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Endoscopic Characterization and Outcome of COVID-19 Patients with Secondary Sclerosing Cholangitis: A Case Series of a Tertiary Center

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ABSTRACT

Background & Aims: During the coronavirus disease 2019 (COVID-19) pandemic a significant proportion of patients with severe acute respiratory distress syndrome (ARDS) due to COVID-19 infection developed secondary sclerosing cholangitis (SSC) as a hepatobiliary complication.
Methods: 17 patients were endoscopically diagnosed and treated with COVID-19 SSC from February 2020 until October 2022 at our center. We retrospectively reviewed and analyzed the data to define risk factors, establish endoscopic treatment options, and to estimate incidence and outcomes.
Results: 258 patients with COVID-19 infection were admitted to our tertiary center and mechanically ventilated. 10 patients developed COVID-19 SSC in-house, and 7 patients were transferred for further endoscopic treatment. All 17 patients were mechanically ventilated, received vasoactive substances and 12 of them were treated with extracorporeal membrane oxygenation therapy. Endoscopic retrograde cholangiography (ERC) was performed in all patients to establish the diagnosis of COVID-19 SSC and evaluate endoscopic treatment options. All ERCs revealed biliary casts. 9 patients had developed severe rarefication of the intrahepatic bile ducts and 4 showed biliary strictures. As endoscopic treatment approaches, casts were removed repeatedly, and strictures were dilated. During the study period, 14 patients died (82%). 3 patients are in follow-up to reassess the need for liver transplantation.
Conclusions: COVID-19 SSC was observed in 2.6 % of the patients with severe COVID-19 in our center. We show that endoscopic approaches offer the opportunity to extract casts and to treat biliary strictures. As the mortality rate of COVID-19 SSC is high, endoscopic treatment can be of great clinical relevance as a bridge to liver transplantation.

Key words: ARDS – acute respiratory distress syndrome – COVID 19 – secondary sclerosing cholangitis.

Abbreviations: AP: alkaline phosphatase; ALT: aslanine aminotransferase; ARDS: acute respiratory distress syndrome; AST: aspartate aminotransferase; CIP: critically ill patients; COVID 19: coronavirus disease 19; ERC: endoscopic retrograde cholangiography; GGT: gamma-glutamyltransferase; ICU: intensive care unit; SSC: secondary sclerosing cholangitis.

INTRODUCTION

Different etiologies of secondary sclerosing cholangitis (SSC) have been described: drug-induced, infectious, autoimmune-associated, ischemic, obstructive as well as SSC in critically ill patients (CIP) [1, 2]. With a significant number of patients developing SSC after intensive care unit (ICU) treatment for pneumonia and acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19) infection, COVID-19 SSC is discussed to emerge as a new disease entity and hepatobiliary long-term complication [3]. The overlap between SSC-CIP and COVID-19 SSC concerning the pathogenesis, clinical course, and risk factors, as two entities of SSC was discussed [3].

The development of COVID-19 SCC is likely the consequence of multiple hits similar to the pathophysiology of SSC-CIP involving ischemia, drug-induced liver damage, toxic bile composition, and cytokine activation [1, 4-7]. In addition, a direct viral effect on cholangiocytes via the ACE2 (angiotensin-converting enzyme) receptor with functional impairment of the epithelial cell has been discussed for COVID-19 SSC [8, 9].

High fibrinogen levels leading to hyperviscosity have been suspected as an amplifying factor in COVID-19 SSC as well [10]. The histopathological findings in liver biopsies of COVID-19 SCC patients show similarity to SSC-CIP, and reveal nonspecific chronic bile duct obstruction [4, 11]. As different studies describe vascular damage in liver biopsies of COVID-19 patients [12-14], endothelial dysfunction may constitute an additional driving factor of cholangiopathy in COVID-19 SSC [15, 16].

Furthermore, a multicenter cohort study revealed similar risk factors and a comparable clinical phenotype of patients with SSC-CIP compared to COVID-19 SSC [3]. Long-term mechanical ventilation, vasoactive agents, extracorporeal membrane oxygenation (ECMO), ketamine usage, and renal replacement therapy as well as obesity, intraperitoneal fat, and prone positioning were considered as playing a role in the pathogenesis of both entities [5, 9, 17, 18].

As pathogenesis and specific risk factors of COVID-19 associated SSC have often been discussed and compared to SSC-CIP in the literature, more endoscopic and clinical data of the COVID-19 SSC patient cohort is lacking. In this study, we aimed to assess the clinical course, evaluate endoscopic treatment options, and analyze outcomes of critically ill patients.

METHODS

Study Design

We conducted a retrospective analysis in our tertiary hepatobiliary center from February 2020 until October 2022. All patients that were admitted to the intensive care units with COVID-19 ARDS and developed SSC in-house and all patients that were transferred to our department for further treatment with COVID-19 SSC were included.

The study was conducted following the declaration of Helsinki and the guidelines of good clinical practice (ICH GCP). After approval of the local ethics committee board of the Medical Faculty (No. 22-3008-104, 18.07.2022) we extracted the laboratory results, clinical data, the cholangiographic images, and reports from the clinical information systems. Moreover, the clinical course was reviewed, and the outcomes of the patients were analyzed. The surviving patients have been scheduled for regular follow-up appointments at our hepatobiliary center and are continuously reevaluated for liver transplantation.

Inclusion and Exclusion Criteria

Only patients with no preexisting liver disease prior to their COVID-19 infection were included in the analysis. The focus goal of the study was to evaluate the endoscopic findings and to establish endoscopic treatment options particularly as a bridge to liver transplantation. Therefore, we only included patients with diagnostic and/or therapeutic ERC in-house. All ERCs were performed by two different examiners to minimize interobserver variability. All patients received rectal diclofenac supposition and infusion with NaCl (0.9 %) 1000 ml for post-ERCP prophylaxis.

Patients lacking significant data due to their ICU stay in referring hospitals were excluded.

Definition of Vasoactive Substances

The dosage of administered vasopressors was categorized as "high" with peak levels of norepinephrine being over 1 mg/h or vasopressin added as a second vasoactive agent. Otherwise, the dosage was categorized as "low".

Statistical Analysis

All data were retrieved from the medical reports and clinical information systems and entered into a clinical database (Microsoft Excel 2016, Microsoft Corp.).

Categorical variables are shown as frequencies and continuous variables as mean with standard deviation when dispersion of the values was limited, else the range was stated. Survival rates are depicted with Kaplan-Meier analysis. Due to the small sample size no further statistical analysis were conducted.

The MELD score (model of end-stage liver disease) was calculated as implemented in Chapter 5 of the Eurotransplant Manual for Liver Allocation [19].

RESULTS

Patient Selection

Between February 2020 and October 2022, 19 patients were treated with COVID-19 SSC at our University Hospital. One patient was excluded from the analysis because the liver biopsy revealed preexisting fatty liver disease. In general, an underlying liver disease was ruled out by transabdominal ultrasound, computed tomography (CT) scans and laboratory values at the time of initial presentation.

Among the remaining 18 COVID-19 SSC patients, 10 developed the condition in-house after being admitted to the ICU with COVID-19 ARDS. 8 patients were transferred for endoscopic intervention after ICU treatment and development of SSC in referring hospitals. One of these 8 patients was endoscopically treated for COVID-19 SSC but was excluded due to insufficient data on the initial ICU stay in the referring hospital. In summary, 17 patients were included in the detailed analysis of this case series.

During the observational period 258 patients in total were admitted with severe COVID-19 ARDS to the intensive care units of our tertiary care university center and mechanically ventilated. 10 of them developed COVID-19 SSC. Thus, the incidence of COVID-19 SSC in this cohort in our center was 2.6 %.

The follow up time defined as time of diagnosis until death or end of the observational period was a mean 4 months (range 0.5 – 15 months).

Baseline Characteristics and Intensive Care Unit Treatment

The baseline characteristics and the features of the ICU treatment of the 17 patients with COVID-19 SSC are summarized in Table I. The mean age of the patients at the time of diagnosis was 60 ± 11.6 years and the majority of the patients were male (n=14). The mean follow-up time was 4 months (range 0.5-15 months).

All patients were intubated and mechanically ventilated with a mean duration of 84 days (range 35-162 days). Treatment of ARDS in prone position was performed in 12 of the 17

Table I. Clinical baseline data and intensive care unit treatment

Number of patients	n = 17
Age (years) mean ± SD	60 ± 11.6
Sex (male/female)	14/3
MELD score on day of COVID-19 SSC diagnosis, mean ± SD	21.0 ± 7.9
Intensive care treatment	
Mechanical ventilation	17
Number of days (mean ± SD)	84 ± 33.2
ECMO therapy	12
Number of days (mean ± SD)	38 ± 38.5
Prone positioning	12
Vasopressor therapy[1]	17
Low dosage	11
High dosage	5
Renal replacement therapy	7
Ketamine therapy[2]	10

[1] information on dosing not obtainable in 1 patient; [2] information on ketamine use not obtainable in 7 patients.

patients. Extracorporeal membrane oxygenation (ECMO) therapy was conducted in 12 patients with a mean duration of 38 days (range 8-133 days).

All patients received vasopressor therapy; the dosages were classified as defined above (see 2.2). Eleven patients received low doses of vasoactive substances under the peak level of 1mg/h noradrenaline during the ICU stay. Five patients required high-dose vasopressor therapy and in one patient the information was retrospectively not obtainable.

Renal replacement therapy was necessary for 7 patients. Ketamine was used verifiably in 10 patients, whilst the data could not be obtained for all patients' due to missing information from the referral hospitals.

Laboratory Findings and Microbiological Results of Bile Fluid Sampling

The first non-transient increase in bilirubin levels occurred on average 101 days after the onset of the first COVID-19 symptoms (range 12-391 days). The mean total bilirubin on the day of the endoscopic diagnosis was 11.9 mg/dl ± 6.6. At the same time alkaline phosphatase (AP) and Gamma-glutamyltransferase (GGT) were highly elevated in each patient. The mean AP was 832 U/l ± 454 and the mean GGT 1023 ± 791 U/l. Levels of liver enzymes [AST (aspartate aminotransferase), ALT (alanine aminotransferase)] were mildly elevated in all patients. Only two patients showed an increase over ten times higher than normal. On average the AST was 145 U/l ± 77, and the ALT 169 U/l ± 121.

The mean MELD score on the day of diagnosis was 21 points ± 7.9, generated mainly due to the high total bilirubin levels. The kidney function was severely impaired in 9 patients, with 7 patients requiring hemodialysis at the time of endoscopic diagnosis of SSC. 16 patients showed mildly elevated INR values with a mean 1.2 ± 0.2 on the day of SSC diagnosis due to impaired liver function. Blood albumin levels were normal in only one patient with a mean value of 26.8 g/l ± 4.2.

In each patient bile samples for microbiological analysis were collected. The bile samples showed predominant biliary colonization with Enterococcus faecium in 13 of the 17 cases (53 % resistant to Vancomycin) and Candida species in 6 patients. The bile sample of one patient was sterile. Other bacteria detected in the bile fluid were Enterococcus faecalis (two patients), Klebsiella species (two patients), Escherichia coli, Enterobacter, Staphylococcus hominis and Pseudomonas aeruginosa.

Endoscopic Findings

COVID-19 SSC was diagnosed by ERC as the diagnostic gold standard in our study cohort. In addition, every ERC was performed as therapeutic intended ERC with respect to suspected cholangitis. Rising laboratory signs of cholestasis paired with the suspicion of an infectious focus indicated the performance of the initial ERC in every patient and led to the diagnosis of COVD-19 SSC after a mean of 110 days (range 20-326 days) following the first symptoms of COVID-19 pneumonia.

At the time of endoscopic intervention by ERC or shortly before, 14 patients received abdominal CT scans with intravenous contrast. In respect to signs of SSC, CT morphological indicators of cholestatic liver disease were detected in only 3 of the patients. These were intrahepatic cholestasis with common bile duct dilatation in two cases and hypodense lesions along the intrahepatic bile ducts. MRI was performed in one patient only and showed SSC typical features.

The need for endoscopic re-intervention was continuously assessed, considering the last cholangiography findings, laboratory values, and the patient's clinical status. The most common reason for re-intervention was suspected cholangioseptic episodes and re-worsening of cholestatic laboratory findings. Scheduled ERC was performed for dilatation or cast extraction in the patients with long-term survival. On average, patients with COVID-19 SCC underwent 2.8 ERCs (range 1-7) during the observational period. The 3 patients with longterm survival received a mean of 5 ERCs (range 2-7). ERC resulted in a transient resolution of septic conditions in every patient. Nonetheless, it did not lead to a lasting decline of cholestatic laboratory parameters during the intensive care stay.

Endoscopic findings in patients with COVID-19 SSC were comparable to cholangiopathy of critically ill patients (SSC-CIP). Fig. 1 demonstrates representative endoscopic images of these findings. An overview of the endoscopic features found over the course of the observational period is listed in Table II. All patients showed biliary casts mainly of the intrahepatic bile ducts. Three patients did not show casts on the initial endoscopic interventions but over the course of intensive care treatment and subsequently performed ERCs.

Table II. Overview of endoscopic features

Endoscopic features	All (n = 17)
ERCs per patient (mean)	2.8
Biliary casts	17
Rarefication intrahepatic bile duct	9
Strictures/ Stenosis	4
Stent placement[1]	6

[1] due to sphincterotomy to prevent bleeding.

Casts were extracted with a balloon catheter or basket. Additionally, saline flushing was performed in the peripheral bile ducts. Follow-up examinations with repeated extraction of casts or bile duct dilatation therapies were conducted when clinically indicated, mainly due to cholangitis.

Rarefication of the biliary ductal system was observed in 9 of the 17 patients on the day of first diagnosis of COVID-19 SSC (Fig. 2). During the follow-up, progressive rarefication led to total occlusion of the peripheral bile duct system in all surviving patients (Fig. 3). We were not able to stop the progression in the peripheral regions with endoscopic interventions. Of clinical importance, the main intrahepatic ducts, as well as the extrahepatic bile ducts, remained mostly unaffected in these patients. The development of a dominant stenosis was detected in 4 patients, and endoscopic dilatation therapy was performed.

Stent placement was necessary for 6 patients for therapy of bleeding direct after endoscopic sphincterotomy. In these cases, fully covered metal stents were inserted. No severe bleeding complications occurred afterwards. Lipase was not determined as post intervention routine. However, patients showed no clinical or radiographic sign of post-ERCP pancreatitis.

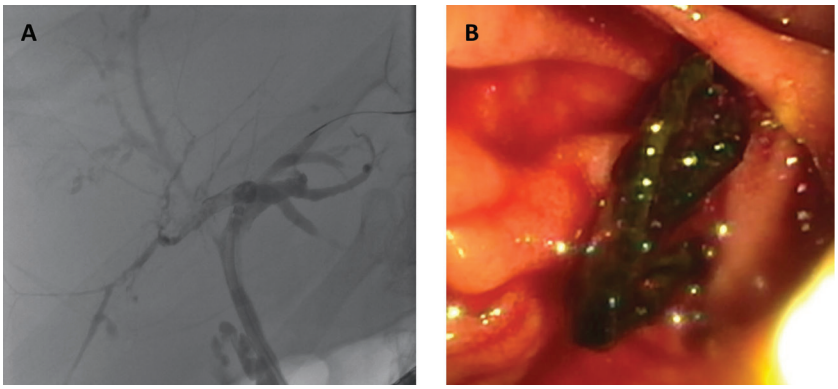

Fig. 1. Representative endoscopic features of COVID-19 SSC A) bile duct system with irregular contrast enhancement and rarefication of the peripheral right-sided bile ducts B) biliary cast.

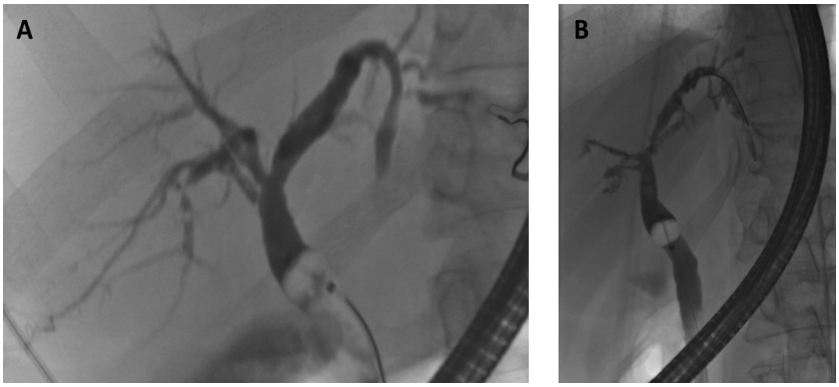

Fig. 2. Progressive rarefication and destruction of the right peripheral bile duct system in a patient with COVID-19 SSC.

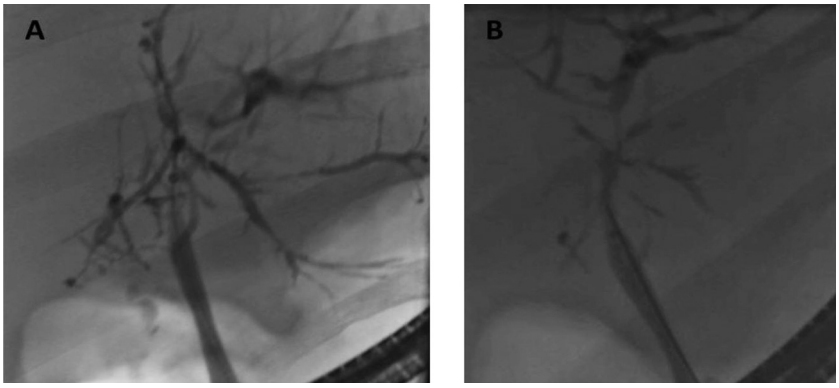

Fig. 3. Total occlusion and rarefication of the peripheral bile ducts over the course of 4 months. The more central localized stenosis underwent dilatation therapy.

Two patients developed hepatic microabscesses, without interventional consequence, as these patients deceased shortly afterwards.

Clinical Outcome

During the observation period, 14 patients (82 %) died (Table III). The underlying pathophysiology was multiple organ failure with predominant acute liver failure in 3 patients, and multiple organ failure without hepatic involvement in 5 cases. Furthermore, 3 patients died of septic shock, one of cardiac arrhythmia, one of cardiac output failure, and one patient due to hemorrhagic shock and coagulopathy associated with ECMO therapy.

Table III. Clinical outcome of the study cohort

Outcome	n = 17
Liver transplantation	0
Death	14/ 17
Mean survival time since diagnosis (months)	10
Cause of death	
Multiple organ failure	8
Septic shock	3
Cardiac complications	2
Hemorrhagic shock	1

Three patients who developed COVID-19 SSC survived and were included in a further clinical follow-up. These received ursodeoxycholic acid and were assessed with regard to the need for liver transplantation. In the case of predominant stenosis, they were included for a scheduled ERC dilatation.

The mean survival time of patients with COVID-19 SSC was 10 months (range 6-15 months) after the first diagnosis of SSC by ERC. Fig. 4 depicts the Kaplan-Meyer survival curve of the study cohort.

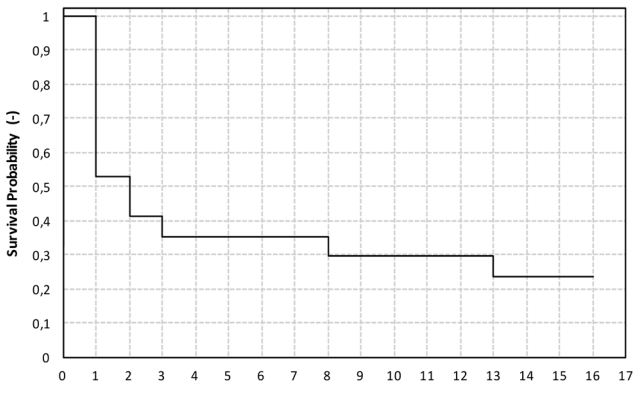

Fig. 4. Kaplan Meier survival rates of patients with COVID-19 SSC. T=0 is defined as the time of COVID-19 SSC diagnosis.

The 3 patients that survived the intensive care treatment presented with stable liver function with no change of the MELD score in the observational period. Hence, none of these 3 patients had to be listed for liver transplantation. Of note, the eligibility for liver transplantation in 2 of the 3 patients is still restricted due to compromised pulmonary function tests and reduced general condition.

DISCUSSION

Prevalence of COVID-19 SSC

Here, we present data on a case series of 17 patients with COVID-19 SSC. Of the 256 patients with COVID-19 ARDS with mechanical ventilation and ICU treatment in our hospital, 10 patients developed COVID-19 SSC. This accounts for an incidence COVID-19 SSC in this cohort of patients of 2.6 % at our center. Leonhardt et al. [10] reported that one in every 43 invasively ventilated COVID-19 patients developed COVID-19 SSC. Another retrospective observational study indicated an incidence of 6 out of 334 COVID-19 ICU admissions with mechanical ventilation developing COVID-19 SSC [20]. In contrast, in the pre-pandemic era Martins and Machado [4] estimated SSC-CIP to occur in 1 of 1990 ICU admissions. With an incidence between 1.8 % (6/334) [20], 2.3 % (25/1082) [10] and 2.6 % of all COVID-19 ICU admissions developing COVID-19 SSC, the incidence of COVID-19 SSC is much higher than the incidence of SSC-CIP in a comparable non-COVID cohort.

Risk Factors of COVID-19 SSC Pathogenesis

Summing up the available knowledge, a multiple hit theory has been assumed causative, similar to the pathogenesis of SSC-CIP [9-11]. The combination of ICU treatment and hypoxemia leading to ischemia, cytokine activation and proinflammatory response, altered bile composition, and drug-induced liver damage are viewed as crucial for both disease entities [9, 14].

A recent study observed that prolonged ketamine usage in COVID-19 ARDS patients led to higher liver cholestatic biomarkers compared to patients without the application of ketamine [6]. In our cohort, treatment with ketamine could be reliably assessed for the 10 patients treated at our center since the beginning of the COVID-19 ARDS symptoms. For the patients that had been referred, the data was not conclusive. Therefore, and as the study was not powered to answer this question, it cannot be reliably contributed to the debate that ketamine usage plays a role in the pathogenesis of SSC. Meanwhile, there have been pharmacological and pathophysiological analyses performed that did not observe a causative link between ketamine and bile duct destruction and this observation is discussed as a typical bias of this association [21].

In addition, our cohort reflects the main risk factors discussed with a mean mechanical ventilation time of 84 days (17 of 17 patients), the average time of 37 days ECMO therapy (12 of 17 patients), renal replacement therapy (7 of 17 patients), and prone positioning (12 of 17 patients).

Of clinical relevance, high-dose vasopressors do not seem to contribute to the development of COVID-19 SSC in our patient cohort. We did not observe a correlation between the required dosing of vasopressors and the occurrence of COVID-19 SSC. Up to now, vasopressor agents have been assumed to be a major risk factor in SSC-CIP pathogenesis [9, 17]. In their review, Martins and Machado [4] discuss the evidence of norepinephrine decreasing the blood flow of the

hepato-splanchnic region. However, a recent case series did not find any correlation between high-dose vasopressor agents and the development of SSC-CIP [5]. Taking into consideration the comparatively low vasopressor dosages in our patient cohort and the incidence of COVID-19 SSC, we do not assume vasopressor therapy to play a major role in the pathogenesis of COVID-19 SSC.

Diagnosis and Treatment Options of COVID-19 SSC

Currently, there is a debate about whether ERC can be regarded as the diagnostic gold standard for SSC. 14 of our patients received an abdominal CT scan with contrast enhancement just before or at the time of ERC, but showed alterations of the bile duct in only 3 cases. These were intrahepatic cholestasis with common bile duct dilatation in two cases and hypodense lesions along the intrahepatic bile ducts. In all other patients with laboratory and endoscopic characteristics of COVID-19 SSC, CT scans failed to raise the suspicion of cholestatic liver disease. Therefore, CT scans cannot be recommended as the primary imaging modality in COVID-19 SSC. However, CT imaging is known to be less effective than MRCP and MR imaging in detecting pathologies of the biliary duct system. MRI was performed in one patient in this case series, resulting in the diagnosis of SSC.

In our cohort of severely critically ill patients, the ability to conduct microbiological cultures of bile and perform endoscopic intervention in the same session when indicated made ERC the preferred technique. Especially in the cohort of COVID-19 ARDS patients ERC had the advantage over MRI that it could be performed under ECMO support. Furthermore, without a necessary change to MRI capable ventilation equipment viral aerosol exposure could be minimized. Another case series in a COVID-19 SSC cohort supports the preference for ERC in these patients as only a few patients showed signs of cholestasis in the imaging modalities performed prior to the ERC. In this study the diagnosis of COVID-19 SSC was made by ERC, as prior imaging modalities failed to show alterations of the bile duct in 34 of the 46 patients [22].

With this large series of COVID-19 SSC cases diagnosed and treated by ERC, we were able to further categorize the endoscopic characteristics and the clinical course of COVID-19 SSC. All patients developed extensive biliary casts, at the latest 100 days after the first respiratory symptoms of COVID-19 ARDS. There was no correlation between cast formation and bilirubin levels. This is supported by another case series with COVID-19 ARDS patients where 25.6 % of the patients demonstrated cholangiographic abnormalities of the bile duct and still had normal bilirubin levels [22].

In SSC-CIP, the destruction of the biliary duct system occurs already during the first 5 to 7 days of ICU treatment [2]. After endoscopic cast removal we demonstrated new formation of biliary casts over a certain period of time in all patients. Leonhardt et al. [2] also reported new cast formation in 7 of their 16 non-COVID-19 patients with SSC-CIP and discussed it as a result of incomplete removal or ongoing inflammatory changes. Furthermore, we noted progressive rarefication of the biliary tract system leading to occlusion of the peripheral intrahepatic bile ducts. The extrahepatic bile duct system was unaffected in all patients of the cohort. A primarily intrahepatic distribution pattern has been reported in a smaller COVID-19 SCC case series before [11]. This appears analogous to the endoscopic features of SSC-CIP [2, 4].

In our case series the endoscopic phenotype of COVID-19 SSC is characterized by predominant cast formation and the progressive rarefication of the peripheral bile duct system, which seems congruent with other data published so far [22]. Furthermore, it is important to note, that in a recent retrospective analysis of 80 patients with SSC of different pathogenetic entities, no beneficial effect of scheduled regular endoscopic interventions on transplant-free survival was documented. The authors described higher survival rates in patients with the detection of bacteria in their bile samples, probably due to specific antibiotic therapeutic regimens. They also discussed a positive effect through the prevention of cholangitis and therefore an improvement of the quality of life [23]. Other retrospective data from a large PSC cohort showed a prolonged transplant free survival time of 17.9 versus 15.2 years in patients with programmed ERC interventions and dominant strictures [24].

In our cohort the indication for repeated endoscopic interventions was mainly due to clinically suspected infections with a rise in the laboratory markers of cholestasis. We did not note a change of the laboratory cholestasis marker during the ICU stay as well as decrease in MELD score as an indicator for the transplant-free survival in the 3 patients with long-term survival and repeated ERCs. Thus, the effect of programmed interventions cannot be assessed in this study.

It seems that in this study cohort, interventions on demand helped to control clinical infections. With few dominant strictures as the therapeutic target in the COVID-19 SSC patients, the improvement of the bile drainage achieved by repeated cast removal may play an important role. This was also observed in another COVID-19 SSC cohort, where the removal of casts did not always correlate with a decrease of laboratory markers of cholestasis. The researchers suspect a benefit in therapeutic re-interventions by prevention of infections and further biliary obstruction [22]. Prospective analysis to further determine the influence of scheduled endoscopic interventions in patients with SSC differentiated into various etiologies are still missing.

Outcome of Patients with COVID-19 SSC

The prognosis of patients with COVID-19 SSC is very limited. In our cohort, 14 of the 17 patients (82%) died during the observational period. Leonhardt et al. [10] reported mortality rates of 60% for the first 12 months and 83% over the course of 24 months. This is in accordance with the outcome of the patients in our cohort. As the mortality rate of patients with COVID-19 ARDS and mechanical ventilation without SSC was found to be around 40-50 % [25, 26], COVID-19 SSC accounts for a dramatic increase of the mortality of critically ill COVID-19 patients. In comparison, the prognosis of SSC-CIP (not associated with COVID-19 ARDS) has been shown to be limited as well with a median transplant-free survival of 40 months and a mortality rate up to 50% [27-29].

The leading cause of death in our study group was multiple organ failure in 8 cases. In 3 of these patients, the liver was the leading organ to fail. The study design does not allow an assessment of the overall transplant-free survival. Until

the end of the study period liver function in the 3 surviving patients according to the MELD score has been stable and no transplantation has been necessary, so far. Treatment with ursodeoxycholic acid should be administered, as it was recently shown to improve transplant-free survival in COVID-19 SCC and SSC-CIP patients in a large multicenter study [3].

The study's limitations mainly result from the unicentric, retrospective study design with a small sample size. Even though, we can present a large single-center study reporting endoscopic findings and treatment options. As prospective studies are lacking, focusing on matched-pair analyses with non-COVID cohorts and multicenter studies to determine interventional benefits might be appropriate to gain further knowledge.

CONCLUSIONS

Besides the analogies in the clinical course and risk factors of COVID-19 SSC and SSC-CIP, we found the endoscopic features to be very similar as well. The impact of therapy with vaso-active substances seems to be less important in COVID-19 SSC when compared to SSC-CIP. However, the mortality rate appears to be even higher in patients with COVID-19 SSC. Endoscopic approaches offer the opportunity to optimize antibiotic treatment in cholangitis episodes, cast extraction and dilatation of biliary stenosis, analogous to SSC-CIP treatment. Endoscopic treatment plays an essential role in the management of acute infectious complications and in serving as a bridge to liver transplantation for patients with COVID-19 SSC. The latter is often limited due to the compromised pulmonary function of these patients.

Conflicts of interest: A.K. received fees for scientific presentations and scientific advisory activities by: Roche Pharma AG, Eisai GmbH, Abbvie Germany AG, Janssen-Cilag GmbH, MSD Sharp & Dohme GmbH, Boston Scientific Corp., Fujifilm Germany, Micro-Tech Germany. All other authors declare no conflict of interest.

Authors' contributions: P.H. and A.K conceived and designed the study. P.H. and S.S. collected the data. P.H., M.M. and A.K analyzed and interpreted the data. P.H., I.Z.J, A.K., S.S., T.M., M.L., B.G and D.L. treated the patients. P.H, A.M. and M.M drafted the manuscript, A.K., M.M., B.G., D.L., M.L and T.M. revised the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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