Secondary sclerosing cholangitis following COVID-19 disease: a multicenter retrospective study

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ABSTRACT

Background: Secondary sclerosing cholangitis (SSC) is a rare disease with poor prognosis. Cases of SSC have been reported following coronavirus disease 2019 (COVID-19), COVID-SSC.

Aims: Aim of this study was to compare COVID-SSC to SSC in critically ill patients (SSC-CIP) and to assess factors influencing transplant-free survival.

Methods: In this retrospective, multicenter study involving 127 patients with SSC from 9 tertiary care centers in Germany, COVID-SSC was compared to SSC-CIP and logistic regression analyses were performed investigating factors impacting transplant-free survival.

Results: 24 patients had COVID-SSC, 77 patients SSC-CIP and 26 patients had other forms of SSC. COVID-SSC developed after a median of 91 days following COVID-19 diagnosis. All patients had received extensive intensive care treatment (median days of mechanical ventilation 48). Patients with COVID-SSC and SSC-CIP were comparable in most of the clinical parameters and transplant-free survival was not different from other forms of SSC (P=0.443 in log-rank test). In the overall cohort, the use of ursodeoxycholic acid (UDCA, OR 0.36, 95%-CI 0.16-0.80, P=0.013; P<0.001 in log-rank test) and high serum albumin levels (OR 0.40, 95%-CI 0.17-0.96, P=0.040) were independently associated with an increased transplant-free survival, while the presence of liver cirrhosis (OR 2.52, 95%-CI 1.01-6.25, P=0.047) was associated with worse outcome. MDRO colonization or infection did not impact patients' survival.

Conclusions: COVID-SSC and CIP-SSC share the same clinical phenotype, course of the disease and risk factors for its development. UDCA may be a promising therapeutic option in SSC, though future prospective trials need to confirm our findings.

Key words: SARS-CoV-2, cirrhosis, cholangiopathy, intensive care unit, multidrug-resistance.

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INTRODUCTION

Secondary sclerosing cholangitis (SSC) is a progressive cholestatic biliary disease which may lead to biliary cirrhosis and liver failure.[1, 2] As an acquired disease, it may develop following different insults on the biliary tree such as ischemia, (biliary) infections, chronic biliary obstruction, toxic effects or immunologic processes.[2] SSC in critically ill patients (SSC-CIP) has been increasingly described and may occur during or following intensive care unit (ICU) treatment in patients without history of prior biliary or liver disease.[3, 4] While no clear trigger can be identified, ischemic injury is believed to play a key role in its initial development.[5] Then, subsequent biliary cast formation with biliary obstruction and recurrent infections are considered the most important pathogenetic drivers of the disease leading to liver fibrosis and even cirrhosis with high mortality rates and a mean transplant-free survival of 13-16 months.[1, 6]

Biliary infections are a common complication in patients with SSC and cholangiosepsis is associated with high mortality rates. Besides the elimination of biliary obstructions, antibiotic therapy plays a pivotal role in these situations.[2, 7] However, recurrent use of antibiotics may lead to the development of multidrug-resistant organisms (MDROs). At the time of SSC-CIP diagnosis, patients may already have acquired MDROs during their intensive care unit stay and are even more vulnerable to MDRO infections.[8] So far, data on the prevalence of MDRO colonization at SSC diagnosis or rates of de-novo MDRO colonization or infections during follow-up are scare. Yet, this information may be critical to guide empirical antibiotic therapy. Additionally, ursodeoxycholic acid (UDCA) is often used in analogy to patients with other chronic biliary disease, e.g. primary biliary cholangitis (PBC).[9] However, UDCA could not slow disease progression in patients with primary sclerosing cholangitis (PSC).[10] Data on UDCA in patients with SSC is limited, yet besides endoscopic biliary cast extraction, UDCA is often used as there are limited therapeutic options in these patients.

Since the emergence of the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19), an ongoing global pandemic has led to

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millions of hospitalizations and more than 4,4 million deaths world-wide.[11] While most COVID-19 patients present with mild flu-like symptoms the development of severe pneumonia resulting in respiratory distress syndrome (ARDS) and organ failure are nowadays a common reason for ICU admission.[12] Most recently, cases of a cholestatic liver disease following ICU stay for COVID-19 have been reported.[13, 14] In these case reports patients presented with similar clinical findings as patients with SSC. A new entity of SSC, SSC precipitated by COVID-19 (COVID-SSC), has been proposed. Interestingly, relevant elevation of liver enzymes, especially alkaline phosphatase (AP) and gamma-glutamyltransferase (GGT), have been described following COVID-19 in patients with and without ICU stay.[15, 16] Thus, it remains unclear if COVID cholangiopathy may be the result of the ICU stay itself – similar to other forms of SSC-CIP – or caused by SARS-CoV-2 leading to a COVID-19 associated cholangiopathy, or a composition of both. So far, only small case series have described patients with COVID-SSC, comparative data to other patients with SSC, especially SSC-CIP are still lacking.

Aim of our multicenter study was to collect data on COVID-SSC patients, to better understand the disease and compare it to other forms of SSC and to assess the impact of MDRO colonization and infection and other factors on the course of SSC disease.

PATIENTS AND METHODS

Study design. This is a retrospective, multicenter study including patients with the established diagnosis of SSC from different tertiary care centers in Germany. Patients from Frankfurt and eight other University Hospitals could be included: Aachen, Cologne, Hamburg, Leipzig, Muenster, Freiburg, Schleswig-Holstein and Wuerzburg (alphabetical order).

SSC was diagnosed by a typical clinical course including an acute deterioration of liver function (i.e. serum bilirubin > 3x ULN, serum GGT > 3x ULN or AP> 3x ULN) with concomitant SSC-typical findings such as strictures or dilatation of the biliary system, rarefication of the biliary tree including contrast filling defects or detection of biliary casts on either of the following modalities:

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endoscopic retrograde cholangiography (ERC), magnetic resonance imaging (MRI), and/or histology. If the diagnosis of SSC remained unclear on MRI, ERC was required to ensure correct diagnosis. Patients had to be eighteen years and older. SSC-CIP was defined as SSC newly diagnosed during or following ICU treatment. COVID-SSC was defined as SSC according to above named criteria in patients with a recently obtained positive COVID-19 test via polymerase chain reaction the onset and course of the disease were associated, and no other cause for SSC could be identified.

The local ethics committee approved this study (vote2021-125).

Patients with SSC were categorized into three groups SSC-CIP, COVID-SSC or SSC due to other causes. Additional Information on identification of patients, exclusion criteria, data collection, definition of multidrug-resistance and statistical analyses can be found in the supporting information (SI).

RESULTS

Patient characteristics. A total of 127 patients from 9 different tertiary care hospitals in Germany were included. SSC was diagnosed by ERC in 120 patients (94.5%) and in 7 cases by MRI. The median follow-up time was 141 days (IQR 489 days). Patients' characteristics are depicted in Table 1. The majority of patients was male (73.2%) with a median age of 61 years (range 19-87 years). 77 patients (60.6%) had SSC-CIP and 24 patients (18.9%) COVID-SSC. Other forms of SSC included chronic biliary obstruction (n=10, 7.9%), ischemia (n=9, 7.1%) and recurrent cholangitis (n=3, 2.4%). Most patients presented with jaundice (n=100, 78.7%) and about a quarter of patients reported pruritus, abdominal pain or fever. Cholestasis was present among 83 patients (65.4%) upon SSC diagnosis, 12 patients (9.4%) had already an abscess or biloma. Among laboratory values bilirubin (median 8.8 mg/dl, IQR 14.1 mg/dl), GGT (median 934 U/l, IQR 1090 U/l) and AP (median 902 U/l, IQR 708 U/l) were markedly elevated. Liver cirrhosis was present at diagnosis in 28 patients (22.0%), 13 patients (10%) presented with relevant signs

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of portal hypertension. Supplementary Table 1 shows characteristics of patients with SSC that were neither categorized as COVID-SSC nor SSC-CIP. Overall, 84 patients (66.1%) received UDCA therapy at a dose of 13.6 mg (IQR 5.2 mg) per kg total body weight. Almost all patients received and ERC (94.5%), Sphincterotomy was performed in 108 patients (85.0%), cast extraction was possible in more than half of the patients (54.3%). 27 patients (21.3%) had a dominant stricture where bougienage/balloon dilation was performed.

Patients with COVID-SSC were diagnosed with COVID-19 between February 2020 and May 2021. SSC was detected after a median of 91 (IQR 90) days after COVID-19 diagnosis and all patients were COVID-negative at the time of diagnosis (median time from negative test to SSC diagnosis 47 days, IQR 60 days, n=15). Laboratory values and patient characteristics upon COVID-19 diagnosis are presented in Table 2. All patients were treated on an ICU, had received vasopressor therapy and mechanical ventilation, with a median number of 48 (IQR 44) days of mechanical ventilation. More than half of them needed renal replacement therapy (60.1%) and 10 patients (7.9%) required ECMO therapy for a median of 21 (IQR 21) days. Sixteen patients (72.7%) received dexamethasone for COVID-19 disease, only a minority received other drugs such as Tocilizumab (n=3, 13.6%) or convalescent plasma therapy (n=2, 9.1%).

As SSC following COVID-19 had been reported especially in patients with long ICU stay we compared patients with COVID-SSC and those with SSC-CIP. Age, gender, laboratory values and initial clinical findings and symptoms were similar between both groups. Duration of initial ICU stay and days until diagnosis of SSC were comparable (p=0.159, and p=0.116 exact dates reported in all COVID-SSC and n=58 and n=56 SSC-CIP patients, respectively). Patients with COVID-SSC were more likely to have diabetes mellitus (P=0.006), and had less often coronary artery disease (p=0.019) or cerebrovascular disease (P=0.006). Liver cirrhosis was rarely found upon diagnosis (4.2% vs. 28.3%, P=0.021) in patients with COVID-SSC.

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Role of biliary infection and MDRO colonization and infection. Cholangitis occurred often in patients with SSC (n=92, 72.4%) and cholangitis was frequently present upon diagnosis (n=58, 45.7%), 22 patients (17.3%) presented with cholangiosepsis. Gram-positive isolates were more likely to be found in bile than gram-negative isolates. Fungi were detected in 26 patients (20.5%). Upon diagnosis of SSC, three quarter of patients were screened for MDRO colonization.

Supplementary Table 2 depicts detailed results of MDRO screening results. MDRO were detected in 35.8% of patients with VRE being the most frequent MDRO in rectal swaps (15.8%) followed by AmpC-resistant Enterobacteriaceae (9.5%) and ESBL E. coli (5.3%). Rates of MDRO colonization were similar between patients with COVID-SSC, SSC-CIP and others. Only half of the patients were screened for MDRO during follow-up. Yet in 54% of cases a new MDRO was found in the course of the disease. Again, VRE (26.5%), but also carbapenem resistant gram-negative MDRO (22.1%) were the most frequent MDROs found upon screening.

Overall, 41 patients (32.3%) developed MDRO infection during follow-up. The most frequent isolates were VRE (in 15.0% of patients), AmpC-resistant Enterobacteriaceae (in 6.3% of patients) and carbapenem resistant gram-negative MDRO (in 4.7% of patients). The majority of MDRO infection were isolated in bile (41.5%) and blood (26.8%) cultures. Patients who were colonized with MDRO were more likely to develop MDRO infection than those without MDRO colonization (51.7% vs. 14.9%, P=0.0001). Overall, in 62.2% of cases, at least one of the MDRO that caused the infection had already been detected in a previous screening.

Factors associated with transplant-free survival. The median survival of the overall cohort was 22 months. Forty-five patients (35.4%) died and 18 patients (14.2%) received a liver transplantation (3 of them with COVID-SSC) during follow-up. Liver transplantation for SSC was performed after a median of 93 (IQR 376) days from SSC diagnosis.

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To investigate factors for liver transplantation or death uni- and multivariate logistic regression analysis was performed (Table 3). As many laboratory values may be influenced by a preexisting medical condition a separate analysis was performed for laboratory values (model 2). Among laboratory values, higher baseline bilirubin levels (OR 1.11, 95% CI 1.04-1.18; P<0.001) were associated with increased mortality, while higher albumin levels were beneficial (OR 0.40, 95% CI 0.17-0.96, P=0.040). Liver cirrhosis present at diagnosis of SSC was an independent risk factor for liver transplantation or death (OR 2.52, 95% CI 1.01-6.25, P=0.047). Neither MDRO colonization at baseline nor during follow-up was associated with increased mortality (OR 1.56, P=0.275; OR 1.44, P=0.352). Kaplan Meier analysis showed numerically more deaths among patients with MDRO infections (SI Figure 1), however this was not statistically significant (P =0.143, log-rank test; OR 1.09, 95% CI 0.51-2.32, P=0.821 in logistic regression analysis).

Most interestingly, the use of additional UDCA therapy for patients with SSC was associated with increased transplant-free survival in uni- and multivariate analysis (OR 0.44, 95% CI 0.21-0.94, P=0.035 and OR 0.36, 95% CI 0.16-0.80, P=0.013). Kaplan Meier curve of patients with and without UDCA therapy is depicted in Figure 1A. Patients with UDCA therapy showed a significantly increased transplant-free survival in comparison to patients not on UDCA therapy (P<0.001, log-rank test). When parameters influencing mortality was compared between groups (UDCA vs. no UDCA) both groups were comparable with respect to preexisting medical conditions or laboratory values at baseline (Supplementary Table 3) Patients receiving UDCA were more likely to have liver cirrhosis upon diagnosis (p=0.013), but were less likely to have received bile duct stenting (p=0.002) and serum albumin was slightly higher (p=0.025). Of note, the effect on survival was even more pronounced when patients after long ICU stay only (i.e. COVID-SSC and CIP-SSC patients) were analyzed (p=0.0001, Figure 1B). When the subgroup of patients limited to COVID-SCC were looked at, there was no significant difference between those with and without UDCA therapy. Similarly, in the subgroup of patients with other forms of

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SSC, UDCA had no effect on survival though the numbers in both subgroups were small (data not shown).

Figure 1C shows overall survival of patients with COVID-SSC and patients with SSC-CIP. There was no significant difference between transplant-free survival (P=0.443, long-rank test). Similar results were observed when COVID-SSC patients were compared with all other SSC patients (Supplementary Figure 1: P=0.216, log-rank test; and logistic regression analysis Table 3: P=0.424 in univariate analysis).

DISCUSSION

In this retrospective, multicenter study we present data on 24 patients with COVID-19 associated SSC from nine tertiary care centers in Germany. So far, only case reports or case series have been reported on COVID-SSC.[13, 14, 16-19]

It still is an ongoing debate if COVID-SSC is the result of the ICU stay itself or constitutes a disease on its own following COVID-19 associated cholangiopathy, or both. In our cohort, patients with COVID-SSC were more likely to have diabetes mellitus – similar results were observed from a group in Zurich with COVID-19 associated cholangiopathy with severe cholestasis (P=0.007)[16] – and had less often coronary artery disease or cerebrovascular disease. Interestingly, liver cirrhosis was rarely found upon SSC diagnosis in our cohort which might be due to an earlier diagnosis of SSC in these patients or due to other still unknown reasons. Yet, patients with COVID-SSC and SSC-CIP shared the same clinical phenotype in most other clinical aspects. Moreover, similar to previous case series, patients with COVID-SSC were critically ill and required extensive intensive care treatment, often involving prolonged mechanical ventilation, the use of vasopressor and renal replacement and/or ECMO therapy. Treatment outcome was not significantly different between both entities. Thus, despite possible – not yet fully understood – differences in its pathogenesis, patients with severe post-COVID-19 cholangiopathy leading to SSC shared the same clinical phenotype upon diagnosis as SSC-CIP

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patients and both entities were comparable with regards to the clinical course of the disease and possible risk factors for its development.

In a case series from Manhasset, NY, USA, three patients with COVID-19 associated SSC were described.[18] Here, liver biopsy was performed and the authors claimed to have found unique histologic features including severe cholangiocyte injury and intrahepatic microangiopathy that they believe were suggestive of direct hepatic injury from COVID-19. They proposed that post-COVID-19 cholangiopathy may represent a confluence of SSC-CIP and direct liver injury from COVID-19.[18] While, attribution to SARS-CoV-2 remained indirect in this study, a recent report has established a clear link to SARS-CoV-2 and liver tropism.[20] In a retrospective study from the University Hospital in Zurich,[16] four patients with COVID-19 developed SSC, yet they reported numerous other patients with cholangiopathy who developed mild to severe cholestasis following COVID-19 compared to none in an influenza A comparative cohort. Yet, all of the patients reported with SSC after COVID-19 were critically ill and required mechanical ventilation, vasopressor therapy and often renal replacement or ECMO therapy[16-18] – all features often seen in patients with SSC-CIP.

In the overall cohort, MDRO colonization was rather frequent: One third of patients was already an MDRO carrier upon SSC diagnosis and de novo colonization occurred in half of the patients screened during follow-up. Similarly, high MDRO rates have been reported in other critically il patients.[21, 22] In our study, MDRO infections were much more frequent among MDRO carriers than those without MDRO colonization. MDRO infection were often caused by the same MDRO that colonized the patient. This highlights the importance of continuous MDRO monitoring via rectal swabs in these critically ill patients to guide empirical antibiotic therapy if cholangitis or cholangiosepsis occur. Interestingly, neither MDRO colonization nor MDRO infection impacted transplant-free survival, as it has been reported in other diseases.[23-25] One possible explanation might be that the high rate of MDRO screening in this cohort may have – at least partially –

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contributed to tailor effective empiric antibiotic therapy in case of an infection. However, this remains speculative.

Interestingly, the use of UDCA (median dose of 13.6 mg/kg TBW) daily was associated with increased transplant-free survival in our overall study cohort while other patients' characteristics possibly influencing mortality were fairly comparable among those with and without UDCA. Moreover, this effect was even more evident in the cohort including only patients with SSC following ICU stay (COVID-SSC and SSC-CIP). UDCA is widely used in chronic biliary disease and has been proven to reduce disease progression and mortality in patients with PBC.[9] However, in patients with PSC no beneficial impact on the course of the disease has been observed with UDCA, while norUDCA might be a future treatment option in these patients.[10, 26] As SSC is a rare disease, data on the use of UDCA is still limited in these patients. So far, no study has systematically investigated the impact of UDCA in SSC patients, though it is often used based on pathophysiological considerations. Our data provides, for the first time, some evidence, that UDCA might be beneficial in these patients. This effect was not shown in the COVID-SSC cohort, though the numbers of patients were low in this subgroup. Of note, due to the nature of a retrospective study the beneficial effects of UDCA are only associative, no causality can be proven and the observed effects are prone to selections bias. Thus, future prospective trials are needed to support our observation.

A limitation of our study is its retrospective design. Data were retrieved from clinical charts and were prone to information bias. Additionally, there was only a limited number of patients with SSC, especially COVID-SSC, that could be included. However, data from this multicenter study is particularly relevant, as SSC is a rare disease and data on SSC and COVID-SSC is scarce as no prospective trials and with respect to COVID-SSC only a few case reports exist.

In conclusion, our multicenter retrospective study presents – for the first time – characteristics and outcome on a relevant number of patients with SSC following COVID-19. Patients with severe post-COVID-19 cholangiopathy leading to SSC were comparable to patients with SSC-

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CIP patients with regards to the clinical course of the disease and possible risk factors for its development. MDRO colonization and infections occurred frequent in the overall SSC cohort and MDRO carriers were prone to MDRO infection. UDCA was associated with an improved transplant-free survival in the overall cohort. Future prospective trials are needed to further validate our observations.

Notes

Abbreviations: AP, alkaline phosphatase; CI, confidence interval; CIP, critical ill patients; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ERC, endoscopic retrograde cholangiography; ESBL, extended-spectrum beta-lactamase; GGT, gamma-glutamyltransferase; ICU, intensive care unit; MDRO, multidrug-resistant organism; MRI, magnetic resonance imaging; MRSA, methicillin resistant staphylococcus aureus; OR, Odds ratio; PBC, primary biliary cholangitis; PSC, primary sclerosis cholangitis; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; SSC, secondary sclerosing cholangitis; UDCA, ursodeoxycholic acid; VRE, vancomycin-resistant *Enterococcus spp*.

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Author contributions:

The authors have contributed to the manuscript by planning the study (PH, OW, MMM), collecting the data (all authors), performing the analyses (PH, MMM), and assessment and interpretation of the data (all authors). MMM wrote the manuscript and all authors read, revised and approved the final version of the manuscript.

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TABLES

Table 1. Patients' characteristics at SSC diagnosis.

Characteristics	All Patients (n=127)	COVID-SSC Patients (n=24)	SSC-CIP Patients (n=77)	P
Age, y, median (range)	61 (19-87)	57 (19-73)	60 (19-87)	0.658
Male sex, n (%)	93 (73.2)	20 (83.3)	55 (71.4)	0.230
Etiology SSC				
Chronic biliary obstruction, n (%)	10 (7.9)			
Recurrent cholangitis, n (%)	3 (2.4)			
Ischemic, n (%)	9 (7.1)			
SSC-CIP, n (%)	77 (60.6)		77 (100)	
COVID-SSC, n (%)	24 (18.9)	24 (100)		
other, n (%)	4 (3.1)			
Baseline chronic diseases, n (%)				
Diabetes mellitus	40 (31.5)	14 (58.3)	20 (26.0)	**0.006**
Chronic obstructive lung disease	16 (12.6)	2 (8.3)	11 (14.3)	0.728
Heart failure	22 (17.3)	3 (12.5)	16 (20.8)	0.551
Arterial hypertension	83 (65.4)	16 (66.7)	51 (66.2)	1.0
Coronary artery disease	31 (24.4)	2 (8.3)	25 (32.5)	**0.019**
Chronic kidney disease	25 (19.7)	3 (12.5)	16 (20.8)	0.392
Cerebrovascular disease	40 (31.5)	2 (8.3)	29 (37.7)	**0.006**
Body weight at baseline [kg]	80.0 (22.5)	80.0 (28.0)	80.0 (20.8)	0.660
Body mass index at diagnosis (n=69)	25.2 (7.3)	26.2 (13.1)	25.3 (8.0)	0.409
Laboratory values at the time of SSC diagnosis				
Serum Sodium (mmol/l)	137 (6)	134 (9)	137 (7)	0.107
Creatinine (mg/dl)	1.0 (1.6)	1.0 (1.6)	1.0 (2.0)	0.965
Bilirubin (mg/dl)	8.8 (14.1)	11.9 (18.3)	8.9 (13.4)	0.358
Aspartate aminotransferase (UI/l)	120 (106)	133 (148)	121 (102)	0.956
Alanine aminotransferase (UI/l)	97 (122)	101 (163)	105 (111)	0.662
Gamma-glutamyltransferase (UI/l)	934 (1090)	856 (1212)	986 (993)	0.770
Alkaline Phosphatase (U/l)	902 (708)	925 (546)	970 (812)	0.707
International normalized ratio	1.1 (0.2)	1.1 (0.2)	1.1 (0.3)	0.971
Albumin (g/dl)	2.7 (1.1)	2.6 (1.6)	2.6 (1.1)	1.0
Platelets (/nl)	288 (196)	287 (128)	293 (230)	0.628
C-reactive protein (mg/dl)	5.9 (10.1)	9.4 (32.1)	6.4 (7.9)	0.645
Leukocytes (/nl)	10.0 (7.7)	9.7 (7.7)	11.2 (8.0)	0.539
Liver cirrhosis present at diagnosis, n (%)	28 (22.0)	1 (4.2)	21 (27.3)	**0.021**
Ascites, n (%)	26 (26.0)	3 (12.5)	20 (26.0)	0.265
Esophageal varices, n (%)	13 (10.2)	1 (4.2)	8 (10.4)	0.682
Initial symptoms				
Jaundice, n (%)	100 (78.7)	21 (87.5)	63 (81.8)	0.756
Pruritus, n (%)	33 (26.0)	5 (20.8)	22 (28.6)	0.600
Abdominal pain, n (%)	31 (24.4)	7 (29.2)	17 (22.1)	0.583
Fever, n (%)	32 (25.2)	5 (20.8)	23 (29.9)	0.445
MDRO colonization/infection	95 (74.8)	16 (66.7)	63 (81.8)	0.156
Initial MDRO colonization, n (%)	34 (35.8)	6 (37.5)	23 (36.5)	1.0
MDRO colonization follow-up, n (%)	37 (54.4)	6 (54.5)	25 (54.3)	0.615
MDRO infection follow-up, n (%)	41 (32.3)	9 (37.5)	25 (32.5)	0.805
ERC performed, n (%)	120 (94.5)	22 (91.7)	75 (97.4)	0.239
Dominant stricture, n (%)	27 (21.3)	6 (25.0)	13 (16.9)	0.381
Sphincterotomy, n (%)	108 (85.0)	20 (83.3)	69 (89.6))	0.472
Bougienage, n (%)	7 (5.5)	0 (0)	5 (6.5)	0.335
(ballon)dilation, n (%)	21 (16.5)	6 (25.0)	9 (11.7)	0.184
Cast extraction, n (%)	69 (54.3)	11 (45.8)	48 (62.3)	0.168
Stenting, n (%)	36 (28.3)	9 (37.5)	19 (24.7)	0.296
Number of ERCPs during stay	2 (2)	2 (2)	2 (2)	0.637
UDCA therapy, n (%)	84 (66.1)	16 (66.7)	50 (64.9)	0.458
UDCA total dose [mg/d] (n=83)	1000 (500)	1000 (400)	1000 (500)	0.635
UDCA dose: mg per kg/TBW (n=62)	13.6 (5.2)	14.6 (9.5)	13.1 (4.0)	0.567

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Data is given as median (IQR), unless otherwise specified.
Abbreviations: COVID-SSC, SSC following COVID-19 disease; ERC, endoscopic retrograde cholangiography; MDRO, multidrug-resistant organism; SSC, secondary sclerosing cholangitis; SSC-CIP, SSC in critically ill patients; TBW, total body weight; UDCA, ursodeoxycholic acid.

Table 2. Characteristics of patients with secondary sclerosing cholangitis following COVID-19 disease from their initial hospital stay following COVID-19 diagnosis.

Characteristics	All Patients (n=24)
Date of COVID-19 diagnosis	02/2020-05/2021
Days from COVID-19 diagnosis to diagnosis of SSC	91 (90)
Laboratory values at hospital admission following COVID-19 diagnosis^	
Serum Sodium (mmol/l)*	133 (9)
Creatinine (mg/dl)*	1.4 (1.4)
Bilirubin (mg/dl)*	0.6 (0.5)
Aspartate aminotransferase (UI/l)[#]	65 (70)
Alanine aminotransferase (UI/l)[#]	45 (39)
Gamma-glutamyltransferase (UI/l)*	54 (85)
Alkaline Phosphatase (U/l)[#]	58 (28)
International normalized ratio*	1.0 (0.1)
Albumin (g/dl)[#]	2.5 (1.1)
Platelets (/nl)*	241 (154)
C-reactive protein (mg/dl)*	12.5 (10.1)
Leukocytes (/nl)*	10.0 (5.4)
Peak ferritin during COVID hospital stay (ng/ml)[$]	2397 (3299)
Peak d-dimer during COVID hospital stay (µg/l)[$]	8600 (13.080)
Vasopressor therapy[?] during ICU stay, n (%)	20 (100)
Renal replacement therapy during hospital/ICU stay, n (%)	14 (58.3)
Mechanical ventilation[+], during ICU stay, n (%)	22 (100)
Number of days	48 (44)
ECMO therapy[+], during ICU stay, n (%)	10 (43.5)
Number of days	21 (21)
Prophylactic anticoagulation with UFH/LMWH, n (%)	12 (50.0)
Therapeutic anticoagulation with UFH/LMWH, n (%)	12 (50.0)
Acetylsalicylic acid[*], n (%)	9 (37.5)
ADP-receptor antagonist[*], n (%)	2 (8.3)
COVID-19-specific therapy° during hospital stay	
Dexamethasone, n (%)	16 (72.7)
Hydroxychloroquine, n (%)	1 (4.5)
Tocilizumab, n (%)	3 (13.6)
Remdesevir, n (%)	1 (4.5)
Convalescent plasma therapy	2 (9.1)
Discharged after initial hospitalization for COVID-19, n (%)	13 (54.6)
Days of hospitalization, overall cohort[?]	82 (47)
Days on ICU, overall cohort[?]	58 (45)

Data presented as median and interquartile range, unless otherwise specified.
^if COVID-19 was diagnosed during hospitalization, data is from the date of COVID-19 diagnosis; no data on the variants that caused COVID-19 was available *Data available in n=19 patients; [#]Data available in n=17 patients; [$]Data available in n=13 patients; [?]Data available in n=20 patients; [+]Data available in n=23 patients; °Data available in n=22 patients; *Abbreviations*: ECMO, extracorporeal membrane oxygenation; LMWH, low molecular weight heparin; SSC, secondary sclerosing cholangitis, UFH, unfractionated heparin.

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Table 3. Uni- and multivariate logistic regression analysis investigating risk factors for liver transplantation or death.

Variables	Univariate Analysis		Multivariate Analysis	
Model 1	**OR (95% CI)**	**P Value**	**OR (95% CI)**	**P Value**
Age	1.01 (0.99-1.04)	P=0.301		
Gender, female	1.12 (0.51-2.50)	P=0.767		
Preexisting medical condition				
Chronic obstruct. pulmonary disease	2.27 (0.76-6.74)	P=0.436		
Diabetes mellitus	1.35 (0.63-2.88)	P=0.146		
Chronic renal impairment	2.14 (0.87-5.27)	P=0.097		
Chronic heart failure	1.60 (0.63-4.06)	P=0.134		
Arterial hypertension	1.28 (0.61-2.70)	P=0.516		
Coronary artery disease	1.02 (0.45-2.31)	P=0.972		
Cerebrovascular disease	0.55 (0.25-1.20)	P=0.068		
Liver cirrhosis present at SSC diagnosis	1.89 (0.80-2.57)	P=0.149	2.52 (1.01-6.25)	**P=0.047**
COVID-19 disease	0.69 (0.27-1.72)	P=0.424		
MRDO status				
MDRO colonization at baseline	1.56 (0.70-3.45)	P=0.275		
MDRO colonization during follow-up	1.44 (0.67-3.13)	P=0.352		
MRGN infection	1.09 (0.51-2.32)	P=0.821		
UDCA therapy for SSC	0.44 (0.21-0.94)	**P=0.035**	0.36 (0.16-0.80)	**P=0.013**
Model 2				
Sodium	0.97 (0.89-1.07)	P=0.551		
Creatinine	1.37 (1.02-1.86)	**P=0.039**		
Bilirubin, baseline	1.11 (1.05-1.18)	**P<0.001**	1.11 (1.04-1.18)	**P<0.001**
Aspartate aminotransferase	1.01 (1.00-1.01)	**P=0.046**		
Alanine aminotransferase	1.0 (0.99-1.00)	P=0.523		
Gamma-glutamyltransferase	0.99 (0.99-1.00)	P=0.820		
Alkaline phosphatase, baseline	1.00 (0.99-1.00)	P=0.350		
Albumin	0.31 (0.15-0.64)	**P=0.001**	0.40 (0.17-0.96)	**P=0.040**
International normalized ratio	1.70 (0.72-3.99)	P=0.220		
Platelets	1.00 (0.99-1.00)	P=0.162		
Leucocytes	1.02 (0.95-1.10)	P=0.550		
C-reactive protein	1.07 (1.00-1.14)	**P=0.045**		
Bilirubin, at discharge	0.98 (0.94-1.03)	P=0.495		
Alkaline phosphatase, at discharge	0.99 (0.99-1.00)	**P=0.047**	0.99 (0.99-1.00)	P=0.052

Note: Laboratory values were from the time of SSC diagnosis, unless otherwise indicated ("at discharge" refers to the laboratory values at discharge of the hospital stay establishing SSC diagnosis/following initial intervention, e.g. ERC). Sample size for model 1 and model 2 was n=127 and n=93 respectively.
Abbreviation: MDRO, multidrug-resistant organism; SSC, secondary sclerosing cholangitis; UDCA, ursodesoxycholic acid.

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FIGURE LEGENDS

Figure 1. Kaplan Meier curve depicting transplant-free survival in patients with secondary sclerosing cholangitis (SSC) stratified according the use of ursodeoxycholic acid in (A) the entire cohort and (B) in patients with SSC following ICU stay (SSC in critically ill patients (SSC-CIP) or following COVID-19 (COVID-SSC). (C) Kaplan Meier curve depicting transplant-free survival in SSC patients with COVID-SSC and SSC-CIP.

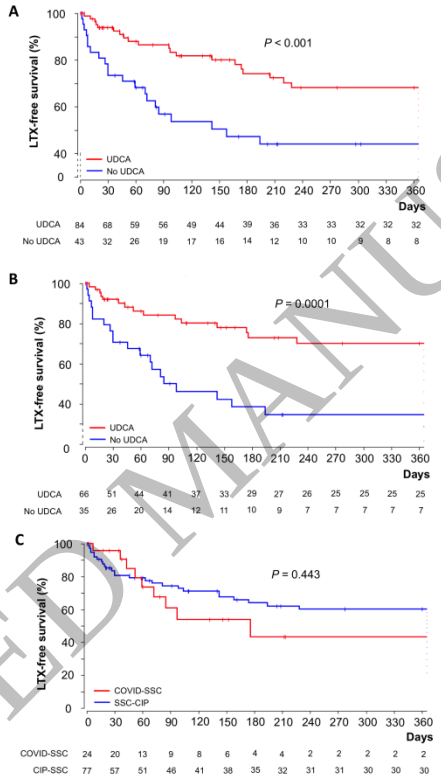

Figure 1
60x106 mm (x DPI)

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