range; ULN, upper limit of normal. Bold *p* values denote statistically significant difference.

NASH as an underlying liver disease, with high rates of obesity and arterial hypertension. Thus, it seems that development of SSC after SARS-CoV-2 infection is a relevant risk, particularly in patients with CLD with metabolic risk factors and/or NAFLD/NASH etiology.

It is generally known that patients who are critically ill and have long ICU stays are at higher risk for developing SSC,[35,36] as multiple risk factors for liver injury, including hypoxemia, endothelial dysfunction, coagulopathy, systemic inflammatory response syndrome (SIRS), ECMO and drug-induced liver injury[37–40] accumulate in these patients. Indeed, these risk factors for bile duct injury were present in the vast majority of patients with CLD developing SSC, with hypoxemia and SIRS due to ARDS in all patients and the need for ECMO in 80%. Moreover, 90% of patients with CLD

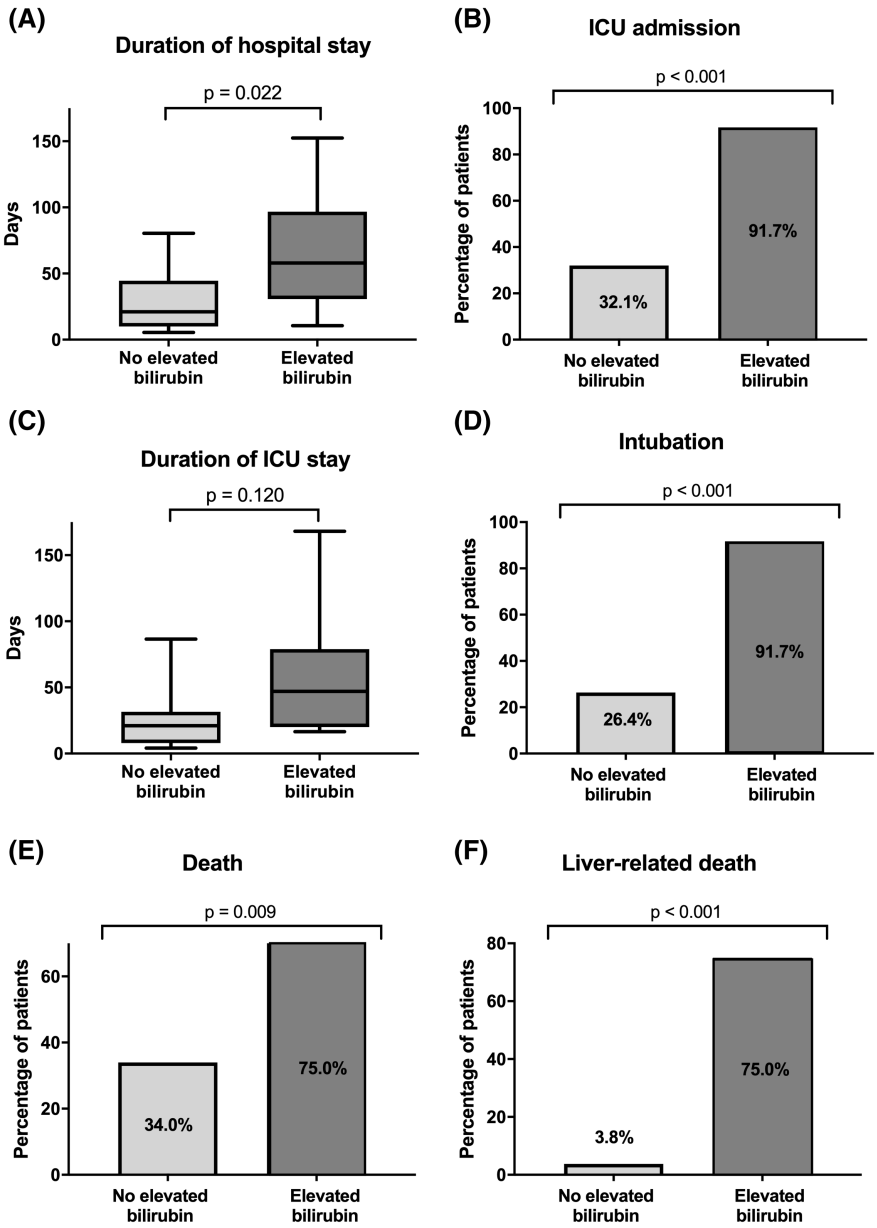

FIGURE 4 Duration of hospital stay and rates of intensive care unit (ICU) admission, intubation, and death in patients with chronic liver disease and COVID-19 according to bilirubin levels. Comparison of (A) duration of hospital stay, (B) rate of ICU admission, (C) duration of ICU stay, (D) rate of mechanical ventilation, (E) rate of death, and (F) rate of liver-related death in patients with liver disease and COVID-19 with and without elevated total bilirubin (BIL ≥1.2 mg/dl) after first positive severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test. The borders of the whiskers are the 10th and the 90th percentile. Group comparison via (A, C) Mann–Whitney *U* test and (B, D–F) Fisher's exact test.

developing SSC were treated with ketamine, which is strongly linked to drug-induced liver injury.[39,41–43] Furthermore, there might also be direct injury of hepatocytes and cholangiocytes by SARS-CoV-2.[3,44] Thus, the sustained elevation of cholestatic parameters and bile duct alterations may be explained by multifactorial liver and bile duct injury in patients who are critically ill with CLD and COVID-19. Of note, SSC takes time to develop.[35,36] Fittingly, patients with CLD and cholestatic liver failure who did not show signs of SSC had shorter time of follow-up, mostly due to earlier death.

Importantly, elevated bilirubin after first positive SARS-CoV-2 PCR test predicted liver-related death among patients with CLD and COVID-19. Bilirubin has been identified a valuable prognostic marker in overall cohorts of patients with COVID-19,[22,24] which also seems to be true in patients with COVID-19 and preexisting CLD. This is expected, as cholestasis and bilirubin elevation are known to develop in patients who are critically ill because of hepatic transport and metabolism alterations, resulting in impaired bile flow and bile acid retention.[45–47] Thus, bilirubin levels should be (re)assessed in patients with

CLD developing COVID-19, and those with elevated bilirubin should be closely monitored.

In line with the literature,[30,31,33] mortality among patients with ACLD was particularly high in our cohort with 27.8% of included patients with ACLD experiencing a decompensation event during or after COVID-19. Despite high rates of mortality among patients with CLD in our cohort, CLD was not a risk factor for mortality in this study. This is probably due to the relatively small sample size of patients with CLD. Of note, well-established risk factors for mortality in patients with COVID-19 also independently predicted survival in our study.

Our study also has limitations: First, because of the retrospective study design, selection bias cannot be ruled out. Moreover, some parameters were not available at all time points. However, by only including well-characterized inpatients with COVID-19, we are confident that our data is reflective of the clinical scenario of hospitalized patients with CLD and COVID-19. Concerning Pre values, we did not discriminate, whether these values were obtained in the context of an outpatient visit or a previous hospitalization, which is a potential confounding factor. Moreover, we did not correct the Cox proportional hazard models for multiple testing, potentially impairing their reproducibility. However, the results are in line with several previous studies, identifying particularly elevated bilirubin as a predictor for poor outcome in patients with COVID-19.[18,22,24] Finally, external validation of our results is required due to our monocentric study design.

In conclusion, we observed a progressive pattern of cholestatic liver injury in a cohort of patients predominantly with NAFLD/NASH with CLD and COVID-19. About one quarter of patients with CLD and COVID-19 developed laboratory signs of cholestatic liver failure and 15.4% were diagnosed with SSC. SSC was indeed more frequent in patients with CLD who were infected with SARS-CoV-2 than in a matched control group of patients with CLD and non–COVID-19 pneumonia. Elevated bilirubin was identified as a strong risk factor for liver-related death among patients with CLD and COVID-19.

AUTHOR CONTRIBUTIONS

All authors contributed either to research design (Lukas Hartl and Thomas Reiberger) and/or the acquisition (Lukas Hartl, Katharina Haslinger, Martin Angerer, Ernst Eigenbauer, Katharina Lampichler, Ahmed Ba-Ssalamah, and Thomas Reiberger), analysis (Lukas Hartl and Thomas Reiberger), or interpretation (all authors) of data. Lukas Hartl, Thomas Reiberger, and Michael Trauner drafted the manuscript, which was critically revised by all other authors.

CONFLICTS OF INTEREST

Dr. Simbrunner received grants from Gilead and AbbVie. Dr. Trauner consults for, is on the speakers' bureau for, and received grants from Falk, Intercept, Gilead, and MSD. He consults for and received grants from Alberio. He consults for BiomX, Boehringer Ingelheim, Genfit, Janssen, Novartis, Shire, Phenex, and Regulus. He received grants from Cymabay, Takeda, Alnylam, Ultragenyx, and AbbVie. He is the coinventor of patents on the medical use of 24-norursodesoxycholic acid. Dr. Mandorfer consults for, advises, is on the speakers' bureau for, and received grants from AbbVie and Gilead. He consults for, advises, and is on the speakers' bureau for Collective Acumen and W.L. Gore & Associates.

ETHICS

The study was approved by the Ethics Committee (EC) of the Medical University of Vienna. It was performed according to the current version of the Helsinki Declaration. Due to the retrospective study design, the need for informed consent was waived by the EC.

DATA AVAILABILITY STATEMENT

Anonymized individual patient data will be made available to interested investigators at the discretion of all authors. Data requests should be sent to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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