Received: 17 January 2022 | Accepted: 11 April 2022

DOI: 10.1002/ueg2.12232

ORIGINAL ARTICLE

ueg journal WILEY

COVID-19 mortality in cirrhosis is determined by cirrhosis-associated comorbidities and extrahepatic organ failure: Results from the multinational LEOSS registry

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Abstract

Background and Objective: International registries have reported high mortality rates in patients with liver disease and COVID-19. However, the extent to which comorbidities contribute to excess COVID-19 mortality in cirrhosis is controversial.

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Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Number: SFB1382 Project ID 403224013/B07; Willy Robert Pitzer Foundation; Deutsches Zentrum für Infektionsforschung
Open access funding enabled and organized by Projekt DEAL.

Methods: We used the multinational Lean European Open Survey on SARS-CoV-2-infected patients (LEOSS) to identify patients with cirrhosis documented between March 2020 and March 2021, when the wild-type and alpha variant were predominant. We compared symptoms, disease progression and mortality after propensity score matching (PSM) for age, sex, obesity, smoking status, and concomitant diseases. Mortality was also compared with that of patients with spontaneous bacterial peritonitis (SBP) without SARS-CoV-2 infection, a common bacterial infection and well-described precipitator of acute-on-chronic liver failure.

Results: Among 7096 patients with SARS-CoV-2 infection eligible for analysis, 70 (0.99%) had cirrhosis, and all were hospitalized. Risk factors for severe COVID-19, such as diabetes, renal disease, and cardiovascular disease were more frequent in patients with cirrhosis. Case fatality rate in patients with cirrhosis was 31.4% with the highest odds of death in patients older than 65 years (43.6% mortality; odds ratio [OR] 4.02; $p = 0.018$), Child-Pugh class C (57.1%; OR 4.00; $p = 0.026$), and failure of two or more organs (81.8%; OR 19.93; $p = 0.001$). After PSM for demographics and comorbidity, the COVID-19 case fatality of patients with cirrhosis did not significantly differ from that of matched patients without cirrhosis (28.8% vs. 26.1%; $p = 0.644$) and was similar to the 28-day mortality in a comparison group of patients with cirrhosis and SBP (33.3% vs. 31.5%; $p = 1.000$).

Conclusions: In immunologically naïve patients with cirrhosis, mortality from wild-type SARS-CoV-2 and the alpha variant is high and is largely determined by cirrhosis-associated comorbidities and extrahepatic organ failure.

KEYWORDS
ACLD, chronic liver disease, cirrhosis, COVID-19, SARS-CoV-2, SBP

INTRODUCTION

As of December 2019, the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the evolving COVID-19 pandemic pose an ongoing threat to both infected individuals and treating physicians. Overburdened health services and mutating viral strains have resulted in more than 476 million cases and more than 6 million deaths worldwide (covid19.who.int, as accessed on 26 March 2022).

SARS-CoV-2 infection can present with a range of symptoms from mild febrile infection to acute respiratory distress syndrome and consecutive multiple organ failure.[1] Older age and pre-existing comorbidities such as obesity, diabetes, cardiovascular disease, respiratory disease, impaired renal function and conditions associated with immunosuppression or immune dysfunction were identified as the most important risk factors for severe disease progression, hospitalisation, and death due to COVID-19.[2–4] Consistent with the fact that many of these conditions frequently diagnosed in patients with liver disease, chronic liver disease and cirrhosis have been identified as risk factors for COVID-19-related deaths in large analyses of electronic health records[4] and meta-analyses of observational studies.[5–7]

Patients with advanced chronic liver disease are at increased risk for infection-related complications and death[8,9] due to multiple contributing pathways including deregulated systemic inflammation, dysfunctional innate and adaptive immune responses, and a predisposition to hepatic and extrahepatic organ failure.[10–12] In addition to bacterial infections, viral respiratory infections can also act as triggers of acute-on-chronic liver failure (ACLF), as shown for the influenza virus[13] and SARS-CoV-2 alike.[14,15] According to available case series, the most common cause of death in SARS-CoV-2-infected patients with chronic liver disease is lung failure followed by liver-related mortality.[15,16]

Given the paucity and heterogeneity of available data, it remains unclear to what extent the presence of liver cirrhosis itself promotes a severe course of COVID-19 in comparison to patients without liver disease but comparable extrahepatic comorbidities. Early publications reported case fatality rates of 24%–35% in SARS-CoV-2-infected patients with cirrhosis but were often limited by the small number of patients included or the lack of a control group of patients without cirrhosis.[5,16–18] A larger data set from an online open-report form confirmed a mortality rate of 32% for cirrhosis, which exceeded 54% for hospitalized patients with decompensated Child-Pugh C cirrhosis and 90% for ventilated patients.[15] A recent analysis of electronic health record data from the US concluded considerably lower estimates: The overall 30-day cumulative mortality rate among patients with cirrhosis, about 50% of whom were

hospitalized, was 9%, with the highest mortality (up to 13%) among patients with decompensated cirrhosis, older age, renal disease, or heart failure.[19]

This wide range of mortality rates has led to discussions about the extent to which cirrhosis per se is a risk factor for a complicated course of COVID-19 or whether these rates can be explained by associated comorbidities.[20,21] These data also highlight the need to interpret mortality rates in the context of time periods, geographical location, ethnicity and severity of underlying disease, cirrhosis-associated extrahepatic comorbidities and complications.

The aim of this study was to determine the presentation, disease course and outcomes of SARS-CoV-2-infected patients with cirrhosis using a matched-control cohort design using the large Lean European Open Survey on SARS-CoV-2-infected patients (LEOSS registry). A second aim of our study was to compare the mortality after SARS-CoV-2 infection to that of a common bacterial infection and well-described precipitator of ACLF in cirrhosis, specifically spontaneous bacterial peritonitis (SBP).

Key summary

What is the established knowledge?

- SARS-CoV-2 infections pose a threat to healthy individuals, but especially to vulnerable patient populations with pre-existing comorbidities, such as chronic liver disease and cirrhosis.
- Viral infections can precipitate acute-on-chronic liver failure (ACLF), and SARS-CoV-2-related mortality in patients with decompensated cirrhosis is extraordinarily high.
- The heterogeneity of available data has sparked debate about whether cirrhosis per se or extrahepatic comorbidities contribute more to the excess mortality rates in cirrhosis.

What are the new findings from this study?

- This large multi-national registry analysis of SARS-CoV-2-infected patients in Europe allows risk factors and comorbidities to be balanced in a propensity score-adjusted case-control design.
- Before matching, the case fatality rate was higher in patients with cirrhosis and SARS-CoV-2 infection than in patients without cirrhosis, whereas the matched patients had a similar case fatality rate, demonstrating a role of cirrhosis-associated extrahepatic comorbidities and complications.
- In contrast to decompensation alone, failure of two or more organs was strongly associated with a high mortality rate, underscoring the importance of ACLF in SARS-CoV-2 infection.
- Patients with cirrhosis and SARS-CoV-2 infection show fewer initial symptoms than patients without cirrhosis.
- SARS-CoV-2 infection poses similar mortality risk to spontaneous bacterial peritonitis (SBP) in patients with cirrhosis.

MATERIALS AND METHODS

Study population

The Lean European Open Survey on SARS-CoV-2 (LEOSS) is an international registry established in March 2020 to address the lack of knowledge about the epidemiology and clinical course of SARS-CoV-2 infections.[22] As of June 2021, the LEOSS registry consists of 146 actively reporting sites across Europe and serves as a large representative multi-national database of adult patients with COVID-19. All patients included were diagnosed by a positive SARS-CoV-2 nucleic acid amplification test from a respiratory specimen. Recorded clinical characteristics included age category, gender, ethnicity, obesity, smoking status, diabetes mellitus (DM), chronic kidney disease (CKD), hypertension, coronary artery disease (CAD), malignancies, asthma, and chronic obstructive pulmonary disease (COPD). In addition, data were collected on treatment options directed against SARS-CoV-2- including antiviral, antibacterial, antifungal, and immunosuppressive or immunomodulatory therapies. In addition to the baseline clinical characteristics, for patients with cirrhosis, the following data were collected: aetiology of cirrhosis; previous decompensation; decompensation at diagnosis of COVID-19; liver transplantation waiting list status; bacterial infections within the last 30 days; laboratory parameters; ascites and hepatic encephalopathy at baseline; presence of ACLF at any point of SARS-CoV-2 infection; severity of cirrhosis as assessed by the Child-Pugh class as well as concomitant medication upon hospitalization (such as proton pump inhibitors, rifaximin and first generation fluoroquinolones). Data on patients, concomitant diseases, and disease progression were entered into the LEOSS registry by the treating physicians at the reporting site and only after the full clinical course of SARS-CoV-2 infection. Cirrhosis and comorbidities were defined at the discretion of the reporting physician based on medical history, previous medical findings, and disease code. Obesity was defined as a documented body mass index of 30 kg/m^2 or more irrespective of the presence of ascites or body composition.

To compare case fatality rates in cirrhosis to non-SARS-CoV-2 infections in patients with cirrhosis, a historical cohort of 169 patients with cirrhosis and SBP recruited for previous studies at the Jena University Hospital was analysed.[23,24] Spontaneous bacterial peritonitis was diagnosed per current guidelines by neutrophil concentration >250/µl ascites fluid and the exclusion of secondary causes of peritonitis. The recorded clinical characteristics included age, aetiology cirrhosis, cirrhosis severity as assessed by Child-Pugh Score, Model-of-End-Stage-Liver-Disease (MELD) score, laboratory parameters, and 28-day mortality.

Ethics approval

Due to all data being collected anonymously, patients can be included in the LEOSS database without further informed consent. Data were recorded anonymously without any patient-identifying information, afterwards categorized and aggregated. In order to ensure anonymity in all steps of the analysis process, an individual LEOSS Scientific Use File was created, which is based on the LEOSS Public Use File principles described in Jakob et al.[25] Approval for LEOSS was obtained by the applicable local ethics committees of all participating centres and registered at the German Clinical Trails Register (DRKS, No. DRKS00021145). Furthermore, in accordance with the 1975 Declaration of Helsinki and the local guidelines and regulations, any patients included in the external cohort with SBP had previously given written informed consent and studies were approved by the local internal review board/ethics committee at the Jena University Hospital (no. 2880-08/10, 3683-02/3).

Study aims

The primary aim of the analysis was to compare the overall mortality after SARS-CoV-2 infection in patients with cirrhosis with that in matched controls without cirrhosis, and only cases for which SARS-CoV-2 outcomes were known as of 15 April 2021 were considered. Secondary aims of the study were (a) to describe group differences between survivors and non-survivors of SARS-CoV-2 infection in patients with cirrhosis, (b) to determine case fatality rates stratified for Child-Pugh stage, previous decompensation state and cirrhosis-associated medication, (c) to determine the frequency of ACLF after SARS-CoV-2 infection in patients with cirrhosis according to the European Foundation for the Study of Chronic Liver Failure (EF-CLIF) criteria,[26,27] (d) to describe group differences in symptoms, inflammatory parameters, liver function tests, and extrahepatic organ failure between patients with cirrhosis and matched controls without cirrhosis, and (e) to compare case fatality rates of SARS-CoV-2 infection in hospitalized patients with cirrhosis with those of a historical cohort of matched patients with cirrhosis and SBP without SARS-CoV-2 infection.

Statistical analysis

Propensity score matching (PSM) was implemented to account for differences in demographical and clinical characteristics of SARS-CoV-2-infected patients with and without cirrhosis. The following variables were used to create a propensity score: age category, gender, obesity, smoking status, DM, CKD, coronary heart disease and a modified Charlson Comorbidity Index (CCI). These eight variables were chosen a priori on the basis of proven or likely association with outcome in COVID-19 but less likely to be otherwise strongly associated with cirrhosis. A Fuzz of 0.0001 was used and cases were matched to 4 controls. In a *post-hoc* sensitivity analysis, an alternative 1:4 PSM controlling for age category, gender, and the modified CCI was also performed.

The modified CCI was calculated as the sum based on the documented comorbidities present at baseline: dementia, cerebrovascular disease, myocardial infarction, chronic heart failure, peripheral vascular disease, chronic obstructive lung disease, connective tissue disease, peptic ulcer disease, diabetes without end-organ damage, CKD (all scores of one point each), hemiplegia, diabetes with end-organ damage, leukemia, lymphoma, solid tumour without metastasis (all scores of two points each) and solid tumour with metastasis (6 points). To avoid overfitting of the propensity score, age category and liver disease were not considered for the modified CCI. The category HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrom) was not evaluated due to potentially identifying information due to a low number of patients.

To compare case fatality rates between SARS-CoV-2 infection and SBP, PSM for patients with cirrhosis and SARS-CoV-2 infection and patients with cirrhosis and SBP was performed 1:1, controlling for age, gender, and Child-Pugh class C (Fuzz 0.0001). As these cohorts contained only patients with cirrhosis, presenting a more homogenous collective, comorbidities were not included in computing a propensity score. For PSM, missing data from the LEOSS registry was imputed as negative or in case of non-numerical scoring systems as the lowest possible category.

Data are expressed as numbers, frequencies or means with standard deviation unless otherwise indicated. Differences between groups were analysed by the Fisher's exact test for categorical variables or the Mann-Whitney *U*-test for continous variables. Binary logistic regression analysis was performed to calculate odds ratio (OR) for predictors of mortality. Multivariable logistic regression analysis was performed for adjusted OR, including parameters that were found to be significant in the univariable analysis. Statistical analysis was performed using SPSS version 25 (IBM, Armonk, NY, USA). Data visualization was performed using GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA) and the SankeyMATIC sankey diagram builder (https://sankeymatic.com/, as accessed August 2021 and March 2022). Reported *p*values are two-sided and were considered significant at a value of <0.05.

RESULTS

SARS-CoV-2-infected patients with cirrhosis have significant extrahepatic comorbidities

Data from 7096 adult patients reported by 15/04/2021 with known (not missing) value of the variable “comorbidity: liver cirrhosis” were eligible for this analysis. Seventy (0.99%) patients with cirrhosis and SARS-CoV-2 infection were identified. Patients with cirrhosis had a different age distribution and presented significantly more often with comorbid conditions, such as DM (35.7 vs. 21.2%, $p = 0.005$), CKD (34.8 vs. 14.1%, $p < 0.001$) or CAD (24.3 vs. 13.2%, $p = 0.012$).

As a result, SARS-CoV-2 infected individuals with cirrhosis had a significantly higher modified CCI than patients without cirrhosis (mean 1.98 ± 1.73 vs. 1.18 ± 1.73, $p < 0.001$) excluding age and pre-existing liver disease. Pre-existing malignancies were present in both unmatched cohorts in similar frequency (4.3 vs. 5.9%, $p = 0.798$). In both cohorts, Caucasian ethnicity was the most common (98.3 vs. 95.4%, $p = 0.522$). Patients with cirrhosis and COVID-19 were statistically more often active smokers, but with similar rates of diagnosed COPD (Table 1).

To account for differences in demographics and comorbidities, we calculated propensity scores for age category, gender, obesity, smoking status, diabetes, CKD, coronary heart disease and modified CCI (without age category, liver disease and HIV). Sixty-six SARS-Cov2-infected patients with cirrhosis were successfully matched to 264 SARS-Cov2-infected patients without cirrhosis resulting in largely balanced baseline characteristics (Table 1).

Only adjusting for age category, gender and the modified CCI in an alternative PSM model, resulted in a less well-balanced patient matching with relevant differences ($p < 0.10$) in the frequency of CKD, diabetes, asthma, malignant disease, and smoking status (Supplementary Table 1).

SARS-CoV-2 infected patients with cirrhosis are frequently asymptomatic at presentation

In 28 (40%) patients, the diagnosis of SARS-CoV-2 infection was made before hospital admission, in 34 (49%) patients, the diagnosis was made on hospital admission or within the first 48 h, and in 8 (11%) patients, the diagnosis was made 3 days or later after hospital admission. The main reasons for consultation/hospitalisation were complications of cirrhosis (33%), respiratory symptoms (21%), gastrointestinal symptoms (16%), or unspecified other reasons (27.1%).

SARS-CoV-2 infected patients with cirrhosis presented significantly more frequent without any COVID-19-associated symptoms (37.5 vs. 10.5% in the matched cohort, $p < 0.001$). The most common symptomatic presentation in both matched cohorts upon admission (baseline) concluded of fever and respiratory symptoms such as a dry cough and dyspnoea (Table 2), followed by gastrointestinal symptoms (diarrhoea, emesis). Additionally, amidst similar clinical patterns, non-cirrhotic controls with SARS-CoV-2 infection were more prone to presenting with fever (18.8 vs. 35.8%, $p = 0.010$) and excessive tiredness/fatigue (4.7 vs. 17.5%, $p = 0.009$) than SARS-CoV-2-infected patients with cirrhosis.

SARS-CoV-2 infected patients with cirrhosis more frequently present with elevated aspartate aminotransferase levels than patients without cirrhosis

Patients with SARS-CoV-2 infection and cirrhosis presented more frequently with at least two-fold elevated aspartate aminotransferase (AST; 27.1 vs. 6.7%, $p < 0.001$) and total serum bilirubin concentrations (21.7 vs. 0.8%, $p < 0.001$) at baseline and during the course of infection (AST: 36.4 vs. 20.1%, $p = 0.005$; bilirubin: 24.2 vs. 6.4%, $p < 0.001$) than patients without cirrhosis. Notably, alanine transaminase (ALT) elevations were not observed more frequently in SARS-CoV2-infected patients with cirrhosis (Table 3).

To investigate whether AST elevations in cirrhosis were a correlate of acute severe alcoholic hepatitis,[28] we applied the published clinical criteria for alcoholic hepatitis.[29] The incidence of patients with alcohol-related liver disease, a total serum bilirubin greater than 2-fold above the upper normal limit, and an aspartate aminotransferase between 1 and 10-fold was 3%.

The high case mortality rates in patients with cirrhosis and COVID-19 is largely determined by cirrhosis-associated extrahepatic comorbidities

All patients with cirrhosis identified from the LEOSS database were hospitalized as compared to 93% of patients without cirrhosis (Table 1). In the unmatched cohorts, admissions to the intensive care unit (ICU) were similar (21.2 vs. 26.9%, $p = 0.432$). Prior to matching, the case fatality rate for patients with cirrhosis was significantly higher than in patients without (31.4 vs. 14.9%, $p < 0.001$).

Following PSM to balance age category, gender, obesity, smoking status, diabetes, CKD, coronary heart disease and the modified CCI, neither the rate of hospitalized patients nor the rate of ICU admissions was different between the groups (Table 1). SARS-CoV-2-infected patients with cirrhosis had a case fatality rate similar to SARS-CoV-2-infected patients without cirrhosis matched for extrahepatic comorbid conditions (28.8 vs. 26.1%, $p = 0.644$).

The 95% confidence intervals of the case fatality rates were 20.0%–42.9% in patients with cirrhosis, 14.0%–15.8% in unmatched patients without cirrhosis, 17.4%–27.7% in matched patients without cirrhosis controlling for age category, gender, and the modified CCI, and 20.7%–31.3% in matched patients without cirrhosis controlling for age category, gender, obesity, smoking status, diabetes, CKD, coronary heart disease and the modified CCI.

Risk factors of SARS-CoV-2-associated mortality in patients with cirrhosis

Among the investigated baseline characteristics and demographics, only older age >65 years (OR 4.02, 95% CI 1.28–12.66, $p = 0.018$) and Child-Pugh class C (OR 4, 95% CI 1.18–13.54, $p = 0.026$) were significantly associated with mortality in this data set (Table 4). The case fatality rate in patients with cirrhosis and SARS-CoV-2 infection aged 65 years and older was nearly three times that in patients younger than 65 years (43.6% vs. 16.1%, Figure 1a). Like-wise, the mortality rate in patients with a Child-Pugh score C was more than twice that in patients with a Child-Pugh class A or B (57.1% vs. 25.0%, Figure 1b). Age over 65 years (adjusted OR 6.61, 95% CI

TABLE 1 Characteristics of SARS-CoV-2 infected patients with and without cirrhosis

	SARS-Cov2- infected patients with cirrhosis, before matching (n = 70)	SARS-Cov2- infected patients without cirrhosis, before matching (N = 7026)	p value	SARS-Cov2- infected patients with cirrhosis, after 1:4 matching[a] (n = 66)	SARS-Cov2- infected patients without cirrhosis, after 1:4 matching[a] (n = 264)	p value
Age categories; n (%)						
18–25 years	1 (1.4)	195 (2.8)	0.004	1 (1.5)	1 (0.4)	0.156
26–35 years	0	527 (7.5)		0	4 (1.5)	
36–45 years	3 (4.3)	617 (8.8)		3 (4.5)	9 (3.4)	
46–55 years	7 (10.0)	1073 (15.3)		7 (10.6)	23 (8.7)	
56–65 years	20 (28.6)	1312 (18.7)		19 (28.8)	49 (18.6)	
66–75 years	20 (28.6)	1178 (16.8)		17 (25.8)	57 (21.6)	
76–85 years	17 (24.3)	1507 (21.4)		17 (25.8)	91 (34.5)	
>85 years	2 (2.9)	617 (8.8)		2 (3.0)	30 (11.4)	
Gender; n (%)						
Male	45 (64.3)	4013 (57.1)	0.275	42 (63.6)	171 (64.8)	0.886
Female	25 (35.7)	3013 (42.9)		24 (36.8)	93 (35.2)	
White ethnicity; n/N (%)	57/58 (98.3)	5512/2779 (95.4)	0.522	54 (98.2)	236 (95.2)	0.475
Obesity; n/N (%)	8/40 (20.0)	1264/4205 (30.1)	0.224	8/37 (21.6)	20/161 (12.4)	0.188
Smoker; n/N (%)						
No	10/23 (43.5)	2028/3042 (66.7)	0.015	10/20 (50.0)	102/142 (71.8)	0.082
Current	9/23 (39.1)	503/3042 (16.5)		7/20 (35.0)	24/142 (16.9)	
Former	4/23 (17.4)	511/3042 (16.8)		3/20 (15.0)	16/142 (11.3)	
Diabetes; n/N (%)	25/70 (35.7)	1486/7000 (21.2)	0.005	23/66 (34.8)	87/259 (33.6)	0.885
Chronic kidney disease; n/N (%)	24/69 (34.8)	984/6998 (14.1)	<0.001	20/65 (30.8)	67/239 (28.0)	0.646
Hypertension; n/N (%)	41/70 (58.6)	3440/6978 (49.3)	0.149	38/66 (57.6)	165/253 (65.2)	0.254
Coronary artery disease; n/N (%)	17/70 (24.3)	917/6940 (13.2)	0.012	14/66 (21.2)	68/248 (27.4)	0.347
Malignancy; n/N (%)	3/70 (4.3)	413/7015 (5.9)	0.798	3/66 (4.5)	29/264 (11.0)	0.161
Asthma; n/N (%)	0/70 (0)	355/7010 (5.1)	0.050	0/66 (0)	12/264 (4.5)	0.134
Chronic obstructive pulmonary disease; n/N (%)	5/70 (7.1)	425/7005 (6.1)	0.615	5/66 (7.6)	27/264 (10.2)	0.819
Modified CCI; mean ± SD	1.98 ± 1.73	1.18 ± 1.73	<0.001	1.83 ± 1.64	2.11 ± 2.20	0.769
SARS-CoV-2-targeted therapy; n (%)						
Anticoagulants and antiplatelet drugs	41 (58.6)	7026 (59.0)	1.000	39 (59.1)	135 (51.1)	0.272
Antiviral drugs	7 (10.0)	1429 (20.3)	0.035	7 (10.6)	46 (17.4)	0.195
Antibiotic and antimycotic drugs	23 (32.9)	2604 (37.1)	0.535	22 (33.3)	128 (48.5)	0.028
Immunomodulatory drugs or steroids	19 (27.1)	1695 (24.9)	0.575	16 (24.2)	50 (18.9)	0.389
Hospitalization; n (%)	70 (100.0)	6489 (93.0)	0.015	66 (100.0)	262 (99.6)	1.000

TABLE 1 (Continued)

	SARS-Cov2- infected patients with cirrhosis, before matching (n = 70)	SARS-Cov2- infected patients without cirrhosis, before matching (N = 7026)	p value	SARS-Cov2- infected patients with cirrhosis, after 1:4 matching[a] (n = 66)	SARS-Cov2- infected patients without cirrhosis, after 1:4 matching[a] (n = 264)	p value
ICU admission; n (%)	15 (21.4)	1606 (22.9)	0.887	14 (21.2)	71 (26.9)	0.432
Case fatality; n (%)	22 (31.4)	1046 (14.9)	<0.001	19 (28.8)	69 (26.1)	0.644

Note: Baseline characteristics are presented as frequencies with percentages or means with standard deviation (SD). p values are based on either Fisher's exact test for categorical variables or Mann-Whitney U-test for continuous variables.

[a]1:4 PSM controlling for age category, gender, obesity, smoking status, diabetes, CKD, coronary heart disease and a modified Charlson's comorbidity index (without age category, liver disease and HIV).

TABLE 2 Symptoms of COVID-19 at presentation

	SARS-Cov2- infected patients with cirrhosis, before matching (n = 70)	SARS-Cov2- infected patients with cirrhosis, after 1:4 matching[b] (n = 66)	SARS-Cov2- infected patients without cirrhosis, after 1:4 matching[b] (n = 264)	p value[a]
Reported symptoms; n/N (%)				
Fever	13/68 (19.1)	12/64 (18.8)	82/229 (35.8)	0.010
Dyspnoea	12/65 (18.5)	11/61 (18.0)	64/220 (29.1)	0.102
Dry cough	12/68 (17.6)	10/64 (15.6)	57/229 (24.9)	0.132
Diarrhea	7/68 (10.3)	6/64 (9.4)	8/229 (3.5)	0.089
Nausea/emesis	6/68 (8.8)	5/64 (7.8)	14/229 (6.1)	0.576
Muscle weakness	5/68 (7.4)	5/64 (7.8)	21/229 (9.2)	1.000
Excessive tiredness/ fatigue	4/68 (5.9)	3/64 (4.7)	40/229 (17.5)	0.009
Productive cough	3/68 (4.4)	2/64 (3.1)	19/229 (8.3)	0.270
Muscle aches	2/68 (2.9)	2/64 (3.1)	18/229 (7.9)	0.264
Wheezing	2/68 (2.9)	2/64 (3.1)	2/229 (0.9)	0.209
Sore throat	2/68 (2.9)	2/64 (3.1)	10/229 (4.4)	1.000
Taste disorder	1/68 (1.5)	1/64 (1.6)	6/229 (2.6)	1.000
Runny nose	1/68 (1.5)	1/64 (1.6)	3/229 (1.3)	1.000
Headaches	1/68 (1.5)	1/64 (1.6)	18/229 (7.9)	0.086
Smell disorder	0/68 (0)	0/64 (0)	4/229 (1.7)	0.580
No reported symptoms; n/N (%)	24/68 (35.3)	24/64 (37.5)	24/229 (10.5)	<0.001

Note: Data are presented as frequencies with percentages.

[a]Fisher's exact test comparing matched cases and controls.

[b]1:4 PSM controlling for age category, gender, obesity, smoking status, diabetes, CKD, coronary heart disease and a modified Charlson's comorbidity index (without age category, liver disease and HIV).

1.66–26.24, p = 0.007) and Child-Pugh class C (adjusted OR 7.33, 95% CI 1.65–32.61, p = 0.009) remained significant in multivariable analysis (Table 4).

Concomitant medications commonly prescribed in patients with cirrhosis, such as proton pump inhibitors, beta blockers, antibiotics, and diuretics, were not significantly associated with mortality in patients with cirrhosis and SARS-CoV-2 infection (Table 4).

Disease course of SARS-CoV-2 infection in patients with cirrhosis

Of the 70 patients with cirrhosis and SARS-CoV-2 infection, 57 initially presented in the uncomplicated phase (UC), meaning they were either asymptomatic or had mild symptoms. Eight patients initially presented with symptoms of complicated disease

TABLE 3 Laboratory parameters of SARS-CoV-2 infected patients in different phases of infection

	SARS-Cov2- infected patients with cirrhosis, before matching (n = 70)	SARS-Cov2- infected patients with cirrhosis, after 1:4 matching[a] (n = 66)	SARS-Cov2- infected patients without cirrhosis, after 1:4 matching[a] (n = 264)	p value[b]
Alanine aminotransferase				
>2×ULN at presentation; n/N (%)	5/54 (9.3)	5/50 (10.0)	10/178 (5.6)	0.330
>2×ULN at any time[c]; n/N (%)	12 (17.1)	9 (13.6)	45 (17.0)	0.580
Aspartate aminotransferase				
>2×ULN at presentation; n/N (%)	13/52 (25.0)	13/48 (27.1)	11/165 (6.7)	<0.001
>2×ULN at any time[c]; n/N (%)	26 (37.1)	24 (36.4)	53 (20.1)	0.005
Gamma-glutamyltransferase				
>5×ULN at presentation; n/N (%)	9/61 (14.8)	9/57 (15.8)	9/242 (3.7)	0.002
>5×ULN at any time[c]; n/N (%)	12 (17.1)	12 (18.2)	26 (9.8)	0.082
Total bilirubin				
>2×ULN at presentation; n/N (%)	10/50 (20.0)	10/46 (21.7)	2/163 (0.8)	<0.001
>2×ULN at any time[c]; n/N (%)	16 (22.9)	16 (24.2)	17 (6.4)	<0.001
Creatinine				
>2×ULN at presentation; n/N (%)	13/58 (25.9)	10/54 (18.5)	25/214 (11.7)	0.182
>2×ULN at any time[c]; n/N (%)	23 (32.9)	19 (28.8)	61 (23.1)	0.339

Note: Data are presented as frequencies with percentages. ULN: Upper limit of normal.

[a]1:4 PSM controlling for age category, gender, obesity, smoking status, diabetes, CKD, coronary heart disease and a modified Charlson's comorbidity index (without age category, liver disease and HIV).

[b]Fisher's exact test comparing matched cases and controls.

[c]missing values of laboratory tests at individual time points were imputed as not increased.

TABLE 4 Associations between patient characteristics at baseline and death in SARS-CoV-2-infected patients with cirrhosis

			Univariable analysis		Multivariable analysis	
	Survived (n = 48)	Died (N = 22)	OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Baseline characteristics; n/N (%)					Model 1	
Age >65 years (vs. 18–65 years)	22/48 (45.8)	17/22 (77.3)	4.02 (1.28–12.66)	0.018	6.61 (1.66–26.24)	0.007
Male gender (vs. Female)	32/48 (66.7)	13/22 (59.1)	0.72 (0.26–2.04)	0.540	-	-
White ethnicity (vs. Other ethnicities)	39/40 (97.5)	18/18 (100)	-	-	-	-
Obesity (yes vs. no)	7/28 (25.0)	1/12 (8.3)	0.27 (0.03–2.51)	0.251	-	-
Alcohol-related liver disease (vs. Other aetiologies)	17/39 (43.6)	6/13 (46.2)	1.11 (0.31–3.91)	0.872	-	-
Acute decompensation in the last 30 days (yes vs. no)	12/35 (34.3)	7/17 (41.3)	1.34 (0.41–4.42)	0.629	-	-
Child-Pugh class C[a] (vs. Child-Pugh A/B)	6/48 (12.5)	8/22 (36.4)	4.00 (1.18–13.54)	0.026	7.33 (1.65–32.61)	0.009
Comorbid conditions; n/N (%)						
Diabetes (yes vs. no)	17/48 (35.4)	8/22 (36.4)	1.04 (0.36–2.98)	0.939	-	-
Chronic kidney disease (yes vs. no)	17/48 (35.4)	7/21 (33.3)	0.92 (0.31–2.69)	0.876	-	-
Hypertension (yes vs. no)	29/48 (60.4)	12/22 (54.5)	0.79 (0.28–2.18)	0.644	-	-
Coronary artery disease (yes vs. no)	14/48 (70.8)	3/22 (13.6)	0.38 (0.10–1.51)	0.170	-	-
Malignancy (yes vs. no)	3/48 (6.3)	0/22 (0)	-	-	-	-
Chronic obstructive pulmonary disease (yes vs. no)	3/48 (6.3)	2/22 (9.1)	1.50 (0.23–9.69)	0.670	-	-
Concomitant medication; n/N (%)						
Beta blockers (yes vs. no)	29/43 (67.4)	7/16 (43.8)	0.38 (0.12–1.22)	0.102	-	-
Diuretics (yes vs. no)	31/44 (70.5)	16/18 (88.9)	3.36 (0.67–16.72)	0.140	-	-
Norfloxacin (yes vs. no)	2/43 (4.7)	0/14 (0)	-	-	-	-
Proton pump inhibitors (yes vs. no)	28/43 (65.1)	14/17 (82.4)	2.50 (0.62–10.10)	0.198	-	-
Rifaximin (yes vs. no)	7/43 (16.3)	2/16 (12.5)	0.74 (0.14–3.98)	0.720	-	-
Statins (yes vs. no)	10/40 (25.0)	4/16 (25.0)	1.00 (0.26–3.82)	1.000	-	-

Note: Data are presented as frequencies with percentages.

[a]Components of the Child-Pugh score that were missing, were imputed as the lowest category. OR are based on binary logistic regression analysis.

(CO) defined by the need for oxygen supplementation, heart failure or hepatocellular damage, and five patients initially presented in the critical phase (CR) with manifest organ failure. Progression of the disease from the UC to the CO or CR phase was frequently observed and was associated with high mortality. Overall, 57% of patients with cirrhosis were in the CO or CR phase at some point during their hospital stay (Figure 2) as compared to 67% of matched controls (Supplementary Figure S1).

Overall, 21.4% of patients with cirrhosis received intensive case treatment comprising of 54.5% of the non-survivors and 6.3% of the survivors. In patients with Child C cirrhosis, ICU admission was 35.7% as compared to 17.9% in patients with Child-Pugh A/B cirrhosis (p = 0.161). Patients with cirrhosis older than 65 years of age were admitted to the ICU in 25.6% of cases as compared to 16.1% in patients 65 years or younger (p = 0.39). The reasons for withholding ICU treatment were not given in the LEOSS registry. Interestingly, there were six deaths reported amongst patients who did not meet the pre-specified LEOSS criteria for complicated or critical disease phase during observation (Figure 2). Reported causes of death in these patients were COVID-19 (n = 1), multiple organ failure (n = 3), comorbid conditions (n = 1), or unknown (n = 1).

Extrahepatic organ failures are predictors of mortality in SARS-CoV-2 infected patients with cirrhosis

To investigate the role of ACLF in patients with COVID-19, we assessed the organ failure criteria of the European Foundation for the Study of Chronic Liver Failure (EF CLIF,[26]). An acute decompensating event, that is, new or worsening ascites, acute hepatic encephalopathy or gastrointestinal bleeding, was observed in 19/52 (36.5%) SARS-CoV2-infected patients with cirrhosis. In contrast, 32 (45.7%) patients experienced organ failure according to the EF-CLIF

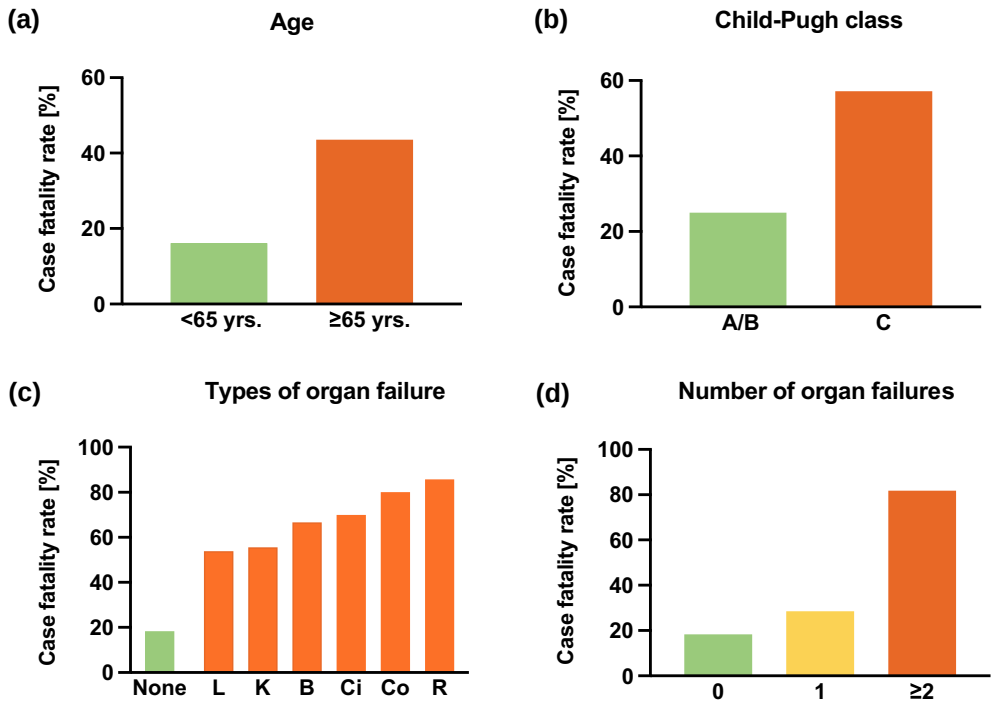

FIGURE 1 Case fatality rates in SARS-CoV-2-infected patients with cirrhosis stratified for age, disease severity, and organ failure. Case fatality rates of 70 SARS-CoV-2 infected patients with cirrhosis are depicted and stratified for (a) age, (b) Child-Pugh class, (c) types of organ failure, and (d) number of organ failures. Organ failures were defined according to the EF CLIF criteria based on the CLIF SOFA score. Case fatality rates were colour coded as follows: ≤25%: green, >25% and ≤40%: yellow, >40% orange. For statistical comparisons and significance levels see Table 4. B, Brain; Ci, Circulatory; Co, Coagulation; K, Kidney; L, Liver; R, Respiratory failure

at some time point (Table 5), suggesting that a relevant number of COVID-19-associated organ failures do not fall within the classical definition of ACLF.

In contrast to liver failure, the occurrence of extrahepatic organ failure was a significant predictor of mortality in patients with cirrhosis and COVID-19 (Table 5). The strongest association was recorded for respiratory failure as defined by a Horowitz index (SpO_2 to FiO_2 ratio) ≤200 mmHg (OR 35.0, 95% CI 3.55–344.69, $p = 0.002$), followed by circulatory failure as defined by vasopressor use (OR 10.79, 95% CI 2.28–51.02, $p = 0.003$), renal failure as defined by serum creatinine ≥2 mg/dl, renal replacement therapy or terlipressin use (OR 4.0, 95% CI 1.24–12.89, $p = 0.020$), central nervous failure defined as hepatic encephalopathy grade 3–4 (OR 7.56, 95% CI 1.19–48.03, $p = 0.032$), and coagulation failure as defined by INR ≥2.0 or platelets <20/nl (OR 11.43, 95% CI 1.18–111.09, $p = 0.036$) as per definitions from the CANONIC study.[26] Case fatality rates were 70% or higher in patients with respiratory failure (85.7%), coagulatory failure (80.0%), or circulatory failure (70.0%; Figure 1c). In patients with cirrhosis and COVID-19 who developed sequential or concurrent failure of two or more organs, the OR for death was 19.93 (95% CI 3.51–113.30, $p = 0.001$; Figure 1d).

Among SARS-CoV-2-infected patients with cirrhosis, 29 (41%) had documented probable or proven bacterial superinfection. The case fatality rate in patients with probable or proven bacterial superinfection was 51.7% as compared to 17.1% in patients without ($p = 0.004$). When the analysis was restricted to patients with proven bacterial infection, this difference was no longer significant (50.0% vs. 26.8%; $p = 0.11$).

Patients with cirrhosis and COVID-19 have a comparable mortality risk to patients with cirrhosis and spontaneous bacterial peritonitis

An external cohort was introduced to compare SARS-CoV-2-associated mortality to that by bacterial infections. For this purpose, data on 169 hospitalized patients with SBP from two previously published studies[23,24] were analysed. Before matching, patients with SBP were younger and had more advanced liver disease than patients with SARS-CoV-2 infection (Table 6). COVID-19 case fatality rate was comparable to 28-day mortality after SBP (31.4 vs. 27.2%, $p = 0.531$).

As age and Child-Pugh stage C were significant predictors of death in SARS-CoV-2 infected patients according to our analysis, we performed a 1:1 PSM controlling for age category, sex and Child-Pugh class C. Using these criteria, 54 patients with SARS-CoV-2 infection were successfully matched with 54 patients with SBP. After matching, markers of systemic inflammation were higher in patients with SBP than in patients with SARS-CoV-2 infection, and elevated bilirubin levels continued to be observed more frequently (Table 6). However, the COVID-19 case-fatality rate remained similar

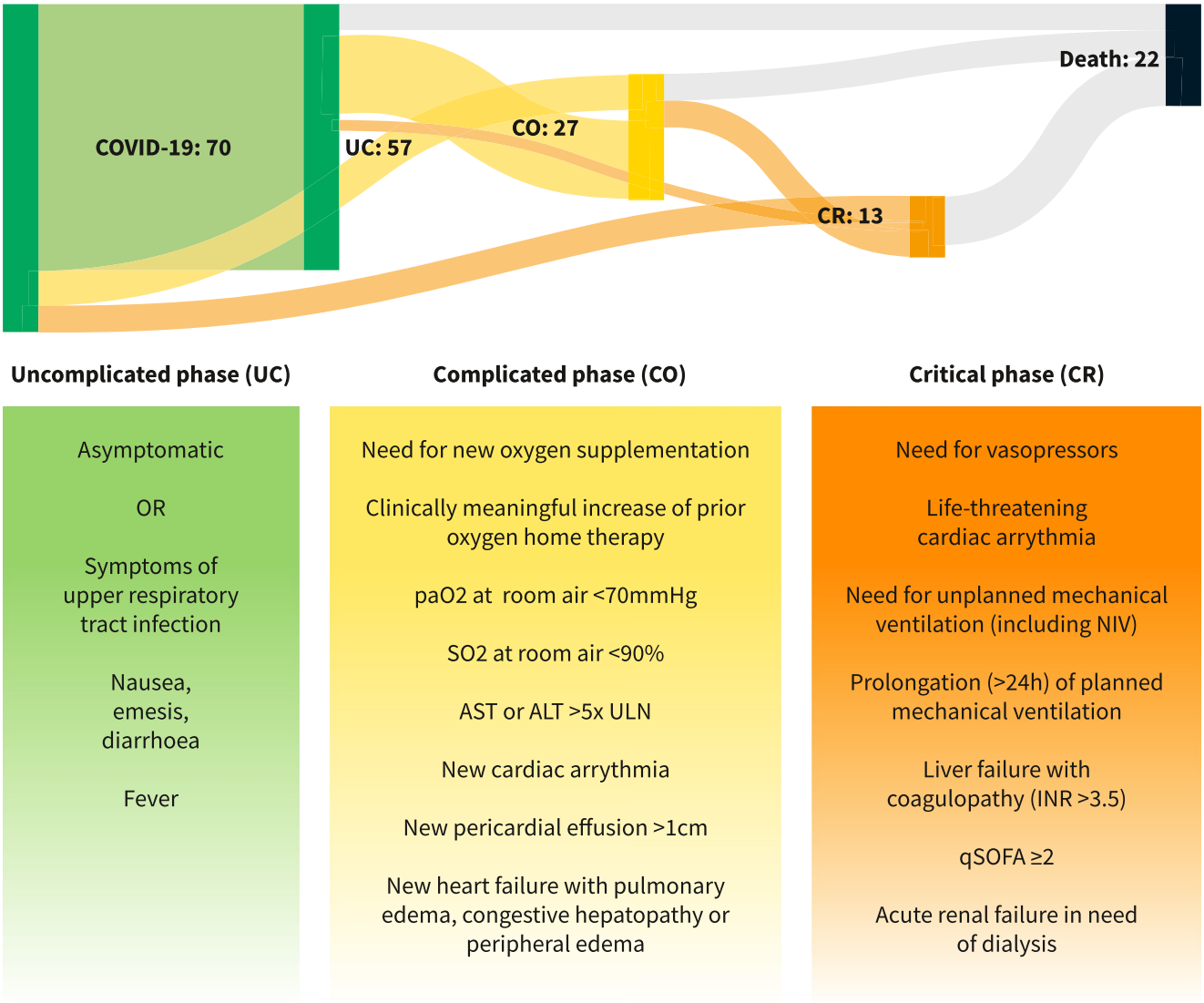

FIGURE 2 COVID-19 disease phases (LEOSS) and phase transition in patients with cirrhosis. Sankey flow diagram of disease courses of patients with cirrhosis and COVID-19 in the UC, the complicated phase and the CR. ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, International Normalized Ratio; NIV, non-invasive ventilation; paO2, partial pressure of oxygen; qSOFA, quick Sequential Organ Failure Assessment; SO2, blood oxygen saturation; ULN, upper limit of the norm. The flow diagram was build using the SankeyMATIC diagram builder (https://sankeymatic.com, as accessed on 16 August 2021)

to 28-day mortality after SBP in the matched cohorts (33.3 vs. 31.5%, $p = 1.000$).

DISCUSSION

By using a large multinational registry analysing real-world data of cases and carefully matched controls, we herein show (i) that SARS-CoV-2 infection is often asymptomatic in patients with cirrhosis; (ii) that older age and advanced cirrhosis stage are the main indicators of mortality after COVID-19 infection, and (iii) that mortality is mainly driven by extrahepatic organ failure. Although the case fatality in patients with cirrhosis was high, in this data set of patients with cirrhosis hospitalized for SARS-CoV-2 between March 2020 and March 2021, COVID-19 case fatality was not statistically different to that of carefully matched patients with comparable comorbidities but without cirrhosis.

In line with international registries[7,15] and observational cohort studies,[16,18] the COVID-19 case fatality rate was 31% in hospitalised patients with cirrhosis with an independent contribution of both older age and more advanced liver disease.[15,19] The high case fatality in cirrhosis could be explained to a significant part by the present extrahepatic comorbidities that exist in SARS-CoV-2 infected patients with cirrhosis. In accordance with a population-based analysis by the US National COVID Cohort Collaborative (N3C),[19] comorbid conditions contributing to a more severe course of COVID-19,[2–4] such as diabetes (N3C: 49 vs. 39%; LEOSS: 36 vs. 21%), CKD (N3C: 25 vs. 19%; LEOSS: 35 vs. 18%), and cardiac comorbidities (N3C: 23

TABLE 5 Associations between organ failure in the disease course and death in SARS-CoV-2-infected patients with cirrhosis

			Univariable analysis	
	Survived (n = 48)	Died (N = 22)	OR (95% CI)	p value
Organ failures[a]; n/N (%)				
Liver failure (yes vs. no)	6/41 (12.8)	7/21 (33.3)	3.42 (0.98–11.90)	0.054
Kidney failure (yes vs. no)	8/40 (20.0)	10/20 (50.0)	4.00 (1.24–12.89)	0.020
Brain failure (yes vs. no)	2/36 (5.6)	4/13 (30.8)	7.56 (1.19–48.03)	0.032
Coagulation failure (yes vs. no)	1/41 (2.4)	4/18 (22.2)	11.43 (1.18–111.09)	0.036
Circulatory failure (yes vs. no)	3/40 (7.5)	7/15 (46.7)	10.79 (2.28–51.02)	0.003
Respiratory failure (yes vs. no)	1/36 (2.8)	6/12 (50.0)	35.00 (3.55–344.69)	0.002
Number of organ failures[a]; n (%)				
0	31 (64.6)	7 (31.8)	1.00 (reference)	-
1	15 (31.3)	6 (27.3)	1.77 (0.51–6.20)	0.371
2 or more	2 (4.2)	9 (40.4)	19.93 (3.51–113.30)	0.001

Note: Odds ratios (OR) are based on binary logistic regression analysis.

[a]Organ failures according to the EF CLIF criteria based on the CLIF SOFA score.

vs. 19%; LEOSS: 24 vs. 13%) were overrepresented in SARS-CoV-2-infected patients with cirrhosis.

In order to carefully balance risk factors between patients with and without cirrhosis, we performed PSM for a large number of covariates within the LEOSS registry database. After adjusting for age, sex, obesity, smoking status, diabetes, CKD, coronary heart disease and the severity of extrahepatic comorbidities, we found similar mortality rates between SARS-CoV-2-infected patients with and without cirrhosis, demonstrating a relevant contribution of cirrhosis-associated comorbidities to the outcome of SARS-CoV-2 infection in patients. The nature of the aggregated data does not allow us to assess the likelihood of the extent to which comorbidities are pathophysiologically linked to the state of cirrhosis.

Whereas mere acute decompensation was not associated with mortality in SARS-CoV-2-infected patients with cirrhosis, the occurrence of organ failure in the course of the disease was. Failure of one or more organs as defined by the CLIF SOFA score[26] occurred in 46% of patients with cirrhosis. We observed the highest mortality in patients fulfilling the criteria for respiratory failure, circulatory failure, or coagulation failure. The sequential or concurrent failure of two or more organs was associated with 80% case fatality. Emphasizing the significance of ACLF in SARS-CoV-2-infected patients with cirrhosis, even patients without documented progression into complicated or critical phases were often classified as having died from multiple organ failure.

One difference between our study and previous literature[15,17] is that SARS-CoV-2 associated mortality in patients with cirrhosis was largely related to extrahepatic comorbidities in our study, although other research groups have also employed matching techniques. Bajaj et al.[17] reported higher mortality rates in inpatients with cirrhosis and COVID-19 as compared to inpatients with COVID-19 without cirrhosis matching for age and gender but not comorbidities. Marjot et al.[15] employed age, sex, COPD, diabetes and heart disease and found increased mortality rates in patients with Child-Pugh B and C cirrhosis as compared to patients without chronic liver disease. The use of both, the CCI and individual comorbidities that are components of it, may have led to repeated adjustment and overfitting of our PSM model. However, an alternative model that considered only age category, sex, and the comorbidities encoded as the modified CCI resulted in a more unbalanced matching with an overrepresentation of diabetes and renal disease in patients with cirrhosis, which are strong determinants of COVID-19 outcome.

In the LEOSS registry CKD was prevalent in 35% of inpatients with cirrhosis and COVID-19. Considering that renal function is one of the main determinants of outcome in cirrhosis and renal failure is the most prognostically relevant single organ failure in cirrhosis,[26] matching for renal function could explain these differences. In contrast to these studies, we demonstrated that the number and severity of 18 predefined comorbidities were well balanced between cases and controls after PSM according to the modified CCI. In line with our study, cirrhosis was not independently associated with the development of severe complications, including mortality, in patients with COVID-19 in a nationwide cohort study from Korea.[21]

Respiratory failure develops in only 2%–5% of patients with acute decompensation of cirrhosis and it is associated with more severe ACLF grades and the highest mortality as observed in the CANONIC and the PREDICT study.[26,30,31] Although respiratory virus infections have been reported in association with acute decompensation of cirrhosis, organ failure, and death,[13] their role as a possible precipitant of ACLF is less well studied as compared to bacterial infections. Bacterial infections are well-known precipitators and perpetuators of systemic inflammation, immune dysfunction, and organ failure in patients with advanced cirrhosis. As infection-related ACLF is most

TABLE 6 Characteristics of SARS-CoV-2 infected patients with cirrhosis compared to a historical cohort of patients with spontaneous bacterial peritonitis (SBP)

	Patients with cirrhosis and COVID-19, before matching (n = 70)	Patients with cirrhosis and SBP, before matching (N = 169)	p value	Patients with cirrhosis and COVID-19, after 1:1 matching[a] (n = 54)	Patients with cirrhosis and SBP, after 1:1 matching[a] (n = 54)	p value
Age categories; n (%)						
18–25 years	1 (1.4)	0	<0.001	0	0	1.000
26–35 years	0	2 (1.2)		0	0	
36–45 years	3 (4.3)	23 (13.6)		2 (3.7)	2 (3.7)	
46–55 years	7 (10.0)	45 (26.6)		7 (13.0)	7 (13.0)	
56–65 years	20 (28.6)	57 (33.7)		20 (37.0)	20 (37.0)	
66–75 years	20 (28.6)	27 (16.0)		15 (27.8)	15 (27.8)	
76–85 years	17 (24.3)	13 (7.7)		9 (16.7)	9 (16.7)	
>85 years	2 (2.9)	2 (1.2)		1 (1.9)	1 (1.9)	
Gender; n (%)						
Male	45 (64.3)	126 (74.6)	0.117	34 (63.0)	34 (63.0)	1.000
Female	25 (35.7)	43 (25.4)		20 (37.0)	20 (37.0)	
Child-Pugh stage C	14 (20.0)	104 (61.5)	<0.001	14 (25.9)	14 (25.9)	1.000
Laboratory parameters at diagnosis						
Bilirubin >2×ULN	10/50 (20.0)	99/160 (62.0)	<0.001	8/38 (21.1)	23/53 (43.4)	0.043
INR >2.0	1/44 (2.3)	34/158 (21.5)	0.001	1/32 (3.1)	3/54 (5.6)	1.000
Creatinine >2×ULN	13/58 (22.4)	33/156 (21.2)	0.853	9/44 (20.5)	10/53 (18.9)	1.000
C-reactive protein >30 mg/l	28/56 (50.0)	125/159 (78.6)	<0.001	19/42 (45.2)	44/52 (84.6)	<0.001
Leukocytes ≥12,000/µl	3/58 (5.2)	64/164 (39.0)	<0.001	3/44 (6.8)	19/54 (35.2)	0.001
Case fatality; n (%)	22 (31.4)	46 (27.2) at 28 days	0.531	18 (33.3)	17 (31.5) at 28 days	1.000

Note: Data are presented as frequencies with percentages.

[a]1:1 PSM controlling for age category, gender, and Child-Pugh class C.

frequent after pneumonia and peritonitis,[32] we compared the mortality after SARS-CoV-2 infection to SBP, a typical bacterial infection in cirrhosis. After controlling for the confounding factors age and Child-Pugh class, case fatality rates of SARS-CoV-2 infected patients with cirrhosis were comparable to the 28-day mortality rates observed after SBP. Although we do not have access to a well-defined cohort of bacterial pneumonia patients in a similar health care setting, pneumonia-associated mortality in patients with cirrhosis is comparable and not significantly higher than SBP based on large international studies and health insurance data.[33,34] In our cohort, suspected or proven bacterial superinfection was associated with increased mortality in SARS-CoV-2-infected patients with liver cirrhosis.

Our study also provides information on the presentation and disease course of SARS-CoV-2 infection in patients with cirrhosis. Elevated aspartate aminotransferase and total serum bilirubin levels were common laboratory findings at presentation, while alanine aminotransferase was less frequently elevated. Patients with cirrhosis reported significantly less fever and fatigue than patients without cirrhosis, and the proportion of patients with cirrhosis who reported no symptoms of COVID-19 was over 35%. Although 81% of patients with cirrhosis and SARS-CoV-2 infection initially had a mild course of disease, more than half of them met the criteria for a complicated or critical COVID-19 LEOSS phase at some point in the course of the disease. It remains unclear, whether a timelier hospitalization and provision of medical care would have prevented such a development.

About 1% of the patients with SARS-CoV-2 infection in the LEOSS registry had cirrhosis. This is well in line with the number of hospitalisations in Germany before the pandemic. According to a nationwide population-based study, a total of 0.94% out of 248,085,936 admissions had cirrhosis.[35] In two large U.S. studies, the incidence of cirrhosis among patients with SARS-CoV-2 was 0.3%–1.8%[36,37] and in a study from a Portuguese referral centre, the frequency was 0.8%.[38]

This registry-based matched cohort study has strengths and limitations. Strengths of the study are the propensity score-matched design, the identical timeframe of hospitalization for multinational cirrhotic and non-cirrhotic patients, the comparatively large cohort of patients with cirrhosis, and the analysis of disease phase transitions. As with any registry study, there is a potential lack of data verification, patients may not have completed follow-up, missing data must be dealt with, and duplicate registration is possible in principle. For example, a small number of patients with cirrhosis were recorded as having died of multiple organ failure following SARS-CoV-2 infection, but were only registered in the LEOSS definition of uncomplicated disease.

Our study has several limitations. One specific limitation of the LEOSS database is the categorization of continuous parameters, which results in the loss of information and may underestimate the true predictive performance of certain variables. Because LEOSS is an anonymized registry, data were not stored under a pseudonym and most data were queried in categories, making reverse database searches in the hospital information system nearly impossible. As a result, we are unable report *post hoc* on composite scores that are computed through continuous variables, such as the MELD score or the CLIF-C ACLF score. Furthermore, the results may not be transferable to all areas of Europe, as the majority of patients in the LEOSS database were documented in Germany. Although university hospitals in larger cities had the highest documentation rates in the LEOSS database, specialised liver departments may be underrepresented as questionnaire items such as “MELD score at diagnosis” and “worst MELD score” were often not reported. Another limitation is the predominance of patients with Caucasian/White ethnicity, which reflects on the European populace, but might limit generalizability for other ethnicities. Although our study provides the opportunity to compare data from patients with and without cirrhosis within one very detailed registry, the relatively small number of patients with cirrhosis (1%) allows only an approximate estimate of mortality within the 95% CI of 20%–43%. In addition, the number of patients with decompensated cirrhosis in this cohort during the first phases of the pandemic is low.

In our analysis, only cases for which SARS-CoV-2 outcomes were known as of 15 April 2021 were included. The last patient with cirrhosis in this analysis was diagnosed with SARS-CoV-2 infection in January 2021. The SARS-CoV2 variants in Germany and Central Europe during that period were B.1.177 (EU1), B.1.221, B.1.258, B.1.160, and the alpha variant B.1.1.7 (https://covariants.org; last accessed March 2022). Limiting the analysis to this time period means that the majority of patients reported were immunologically naïve to the SARS-CoV-2 virus, as vaccination against COVID-19 began in Germany in late December 2020. This is why our results may not be transferable to newer variants or disease course in immunized and vaccinated individuals.

As the prevalence of liver disease and cirrhosis has plateaued at 850 per 100,000 population in Europe,[39] patients with chronic liver disease remain a group at increased risk of severe disease and death. This European registry study analysing real-world data confirms a high risk of death in hospitalised patients with cirrhosis and SARS-CoV-2 infection comparable to that of specific bacterial infections such as SBP. Patients over 65 years of age and patients with cirrhosis were at the highest risk. Propensity score matching suggests that a large proportion of this excess mortality is due to cirrhosis-associated extrahepatic comorbidities. The development of respiratory failure and two-organ failure were associated with a mortality rate of 80%.

ACKNOWLEDGEMENTS

Jonathan F. Brozat, Jacob Nattermann, and Tony Bruns conceived of the study. Jonathan F. Brozat and Tony Bruns performed statistical analyses and drafted the manuscript. Jonathan F. Brozat, Michael Dreher, Christian Trautwein, and Andreas Stallmach helped shape the research, analysis and manuscript. Tony Bruns, Philipp A. Reuken, and Andreas Stallmach provided clinical data. All authors discussed the results and critically revised the manuscript for important intellectual content. We express our deep gratitude to all study teams supporting the LEOSS study. The LEOSS study group contributed at least 5 per mille to the analyses of this study: Technical University of Munich (Christoph Spinner), University Hospital Regensburg (Frank

Hanses), Hospital Passau (Julia Lanznaster), Hospital Ernst von Bergmann (Lukas Tometten), University Hospital Jena (Maria Madeleine Ruethrich), Hospital Ingolstadt (Stefan Borgmann), University Hospital Frankfurt (Maria Vehreschild), Johannes Wesling Hospital Minden Ruhr University Bochum (Kai Wille), Catholic Hospital Bochum (St. Josef Hospital) Ruhr University Bochum (Kerstin Hellwig), University Hospital Wuerzburg (Nora Isberner), Marien Hospital Herne Ruhr University Bochum (Timm Westhoff), University Hospital Schleswig-Holstein Luebeck (Jan Rupp), German Heart Centre Munich (Markus Freissmuth), Elbland Hospital Riesa (Joerg Schubert), Elisabeth Hospital Essen (Ingo Voigt), Hospital Bremen-Centre (Bernd Hertenstein), Hospital St. Joseph-Stift Dresden (Lorenz Walter), Municipal Hospital Karlsruhe (Christian Degenhardt), University Hospital Dresden (Katja de With), University Hospital Freiburg (Siegbert Rieg). The LEOSS study infrastructure group: Jörg Janne Vehreschild (Goethe University Frankfurt), Carolin E. M. Jakob (University Hospital of Cologne), Lisa Pilgram (Goethe University Frankfurt), Melanie Stecher (University Hospital of Cologne), Susana M. Nunes de-Miranda (University Hospital of Cologne), Nick Schulze (University Hospital of Cologne), Sandra Fuhrmann (University Hospital of Cologne), Max Schons (University Hospital of Cologne), Annika Claßen (University Hospital of Cologne), Bernd Franke (University Hospital of Cologne) und Fabian Praßer (Charité, Universitätsmedizin Berlin). The LEOSS registry was supported by the German Centre for Infection Research (DZIF) and the Willy Robert Pitzer Foundation. TB is supported by the German Research Foundation (SFB1382 Project ID 403224013/B07).

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data availability is described here: https://leoss.net/wp-content/uploads/2020/04/Appendix-C_Data-Use-and-Access-Policy-V2.1.pdf.

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How to cite this article: Brozat JF, Hanses F, Haelberger M, Stecher M, Dreher M, Tometten L, et al. COVID-19 mortality in cirrhosis is determined by cirrhosis-associated comorbidities and extrahepatic organ failure: results from the multinational LEOSS registry. United European Gastroenterol J. 2022;10(4):409–24. https://doi.org/10.1002/ueg2.12232