Original Article

# Impact Of COVID – 19 On The Outcomes Among Patients With Chronic Liver Disease Along Comorbidities - A Prospective Cross-Sectional Study

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**DOI:** 10.47750/pnr.2022.13.03.180

## Abstract

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 Prospective Observational 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-19infectionondiseaseseverityandthecourseofliverdisease. We included all patients with chronic liver disease and a positive RT-PCR test for SARS-CoV-2 between March 2021 to June 2021. 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% versus16.2%, 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 our study 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. Patients with chronic liver disease, especially those with cirrhosis, are at major risk of a severe COVID-19 disease course and higher mortality.

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel corona virus first detected in Wuhan, China, that causes coronavirus disease 2019 (COVID-19) [1]. Corona viruses 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 diseases, immunosuppression, chronic liver diseases 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 immuno-suppressed patients [8]. Prior studies have found that patients with CLD or cirrhosis experienced more frequent adverse outcomes of 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 liverfailure (ACLF) [11]. Mortality has been proven to increase for patients with cirrhosis and COVID-19. 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 non-generalizable, hospital-based studies. This lack of data about non-hospitalized 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 observational study, including all patients with preexisting

CLDand 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 with comorbidities.

## Materials and Methods

### Study Design and Population

We established a population-based study, COVID-19 Chronic Liver Disease, comprising all patients and a positive reverse transcription-polymerase chain reaction test for SARS-CoV-2. The inclusion period was March 2021 to June 2021. Eligible patients were identified based on confirmed the diagnosis systematically though critical examination of biochemistry, ultrasound, computed tomography and clinical examination.

### Data Collection

The primary outcomes were measurements of disease severity among COVID-19 patients were hospitalization, admission to intensive care and 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 RT-PCR analysis of a specimen from either a nasopharyngeal swab or tracheal suctioning.

### Study site

Amaravathi Institute of Medical Sciences, Guntur

### Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version25). Continuous variables were reported as means with standard deviations (SD) and compared using the independent t-test for normally distributed data. A p value smaller than 0.05 was considered as significant value.

## Results

### Baseline Characteristics of Patients with CLD and COVID-19

A total of 261 CLD patients with COVID-19 were therefore included in the present study, 64 patients (24.2%) had cirrhosis and197 (75.8%) had CLD without cirrhosis. 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 27.1.50 (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%).

A majority of patients (162, 62%) had atleast one comorbid medical condition in addition to CLD. The most common comorbidities were obesity (72,27.6%), hypertension (63, 24.1%), and diabetes mellitus type 2 (53, 20.3%).

| Variables | Cirrhosis (n=64) (n(%)) | Non cirrhotic 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 |
| 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) | 12.5(19) | 6(16) | 0.04 |

## COVID-19-specific therapy in hospitalized patients

| Variables | Cirrhosis (n=64) (n(%)) | Non cirrhotic CLD (n=197) (n(%)) | P value |
|---|---|---|---|
| Oxygen | 24(37.5) | 27(13.5) | <0.001 |
| Piperacillin/tazobactam | 20(31.3) | 19 (9.5) | <0.001 |
| Enoxaparin | 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 |

## Chest X Ray

| Variables | Cirrhosis (n=64) (n(%)) | Non cirrhotic CLD (n=197) (n(%)) | P value |
|---|---|---|---|
| Normal | 9(28.1) | 8 (17.4) | 0.259 |
| Ground-glassopacities | 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 |

## Outcome of Hospitalization

| Variables | Cirrhosis (n=64) (n(%)) | Non cirrhotic CLD (n=197) (n(%)) |
|---|---|---|
| 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) |
| Hospital | 1(3.1) | 0(0) |

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 CI (5.4vs.2.6,p= 0:001). The mean number of hospital admissions in the 3 months prior to a COVID-19 diagnosis was 1 (±2.6), and the median number of in-hospital days was 13.

| **Variables** | **Number of Patients** n (%) |
|---|---|
| Female, | 122 (46.7) |
| Age (years), mean (SD) | 56.13 (15.8) |
| BMI (n = 235), mean(SD) | 27.1(6.1) |

## Life Style

| **Variables** | **Number of Patients** n (%) |
|---|---|
| Smokers (n=243), n (%) | 50 (19.2) |
| Current alcohol (n=246), n(%) | 129 (49.4) |
| Overuse alcohol, n (%) | 42 (16.1) |

## Comorbidities

| **Variables** | **Number of Patients** n (%) |
|---|---|

| | |
|---|---|
| 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) |
| Obesity,n(%) | 72(27.6) |
| Hypertension, n(%) | 63(24.1) |

## Biochemistry in Plasma

| **Variables** | **Number of Patients** n (%) |
|---|---|
| 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) |

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).

| | |
|---|---|
| VitaminB, n(%) | 44(16.9) |
| Furosemide, n(%) | 32(12.3) |
| Spironolactone, n(%) | 29(11.0) |
| Antiviral nucleoside analogues, n(%) | 14(5.4) |
| Propranolol, n(%) | 10(3.8) |
| Nutrients (calcium, vitaminD, zinc, magnesium), n(%) | 7(2.7) |
| Ursodeoxycholic acid, n(%) | 7(2.7) |
| Rifaximin, n(%) | 6(2.3) |
| Albuminin fusion,n(%) | 5(1.9) |
| Ciprofloxacin (Prophylaxis),n(%) | 4(1.5) |
| Anticoagulation therapy, n(%) | 3(1.1) |
| Prednisolone, n(%) | 3(1.1) |
| Immune modulation, n(%) | 2(0.8) |

## 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 tazobactum (intravenous infusion), tinzaparin, corticosteroids,

## Cirrhosis characteristics and etiology

| | |
|---|---|
| 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 + hepatitisB, n (%) | 1(1.6) |
| Alpha-1-antitrypsindeficiency,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) |

Continuous positive airway pressure, remdesivir, or noninvasive ventilation (p<0:05).

In invariable analyses controlled for age, gender, hypertension, obesity, diabetes, cardiac disease, and chronic pulmonary disorders, cirrhosis remained an independent predictor of severe COVID-19. 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. No independent risk factors were associated with mortality.

## 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.

Regarding biochemistry, we did not find any aggravation in either the cirrhosis or then on cirrhotic 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).

## Discussion

In this 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 at 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 [13]. However, the rate of COVID-19 related hospital admissions for patients with cirrhosis in our study is lower than that reported. This discrepancy in the hospitalization rates might be explained by limitations in the data sourced from non-hospitalized patients, as the design of the studies relied on hospitalized patients. Admission rates to an intensive care unit (ICU) were 10.9% and 2.5% for cirrhosis and noncirrhotic CLD, respectively. A large, international cohort study of 359 noncirrhotic CLD patients and 386 cirrhosis patients found COVID-19 related mortality to occurring 32% of patients with cirrhosis, compared with 8% in noncirrhotic CLD. 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% [14]. 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

| **Variables** | **Hospitalization** | **p** | **Bacterial infection** | **p** | **Intensive care Unit** | **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 |
| F/M | 1(0.4-2.9) | 1 | 1.12(0.3- | 0.9 | 1.95(0.5-8.2) | 0.36 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | 4.3) | | | |

## Life Style

| Variables | Hospitalization | p | Bacterial infection | p | Intensive care Unit | p |
|---|---|---|---|---|---|---|
| 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 |
| 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 |

## Co-morbidities

| Variables | Hospitalization | p | Bacterial infection | p | Intensive care Unit | p |
|---|---|---|---|---|---|---|
| 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 |
| Obesity | 1(0.3-3) | 1 | 0.32(0.1-1.2) | 0.08 | 0.35(0.1-1.6) | 0.17 |
| Type 2diabetes | 0.7(0.3-1.9) | 0.4 | 0.58(0.2-2.0) | 0.39 | 0.46(0.1-1.9) | 0.28 |
| 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 |
| 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 |
| 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 |
| Stroke and hemiplegia | 1.8(0.4-8.2) | 0.5 | — | | — | |
| 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 |

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 [15]. 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 predict or for liver deterioration was COVID-19-related hospitalization [16]. 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 inpatient 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 [17]. In our study, we looked at liver function and did not find any aggravation in hepatic biochemistry in either the cirrhosis or noncirrhotic group during and after COVID - 19 infections. Studies have reported aggravation of the hepatic bio-chemistry, especially ALT, 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 ALT, among patients who died of COVID-19 than among those who survived [19]. Many of these papers have not considered the clinical significance of this aggravation.

The pathophysiological mechanisms of how COVID-19 affects the liver remain unknown. It has been reported that SARSCoV-2 enters directly through the angiotensin-converting enzyme 2 (ACE 2) receptor, causing liver damage through over expression of ACE2 in cyto membranes by liver cells and in the bile duct. Damage to both hepatocytes and cholangiocytes has been reported in COVID-19 [20]. Drug-induced liver injury is another possible contributing factor to abnormal hepatic biochemistry, something that might occur after initiating therapeutic drugs [21]. 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 [22]. 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 [23]. 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 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. We attempted to standardize the definitions for cirrhosis as confirmed by 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.

## Conclusion

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

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