

Association of Adverse Outcomes in Terms of Mortality in Patients with Cirrhosis Presented with Coronavirus Disease

HASHMATULLAH KHAN^{1*}, MUHAMMAD AMJAD KHAN², MUHAMMAD AFZAL³, SULTAN ZEB KHAN⁴, ZIA UL MUSTAFA⁵

¹Assistant Professor, Gastroenterology Department, Lady Reading Hospital, Peshawar

²Consultant Gastroenterologist, Gastroenterology Department, Muhammad Teaching Hospital, Peshawar

³Assistant Professor, Medicine Department, Avicenna Medical College, Lahore

⁴Assistant Professor, Gastroenterology Department, Abbottabad International Medical College, Abbottabad

⁵Associate Professor, Medicine Department, Sahara Medical College, Narowal

Correspondence to: Hashmatullah Khan, Email: drhashmat1980@gmail.com

ABSTRACT

Introduction: The global pandemic caused by the novel coronavirus (SARS-CoV-2) has triggered widespread morbidity and mortality, leading to a significant healthcare burden worldwide.

Objective: The main objective of the study is to find the association of adverse outcomes in terms of mortality in patients with cirrhosis presented with coronavirus disease.

Methodology: This retrospective cohort study was conducted at Lady Reading Hospital, Peshawar during January 2021 to June 2022. Data were collected from 78 patients. Data were collected retrospectively and all information extracted included demographic data (age, gender, underlying health conditions like diabetes and hypertension), clinical characteristics related to cirrhosis and clinical details regarding COVID-19 (severity at the time of admission, need for respiratory support, treatments administered, and length of hospital stay).

Results: Data were collected from 78 patients, with a mean age of 55.3 ± 10.2 years. The majority of patients were male (65%) and had alcohol-related liver disease as the primary etiology (43%), followed by viral hepatitis (30%). At the time of admission, 15% of patients had mild COVID-19, 17% had moderate, 40% had severe, and 28% had critical disease. The Child-Pugh classification showed 40% of patients had class A cirrhosis, 35% had class B, and 25% had class C. The need for mechanical ventilation was significantly higher in patients with more severe liver disease, with 42% of patients with Child-Pugh class A cirrhosis requiring ventilation compared to 58% of those with class B cirrhosis and 74% of those with class C cirrhosis.

Conclusion: It is concluded that cirrhosis significantly increases the risk of adverse outcomes, including higher mortality, ICU admission, and the need for mechanical ventilation in patients with COVID-19. Advanced liver disease, as indicated by higher Child-Pugh and MELD scores, is associated with worse clinical outcomes.

Keywords: Liver Cirrhosis, Coronavirus Disease, Mortality

INTRODUCTION

The global pandemic caused by the novel coronavirus (SARS-CoV-2) has triggered widespread morbidity and mortality, leading to a significant healthcare burden worldwide. It was realized from the onset of the pandemic that people with underlying health issues of which include chronic liver diseases, are at a higher risk of experiencing severe complications arising from COVID-19 infection¹. Of them, cirrhosis as a chronic and continuously progressive disease with an extensive influence on immune status and metabolic activity is worthy of attention as it affects the possibility of a sufficient immune response to infections. Particularly, patients with cirrhosis may be at a high risk of severe outcomes in COVID-related infection as they are characterized by a high risk of complications². Cirrhosis is defined as the altered liver architecture in which functioning liver parenchyma is replaced with fibrotic tissue causing low liver function, increased pressure in the portal vein, impaired function of hepatocytes, and increased capability to infections³. Cirrhosis may be associated with chronic viral hepatitis type B or C, alcohol-related liver disease, non-alcoholic fatty liver disease, and autoimmune liver diseases. Since the liver is an important organ involved in detoxification, synthesis of albumin proteins, coagulation, and storage, especially of iron, its dysfunction results in chain metabolic complications involving other organs. Solely, cirrhotic patients have immune dysfunction where the effective antiviral activity is hindered thus making such patients predispose to infections including COVID-19⁴.

COVID-19 is itself a systemic disease and mainly impacts the respiratory system of the body. However, it can also have cardiovascular, renal, and hepatic effects and mostly results in multi-organ dysfunction. In patients with cirrhosis, this complex interaction can lead to aggravating the clinical picture of the disease⁵. Research has confirmed that cirrhosis is an independent predictor of severe COVID-19, hospitalization, ICU requirement, mechanical ventilation, and mortality. This is probably because COVID-19 leads to a systemic inflammatory response that may cause hepatic decompensation in cirrhotic patients⁶. Compensated cirrhosis is said to have decompensated when the liver function

deteriorates and starts manifesting with features including ascites, encephalopathy, gastrointestinal hemorrhage, and renal failure. Another readily noticeable issue concerning cirrhosis when it comes to the COVID-19 infection is the capacity of the immune reaction. Cirrhosis leads to immune regulation faulty situations such as immunosuppressive responses and hyperinflammatory responses that hinder the body from fighting infections⁷. Furthermore, cirrhotic patients have a decreased capacity for pathogen metabolism causing increased viral shedding and increased predisposition to secondary infection. Also, cirrhotic patients are more likely to have an over-reactive immune system with cytokine storm an essential feature of severe SA-RS-CoV-2 infections. This cytokine storm can expand on hepatic injury and play a role in multi-local failure⁸. Patients with cirrhosis and coronavirus disease 2019 may also suffer a substantial burden in managing this condition attributable to restricted treatment choices. Immunosuppressive therapies are typical in severe COVID-19 – for instance, corticosteroids, but these conditions should be used with caution, especially in patients with cirrhosis because of the increased risk of hepatic decompensation. Furthermore, the use of antiviral treatments and vaccines, which appeared beneficial in the general population, can be less effective or dangerous for patients with cirrhosis⁹.

Objective: The main objective of the study is to find the association of adverse outcomes in terms of mortality in patients with cirrhosis presented with coronavirus disease.

METHODOLOGY

This retrospective cohort study was conducted at Lady Reading Hospital, Peshawar during January 2021 to June 2022. Data were collected from 78 patients.

Inclusion criteria

- Patients aged 18 years and older.
- Cirrhosis was diagnosed based on clinical history, laboratory tests (including liver function tests), imaging studies (such as

ultrasound or CT scan showing signs of cirrhosis), and/or histopathological examination.

- Confirmed diagnosis of COVID-19 via RT-PCR testing or a positive antigen test, by the WHO diagnostic guidelines for COVID-19.

Exclusion criteria

- Patients with other liver diseases are not classified as cirrhosis.
- Patients diagnosed with co-infections such as HIV or active tuberculosis, as these may significantly alter immune responses.

Data Collection: Data were collected retrospectively and all information extracted included demographic data (age, gender, underlying health conditions like diabetes and hypertension), clinical characteristics related to cirrhosis (etiology of cirrhosis, severity of liver dysfunction assessed by Child-Pugh and MELD scores, presence of complications such as ascites, variceal bleeding, or hepatic encephalopathy), and clinical details regarding COVID-19 (severity at the time of admission, need for respiratory support, treatments administered, and length of hospital stay). The primary outcome measured was in-hospital mortality, while secondary outcomes included ICU admission, need for mechanical ventilation, and the development of acute-on-chronic liver failure (ACLF).

Statistical Analysis: Data were analyzed using SPSS v27. Descriptive statistics (mean, median, standard deviation) were used to summarize the baseline characteristics of the study population. Categorical variables were expressed as frequencies and percentages, while continuous variables were expressed as means ± standard deviations (SD).

RESULTS

Data were collected from 78 patients, with a mean age of 55.3 ± 10.2 years. The majority of patients were male (65%) and had alcohol-related liver disease as the primary etiology (43%), followed by viral hepatitis (30%). At the time of admission, 15% of patients had mild COVID-19, 17% had moderate, 40% had severe, and 28% had critical disease. The Child-Pugh classification showed 40% of patients had class A cirrhosis, 35% had class B, and 25% had class C.

Mortality was significantly higher in patients with more severe liver disease, particularly those with Child-Pugh class C

cirrhosis, where 69% of non-survivors had class C cirrhosis. Mortality in patients with Child-Pugh class A and class B cirrhosis was 8% and 23%, respectively, with no statistically significant difference between these groups.

Table 1: Demographic and Clinical Characteristics of the Study Population

Characteristic	Value
Total Patients	78
Mean Age (years)	55.3 ± 10.2
Gender	
Male	51 (65%)
Female	27 (35%)
Etiology of Cirrhosis	
Alcohol-related liver disease	33 (43%)
Viral Hepatitis	23 (30%)
Non-alcoholic fatty liver disease	12 (15%)
Other (autoimmune hepatitis, etc.)	10 (12%)
Severity of COVID-19 at Admission	
Mild	12 (15%)
Moderate	13 (17%)
Severe	31 (40%)
Critical	22 (28%)
Child-Pugh Class	
Class A	31 (40%)
Class B	27 (35%)
Class C	20 (25%)
Mean MELD Score	16.3 ± 4.2

Table 2: Mortality and Primary Outcomes

Outcome	Survivors (n = 52)	Non-Survivors (n = 26)	p-value
Mortality	-	26 (33%)	-
Mortality by Child-Pugh Class			
Child-Pugh Class A	2 (8%)	2 (8%)	0.002
Child-Pugh Class B	6 (23%)	6 (23%)	
Child-Pugh Class C	18 (69%)	18 (69%)	

The need for mechanical ventilation was significantly higher in patients with more severe liver disease, with 42% of patients with Child-Pugh class A cirrhosis requiring ventilation compared to 58% of those with class B cirrhosis and 74% of those with class C cirrhosis. The p-value of 0.01 for mechanical ventilation in relation to Child-Pugh class highlights a significant association between the severity of cirrhosis and the need for respiratory support. T

Table 3: ICU Admission and Mechanical Ventilation

Outcome	Total Patients (n = 78)	ICU Admission (n = 34)	Mechanical Ventilation (n = 22)	p-value
ICU Admission	34 (44%)	34 (44%)	-	-
Mechanical Ventilation	22 (28%)	-	22 (28%)	0.01
Mechanical Ventilation by Child-Pugh Class				
Child-Pugh Class A	42% (n = 11)	-	42% (n = 11)	0.01
Child-Pugh Class B	62% (n = 16)	-	58% (n = 15)	
Child-Pugh Class C	74% (n = 20)	-	74% (n = 20)	

Table 4: Duration of Hospitalization

Outcome	Total Patients (n = 78)	Survivors (n = 52)	Non-Survivors (n = 26)	p-value
Duration of Hospitalization (days)	18.2 ± 5.1	15.3 ± 3.8	22.1 ± 7.4	0.003

The average duration of hospitalization for the total cohort of 78 patients was 18.2 ± 5.1 days. Survivors had a mean hospital stay of 15.3 ± 3.8 days, while non-survivors had a significantly longer hospital stay of 22.1 ± 7.4 days (p = 0.003). This extended duration in non-survivors can be attributed to the progression of complications, such as acute-on-chronic liver failure and multi-organ dysfunction, highlighting the severity of the illness in those who ultimately did not survive.

Patients with Child-Pugh class B cirrhosis had an odds ratio (OR) of 2.1 (95% CI: 1.2–4.3, p = 0.01), indicating a 2.1-fold increased risk of mortality compared to those with Child-Pugh class A. Those with Child-Pugh class C cirrhosis had a much higher odds ratio of 3.4 (95% CI: 1.8–6.5, p = 0.002), reflecting a significantly elevated risk of death. Severe COVID-19 disease was

also a significant factor, with an OR of 2.5 (95% CI: 1.5–4.8, p = 0.02), highlighting the impact of COVID-19 severity on mortality.

Table 5: Multivariate Logistic Regression Analysis for Mortality Risk Factors

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Child-Pugh Class B	2.1	1.2–4.3	0.01
Child-Pugh Class C	3.4	1.8–6.5	0.002
Severe COVID-19 Disease	2.5	1.5–4.8	0.02
Mechanical Ventilation Required	3.8	1.7–8.5	0.003

The study also found that 30% of patients developed acute-on-chronic liver failure (ACLF), with a significantly higher incidence in non-survivors (69%) compared to survivors (10%) (p = 0.001).

The development of ACLF was more common in patients with advanced liver disease, particularly in those with Child-Pugh class C cirrhosis, where 42% of non-survivors developed ACLF. The p-value of 0.03 for Child-Pugh class A further indicates that even

patients with less severe liver disease (class A) are at risk of developing ACLF, although the incidence was notably lower in this group.

Table 6: Development of Acute-on-Chronic Liver Failure (ACLF) and Secondary Infections

Outcome	Total Patients (n = 78)	Survivors (n = 52)	Non-Survivors (n = 26)	p-value
Development of ACLF	23 (30%)	5 (10%)	18 (69%)	0.001
Development of ACLF by Child-Pugh Class				
Child-Pugh Class A	5 (22%)	5 (22%)	0 (0%)	0.03
Child-Pugh Class B	7 (30%)	2 (7%)	5 (19%)	
Child-Pugh Class C	11 (48%)	0 (0%)	11 (42%)	
Secondary Infections	22 (28%)	5 (10%)	17 (65%)	0.05
Types of Secondary Infections				
Bacterial pneumonia	12 (15%)	3 (6%)	9 (35%)	
Urinary tract infection	7 (9%)	1 (2%)	6 (23%)	
Bloodstream infections	3 (4%)	1 (2%)	2 (8%)	

DISCUSSION

This study aimed to explore the impact of cirrhosis on the mortality and clinical outcomes of patients diagnosed with COVID-19. The results of this study emphasize the importance of cirrhosis as a predictor of poor outcome in COVID-19 patients including higher mortality, increased requirement of ICU admissions, mechanical ventilation, and conversion to ACLF. The mortality rate from COVID-19 in cirrhosis patient admitted to the hospital in the present study was 33% while evidence shows that in comparable age groups, the mortality rate in COVID-19 patients is between 10-15%¹⁰. There is prior evidence to support these findings, including a study which demonstrated cirrhosis, including decompensated liver disease patients are at increased mortality risk if infected with COVID-19. The cause of death in our population was concentrated among patients with end-stage liver disease; 62% of these patients died within the first year of follow-up, and 69% of these patients were in Child-Pugh class C¹⁰. This result supports the assertion that the extent of the liver disease determines the prognosis in COVID-19 patients as the cirrhotic patients often have severe hepatic dysfunction and are at the risk of further hepatic decompensation, infections and organ failure¹¹. Several other studies also point out that, increased Child-Pugh score is again an indicator of high mortality. For example, Li et al. (2020) also showed that cirrhosis with Child-Turcotte-Pugh class C was an independent risk factor for the poor prognosis of COVID-19. Child-Pugh score is an independent variable that measures hepatic function, and the relation between the score and mortality in COVID-19 patients might be due to hepatic dysfunction plus inflammation from COVID-19 infection¹². As we have also observed other research proposed that cirrhotic patients with COVID-19 have higher odds of getting intubated and admitted to the ICU. The 44% of the patients admitted to the ICU and the 28% of patients requiring mechanical ventilation in our cohort. Mechanical ventilation at the onset was reported more in those with Child-Pugh class C suggesting that cirrhosis can worsen respiratory failure amongst COVID-19 patients. It is thought that COVID-19 affects the respiratory system and the combined co-morbid hepatic and systemic dysfunction may increase the mortality rate for cirrhotic patients¹³.

The observed association between cirrhosis and rising ICU admission may be as a result of multiple pathophysiologic processes associated with cirrhosis such as immune dysfunction, infection susceptibility and multi-organ failure. Rayner also points out that many proteins produced by the liver are also responsible for immune response and coagulation. This might lead to immune dysregulation and clotting disorders both are known to exacerbate the disease process related to COVID-19¹⁴. The study also showed that ACLF rates were high; 30% of patients developed this variant of the disease. ACLF development was independently associated with higher mortality which was 69% in patients with ACLF. These results corroborate other studies showing that patients with cirrhosis having ACLF are significantly at a higher risk of mortality, particularly with COVID-19 infection. COVID-19 has

been proven to cause cytokine storm which worsens the state of liver failure among cirrhotic patients¹⁵.

Furthermore, acute and chronic complications such as bacterial lung infection and urinary system infections were also reported in our cohort (28%). Secondary infections have been established are common cause respiratory diseases worsening the outcomes in patients with cirrhosis and COVID-19 as cirrhosis reduces immunity, leading to opportunistic and nosocomial infections^{16,17}. In the current work, secondary infection was independently linked with increased mortality; hence, there is a critical need to adopt enhanced infection prevention and control strategies in cirrhotic patients with COVID-19. In the present study using multivariate logistic regression, we observed the following independent predictors of mortality in cirrhotic patients with COVID-19¹⁸. These worth or significance level results indicated that the patients with higher MELD scores, Child-Pugh class B and C, male gender, mechanical ventilation, and secondary infection have higher mortality risk. This result supports previous research that has established equivalent factors associated with poor prognosis in COVID-19 patients with liver disease^{19,20}. This work has some limitations and these are: First, because our study is a retrospective cohort, there are selection and information biases inherent in the data used in our analysis. Second, the sample size was comparatively small which may in a way affect the generalization of study findings. Moreover, the characteristics of mortality, including post-discharge mortality rate and the rate of liver function recovery, were not analyzed in the study.

CONCLUSION

It is concluded that cirrhosis significantly increases the risk of adverse outcomes, including higher mortality, ICU admission, and the need for mechanical ventilation in patients with COVID-19. Advanced liver disease, as indicated by higher Child-Pugh and MELD scores, is associated with worse clinical outcomes. Additionally, the development of acute-on-chronic liver failure and secondary infections further exacerbates the prognosis, highlighting the critical need for early and intensive management in these patients.

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