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Study of Predictors of Outcomes and Severity of Corona Virus Disease in Patients with Liver Cirrhosis

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ABSTRACT
Background: Hepatic decompensation and mortality are common after COVID-19 infection in patients with cirrhosis. According to Child-Pugh class, mortality rose in a linear pattern. **Objective:** The aim of the current study is to predict outcome of COVID-19 infection in cirrhotic patients. **Patient and methods:** A total of 104 patients with COVID-19 infection with history of cirrhosis admitted to Zagazig University Hospital and El-Ahrar Teaching Hospital participated in our case control study. Patients were divided into 2 groups: The case group included 52 COVID-19 cirrhotic patients, and the control group included 52 patients with cirrhosis but with no evidence of COVID-19 infection. All subjects were subjected to full history taking, clinical examination, laboratory investigations, and radiological findings. **Results:** The inflammatory markers (D-dimer, CRP, ESR first hour, ESR second hour and WBC) and Ferritin were statistically significant higher in the case group compared with the control group. There were high significant correlations between severity COVID-19 and Child Pugh classification. There were high significant correlations between laboratory parameters and severity of COVID-19. Mortality rate was significantly higher in the case group compared with the control group (13.4% vs. 25%, respectively). Length of hospital stay, Child Turcot Pugh, fresh frozen plasma transfusion to correct coagulopathy, ascites and hepatic encephalopathy could predict hospital mortality among COVID-19 patients. **Conclusion:** The in-hospital mortality rate for patients hospitalized with COVID-19 in the context of cirrhosis is higher than the in-hospital mortality rate for patients hospitalized for cirrhosis alone. It is essential to acknowledge that hospitalized patients with cirrhosis are at an elevated risk of mortality regardless of the presence of COVID-19.
Keywords: Predictors, COVID-19, Liver Cirrhosis, Child-Pugh classification.

INTRODUCTION
An outbreak of pneumonia caused by a newly discovered coronavirus that began in Wuhan, Hubei Province, China, at the end of 2019 quickly expanded across the country and is now threatening to become a global pandemic [(1)]. Liver disorders and conditions including hepatitis and prolonged alcoholism can lead to the advanced scarring (fibrosis) of the liver known as cirrhosis [(2)].

The liver strives to heal itself whenever it is damaged, be it through disease, excessive alcohol usage, or some other source. This causes the formation of scar tissue. Scar tissue accumulates in a cirrhotic liver, limiting its ability to perform its normal functions (decompensated cirrhosis). Cirrhosis in its later stages is fatal [(3)].

There is speculation that the gastrointestinal and hepatic signs of SARS-CoV-2 are attributable to the widespread expression of the angiotensin-converting enzyme-2 (ACE-2) receptor in these organs [(4)].

The virus appears to contribute to disease by stimulating an intense immunological response. Almost half of the patients had abnormal liver function tests due to the infection [(5)].

Patients with liver cirrhosis, particularly those who have experienced decompensation, may be at a higher risk of contracting SARS-CoV-2 due to systemic immunological failure. The real prevalence of infected cirrhotic people is unknown; while a preliminary investigation found that 2-12% of COVID-19 infected individuals have a history of liver illness. Hepatic decompensation and mortality are common after COVID-19 infection in patients with cirrhosis. According to Child-Pugh class, mortality rose in a linear pattern [(6)].

Age and alcohol-related liver illness were also contributors to mortality rates. Patients with advanced cirrhosis had a greater mortality risk compared to controls without liver disease who were matched on propensity scores. Patients with cirrhosis were especially vulnerable to COVID-19-related lung illness, which accounted for the vast majority of fatalities [(7)].
The aim of the current study is to predict outcome of COVID-19 infection in cirrhotic patients to improve the prognosis of the disease.

PATIENTS AND METHODS
A total of 104 patients with COVID-19 infection with history of cirrhosis admitted to Zagazig University Hospital and El-Ahrar Teaching Hospital participated in our case control study.
Patients were divided into 2 groups, 52 case in each group:

Case group: Cirrhotic patients with COVID-19 infection (Group I): 52 patients.

Control group: Cirrhotic patients without COVID-19 infection (Group II): 52 patients.

Inclusion criteria: Evidence of liver cirrhosis by laboratory and radiological like US, evidence of COVID-19 infection indicated by laboratory and radiological findings, and their ages above 18 years.

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Exclusion criteria: Patients who are uncooperative with study procedure, Covid19 patients who have no evidence of cirrhosis, and ages below 18 years old.

All subjects were subjected to full history taking, clinical examination, laboratory investigations, and radiological findings.

Laboratory investigations included any investigations that verify inclusion and exclusion criteria: Complete blood picture, liver function tests, serum LDH, coagulation profile: PT, PTT, INR, D-Dimer and fibrinogen, Inflammatory parameters: CRP, Ferritin and ESR, and serum electrolytes: Na, k, Mg and ca.

PCR test for COVID-19 was used to detect the presence of viral RNA of covid19, which indicates that a person has been infected with the virus, by using the nose swab (Positive: highly likely patient has COVID-19, and Negative: means probably not having COVID-19).

Laboratory findings suggestive of cirrhosis: CBC: thrombocytopenia, abnormal LFTs: decrease albumin <3.5 mg/dl, increase globulins and A/G ratio is decrease and may be reversed, serum bilirubin increased, transaminases and alkaline phosphatase are moderately elevated. Prothrombin time: prolonged.

Laboratory findings in COVID-19 patients: lymphopenia, increase ALT and AST increase LDH increase ferritin and D Dimer increase levels of proinflammatory and chemokines like IL6 increase CRP.

Radiological Findings:

Abdominal US, to identify cirrhotic patients, and its complications. As a simple method to identify the target groups, Appearances in abdominal US include: nodular Surface, Segmental hypertrophy or atrophy, overall coarse and heterogeneous echotexture, Signs of portal hypertension, Splenomegaly and ascites.

Chest CT, to suggest patients with COVID-19 infection.

Ethical Approval:

This study was ethically approved by the Ethical Committee of the Faculty of Medicine, Zagazig University (IRB #9256/31-1-2022). Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test, Fisher's exact test and Chi-Square for Linear Trend were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test was used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

RESULTS

There was no statistically significant difference between the 2 studied groups regarding the age and gender (**Table 1**).

Table (1): Demographics characteristics of the studied groups.

Variables	Control Group (N=52)		Case Group (N=52)		T test	P-value
Age (years) Mean ± SD Range	55.96 ± 4.6 48 – 64		58 ± 2.2 56 – 60		**5.23**	**0.57** **NS**
Sex	**N**	**%**	**N**	**%**	**X^2**	**P-value**
Male	24	46.2	26	50	0.43	0.81
Female	28	53.8	26	50		NS

Patients in case group had a significantly higher incidence of infection, paracentesis, variceal bleeding and hepatic encephalopathy as the leading causes of hospitalization (**Table 2**).

Table (2): Causes of hospital admission in the studied groups.

Variable	Control Group (N=52)		Case Group (N=52)		P-value
	N	%	N	%	
Infection as reason for admission	13	-25%	20	-38%	<0.0001 (H.S)
Paracentesis	3	-5.70%	10	-19%	<0.0001 (H. S)
GI bleeding	15	-28.80%	26	-50%	<0.0001 (H. S)
Variceal banding	1	-1.90%	11	-21.10%	0.001 (H. S)
Hepatic encephalopathy	5	-9.60%	13	-25%	<0.0001

Table 3 summarizes and compares ultrasonographic examination of the 2 studied groups.

Table (3): Ultrasonographic examination of the studied groups.

	Ultrasonographic examination	Control Group (N=52)		Case Group (N=52)		P-value
		No.	%	No.	%	
Liver	Abnormal echopattern	**26**	**50%**	**13**	**25%**	<0.001 (HS)
	Cirrhotic echopattern	**26**	**50%**	**39**	**75%**	<0.001 (HS)
Spleen	Average	29	80.60%	24	46.20%	0.389 (NS)
	Enlarged	23	19.40%	28	53.80%	<0.001 (HS)
Ascites	No ascites	16	30.80%	0	0%	<0.001 (HS)
	Mild ascites	10	19.20%	20	38.40%	<0.001 (HS)
	Moderate ascites	13	25%	19	36.60%	<0.001 (HS)
	Tense ascites	13	25%	13	25%	<0.001 (HS)

The inflammatory markers (D-dimer, CRP, ESR first hour, ESR second hour and WBC) and Ferritin were statistically significant higher in the case group compared with the control group (**Table 4**).

Table (4): Levels of Inflammatory markers and serum Na, K, Ca and Mg of the studied gropus.

Variable	Control Group (N=52)	Case Group (N=52)	P-value
D-Dimer (ng/mL)	0.4 (0-4.9)	3.3 (0.2-4.3)	<0.001 (HS)
CRP (mg/dL)	48 (1.57-317.3)	125 (10.2-296)	<0.001 (HS)
ESR first hour (mm/hr)	30 (5-98)	86 (10-95)	<0.001 (HS)
ESR second hour (mm/hr)	58 (12-115)	100 (15-107)	<0.001 (HS)
WBC (mcL)	14.6 (3.2-33.9)	24.8 (9-29.8)	<0.001 (HS)
Ferritin (nmol/L)	583.7 (6.2-3491)	916 (363-1602/)	<0.001 (HS)
Na (mEq/L)	130.23 ± 4.21	133.23 ± 4.21	0.76 (NS)
K (mEq/L)	4.02 ± 0.48	3.88 ± 0.69	0.43 NS
Ca (mg/dL)	8.68 ± 1.06	8.40 ± 0.59	0.321 (NS)
Mg (mg/dL)	2.03 (1.03-13.9)	2.23 (1.4-2.6)	0.98 (NS)

Median, range: non-parametric test.

There were high significant correlations between severity COVID-19 and Child Pugh classification (**Table 5**).

Table (5): Correlation between COVID-19 severity and Child Pugh classification.

Variable	R	P	Significance
Child A (5 to 6)	0.5	0.05	S
Child B (7 to 9)	0.08	0.05	S
Child C (10 to 15)	**0.4**	**0.001****	**HS**

There were significant correlations between laboratory parameters and severity of COVID-19 in case group (**Table 6**).

Table (6): Correlation coefficient between laboratory parameters and severity of COVID-19 in case group.

Variable	R	P-value	Significance
INR	**0.6**	**0.05**	**S**
ALT (U/L)	**0.5**	**0.05**	**S**
AST (U/L)	**0.08**	**0.05**	**S**
Bilirubin (µmol/L)	**0.4**	**0.001****	**HS**
Creatinine (mg)	**0.2**	**0.05**	**S**
Urea (mg/dL)	**0.6**	**0.05**	**S**
Platelets (mcL)	**0.6**	**0.05**	**S**
S. Ferritin (nmol/L)	**0.41**	**0.01****	**HS**
WBCs (mcL)	**0.08**	**0.05**	**S**
D-Dimer (ng/mL)	**0.6**	**0.05**	**S**
CRP (mg/L)	**0.5**	**0.05**	**S**
ESR first hour (mm/hr)	**0.08**	**0.05**	**S**
ESR second hour (mm/hr)	**0.4**	**0.001****	**HS**
Fasting blood sugar (mg/dL)	**0.2**	**0.05**	**S**
K (mEq/L)	**0.6**	**0.05**	**S**
Ca (mg/dL)	**0.6**	**0.05**	**S**
Mg (mg/dL)	**0.41**	**0.01****	**HS**

Mortality rate was significantly lower in the control group than the case group (**Table 7**).

Table (7): Mortality among studied patients.

Variables	Control Group (N=52)		Case Group (N=52)		P-value
	N	%	N	%	
Mortality	7	13.4%	13	25%	**0.01* (HS)**

This table shows that: in univariate logistic regression, length of hospital stays, Child Turcot Pugh, FFP transfusion to correct coagulopathy, ascites and Hepatic encephalopathy could predict in hospital mortality among COVID-19 patients (Table 8).

Table (8): Predictors of mortality among studied groups.

Variables	Univariate				Multivariate			
	Coefficients β	Std. Error	OR	P-value	Coefficients β	Std. Error	OR	P-value
Age	0.004	0.01	1.004	0.697 (S)	--	--	--	--
Sex	-0.014	0.155	0.986	0.953 (NS)	--	--	--	--
HE	-0.536	0.256	1.71	**0.03 (S)**	0.371	0.307	1.45	S
HCC	0.182	0.266	1.20	0.494 (S)	--	--	--	--
Hydrothorax	0.069	0.257	1.07	0.789 (S)	--	--	--	--
Infection	-0.474	0.265	0.623	0.07 (S)	--	--	--	--
Ascites **I** **II** **III**	 -0.517 0.715 0.468	 0.454 0.325 0.412	 0.596 2.04 1.6	 0.255 (S) **0.028 (S)** 0.255 (S)	 -0.639 0.6 0.33	 0.470 0.358 0.449	 0.528 1.82 1.39	0.01 (S)
OV **I** **II** **III** **IV** **GV**	 0.163 -0.504 -0.774 -1.21 0.419	 0.605 0.385 0.454 0.784 0.429	 1.18 0.604 0.461 0.299 1.52	 0.788 (NS) 0.189 (S) 0.088 (S) 0.124 (S) 0.329 (S)	--	--	--	0.05 (S)
Intractable ascites	0.375	0.305	1.46	0.219 (S)	--	--	--	S
Coagulopathy	-0.015	0.243	0.985	0.95 (S)	--	--	--	-S
Hyponatremia	0.388	0.245	1.474	0.114 (NS)	--	--	--	S
Mechanical ventilation	0.355	0.773	1.42	0.646 (S)	--	--	--	--
Serum ferritin	0.59	0.254	1.81	**0.0186 (S)**	0.527	0.262	1.69	**0.045 (S)**
Length of stay (LOS) *2-5 days* *5-13 days* ≥ 13 days	 0.86 1.157 1.57	 0.351 0.473 0.68	 2.38 0.3143 0.220	 **0.0135 (S)** **0.0145 (S)** **0.026 (S)**	 0.981 -1.12 -1.52	 0.375 0.491 0.7	 2.67 0.33 0.218	 **0.009 (S)** **0.023 (S)** **0.029 (S)**
CTP	0.410	0.203	1.5	**0.043 (S)**	0.04	0.266	1.04	0.88
MELD	0.0001	0.017	1	0.99 (S)	--	--	--	--

DISCUSSION

Damage from cirrhosis causes the liver's structure to disintegrate and the vascular architecture to become distorted. Patients with cirrhosis are more vulnerable to infections and other complications due to the disease's underlying link to immunological failure [8].

COVID-19 infection was associated with more severe consequences in cirrhotic patients than in those without cirrhosis [9].

In our study, age was distributed as 58 (SD 2.2) years old, and no appreciable distinction could be found between the two groups. These findings came in agreement with study by **Zhang *et al.*** [5] that enrolled 112 covid-19 patients and revealed that the age ranged from 39-67 years old.

We found no evidence of a statistically significant gender difference in any of our sampled populations.

This in agree with **Barman *et al.*** [10] enrolled 90 COVID-19 patients, 54% of patients were males and 47% of patients were females, and showed that no statistically-significant gender difference was found in terms of severity (P =0.524).

In this study, laboratory investigations have significant difference between the studied groups. Group II showed a significant increase in biomarkers like D. Dimer, CRP, serum ferritin, fibrinogen and lactate dehydrogenase (serum LDH) with elevation of direct and total bilirubin and significant decrease in WBCs, HB and total protein. The risk of major and small vessel thrombosis is raised in patients with COVID-19, who may show indications of a hypercoagulable state. Mild thrombocytopenia, elevated D-Dimer levels, elevated fibrin degradation products, and an increased international normalized ratio (INR) are some of the laboratory abnormalities seen in inpatients with C0VID-19 related coagulopathy. Hypercoagulability related with COVID-19 has yet to have a definitively determined cause. In agreement with **Ahmed and Ghani** [10] study's which showed that when a patient's COVID-19 test comes back positive, it is now standard practice to run additional tests for these prognostic biomarkers because doing so has been shown to improve patient treatment and outcomes.

In our study, electrolytes distribution in blood of patients in studied groups have no significant difference as change in serum sodium (Na), magnesium (Mg), Ca and K. In contrast with **Ahmed and Ghani** [11] who confirmed Serum sodium, potassium, and calcium levels are lower in severely COVID-19 infected people. Some of these abnormalities, such as hypokalemia, may have serious consequences for patient care. Some of the most prevalent side effects of COVID-19 are respiratory distress and cardiac damage, both of which are made worse by hypokalemia. Leukopenia, lymphopenia, high liver transaminases, elevated LDH, and elevated CRP are the most prevalent laboratory abnormalities seen in cirrhotic patients with COVID-19. The second group was shown to have a highly significant difference in terms of the association between COVID-19 severity and prognosis, with increasing severity of COVID-19 related with a worse prognosis (P =0.00). In agreement with **Galiero *et al.*** [12] which showed that extremely high rates of hospitalization and mortality are seen among CLD patients with COVID-19.

In univariate logistic regression, length of hospital stays, Child Turcot Pugh, FFP transfusion, ascites and Hepatic encephalopathy could predict in hospital mortality among COVID-19 patients with further multivariate logistic regression, length of stay, FFP transfusion, higher D-dimer and higher CRP could predict.

In a study by **Galiero *et al.*** [12], age >60-year, ischemic heart disease, DM, chronic obstructive pulmonary disease, ascites and hepatic encephalopathy were predictors of mortality.

In this study, there is a significantly higher morbidity and mortality due to COVID-19 in patient with cirrhosis in comparison to patients with cirrhosis without COVID-19. This coincides with the study done by **Bajaj *et al.*** [8], baseline pulmonary compromise due to factors such as sarcopenia and poor respiratory excursion, ascites raising the diaphragms, and pleural effusions may account for the increased need of BiPAP in cirrhosis and COVID-19. Although these measures were taken, the mortality rate for individuals with cirrhosis and COVID-19 was higher than that for those with cirrhosis alone. An increased anaerobic milieu has been linked to increased mortality, and elevated serum lactate levels in people with cirrhosis and COVID-19 may be an indicator of this.

Therefore, a lesser hepatic reserve and worse CCI (Charlson Comorbidity Index) could predispose to this greater fatality rate. The CCI was the only factor that showed any statistically meaningful relationship to mortality [13].

Another explanation by **Satapathy *et al.*** [4] reported that patients with cirrhosis and a positive COVID-19 test were detected at admission or within 2 days of admission in the majority of cases, but because of the variability in their presentations, the individualized care they require is typically delayed. Patients with cirrhosis and COVID-19 showed an increased prevalence of comparable respiratory, taste/smell, and cardiovascular symptoms but a decreased prevalence of gastrointestinal symptoms. Differentials may be explained by the increased baseline prevalence of gastrointestinal symptoms in cirrhotic individuals, albeit this remains a conjecture. If patients with cirrhosis use lactulose, they may not develop these symptoms of COVID-19 infection [4].

In our opinion the higher mortality rate may be due to: The majority of COVID-19 and cirrhosis patients admitted to the hospital had respiratory problems that necessitated the use of respiratory and critical care. Patients admitted within the same time period who were diagnosed with cirrhosis but had no other underlying conditions required only a therapy for cirrhosis-specific consequences.

Patients with cirrhosis have been less likely to be hospitalized during the pandemic, but those who

experience complications that require immediate attention will still be kept there. Possible explanations for the lack of effect of the COVID-19 pandemic on cirrhotic patients include the fact that only the sickest patients with cirrhosis were admitted, and the fact that the additional infection was already there [(4)].

Our data shows that compared to individuals with cirrhosis and COVID-19, those with cirrhosis alone were more likely to be hospitalized, undergo cirrhosis-specific procedures such large-volume paracentesis and variceal banding, and be diagnosed with grade III/IV hepatic encephalopathy. This is despite the fact that isolation protocols probably would have restricted these cases' entrance to only the direst of circumstances. Both groups showed reduced levels of biochemical indicators indicative of cirrhosis, including albumin, salt, and creatinine. The peak MELD score was higher in the COVID-19 and cirrhosis group, but the ACLF rates were equal, perhaps because patients with cirrhosis alone developed more grade III/IV hepatic encephalopathy and liver failure.

In agree with our study, **Jeon *et al.* [(9)],** patients with cirrhosis and COVID-19 are more likely to experience hypertension and respiratory problems. Notably, there was no significant difference in the prevalence of CKD or the need for hemodialysis or a kidney transplant. This is intriguing because both cirrhotic patients and those without cirrhosis have a significant chance of developing renal impairment, either as a novel symptom or as a result of the disease itself **[(9)].**

The strengths of the study are inclusion of the control groups with cirrhosis but without COVID-19 to allow better characterization of the impact of COVID-19 in patients with cirrhosis. In addition, Patients were hospitalized during the identical period to better understand the impact of COVID-19.

The weaknesses of the study were the relatively small number of patients with cirrhosis and COVID-19, to that end, our observation will need to be validated in larger cohorts. Furthermore, the mortality in the cirrhosis+COVID-19 group might be even higher than that in the cirrhosis alone group when effective treatment is available for COVID-19 since patients with cirrhosis are likely to be denied such treatment until safety in cirrhosis is demonstrated. Finally, larger cohort studies are needed to be compared with our findings regarding predicting outcome of COVID-19 infection in cirrhotic patient to improve prognosis of the disease. Patients with cirrhosis who are hospitalized should be considered high risk for death regardless of the presence of COVID-19. This discovery needs to be further examined in bigger cohorts; however, our data imply that COVID-19 considerably increases mortality risk in cirrhosis.

CONCLUSION

The in-hospital mortality rate of individuals hospitalized with COVID-19 in the context of cirrhosis is greater than that of people treated for cirrhosis alone. Child Turcot Pugh, FFP transfusion to correct coagulopathy, ascites and Hepatic encephalopathy could predict in hospital mortality among COVID-19 patients. Patients with cirrhosis who are hospitalized should be considered high risk for death regardless of the presence of COVID-19.

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