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Research Article

Outcomes of COVID-19 among Patients with Chronic Liver Disease: A Danish Prospective, Population-Based Cohort Study

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Aims. Chronic liver disease and cirrhosis are associated with immune dysregulation and might increase the risk of acquiring COVID-19 and developing more severe outcomes of it. In a population-based cohort study of patients with chronic liver disease and cirrhosis, we investigated the association between liver disease and COVID-19. We assessed the impact of COVID-19 infection on disease severity and the course of liver disease. *Methods.* We included all patients living in the Capital Region of Denmark and Region Zealand with chronic liver disease and a positive RT-PCR test for SARS-CoV-2. The background population was 2.7 million people; of these, 19,743 people had a diagnosis of liver disease. Between Feb 1, 2020, and Feb 27, 2021, 7,240 people with chronic liver disease were tested for SARS-CoV-2. *Results.* There were 261 patients with chronic liver disease and COVID-19 in the study. Sixty-four (24.2%) patients had cirrhosis. People with cirrhosis were more likely to require hospitalization than patients with chronic liver disease (71.8% versus 16.2%, $p < 0.001$) and more likely to be admitted to an intensive care unit (7.8% versus 3.6%, $p = 0.005$) and had higher rates of mortality (18.7% versus 1.5%, $p = 0.001$). In univariate analyses controlled for age, gender, and comorbidities, cirrhosis remained an independent predictor of severe COVID-19. Of hospitalized patients with cirrhosis, 41% experienced a worsening of their liver disease during their COVID-19 infection. *Conclusion.* Patients with chronic liver disease, especially those with cirrhosis, are at major risk of a severe COVID-19 disease course and higher mortality.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus first detected in Wuhan, China, that causes coronavirus disease 2019 (COVID-19) [1]. Coronaviruses are enveloped RNA viruses that are distributed broadly among humans and cause respiratory, enteric, hepatic, and neurological diseases [1]. More than 170 million cases of COVID-19 have been reported globally, and the disease has resulted in more than three million deaths as of June 2021 [2]. Several studies have demonstrated that advanced age, chronic cardiopulmonary dis-

eases, immunosuppression, and obesity are potential risk factors for severe outcomes of COVID-19 [3].

Chronic liver disease (CLD) and cirrhosis are associated with immune dysregulation [4], resulting in an increased susceptibility to bacterial infections [5]. It has been hypothesized that patients with CLD might be at increased risk of acquiring COVID-19, although this has not been proven in any study [6, 7]. However, increased susceptibility to acquiring COVID-19 has been observed in chronically immunosuppressed liver transplant patients [8].

Prior studies have found that patients with CLD or cirrhosis experienced more frequent adverse outcomes of
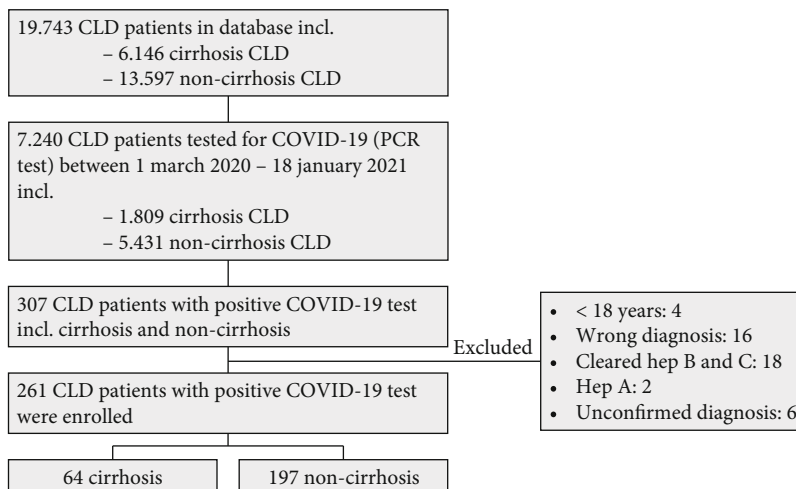
FIGURE 1: Flowchart of patient selection.

COVID-19 than the background population [9, 10] and that patients with CLD were at risk of developing acute liver injury, hepatic decompensation, or acute-on-chronic liver failure (ACLF) [11]. Mortality has been proven to increase for patients with cirrhosis and COVID-19 [6].

Current evidence suggests that comorbidities such as diabetes, obesity, and chronic obstructive pulmonary disease and smoking status predict a higher mortality among patients with CLD, decompensated cirrhosis, and hepatocellular carcinoma (HCC), when infected with COVID-19 [12].

However, the literature to date has been based mainly on nongeneralizable, hospital-based cohorts. This lack of data about nonhospitalized patients distorts our understanding of the impact of CLD on the course of COVID-19 and vice versa.

We therefore aimed to conduct a population-based cohort study, including all patients with preexisting CLD and cirrhosis, to generate an unselected dataset for examining the association, if any, between CLD and COVID-19. Our primary aim was to investigate the disease course and prognosis of COVID-19 among patients with CLD. Our secondary aim was to examine the impact of COVID-19 infection on the disease severity and course of CLD.

2. Materials and Methods

2.1. Study Design and Population. We established a population-based cohort (the Danish COVID-19 Chronic Liver Disease Cohort), comprising all patients living in the Capital Region of Denmark and Region Zealand with chronic liver disease and a positive reverse transcription-polymerase chain reaction test for SARS-CoV-2. In total, these two regions have 2.7 million inhabitants or 45.5% of the Danish population.

The inclusion period was March 1, 2020, until January 18, 2021, and the follow-up was completed on February 27, 2021. The first testing for SARS-CoV-2 took place in Denmark on January 28, 2020, and the first case of COVID-19 was detected there on February 27, 2020.

In April 2021, the Danish Vaccination Program offered patients with CLD the first dose of a COVID-19 vaccination, and it was at this time that we chose to stop recruiting for the study.

Eligible patients were identified using the International Classification of Diseases (Tenth Revision) codes for CLD (Supplementary Table 1), sourced from the Epic Health Care System in which all Danish residents are registered with a unique 10-digit identification number. We confirmed the diagnosis systematically though critical examination of biochemistry, ultrasound, computed tomography, biopsied material, and clinical examination as per guidelines.

Permission to retrieve health care data was approved by the Danish Patient Safety Authority (Jr. no: 31-1521-374) and Knowledge Center on Data Protection Compliance (Jr. no: P-2020-776).

2.2. Outcomes, Definitions, and Data Collection. The primary outcomes were measurements of disease severity among COVID-19 patients: (i) hospitalization, (ii) admission to intensive care, and (iii) mortality. Secondary outcomes for either cirrhosis or noncirrhotic CLD were defined as severe COVID-19 and deterioration of liver disease, including the prevalence of bacterial infections.

A positive test result for SARS-CoV-2 was defined as the presence of SARS-CoV-2 genomic material as determined by reverse transcription-polymerase chain reaction (RT-PCR) analysis of a specimen from either a nasopharyngeal swab or tracheal suctioning.

Bacterial infection involved a positive blood culture, bacterial pneumonia, or sepsis [13].

Intensive care was defined as admission to an intensive care unit, noninvasive ventilation, or mechanical ventilation.

The deterioration of cirrhosis was defined as either the progression of a patient's Child-Pugh class (A to B, A to C, or B to C) or an increase in their Model for End-Stage Liver Disease (MELD) score of more than 15 during a COVID-19 infection, with or without the development of clinical manifestations such as jaundice, ascites, or bleeding from gastro-oesophageal varices.

TABLE 1: Baseline characteristics of patients with chronic liver disease and COVID-19.

Variables	
Female, n (%)	122 (46.7)
Age (years), mean (SD)	56.13 (15.8)
BMI ($n = 235$), mean (SD)	27.1 (6.1)
Lifestyle	
Smokers ($n = 243$), n (%)	50 (19.2)
Current alcohol ($n = 246$), n (%)	129 (49.4)
Overuse alcohol, n (%)	42 (16.1)
Etiology of liver disease	
Hepatitis B, n (%)	79 (30.3)
Liver cirrhosis, n (%)	64 (24.5)
Alcoholic liver disease, n (%)	63 (24.1)
Nonalcoholic fatty liver disease, n (%)	52 (19.9)
Hemochromatosis, n (%)	23 (8.8)
Alcoholic liver insufficiency, n (%)	19 (7.3)
Chronic liver insufficiency, n (%)	17 (6.5)
Hepatitis C, n (%)	15 (5.7)
Autoimmune hepatitis, n (%)	9 (3.4)
Hepatocellular carcinoma, n (%)	9 (3.4)
Primary biliary cholangitis, n (%)	8 (3.1)
Alfa-1-antitrypsin deficiency, n (%)	6 (2.3)
Wilsons, n (%)	1 (0.4)
Primary sclerosing cholangitis, n (%)	1 (0.4)
Budd-Chiari, n (%)	1 (0.4)
Comorbidities	
Obesity, n (%)	72 (27.6)
Hypertension, n (%)	63 (24.1)
Type 2 diabetes, n (%)	53 (20.3)
Cardiac disease, n (%)	38 (14.6)
Autoimmune diseases, n (%)	37 (14.2)
Chronic pulmonary disease, n (%)	32 (12.3)
History of stroke or hemiplegia, n (%)	15 (5.7)
Asthma, n (%)	11 (4.2)
Localized solid tumor, n (%)	11 (4.2)
Chronic kidney disease, n (%)	9 (3.4)
Dementia, n (%)	6 (2.3)
No comorbidities, n (%)	99 (37.9)
Charlson Comorbidity Index, mean (SD)	3.26 (2.5)
Number of hospital admissions in the last 12 months prior to COVID-19 diagnosis, mean (SD)	1.0 (2.6)
Hospitalization length (cumulated), median (IQR)	13 (3-33.50)
Biochemistry in plasma	
Hemoglobin, mean (SD)	8.2 (1.3)
Platelet ($\times 10^9$/L), mean (SD)	219 (97.7)
ALAT (U/L), mean (SD)	40.9 (35.1)
Albumin (g/dL), mean (SD)	34.8 (8.1)
Bilirubin (μmol/L), mean (SD)	17 (29.4)
INR, mean (SD)	1.1 (0.3)
Creatinine (μmol/L), mean (SD)	89.8 (110.7)
Sodium (mmol/L), mean (SD)	137.3 (11)
C-reactive protein (mg/dL), mean (SD)	11.2 (24.6)

TABLE 1: Continued.

Variables	
Treatment ($n = 103$)	
Specific medication therapy of CLD	
Vitamin B, n (%)	44 (16.9)
Furosemide, n (%)	32 (12.3)
Spironolactone, n (%)	29 (11.0)
Venesection, n (%)	16 (6.1)
Antiviral nucleos(t)ide analogues, n (%)	14 (5.4)
Propranolol, n (%)	10 (3.8)
Nutrients (calcium, vitamin D, zinc, magnesium, etc.), n (%)	7 (2.7)
Ursodeoxycholic acid, n (%)	7 (2.7)
Rifaximin, n (%)	6 (2.3)
Albumin infusion, n (%)	5 (1.9)
Ciprofloxacin (SBP prophylaxis), n (%)	4 (1.5)
Anticoagulation therapy, n (%)	3 (1.1)
Prednisolone, n (%)	3 (1.1)
Immune modulation, n (%)	2 (0.8)

COVID-19-related mortality was defined as death occurring during an infection with COVID-19, with the disease as the primary or secondary cause of death. Severe COVID-19 was defined as the need for hospitalization during infection with COVID-19.

To investigate whether CLD or cirrhosis was an independent risk factor for the disease course of COVID-19, we divided our cohort into two groups: cirrhosis vs. noncirrhotic CLD.

The categories of the univariate analysis were a priori selected.

Data collection included patient demographics, symptoms, and disease course of COVID-19 (treatments, hospitalizations, admission to intensive care units, requiring invasive or noninvasive respiratory support, and mortality) and liver disease characteristics (etiology, biochemical activity, treatment, cirrhosis and disease severity according to the MELD score, Child-Pugh class, and Charlson Comorbidity Index (CCI)). No corrections were made for missing data, although for the purposes of logistical analysis, missing data for smoking and alcohol were considered to be no smoking or no alcohol abuse.

We collected the data closest to, and following, a diagnosis of COVID-19. We also collected short-term data from the three months after a diagnosis of COVID-19 and long-term data from 3-12 months after diagnosis. Data were registered in the Research Electronic Data Capture (REDCap) system [14, 15].

2.3. Statistical Analysis. Statistical analyses were performed using IBM SPSS Statistics (version 25 64-bit).

Continuous variables were reported as means with standard deviations (SD) and compared using the independent t-test for normally distributed data. For skewed distribution data, variables were reported as medians (interquartile ranges (IQR)) and compared using the Mann–Whitney U test. Categorical variables were presented as numbers with percentages and compared using the chi-squared test or Fisher's exact test, as appropriate. A p value smaller than 0.05 was considered significant.

Univariable logistic regression was performed to determine the independent risk factors for severe COVID-19 and liver deterioration. To evaluate liver deterioration, we analyzed only patients for whom we had a Child-Pugh class or a MELD score from both before and during their COVID-19 infection.

3. Results

3.1. Baseline Characteristics of Patients with CLD and COVID-19. We searched registries between March 1, 2020, and February 27, 2021. Of the 2,712,695 individuals living in the catchment area (i.e., 45% of the Danish population) [16], we identified 19,743 patients with a diagnosis of CLD or cirrhosis. Of these, 307 patients with CLD had been infected with SARS-CoV-2 during the study period. After the initial screening of records, forty-six people were excluded due to a lack of evidence for chronic liver disease. A total of 261 CLD patients with COVID-19 were therefore included in the present study: 64 patients (24.2%) had cirrhosis and 197 (75.8%) had CLD without cirrhosis (Figure 1).

Of the 261 patients, 139 (53.3%) were male. The mean age at the time of a COVID-19 diagnosis was 56.1 (±15.8) years, and the mean body mass index (BMI) was 27.1.

Fifty (19.2%) patients were smokers, and 42 patients (16.1%) reported current excessive alcohol consumption. Major liver disease etiologies included chronic hepatitis B infection in 79 patients (30.3%), alcoholic liver disease in 63 patients (24.1%), and nonalcoholic fatty liver disease (NAFLD) in 52 patients (19.9%) (Table 1).

A majority of patients (162, 62%) had at least one comorbid medical condition in addition to CLD. The most

TABLE 2: Characteristics of patients with liver cirrhosis and noncirrhotic CLD during COVID-19 and during hospitalization.

Variables	Cirrhosis ($n = 64$) (n (%))	Noncirrhotic CLD ($n = 197$) (n (%))	p value
Female	20 (31.3)	102 (51.8)	0.004
Age (years), mean (SD)	66.66 (11.1)	52.71 (15.6)	<0.001
Charlson Comorbidity Index, mean (SD)	5.4 (1.8)	2.6 (2.3)	<0.001
Hospitalization due to COVID-19	32 (50)	46 (23)	<0.001
Admitted to intensive care unit	7 (10.9)	5 (2.5)	0.005
Mechanical ventilation	5 (7.8)	5 (2.5)	0.066
Noninvasive ventilation	3 (4.7)	0 (0)	0.01
Hospitalization length (days), median[a] (IQR)	12.5 (19)	6 (16)	0.04
COVID-19-specific therapy in hospitalized patients			
Oxygen	24 (37.5)	27 (13.5)	<0.001
Piperacillin/tazobactam	20 (31.3)	19 (9.5)	<0.001
Tinzaparin	19 (29.7)	22 (11)	<0.001
Central vein catheter	13 (20.3)	2 (1)	<0.001
Corticosteroids	12 (18.8)	18 (9)	0.032
Continuous positive airway pressure	11 (17.2)	6 (3)	<0.001
Remdesivir	9 (14.1)	12 (6)	0.038
Penicillin	2 (3.1)	7 (3.5)	0.886
Chest X-ray			
Normal	9 (28.1)	8 (17.4)	0.259
Ground-glass opacities	4 (12.5)	6 (13.0)	1
Pneumonia	15 (46.9)	20 (43.5)	0.767
Pleural effusions	5 (15.6)	2 (4.3)	0.116
Pulmonary edema	4 (12.5)	1 (2.2)	0.153
Pneumothorax	2 (6.3)	0	0.165
Bacterial infection[b]	21 (65.6)	32 (69.6)	0.714
Outcome of hospitalization			
Own home without help	12 (37.5)	35 (76.1)	
Own home with help	2 (6.3)	2 (4.3)	
Rehabilitation centers	5 (15.6)	5 (10.9)	
Nursing home	0 (0)	1 (2.2)	
Hospice	1 (3.1)	0 (0)	
Death	12 (37.4)	3 (6.5)	0.001

[a]Median. [b]Bacterial pneumonia and/or positive blood culture and/or sepsis.

common comorbidities were obesity (72, 27.6%), hypertension (63, 24.1%), and diabetes mellitus type 2 (53, 20.3%). The mean Charlson Comorbidity Index (CCI) was 5.4 among the cirrhosis patients.

Patients with cirrhosis had a significantly higher mean age than patients with noncirrhotic CLD (66.66 vs. 52.71, p < 0.001) and a higher CCI (5.4 vs. 2.6, $p = 0.001$) (Table 2).

The mean number of hospital admissions in the 12 months prior to a COVID-19 diagnosis was 1 (±2.6), and the median number of in-hospital days was 13 (IQR 3-33.5) (Table 1).

The most frequent etiology of cirrhosis, in 40 patients (62.5%), was alcohol consumption. The baseline MELD score was known for 56 (87.5%) patients with cirrhosis, with a mean MELD score of 13.34 (±6.4). A baseline Child-Pugh class was known for 43 (67%) patients, 18 (41.9%) of whom were class A, another 18 (41.9%) were

class B, and seven patients (16.3%) were class C. No patients underwent liver transplantation during study follow-up (Table 3).

3.2. COVID-19 Course among Patients with CLD. A total of 78 (29.9%) patients in the study required COVID-19-related hospitalization, 12 (4.6%) of whom were admitted to an intensive care unit, and 15 (5.7%) patients died due to COVID-19.

Comparing noncirrhotic CLD with cirrhosis, we found a significantly higher rate of hospitalization in the latter ($N = 32$ (15.7%) vs. $N = 46$ (71.8%), $p < 0.001$), admission to intensive care unit (7 vs. 5, $p = 0.005$), length of hospital stay (12.5 vs. 6, $p = 0.01$), and death (12 vs. 3, $p = 0.001$). Patients with cirrhosis more often required a central vein catheter and received nasal oxygen supply, piperacillin and tazocin (intravenous infusion), tinzaparin, corticosteroids,

TABLE 3: Characteristics of patients with liver cirrhosis prior to COVID-19.

Liver status prior to COVID-19	
Cirrhosis, n (%)	64 (24.2)
Cirrhosis characteristics and ethology	
Alcohol, n (%)	40 (62.5)
Nonalcoholic steatohepatitis, n (%)	8 (12.5)
Unknown, n (%)	5 (7.8)
Hepatitis C, n (%)	3 (4.7)
Hepatitis B, n (%)	2 (3.1)
Alcohol+hepatitis C, n (%)	2 (3.1)
Alcohol+nonalcoholic steatohepatitis, n (%)	1 (1.6)
Alcohol+autoimmune hepatitis, n (%)	1 (1.6)
NASH+hepatitis B, n (%)	1 (1.6)
Alpha-1-antitrypsin deficiency, n (%)	1 (1.6)
Acute on chronic liver failure, n (%)	11 (17.2)
MELD score (n = 56), mean (SD)	13.34 (6.4)
MELD score ≥ 15, n (%)	19 (33.9)
Charlson Comorbidity Index, mean (SD)	5.41 (1.8)
Child-Pugh score (n = 43)	
Child-Pugh A (5, 6), n (%)	18 (41.9)
Child-Pugh B (7–9), n (%)	18 (41.9)
Child-Pugh C (10–15), n (%)	7 (16.3)
Procedures	
Large volume paracentesis, n (%)	4 (6.3)
Banding of varices, n (%)	6 (9.4)
TIPS placement, n (%)	2 (3.1)
Liver transplantation, n (%)	0 (0)

continuous positive airway pressure, remdesivir, or noninvasive ventilation ($p < 0.05$) (Table 2).

In univariable analyses controlled for age, gender, hypertension, obesity, diabetes, cardiac disease, and chronic pulmonary disorders, cirrhosis remained an independent predictor of severe COVID-19 (Table 4(a)). Among patients with noncirrhotic CLD, age, hypertension, diabetes type 2, cardiac failure, and chronic pulmonary disease were associated with hospitalization. Age, hypertension, excessive alcohol consumption, and chronic pulmonary disease were associated with bacterial infection. Age, hypertension, diabetes type 2, and chronic pulmonary disease were associated with requiring intensive care (Table 4(b)). No independent risk factors were associated with mortality.

3.3. Cirrhosis Deterioration during COVID-19. Forty-one percent of hospitalized patients with cirrhosis experienced a worsening of their liver disease during a COVID-19 infection. Hospitalization and death were independently associated with cirrhosis deterioration. Age, gender, and etiology of cirrhosis were not found to be predictors of deterioration of liver disease (Table 5).

Regarding biochemistry, we did not find any aggravation in either the cirrhosis or the noncirrhotic CLD groups regarding bilirubin, international normalized ratio (INR),

or creatinine during a COVID-19 infection, nor in the six months afterwards. We found higher levels of albumin in the noncirrhotic CLD group 1-3 months after a COVID-19 infection ($p = 0.02$) (Supplementary Table 2).

4. Discussion

In this population-based cohort study, we investigated the disease course and prognosis of COVID-19, as well as the progression and course of liver disease, among patients with preexisting CLD and a confirmed SARS-CoV-2 infection.

We found that patients with cirrhosis had a significantly higher hospitalization rate than noncirrhotic CLD patients (50% vs. 32%, $p = 0.001$). We found that 30% of patients with CLD and a COVID-19 infection required hospitalization. This rate is considerably higher than that reported for the background population [17]. However, the rate of COVID-19-related hospital admissions for patients with cirrhosis in our study is lower than that reported in a small cohort in northern Italy [18] and as compared to that reported in another, larger, international cohort [6]. This discrepancy in the hospitalization rates might be explained by limitations in the data sourced from nonhospitalized patients, as the design of the Italian and international studies relied on hospitalized patients. As the Danish Health Authorities carried out an extensive testing strategy comprising between 200,000 and 400,000 PCR tests daily between December 2020 and March 2021, we assume the number of unregistered COVID-19 infections to be low [19].

Admission rates to an intensive care unit (ICU) were 10.9% and 2.5% for cirrhosis and noncirrhotic CLD, respectively. These rates are similar to those reported in a multicenter cohort collected 5in the United States between March 1, 2020, and May 30, 2020 [12] but are lower than the rates from similar, register-based studies conducted in the United States and England, as well as an international register-based study across four continents [6, 9, 10]. However, these studies relied on a majority of patients hospitalized at baseline, suggesting a higher rate of patients requiring admission to ICU during the study period. Denmark never reached the max capacity of ICU, which is not a reason for lower admissions. We do not have any detailed information about the criteria for admission to an ICU in Denmark for the present study nor were they described in the prior studies [6, 9, 12].

A large, international cohort study of 359 noncirrhotic CLD patients and 386 cirrhosis patients found COVID-19-related mortality to occur in 32% of patients with cirrhosis, compared with 8% in noncirrhotic CLD. Mortality increased with the severity of cirrhosis as indicated by the Child-Pugh score (i.e., it was highest in patients in Child-Pugh class C) and was positively associated with alcoholic liver disease [6].

The mortality rate of 37% among cirrhosis patients reported here is line with this and other previous studies, which report mortality rates of 34% and 30% [11, 20]. The present study has allowed us the opportunity to follow the mortality rate for almost twelve months, whereas the prior studies took place across one to four months.

Generally, patients with CLD including cirrhosis had longer stays in the hospital than patients without liver disease

Table 4: Clinical predictors of severe COVID-19 among patients with cirrhosis and noncirrhosis chronic liver diseases.

(a) Cirrhosis

Variables	Hospitalization Univariate analysis		Bacterial infection Univariate analysis		Intensive care Univariate analysis		Mortality Univariate analysis	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (years)	0.98 (0.94-1.03)	0.4	0.97 (0.9-1.0)	0.3	1.01 (0.9-1.1)	0.77	0.98 (0.9-1.0)	0.52
F/M	1 (0.4-2.9)	1	1.12 (0.3-4.3)	0.9	1.95 (0.5-8.2)	0.36	1.50 (0.4-5.3)	0.53
Lifestyle								
Smoking (active)	1.99 (0.7-5.8)	0.2	0.31 (0.1-1.6)	0.2	4.24 (0.5-37.1)	0.19	3.60 (0.7-18.1)	0.12
Alcohol overuse	0.63 (0.2-1.9)	0.4	0.54 (0.1-2.0)	0.36	1.65 (0.31-8.82)	0.56	0.64 (0.18-2.29)	0.49
Comorbidities								
Hypertension	1.3 (0.5-3.9)	0.6	0.57 (0.2-2.1)	0.39	0.89 (0.2-4.0)	0.88	1.67 (0.4-6.9)	0.48
Obesity	1 (0.3-3)	1	0.32 (0.1-1.2)	0.08	0.35 (0.1-1.6)	0.17	1.39 (0.3-5.8)	0.65
Type 2 diabetes	0.7 (0.3-1.9)	0.4	0.58 (0.2-2.0)	0.39	0.46 (0.1-1.9)	0.28	1.03 (0.3-3.6)	0.96
Cardiac disease	0.6 (0.2-1.9)	0.4	1.33 (0.3-5.6)	0.69	0.82 (0.1-3.7)	0.79	0.65 (0.2-2.7)	0.56
COPD	0.6 (0.2-2.4)	0.5	0.47 (0.1-2.2)	0.33	0.59 (0.1-3.4)	0.56	0.30 (0.07-1.28)	0.10
Chronic kidney disease	1 (0.2-5.4)	1	0.42 (0.1-2.6)	0.35	0.28 (0.0-1.8)	0.18	1.30 (0.14-12.2)	0.81
Stroke and hemiplegia	1.8 (0.4-8.2)	0.5	—		—		0.73 (0.13-4.14)	0.76
Autoimmune diseases	0.7 (0.23.5)	0.7	0.53 (0.1-3.1)	0.49	1.02 (0.1-9.6)	0.99	1.60 (0.18-14.59)	0.68
Asthma	—	—	—		—		—	
Localized solid tumor	0.3 (0.03-3.2)	0.3	—		—		0.22 (0.03-1.77)	0.16
Treatment								
Vitamin B	0.8 (0.3-2.1)	0.6	1.0 (0.29-3.51)	1.00	1.29 (0.31-4.35)	0.72	0.82 (0.24-2.79)	0.76

Severe COVID-19 was defined as requirement of hospitalization during COVID, bacterial infection involves positive blood culture or bacterial pneumonia or sepsis, and intensive care involves admission to an intensive care unit or noninvasive ventilation or mechanical ventilation. COPD: chronic pulmonary disease.

(b) Noncirrhosis CLD

Variables	Hospitalization Univariate analysis		Bacterial infection Univariate analysis		Intensive care Univariate analysis		Mortality Univariate analysis	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (years)	1.07 (1.04-1.10)	<0.001	1.06 (1.02-1.10)	0.004	1.07 (1.01-1.14)	0.015	1.04 (0.97-1.07)	0.289
F/M	0.91 (0.47-1.76)	0.78	0.93 (0.31-2.75)	0.89	0.36 (0.07-1.90)	0.22	2.85 (0.29-27.87)	0.37
Lifestyle								
Smoking (active)	1.69 (0.61-4.75)	0.31	2.60 (0.33-20.69)	0.37	1.14 (0.13-9.86)	0.90	—	
Alcohol overuse	0.42 (0.17-1.05)	0.06	0.196 (0.06-0.65)	0.008	0.31 (0.06-1.70)	0.18	0.39 (0.04-3.87)	0.42
Comorbidities								
Hypertension	0.098 (0.05-0.22)	<0.001	0.09 (0.03-0.289)	<0.001	0.04 (0.01-0.35)	0.003	0.27 (0.04-1.97)	0.197
Obesity	0.55 (0.27-1.12)	0.10	0.47 (0.56-1.44)	0.19	0.94 (0.18-5.01)	0.94	1.14 (0.12-11.16)	0.91
Type 2 diabetes	0.35 (0.15-0.78)	0.01	0.99 (0.21-4.69)	0.99	0.20 (0.04-0.96)	0.04	0.16 (0.02-1.15)	0.07
Cardiac disease	0.18 (0.07-0.48)	0.001	0.61 (0.13-2.98)	0.55	0.25 (0.04-1.36)	0.11	—	—
Chronic pulmonary disease	0.16 (0.06-0.41)	<0.001	0.13 (0.04-0.41)	0.001	0.04 (0.01-0.22)	<0.001	0.37 (0.04-3.68)	0.39
Chronic kidney disease	0.60 (0.05-6.82)	0.68	—	—	—	—	—	—
Story of stroke and hemiplegia	0.39 (0.08-1.8)	0.23	0.44 (0.049-3.94)	0.46	0.196 (0.02-1.89)	0.16	0.096 (0.01-1.07)	0.056
Autoimmune diseases	0.55 (0.24-1.28)	0.17	0.64 (0.17-2.43)	0.51	1.08 (0.13-9.31)	0.94	—	
Asthma	0.28 (0.08-1.01)	0.05	0.67 (0.08-5.72)	0.72	—		—	
Localized solid tumor	0.21 (0.05-0.99)	0.048	0.44 (0.05-3.94)	0.46	0.196 (0.02-1.89)	0.16	—	
Treatment								
Vitamin B	0.19 (0.06-0.63)	0.007	0.19 (0.45-0.80)	0.024	0.37 (0.41-3.34	0.38	—	

Severe COVID-19 was defined as requirement of hospitalization during COVID, bacterial infection involves positive blood culture or bacterial pneumonia or sepsis, and intensive care units involve admission to intensive care or noninvasive ventilation or mechanical ventilation and mortality.

TABLE 5: Predictors of liver deterioration during COVID-19.

Variables	Child-Pugh[a] score deterioration During COVID ($n = 9$) Univariate analysis OR (95% CI)	p	MELD[b] score deterioration During COVID ($n = 13$) Univariate analysis OR (95% CI)	p
Age	0.96 (0.9-1.02)	0.2	0.97 (0.9-1.03)	0.4
F/M	3.3 (0.8-14.1)	0.1	2.3 (0.7-7.9)	0.2
Etiology of cirrhosis				
Alcohol	0.6 (0.1-3.1)	0.5	0.97 (0.3-3.6)	0.97
Nonalcoholic steatohepatitis	0.3 (0.1-1.4)	0.1	0.5 (0.12-2.4)	0.4
Hepatitis C	0.2 (0.3-1.4)	0.1	0.34 (0.05-2.3)	0.3
Hepatitis B	—		0.5 (0.04-5.9)	0.6
Alfa-1-antitrypsin deficiency	—		0.000	1
COVID-19-related hospitalization	0.1 (0.01-0.83)	0.03	0 (0)	0.998
COVID-19-related intensive care	0.3 (0.05-1.2)	0.09	0.9 (1.2-4.8)	0.9
COVID-19-related mortality	0.3 (0.06-1.1)	0.07	0.04 (0.008-0.2)	0.0001

Deterioration of cirrhosis was defined as requirement of [a]Child-Pugh score (A-B, A-C, and B-C), increase in [b]MELD scores > 15 during hospitalization for COVID-19, or/and developed clinical manifestations such as jaundice, ascites, and varicose veins.

(13.4 vs. 10.1 days) [21]. We found that cirrhosis prolongs the duration of hospitalization as compared to noncirrhotic CLD, an observation also made by Moon et al. [9].

The presence of comorbidities had a negative impact on noncirrhotic CLD and increased the risk of severe COVID-19, while comorbidities in the cirrhosis group did not appear to affect the course of COVID-19. This finding suggests that cirrhosis is the main risk factor. We did not find obesity to be a risk factor for severe COVID-19 in either of the study groups, a finding similar to that in previous studies [22, 23].

To our knowledge, no other studies have investigated liver deterioration during and after a COVID-19 infection, other than those examining ACLF or decompensation. Liver deterioration is a difficult process to assess, but here we have defined it as an increase in MELD score or a more severe Child-Pugh class. We found that the only predictor for liver deterioration was COVID-19-related hospitalization and death. Our study sample was unfortunately too small to assess the long-term effects of COVID-19 on liver disease severity. However, we did not notice higher in- or outpatient visits among patients recovering from COVID-19.

A rise in liver enzymes has been reported in patients with CLD, leading some to speculate whether COVID-19 might exacerbate CLD [19, 22, 24]. In our study, we looked at liver function (albumin, bilirubin, and INR) and did not find any aggravation in hepatic biochemistry in either the cirrhosis or noncirrhotic group during and after COVID-19 infection. The same finding has been reported by Ji et al. [25].

Studies have reported aggravation of the hepatic biochemistry, especially ALAT, where a raise between 14% and 53% in patients without known liver disease has been seen. Scientifically, aggravation in hepatic biochemistry among cirrhosis patients at the time of a COVID-19 diagnosis is also found by the same study [18]. Other studies have reported higher MELD scores, as well as higher ALAT, among patients who died of COVID-19 than among those who survived [7]. Many of these papers have not considered the clinical significance of this aggravation in terms of morbidity and mortality.

The pathophysiological mechanisms of how COVID-19 affects the liver remain unknown. It has been reported that SARS CoV-2 enters directly through the angiotensin-converting enzyme 2 (ACE2) receptor, causing liver damage through overexpression of ACE2 in cytomembranes by liver cells and in the bile duct. Damage to both hepatocytes and cholangiocytes has been reported in COVID-19 [26].

Drug-induced liver injury is another possible contributing factor to abnormal hepatic biochemistry, something that might occur after initiating therapeutic drugs [26]. In general, medical treatments for COVID-19 have been experimental and varied since the pandemic emerged. Antiviral therapeutics might have a deleterious impact on hepatic biochemistry.

Our results confirm that CLD patients, especially patients with cirrhosis, have significantly higher rates of hospitalization, admission to an intensive care unit, and mortality. This should enable a risk stratification which, in parallel with clinical assessment, can help determine who should receive immediate intensive care if resources are scarce. However, personalized management will be dependent on the disease stage, individual risk, and COVID-19 disease course.

Priority of CLD patients in the vaccination program has been discussed in various liver societies due to high mortality and immune dysfunction, and many have recommended prioritization of their members for COVID-19 vaccination [26, 27]. Regardless of their etiology, CLD and cirrhosis have been implicated in impaired and altered immune responses to earlier, non-COVID vaccinations, as well as immune memory against certain vaccine-delivered antigens [28]. As such, the duration of protection and

long-term protective response imparted by immunization in patients with CLD and cirrhosis remain unclear. This vulnerable group of patients will perhaps benefit from a third dose of a COVID-19 vaccine in order to ensure the desired immune response.

The strength of the present study is its population-based design, which included all patients with preexisting CLD from a geographically defined population, to offer unselected data, thus minimizing selection bias and providing an accurate reflection of the impact of COVID-19 infection on cirrhosis and CLD. Furthermore, Denmark has provided free and unlimited access to SARS-CoV2 testing, meaning that the number of undiagnosed cases is hoped to be low.

We attempted to standardize the definitions for cirrhosis as confirmed by biopsy, computed tomography (CT), or clinical decompensation such as varices and ascites. All study patients had a confirmed laboratory PCR test result for COVID-19 which ensures standardization, and the same comparisons are being made between study groups.

We are aware of some limitations to the study. Although we attempted to collect detailed, standardized data according to clear definitions, there still exists the possibility of missing data and confounding variables not captured in our report. A cohort study of unselected patients necessarily results in large variations in the data. While we included all patients with CLD from 45.5% of the total Danish population, the study population was nonetheless rather small, because of the small population of Denmark and a fairly low incidence of COVID-19 in the country.

5. Conclusion

This study supports the concerns raised in earlier studies about patients with CLD, especially patients with cirrhosis, being at greater risk of a severe COVID-19 disease course and facing a higher rate of mortality.

Abbreviations

ACLF:	Acute-on-chronic liver failure
ALAT:	Alanine aminotransferase
BMI:	Body mass index
COVID-19:	Coronavirus disease 2019
CLD:	Chronic liver disease
CP:	Child-Pugh
CCI:	Charlson Comorbidity Index
COPD:	Chronic pulmonary disease
HCC:	Hepatocellular carcinoma
NAFLD:	Nonalcoholic fatty liver disease
IQR:	Interquartile range
ICU:	Intensive care unit
INR:	International normalized ratio
MELD:	Model for End-Stage Liver Disease
RT-PCR:	Reverse transcription-polymerase chain reaction
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus 2
SD:	Standard deviation
SBP:	Spontaneous bacterial peritonitis
TIPS:	Transjugular intrahepatic portosystemic shunt.

Data Availability

The underlying data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

Supplementary material 1. Table 1: International Classification of Diseases (Tenth Revision) codes for CLD. Supplementary material 2. Table 2: impact of COVID-19 on biochemical appearances of cirrhosis and other chronic liver disease. (Supplementary Materials)

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