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Impact of chronic liver disease on COVID-19 infection at Zagazig University Hospitals

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Abstract

Background. Chronic liver disease (CLD) is linked to immune system failure, which increases the risk of infections and consequences brought on by COVID-19. Therefore, we aimed to compare hospitalized COVID -19 patients with and without CLD to assess the effect of CLD on the severity of COVID-19 infection. **Methods.** The study was conducted between April and October 2022 at Zagazig university hospitals. It enrolled 108 subjects admitted at the isolation hospital for COVID-19 illness. The cases were allocated equally into three groups, group (I): Patients without evidence of liver disease. Group (II): patients with chronic hepatitis, and group (III): patients with cirrhotic liver. **Result.** There were significant correlations between the severity of COVID -19 and the CTP classification of Group III ($r=0.5$ $p=0.05$ in child A, $r=0.08$ $p=0.05$ in child B, $r=0.4$ $p=0.001$ in child C). In addition, there were significant correlations between laboratory parameters such as INR ($r=0.6$, $p=0.05$), bilirubin ($r=0.4$, $p=0.001$), ALT ($r= 0.5$, $p=0.05$), and AST ($r=0.08$, $p=0.05$) and severity of COVID -19 in studies groups. **Conclusion:** Those with CLD and cirrhosis had a higher death rate. COVID-19 severity related to the Child-Turcotte-Pugh score (CTP) score.

Keywords: COVID-19, chronic liver disease, Child-Turcotte-Pugh, Zagazig.

Introduction

In December 2019, the World Health Organization (WHO) declared a new coronavirus known as "SARS-CoV2" to be the cause of the COVID-19 outbreak [1].

Positive-sense single-stranded RNA [(+) ssRNA] with a 5'cap and 3'UTR poly(A) tail makes up the SARS-CoV2 genome [2]. The virus enters respiratory tract cells via the angiotensin-converting enzyme receptor 2. The structural proteins play an essential role in budding the virus particles released from different host cells [3].

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Chronic liver disease (CLD) is linked to immune system failure, which increases the risk of infections and consequences brought on by COVID-19[4]. Furthermore, hepatic patients experiencing acute respiratory distress syndrome (ARDS), independent of the underlying reason, have a worse prognosis than patients without CLD [5]. IL-2 and IL-17A are critical inflammatory factors causing liver injury in COVID-19 patients. The early increase in AST level and its correlation with disease severity indicate that immune-mediated inflammation plays a vital role in liver injury in severe COVID-19 patients [6].

Nevertheless, there is mixed evidence about the potential that CLD is a risk factor for a more severe COVID-19[7]. Since COVID-19 was identified as a pandemic by the WHO on 12 March 2020, numerous types of research have been conducted. According to these researches, the SARS-CoV-2 infection causes abnormal liver tests in the general population, including elevated levels of the alanine-transaminase (ALT) and aspartate-transaminase (AST), total bilirubin, and prothrombin time (PT) [8,9,10]. In addition, higher mortality is linked to advanced age, reduced levels of platelets albumin and lymphocytes, and increases in ALT, leucocytes, lactate dehydrogenase, ferritin, PT, and creatinine [8,10].

Although research is relatively limited, some evidence suggests that individuals with CLD, particularly those with cirrhosis, are more vulnerable to poorer clinical consequences, specifically COVID-19, with a more severe course and greater death risk [11]. Obesity, hypertension, and diabetes mellitus are metabolic comorbidities that patients with non-alcoholic fatty liver disease (NAFLD) or steatohepatitis (NASH) may have. These conditions are risk factors for COVID-19's severe outcome [10]. Our aim in this study was to compare hospitalized COVID -19 patients with and without CLD to assess the effect of CLD on the severity of COVID-19 infection.

CT scanning in patients with COVID-19–associated pneumonia usually shows ground-glass opacification, possibly with consolidation. Some studies have reported that abnormalities on chest CT scans are typically bilateral, involve the lower lobes, and have a peripheral distribution. However, pleural effusion, pleural thickening, and

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lymphadenopathy have also been reported with less frequency [12]. Therefore, COVID-19 CO-RADS classification is widely used to assess patients (COVID working group of the Dutch Radiological Society, The Radiology Assistant 2020).

Methods

Study Design

This is a prospective case-control study of 6 months. It was conducted between April and October 2022 at Zagazig university Hospital. The patients' informed consent was obtained before being included in the study. The Zagazig University Institutional Review Board (IRB) approved the study.

The study enrolled 108 subjects admitted at the isolation hospital for COVID-19 infection. The cases were allocated equally into three groups, group (I): Patients without evidence of liver disease. Group (II): patients with chronic hepatitis, and group (III): patients with cirrhotic liver. All patients were HCV Ab positive.

Being under 18 years old has undergone a liver transplant, and combined infection with HBV or HIV were exclusion factors. The hospitalization criteria were those established by the Zagazig university hospitals, including positive COVID-19 PCR in nasopharyngeal swabs and CT chest findings with dyspnea and oxygen saturation below 90. Also, patients with comorbid conditions or emergency cases requiring hospital admission are discovered to be positive for COVID-19 PCR nasopharyngeal swabs.

Clinical, laboratory, and radiological evaluation

Adulthood and diagnosing a COVID-19 infection by reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swab specimens were inclusion criteria. The participants did not receive the COVID-19 vaccine.

The medications used to treat COVID-19 in hospitalized patients were Dexamethasone and Remdesivir (200 mg on day one, proceeded by four days of 100 mg each day). All

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hospitalized patients received this treatment the Egyptian Ministry of Health recommended during the study period. In addition, antibiotic therapy was added to patients who had concurrent bacterial infections. All patients underwent a clinical examination, laboratory tests, and radiological investigations.

Clinical information included the patient's age, sex, and the existence of comorbid disorders such as hypertension, diabetes mellitus, hyperlipidemia, obesity, and as pulmonary, cardiac, and renal diseases. In addition, at admission, laboratory testing for liver and renal function and as inflammatory markers for COVID-19 were obtained.

A history of HCV viremia, even individuals who have had their infection treated and showed abnormalities in liver functions and signs of liver fibrosis on ultrasound, fibroscan, or histology are considered to have chronic hepatitis C virus (HCV). On radiological examination of the abdomen and liver histology, the existence of morphological signs of cirrhosis with or without portal hypertension was used to identify the disease. Ascites, hepatic encephalopathy while receiving treatment, and a history of hematemesis were all considered signs of decompensation. We followed the patients to notice their hospital discharge or death.

The child-Turcotte-Pugh score was used where 1 to 3 points can be assigned for each variable (albumin, bilirubin, ascites, encephalopathy, and PT, /INR,) and according to the combination of these elements, there are three prognosis subgroups for patients.

Class A (5–6 points), B (7-9 points), and C (10–15 points).

According to WHO, the severity of COVID-19 ranges from:

- (1) **Mild COVID-19:** Respiratory symptoms unrelated to pneumonia or hypoxia.
- (2) **Moderate COVID-19:** The existence of clinical pneumonia and, on radiographs, oxygen saturation equal to or greater than 90% in room air at sea level.
- (3) **Severe COVID-19:** The existence of clinical pneumonia and on radiographs, oxygen saturation less than 90% on room air at sea level, a respiratory rate greater than 30 breaths per minute, or lung infiltration greater than 50% [13].

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The outcome was the assessment of disease severity and the mortality rate among hospitalized COVID-19 patients having or not having chronic liver disease.

Statistical analysis

Data analysis was done using SPSS version 26. Frequencies and percentages were used to define categorical variables, while the mean and standard deviation were used to describe continuous variables (SD). The continuous variables' means were compared using independent t-tests (for two groups) and a 1-way ANOVA test (for more than two groups). Not-normally distributed data was represented as median and interquartile range and compared using Kruskal Wallis (for more than two groups) and Mann Whitney test (to compare two groups). Spearman rank correlation coefficient was used to assess the direction and strength of association between ordinal data. Using the chi-square test, categorical variables were compared. A p-value of 0.05 or less was deemed significant.

All tests were run utilizing the statistical analysis program IBM SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

Results**3.1. Demographic data and comorbid conditions:**

In the current study, no significant differences concerning sex and concomitant illnesses such as heart disease, kidney disease, connective tissue disease, hypertension, diabetes mellitus, hyperlipidemia, and obesity were found. However, a statistically significant difference was found among the studied groups related to age. In making a Tukey HSD comparison, the difference is substantial between group I and each other group (Tab 1).

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Table 1. Demographic and comorbid conditions.

Variables	Group I (N=36)		Group II(N=36)		Group III (N=36)		F	p
Age (years)	55.96 ± 4.6		59.5 ± 5.1		58 ± 2.2		6.556	0.002*
Mean ±SD								
Tukey HSD	P ₁ 0.003*		P ₂ 0.11		P ₃ <0.001**			
	N	%	N	%	N	%	χ ²	p
Sex								
Male	20	76.9	18	50	16	23.1	0.889	0.641
Female	16	23.1	18	50	20	76.9		
Hypertension	2	5.5%	5	13.9%	5	13.9%	MC	0.574
Diabetes	1	2.8%	3	8.3%	6	16.7%	MC	0.194
Obesity	8	22.3%	7	19.4%	7	19.4%	MC	>0.999

MC Monte Carlo test F One way ANOVA test χ² Chi square test p₁ difference between group I and II p₂ difference between group II and group III p₃ difference between group I and III *p<0.05 is statistically significant.

3.2. Clinical presentation

At the time of admission, fever was represented in 61.1%, 83.3%, and 75% of group (I), group (II), and group (III), respectively. Cough was present in 83.3%, 58.3%, and 69.4% within the group (I), group (II), and group (III), respectively. Loss of smell, sore throat, or rhinorrhea were represented in 83.3%, 69.4%, and 83.3% of the group (I), group (II), and group (III), respectively. Malaise, fatigue, chest pain, and shortness of breath were represented in 50%, 72.2%, and 72.2% of the group (I), group (II), and group (III), respectively. Hepatic encephalopathy was represented in 16.7% and 22.2% of the group (II) and group (III), respectively, which significantly differs from group I compared with groups II and III. There is a non-significant difference between groups regarding the duration of symptoms or presenting symptoms other than HE (Tab 2)

Table 2. Clinical presentation of the studied groups.

Clinical presentations	Group I (N=36)		Group II (N=36)		Group III (N=36)		P [§]
	N	%	N	%	N	%	
Fever	22	61.1	30	83.3	27	75	0.099
Cough	30	83.3	21	58.3	25	69.4	0.066

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Loss of smell	30	83.3	25	69.4	30	83.3	0.251
Sore throat /rhinorrhea							
Malaise/Fatigue/							
Chest pain/shortness of breath	18	50	26	72.2	26	72.2	0.074
Hepatic encephalopathy	0	0	6	16.7	8	22.2	<0.001**
	P1 0.025*		P2 0.769		P3 0.005*		
Duration of symptoms before admission [‡]	3.5(3 – 4)		4(3 – 4)		4(3 – 5)		0.1

*‡data is represented as median and interquartile range and compared using Kruskal Wallis test §symptoms are compared using Chi-square test p1 difference between group I and II p2 difference between group II and group III p3 difference between group I and III *p<0.05 is statistically significant **p≤0.001 is statistically highly influential.*

O₂ saturation was higher in group I (93.21±4.6) than in group II (91.21±4.6) and group III (88.21±4). On making a pairwise comparison, the difference is significant between group III and each other group (Table 4).

3.3. Laboratory investigations conducted at the time of admission

There is a statistically significant difference between the studied groups regarding INR, ALT, AST, serum bilirubin, CRP, ESR, ferritin, D dimer, and WBCs. On comparing every two individual groups. Regarding INR, ESR the difference is significant between each two groups

Concerning ALT, the difference is significant between group II and each other group (the highest level was reported in group II). While group III had significantly higher AST when compared with groups II and I. In contrast, groups II and I did not differ substantially. The same for total bilirubin, and D dimer. The difference was significant only when comparing group III and each group.

Group (I) had significantly lower serum ferritin, WBCs, and CRP than groups II and III. That difference was non-significant on comparing groups II and III.

There is a non-significant difference between groups concerning serum urea or creatinine (Tab 3).

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Table 3. INR, Kidney functions, Liver functions, and inflammatory markers among the different studied groups.

	Group I (N=36)	Group II (N=36)	Group III (N=36)	p [§]
	Mean±SD	Mean±SD	Mean±SD	
INR	0.90 ± 0.17	1.3 ± 0.19	1.14 ± 0.23	<0.001**
Tukey HSD	P ₁ <0.001**	P ₂ 0.002*	P ₃ <0.001**	
ALT (IU/L)	23.9 ± 0.7	70.35 ± 10.5	20.7 ± 14.29	<0.001**
Tukey HSD	P ₁ <0.001**	P ₂ <0.001**	P ₃ 0.184	
AST IU/L	28.1 ± 10.9	31.95 ± 9.98	118.23 ± 65.89	<0.001**
Tukey HSD	P ₁ 0.123	P ₂ <0.001**	P ₃ <0.001**	
Bilirubin(mg/dL)	0.95 ± 0.17	1.0 ± 0.20	2.33 ± 0.22	<0.001**
Tukey HSD	P ₁ 0.257	P ₂ <0.001**	P ₃ <0.001**	
Creatinine mg/dL	0.94 ± 0.41	0.86 ± 0.47	1.13 ± 0.38	0.236
Urea mg/dl	25.65 ± 10.94	29.65 ± 9.98	31.37 ± 12.41	0.089
	Median (IQR)	Median (IQR)	Median (IQR)	p [¥]
D dimer ng/mL	0.69(0.4-2.03)	0.8(0.41-2.01)	2.75(0.47-3.88)	0.007*
Pairwise	P ₁ >0.999	P ₂ 0.032*	P ₃ 0.013*	
CRP mg/L	44(5.25-96.75)	117.5(62.28-190)	182.5(92.5-210)	<0.001**
Pairwise	P ₁ <0.001**	P ₂ 0.258	P ₃ <0.001**	
ESR (mm/hr)	23.5(13.0 – 40.75)	53 (23 – 77)	77 (68 – 90)	<0.001**
Pairwise	P ₁ 0.002*	P ₂ 0.003*	P ₃ <0.001**	
Ferritin (ng/ mL)	250(107.5-890)	879(363-1706)	879(278.3-1681.5)	<0.001**
Pairwise	P ₁ 0.001**	P ₂ >0.999	P ₃ 0.004*	
WBC	8.85(4.83-11.33)	18.9(11.7-23.35)	20.8(12-23.68)	<0.001**
Pairwise	P ₁ <0.001**	P ₂ >0.999	P ₃ <0.001**	

[¥]p for Kruskal Wallis test p₁ difference between group I and II p₂ difference between group II and group III p₃ difference between group I and III *p<0.05 is statistically significant **p≤0.001 is statistically highly substantial §p for One way ANOVA test.

3.4. Radiological investigations

Upon ultrasonographic examination of the studied groups, neither group I nor group II patients had ascites, while 72.2 % of group III patients had ascites (p=<0.001).

Regarding CT chest, positive findings were detected in 19.4% of group I patients, while 33.6% of group II patients and 52.7% of group III patients (p= 0.01). On comparing the two groups, the difference is significant between groups I and III (Table 4).

Table 4. O2 saturation and CT findings of the studied groups.

Clinical presentations	Group I (N=36)		Group II (N=36)		Group III (N=36)		P-value
O2 saturation (Mean ± SD)	93.21±4.6		91.21±5.9		88.2 ± 6.8		0.002**¥
Tukey HSD	P ₁ 0.113		P ₂ 0.048*		P ₃ <0.001**		
	N	%	N	%	N	%	p [§]
Ascites (US)	-	-	0	0	26	72.2	<0.001**
Positive CT findings	7	19.4	12	33.3	19	52.8	0.012*
	P ₁ 0.285		P ₂ 0.153		P ₃ 0.006*		

[¥]P for One way ANOVA test §symptoms are compared using Chi-square test p₁ difference between group I and II p₂ difference between group II and group III p₃ difference between group I and III *p<0.05 is statistically significant **p≤0.001 is statistically highly substantial US ultrasound CT Computed tomography.

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3.5. Assessment of COVID severity and liver disease and the correlation between them

About two-thirds of the studied patients had mild COVID-19 disease (66.7%) in Group I. In comparison, about 66.7% of the studied patients had moderate COVID-19 illness (66.8%) in Group II. On the other hand, in Group III, about 58.4% of the studied patients had moderate COVID-19 illness, and 30.5% of our patients had severe COVID-19 disease. On comparing every two groups, there is a significant difference between groups I and II, and III, while there is a non-significant difference between groups II or III (Tab 5).

Table 5. The severity of COVID-19 among the studied patients.

Variables	Group I (N=36)		Group II (N=36)		Group III (N=36)		P
Mild	24	66.8%	6	16.6%	4	11.1%	<0.001**
Moderate	6	16.6%	24	66.8%	21	58.4%	
Severe	6	16.6%	6	16.6%	11	30.5%	
	P ₁ 0.004*		P ₂ 0.175		P ₃ 0.002*		

*P for Chi-square test p₁ difference between group I and II p₂ difference between group II and group III p₃ difference between group I and III *p<0.05 is statistically significant **p<0.001 is statistically highly influential.*

Regarding CTP classification among group III patients, Child A was 22.2% of the patients, while CTP B and C were 50 % and 27.8 %, respectively (Tab 5). In addition, significant correlations existed between the severity of COVID -19 and CTP classification (Tab 6).

Table 6. Different grades of CTP classification among studied patients.

	Group II (N=36)		Group III (N=36)		P
	N	%	N	%	
Child A	36	100%	8	22.2%	<0.001**
Child B	0	0%	18	50%	
Child C	0	0%	10	27.8%	

***p<0.001 is statistically highly significant p for Chi-square for trend test.*

3.6. Assessment of the outcomes.

CLD Patients had more mortality rates than patients without CLD, and cirrhotic patients had a significantly greater death rate than hepatic patients without cirrhosis (8.3%, 19.4%, and 33.3%) in groups I, II, and III, respectively. On comparing every two individual groups, the difference is significant between groups I and III (tab 8).

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Table 7. The correlation coefficient between Child-Turcotte-Pugh score (CTP) and severity of covid -19 in studies groups.

	r	P
CTP	0.49	<0.001**

r Spearman rank correlation coefficient **p<0.001 is statistically highly significant.

Table 8. Comparison between the studied groups regarding mortality.

Variables	Group I (N=36)		Group II (N=36)		Group III (N=36)		P
	N	%	N	%	N	%	
Mortality	3	8.3%	7	19.4%	12	33.3%	0.046*
	P ₁ 0.307		P ₂ 0.284		P ₃ 0.018*		

P for Chi-square test p₁ difference between group I and II p₂ difference between group II and group III p₃ difference between group I and III *p<0.05 is statistically significant.

DISCUSSION

Patients with more severe COVID-19 infections and those needing intensive care unit (ICU) admission have higher rates of liver impairment than other patient groups [14]. In addition, the current investigation demonstrated that the severity of pre-existing liver illness significantly predicts the outcome.

In patients with COVID-19, whether or not CLD is present, a high bilirubin and transaminases (AST and ALT) signify liver damage directly or indirectly [15]. Initial investigations found that elevated AST and ALT levels in over a third of patients (transaminitis), which were linked to a more extended hospital stay [16], were present.

According to research by Cai et al., the liver tests of 76.3% of COVID-19 patients were abnormal. During hospitalization, 21.5% of these patients experienced a liver injury as indicated by ALT, AST, and total bilirubin levels that were raised more than three times the normal levels. Additionally, the study showed that patients' chances of acquiring severe pneumonia increased when they had abnormal liver tests [17]. These results align with our research, which found that individuals with COVID-19 had significantly elevated AST, ALT, bilirubin, and INR levels. These findings may help predict poor outcomes in these patients.

Uncertainty surrounds the method through which COVID-19 infection causes liver damage. In one sense, a direct cytotoxic effect of the virus has been hypothesized because

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liver and bile duct cells contain large numbers of angiotensin-converting enzyme-2 receptors, which permit their entry [18]. However, because COVID-19 affects multiple systems, liver damage is expected to be multifactorial, with the participation of systemic inflammatory response, cytokine release, and microvascular thrombosis [19].

Even without respiratory symptoms, COVID-19 infection in CLD patients, notably cirrhosis, seems to cause a fast decline in liver function and higher levels of decompensation [11].

According to the current study, individuals with CLD had significantly reduced O₂ saturation, which may indicate that the necessity for hospitalization was more likely brought on by CLD decompensation.

The APCOLIS study [20] found a higher incidence of liver-related complications in CLD patients infected with COVID-19, including aggravation of jaundice, ascites, hepatic encephalopathy, hematemesis, and spontaneous bacterial peritonitis. These consequences were more common in patients with decompensated cirrhosis and smaller baseline hepatic reserves.

Our study detected a significant correlation between the severity of COVID -19 and CTP classification. This implies that the intensity of liver illness present at the time of admission in COVID-19 patients predicts worsening patient condition and transfer to the ICU.

Patients with CLD in our study showed higher mortality rates than patients without CLD. These results concur with Ji et al., 2020. They claimed that compared to COVID-19 patients without chronic liver disease, those with chronic liver disease, including cirrhosis, experienced a more significant rate of disease progression [21]. Furthermore, according to a study by Iavarone et al., 2019, 29% of patients who died had end-stage liver disease, and 34% of patients passed away after a median of 10 days following their diagnosis of COVID-19 infection [22].

The current study had several advantages. First, this research, carried out in a hospital in Egypt, comprises the most significant number of individuals with CLD. Additionally, it is a follow-up study independent of hospital data.

Conclusion

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Those with CLD and cirrhosis had a greater death rate. COVID-19 severity was related to CTP score. Physicians should be mindful of the possible negative consequences of this virus on short-term outcomes in vulnerable patients, such as those with cirrhosis.

Footnotes.

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Declaration of competing interest

There are no conflicts of interest related to this study.

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Data availability

The corresponding author will supply the data supporting our study's findings upon reasonable request.

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