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Contents

Weekly Volume 27 Number 42 November 14, 2021

FRONTIER

OPINION REVIEW

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Cohort Study

Survival and outcomes for co-infection of chronic hepatitis C with and without cirrhosis and COVID-19: A multicenter retrospective study

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Author contributions: Afify S and Omran DA were the guarantors and designed the study; Afify S, Maher R, Eysa B, Abdel Ghaffar MM, Abdelhalim A and Edris MA participated in the acquisition of the data; Abo-Elazm OM participated in the analysis, and interpretation of the data; Shousha HI and Hamid FA drafted the initial manuscript; Afify S, Maher R, Omran DA, and Eysa B revised the article critically for important intellectual content.

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Abstract

BACKGROUND

Chronic liver disease, particularly cirrhosis, is associated with worse outcomes in patients infected with coronavirus disease 2019 (COVID-19).

AIM

To assess outcomes of COVID-19 infection among patients with pre-existing hepatitis C with or without liver cirrhosis.

METHODS

This multicenter, retrospective cohort study included all cases of confirmed co-infection of severe acute respiratory syndrome coronavirus 2 and chronic hepatitis

Informed consent statement: All study subjects gave written informed consent before study inclusion.

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C with or without liver cirrhosis who were admitted to six hospitals (Al-Sahel Hospital, Al-Matareya Hospital, Al-Ahrar Hospital, Ahmed Maher Teaching Hospital, Al-Gomhoreya Hospital, and the National Hepatology and Tropical Medicine Research Institute) affiliated with the General Organization for Teaching Hospitals and Institutes in Egypt. Patients were recruited from May 1, 2020, to July 31, 2020. Demographic, laboratory, imaging features, and outcomes were collected. Multivariate regression analysis was performed to detect factors affecting mortality.

RESULTS

This retrospective cohort study included 125 patients with chronic hepatitis C and COVID-19 co-infection, of which 64 (51.20%) had liver cirrhosis and 40 (32.00%) died. Fever, cough, dyspnea, and fatigue were the most frequent symptoms in patients with liver cirrhosis. Cough, sore throat, fatigue, myalgia, and diarrhea were significantly more common in patients with liver cirrhosis than in non-cirrhotic patients. There was no difference between patients with and without cirrhosis regarding comorbidities. Fifteen patients (23.40%) with liver cirrhosis presented with hepatic encephalopathy. Patients with liver cirrhosis were more likely than non-cirrhotic patients to have combined ground-glass opacities and consolidations in CT chest scans: 28 (43.75%) *vs* 4 (6.55%), respectively (P value < 0.001). These patients also were more likely to have severe COVID-19 infection, compared to patients without liver cirrhosis: 29 (45.31%) *vs* 11 (18.04%), respectively (P value < 0.003). Mortality was higher in patients with liver cirrhosis, compared to those with no cirrhosis: 33 (51.56%) *vs* 9 (14.75%), respectively (P value < 0.001). All patients in Child-Pugh class A recovered and were discharged. Cirrhotic mortality occurred among decompensated patients only. A multivariate regression analysis revealed the following independent factors affecting mortality: Male gender (OR 7.17, 95%CI: 2.19–23.51; P value = 0.001), diabetes mellitus (OR 4.03, 95%CI: 1.49–10.91; P value = 0.006), and liver cirrhosis (OR 1.103, 95%CI: 1.037–1.282; P value < 0.0001). We found no differences in liver function, COVID-19 disease severity, or outcomes between patients who previously received direct-acting antiviral therapy (and achieved sustained virological response) and patients who did not receive this therapy.

CONCLUSION

Patients with liver cirrhosis are susceptible to higher severity and mortality if infected with COVID-19. Male gender, diabetes mellitus, and liver cirrhosis are independent factors associated with increased mortality risk.

Key Words: COVID-19; Egypt; Outcome; Liver cirrhosis; Chronic hepatitis C

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Core Tip: Chronic liver disease, particularly cirrhosis, is associated with worse outcomes in patients infected with coronavirus disease 2019 (COVID-19). This study examined the impact of COVID-19 infection on patients with chronic hepatitis C during the first COVID-19 peak in Egypt. This retrospective cohort study was performed in six Egyptian hospitals. We found that cirrhotic patients had higher rates of pneumonia, severe COVID-19, and mortality. Cirrhotic mortality was observed among decompensated patients only. Male gender, diabetes mellitus, and liver cirrhosis were independent factors associated with increased mortality risk in Egyptian patients with COVID-19 and chronic hepatitis C.

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INTRODUCTION

On March 11, 2020, WHO declared severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), also known as coronavirus disease 2019 (COVID-19), as the sixth pandemic of the 21st century[1]. As of January 2021, the virus has caused more than 85 million confirmed infections and about 2 million deaths worldwide[2]. In Egypt, about 140000 confirmed infections and about 8000 deaths were recorded by the Egyptian Ministry of Health and Population as of January 2021[3]. Lung lesions can cause major damage in those infected with COVID-19, and liver injury also has been reported[4]. Studies conducted in Wuhan early in the epidemic outbreak found that up to 50% of infected patients had abnormal liver enzymes. Zhang *et al*[5] showed that SARS-CoV-2 infection occurs in 2%–11% of patients with pre-existing liver conditions.

COVID-19's adverse effects on the liver could be explained by both direct cytopathic injury and indirect effects of the virus[4]. It is well-established that SARS-CoV-2 uses angiotensin-converting enzyme receptors to gain entry into cells. These receptors are much more abundant in cholangiocytes (59.70%) than in hepatocytes (2.60%)[6]. The bile duct epithelium also plays an important role in regeneration after injury and immune response. Thus, the indirect effects may be due to exposure to multiple insults. For example, in severe cases admitted to intensive care, hemodynamic instability can lead to hypoperfusion and ischemic liver injury. Pneumonitis-associated hypoxia can lower mean arterial pressure, causing a synergistic effect contributing to this ischemic insult[4]. Another contributing factor could be toxic effects of medications (*e.g.*, steroids, non-steroid anti-inflammatory drugs, antibiotics, anticoagulants, antivirals), which are associated predominantly with hepatocellular rather than cholestatic liver injury[6,7]. Finally, immune dysregulation can lead to systemic inflammatory response syndrome, or cytokine storm, which is the release of inflammatory mediators (*e.g.*, interleukins IL-6 and IL-1, TNF- α, and interferon) that can cause and exacerbate liver injury[8].

Hepatitis C virus remains the most common etiology of overt and occult chronic liver diseases, liver cirrhosis, and risk of hepatocellular carcinoma in Egypt[9]. Chronic liver disease is associated with immune dysregulation and multiple system involvement (*e.g.*, cardiomyopathy, hepatopulmonary syndrome, and coagulopathy)[9]. Patients in Child-Pugh classes B and C and those with higher MELD scores have much higher mortality rates than patients in class A or with lower MELD scores[10]. Importantly, the cause of death in most of these patients is respiratory failure rather than acute on top of chronic liver failure[10].

Transaminitis, which is abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), is the most frequent and direct cause of disease severity in patients without cirrhosis[4]. Decompensation with worsening liver symptoms (*e.g.*, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and variceal hemorrhage) has been reported in patients with chronic liver disease and is associated with a high risk of death. Interestingly, decompensation occurs without respiratory symptoms[11]. This study aimed to demonstrate the impact of COVID-19 infection on patients with pre-existing hepatitis C with or without liver cirrhosis during the first COVID-19 peak in Egypt.

MATERIALS AND METHODS

Study design and patient selection

This multicenter, retrospective cohort study included all cases of confirmed co-infection of SARS-CoV-2 and chronic hepatitis C with or without liver cirrhosis who were admitted to six hospitals (Al-Sahel Hospital, Al-Matareya Hospital, Al-Ahrar Hospital, Ahmed Maher Teaching Hospital, Al-Gomhoreya Hospital, and the National Hepatology and Tropical Medicine Research Institute) in the General Organization for Teaching Hospitals and Institutes in Egypt. Patients were recruited from May 1, 2020, to July 31, 2020. The diagnosis of COVID-19 was based on a positive RT-PCR from nasopharyngeal swabs. Patients with negative RT-PCR results or those who did not undergo the swab were excluded.

Ethics statement

The authors assert that all procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects and patients were approved by the research

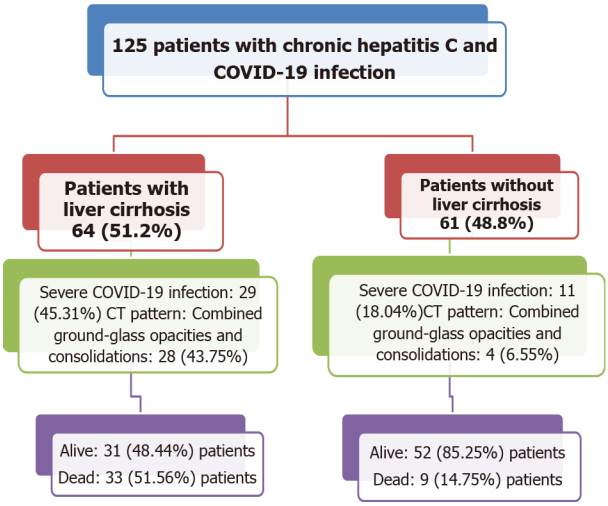

Figure 1 Flow chart of the study cohort.

ethics committee of the General Organization for Teaching Hospitals and Institutes. Written informed consent was obtained from all patients.

Methods

Baseline demographic data collected included age, gender, cigarette smoking status, and comorbidities. Other information recorded included general respiratory and gastrointestinal symptoms, chest CT scans, and laboratory results (complete blood count, liver and renal function, coagulation, D-dimer, ferritin, and C-reactive protein). We also included treatments administered to the patients and COVID-19 disease classification and outcome. COVID-19 severity was categorized as mild, moderate, or severe, according to the management protocol of the Egyptian Ministry of Health and Population[12]. Mild cases were symptomatic with lymphopenia or leucopenia and no radiological lung affection by pneumonia. Moderate cases were symptomatic with radiological features of pneumonia with or without leucopenia and lymphopenia. Severe and critical cases included any of the following: respiratory rate > 30 per minute; SaO_2 < 92 in room air; PaO_2/FiO_2 ratio < 300; chest radiology showing > 50% lung affection or progressive lung affection within 24 to 48 h; or critically ill at SaO_2 < 92, respiratory rate > 30 per minute, or PaO_2/FiO_2 ratio < 200 despite oxygen therapy. Severe and critical cases were indicated for intensive care unit (ICU) admission. Treatments were applied according to the protocol[12].

Statistical analysis

Data were analyzed using SPSS version 25 (SPSS Inc., Chicago, IL, United States). Numerical data are expressed as mean and standard deviation or median and range, as appropriate. Qualitative data are expressed as frequency and percentage. The Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, Student's *t*-test or the Mann-Whitney test (non-parametric *t*-test) was used to compare groups, as appropriate. A P value ≤ 0.05 was considered significant. To study possible associations between selected variables (gender, liver cirrhosis, and diabetes mellitus) and mortality, we fitted multiple logistic regression models. The results are expressed as the odds ratio (OR) with 95% confidence interval (CI).

RESULTS

This study included 125 patients infected with chronic hepatitis C virus and COVID-19 (Figure 1). Of those, 64 (51.2%) patients had liver cirrhosis: 25 (39.06%) were classified as Child-Pugh class A, 22 (34.38%) as class B, and 17 (26.56%) as class C. Patient residences included five Egyptian governorates: Cairo, Giza, Al-Behera, Al-Qalubya, and Al-Menofeya. Over half (61.2%) were older than 60 years, and most (68.8%) were men. Table 1 presents the baseline demographic features. Regarding COVID-19 symptoms, five (4.0%) patients were asymptomatic. The most common symptoms

Table 1 Baseline demographic features of patients (*n* = 125 patients)

Item	*n* (%)
Egyptian governorate	
Cairo	78 (62.4)
Al-Menofeya	17 (13.6)
Giza	14 (11.2)
Al-Qalubya	9 (7.2)
Al-Behera	7 (5.6)
Age (yr)	
20 to 30	1 (0.8)
30 to 40	6 (4.8)
40 to 50	10 (8.1)
50 to 60	31 (25.0)
60 to 70	35 (28.2)
70 to 80	35 (28.2)
80 to 90	6 (4.8)
Gender	
Male	86 (68.8)
Female	39 (31.2)
Cigarette smoking	10 (8.0)
History of contact with COVID-19 case	32 (25.6)
Diabetes mellitus	52 (41.6)
Hypertension	52 (41.6)
Direct-acting antiviral therapy treatment	
Not previously treated	108 (86.4)
Sustained virological response	17 (13.6)
COPD	1 (0.8)
Coronary artery disease	12 (9.6)
Acute kidney injury	1 (0.8)
Chronic renal insufficiency	8 (6.4)
Heart failure	2 (1.6)
Bronchial asthma	1 (0.8)
CT pattern	1 (0.8)
Consolidations and ground-glass opacities	31 (24.8)
Ground-glass opacities	94 (75.2)
Lesion distribution on CT	
Bilateral	122 (97.6)
Unilateral	3 (2.4)
COVID-19 case severity	
Moderate	86 (68.8)
Severe	39 (31.2)
Admission zone	
ICU	24 (19.2)

Intermediate care	6 (4.8)
Ward	95 (76.0)

COVID-19: Coronavirus disease 2019; COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; ICU: Intensive care unit.

were dyspnea (80 patients, 64.0%), fever (78 patients, 62.4%), and cough (55 patients, 44.0%), and five (4.0%) had diarrhea. Table 2 summarizes the patient symptoms. Table 3 summarizes the baseline laboratory results and treatment protocols among the studied patients.

We compared the characteristics of patients with and without liver cirrhosis. Fever, cough, dyspnea, and fatigue were the most frequent symptoms in patients with liver cirrhosis. Cough, sore throat, fatigue, myalgia, and diarrhea were significantly more common in patients with liver cirrhosis than non-cirrhotic patients. There was no difference between patients with and without cirrhosis regarding comorbidities. Fifteen (23.4%) patients with liver cirrhosis presented with hepatic encephalopathy (Table 4).

Patients with liver cirrhosis were more likely to show combined ground-glass opacities and consolidations in their chest CT scans: 28 (43.75%) *vs* 4 (6.55%), respectively (P value < 0.001). These patients also were more likely to present with severe COVID-19 infection: 29 (45.31%) *vs* 11 (18.04%), respectively (P-value 0.003), compared to patients without liver cirrhosis. Mortality was higher in patients with liver cirrhosis: 33 (51.56%) *vs* 9 (14.75%), respectively (P value < 0.001) (Table 5). All patients classified as Child-Pugh class A recovered and were discharged, whereas 18 (45%) mortalities occurred among patients considered class B and 15 (37.5%) among those considered class C.

A multivariate logistic regression revealed that male patients were more likely than female patients to die, after adjusting for liver cirrhosis and diabetes mellitus status (OR 7.166, 95%CI: 2.185–23.506; P value 0.001). Mortality was four times more likely among patients with diabetes mellitus, after adjusting for other factors in the model (OR 4.029, 95%CI: 1.488–10.906; P value 0.006). Patients with liver cirrhosis also were more likely to die (OR 1.103, 95%CI: 1.037–1.282; P value 0.0001), compared to those without cirrhosis (Table 6).

Within our cohort, 17 (13.6%) patients received direct-acting antiviral therapy (DAA) and achieved sustained virological response before acquiring COVID-19 infection. Among them, 10 (15.6%) patients had liver cirrhosis and seven (11.5%) did not. Three (17.6%) DAA recipients had severe COVID-19 disease, and the rest had moderate COVID-19 disease on admission. Regarding liver function, COVID-19 disease severity, and outcome, we found no difference between patients who previously received DAA and those who did not (Table 7).

DISCUSSION

Little research has assessed outcomes of patients co-infected with chronic hepatitis C virus and COVID-19, and existing studies include either a small number of patients or report data from patients with chronic liver disease and multiple underlying etiologies (viral and non-viral). This is the first Egyptian study reporting the outcome of SARS-CoV-2 infection in patients with isolated chronic hepatitis C as the etiology of their underlying chronic liver disease. We found a substantially increased incidence (23.43%) of hepatic encephalopathy in our cirrhotic patients infected with COVID-19. The 1-year cumulative incidence of hepatic encephalopathy in liver cirrhosis ranges from 0% to 21%[13]. We also found that the severity of COVID-19 symptoms and mortality rates were significantly higher in patients with liver cirrhosis. All patients assigned to Child-Pugh class A recovered and were discharged, but mortalities occurred among patients assigned to Child-Pugh class B or class C on admission. Male gender, diabetes mellitus, and liver cirrhosis were independent factors affecting mortality in our cohort.

In our study, fever (67.2%), cough (57.8%), dyspnea (56.3%), and fatigue (32.8%) were the most frequent symptoms in patients with liver cirrhosis, followed by diarrhea (7.8%). Among patients with cirrhosis, 6.3% were asymptomatic. Iavarone *et al*[14] studied 50 patients with liver cirrhosis with hepatitis C, hepatitis B, non-viral (*e.g.*, alcoholic), or multiple etiologies and reported fever in 64%, fatigue in 60%, dyspnea in

Table 2 Symptoms of the studied patients

Symptom	*n* (%)
Dyspnea	80 (64.0)
Fever	78 (62.4)
Cough	55 (44.0)
Fatigue	26 (20.8)
Disturbed consciousness	22 (17.6)
Sore throat	15 (12.0)
Newly developed hepatic encephalopathy	15 (12.0)
Hepatocellular carcinoma	15 (12.0)
Myalgia	12 (9.6)
Current ascites	9 (7.2)
History of hematemesis from esophageal varices	9 (7.2)
Asymptomatic	5 (4.0)
Diarrhea	5 (4.0)
Arthralgia	5 (4.0)
Anorexia	4 (3.2)
Nausea	3 (2.4)
Vomiting	3 (2.4)
Loss of taste	2 (1.6)
Hemoptysis	1 (0.8)
Abdominal pain	1 (0.8)
Loss of smell	1 (0.8)
Jaundice	1 (0.8)
Rhinorrhea	1 (0.8)

42%, and cough in 36%, followed by diarrhea in 10% and no symptoms in 12% of patients. In our study, 15 (23.4%) patients with liver cirrhosis presented with hepatic encephalopathy, compared with 11 (22%) of patients in Iavarone *et al*[14]. For ALT levels in our cohort, 58 (46.4%) were normal, 40 (32%) were elevated 1-2 times above the upper limit of normal, 7 (5.6%) were elevated 2-3 times above the upper limit, 20 (16%) were three times above normal, and 1 patient was five times over the upper limit. Iavarone *et al*[14] define ALT elevation at five times over the upper limit of normal as hepatic flare.

Our results revealed higher mortality among male patients, compared to female patients. Nasiri *et al*[15] similarly reported COVID-19-related mortality to be higher among males, and cohorts from China, Italy, Denmark, and the United States confirmed these findings[16-20]. Underlying sex-related mechanisms could include chromosomal immunological response, lifestyle (alcohol, smoking, and obesity), and comorbidities[19]. We also found that mortality was significantly higher in patients with liver cirrhosis, particularly those with decompensated cirrhosis. Boettler *et al*[21] reported that chronic viral hepatitis did not seem to raise the risk of a severe COVID-19 in a study by Guan *et al*[22], which included patients in China with chronic hepatitis B only. Shalimar *et al*[23] found no difference in mortality among patients with and without cirrhosis, but their sample size was small. An Italian study by Mangia *et al*[24] found that cirrhosis of metabolic origin, older age, leucopenia, and lymphopenia were risk factors for mortality. They also suggested that the very low prevalence of SARS-CoV-2 infection in patients with chronic hepatitis C infection could play a protective role against SARS-CoV-2 infection.

A meta-analysis by Váncsa *et al*[25], which included mainly studies of chronic hepatitis B in China, reported that liver failure and platelet count could predict in-hospital mortality with high specificity and lactate dehydrogenase with moderate

Table 3 Baseline laboratory results and treatments of the studied 125 patients

	mean ± SD/*n* (%)
Pulse rate	92 ± 17
Temperature	37 ± 1
Respiratory rate	23 ± 5
Oxygen saturation	93 ± 5
Hemoglobin (gm/dL)	12 ± 2
Platelet count (× 1000/cmm)	183 ± 107
Total leucocyte count (× 1000/cmm)	10 ± 8
Neutrophil : Lymphocyte ratio	1 ± 0
INR	1.16 ± 0.29
PTT	33.9 ± 13.2
Serum creatinine (mg/dL)	1.39 ± 1.43
Serum sodium (mEq/L)	137 ± 9
Serum potassium (mEq/L)	4.18 ± 0.77
Total bilirubin (mg/dL)	3 ± 5
Direct bilirubin (mg/dL)	2.1 ± 3.8
Serum albumin (g/dL)	3.2 ± 0.7
Alanine Transaminase (U/L)	58 ± 53
Aspartate Transaminase (U/L)	92 ± 123
Alkaline phosphatase (U/L)	262 ± 226
Serum ferritin (ng/mL)	667 ± 483
D-dimer (mg/mL)	1560 ± 2503
Fibrinogen (mg/dL) × 100 if presented in g/L	77
Azithromycin	72 (57.6)
Paracetamol	45 (36.0)
Supplementary vitamin C	85 (68.0)
Zinc	69 (55.2)
Colchicine	2 (1.6)
Lactoferrin	18 (14.4)
Other antibiotics	71 (56.8)
Steroids	38 (30.4)
Hydroxyl-chloroquine	29 (23.2)
Low-molecular weight heparin	56 (44.8)
Warfarin	3 (2.4)

PTT: Partial thromboplastin time; INR: International normalized ratio.

specificity. Singh *et al*[26] found that patients with cirrhosis had a higher relative risk of mortality and a higher risk of hospitalization, compared to patients without liver disease. Another study by Galiero *et al*[27] described outcomes in 35 patients with liver cirrhosis, though they did not compare cirrhotic *vs* non-cirrhotic patients, they found that male sex, chronic liver disease, and malignancies were independent factors of poor prognosis in hospitalized patients with COVID-19. They also reported that patients with advanced chronic liver disease had worse clinical conditions compared to patients with no liver disease[27].

Table 4 Baseline features and symptoms of patients with and without liver cirrhosis

Variable		No liver cirrhosis61 (48.8%)	Liver cirrhosis 64 (51.2%)	*P* value
Gender	Male	42 (68.9%)	44 (68.8%)	0.57
	Female	19 (31.1%)	20 (31.3%)	
Age (yr)	20 to 30	0 (0.0%)	1 (1.6%)	0.004
	30 to 40	3 (4.9%)	3 (4.8%)	
	40 to 50	0 (0.0%)	10 (15.9%)	
	50 to 60	19 (31.1%)	12 (19.0%)	
	60 to 70	14 (23.0%)	21 (33.3%)	
	70 to 80	21 (34.4%)	14 (22.2%)	
	80 to 90	4 (6.6%)	2 (3.2%)	
Cigarette smoking		2 (3.2%)	8 (11.5%)	0.06
Diabetes mellitus		24 (39.3%)	28 (43.8%)	0.71
Hypertension		23 (37.7%)	29 (45.3%)	0.46
COPD		0 (0.0%)	1 (1.6%)	1
Coronary artery disease		5 (8.2%)	7(10.9%)	0.76
Chronic renal insufficiency		4 (6.6%)	4 (6.3%)	1
Heart failure		0	2 (3.1%)	0.49
Hepatocellular carcinoma		3 (4.9%)	12 (18.8%)	0.026
Esophageal varices		0 (0.0%)	9 (14.1%)	0.003
Asymptomatic		1 (1.6%)	4 (6.3%)	0.36
Fever		35 (57.4%)	43 (67.2%)	0.27
Cough		18 (29.5%	37 (57.8%)	0.002
Dyspnea		44 (72.1%)	36 (56.3%)	0.09
Sore throat		2 (3.3%)	13 (20.3%)	0.005
Hemoptysis		0 (0.0%)	1 (1.6%)	1
Fatigue		5 (8.2%)	21 (32.8%)	0.001
Anorexia		1 (1.6%)	3 (4.7%)	0.62
Diarrhea		0 (0.0%)	5 (7.8%)	0.05
Nausea		1 (1.6%)	2 (3.1%)	1
Vomiting		1 (1.6%)	2 (3.1%)	1
Abdominal pain		1 (1.6%)	0 (0.0%)	0.48
Arthralgia		1 (1.6%)	4 (6.3%)	0.36
Myalgia		1 (1.6%)	11 (17.2%)	0.004
Loss of taste		0 (0.0%)	2 (3.1%)	0.49
Loss of smell		0 (0.0%)	1 (1.6%)	1
Disturbed consciousness		3 (4.9%)	19 (29.7%)	0.001
Hepatic encephalopathy		0 (0.0%)	15 (23.4%)	0.033
Direct-acting antiviral therapy with sustained virological response before COVID-19 infection		7 (11.5%)	10 (15.6%)	0.61

COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019.

In a retrospective multicenter study from 16 hospitals in China that included 21

Table 5 Comparison between patients with and without liver cirrhosis

		No liver cirrhosis 61 (48.8%)	Liver cirrhosis 64 (51.2%)	*P* value
Hemoglobin (mg/dL)		12 ± 2	12 ± 2	0.85
Platelet count (× 1000/cmm)		193 ± 107	171 ± 107	0.36
TLC (× 1000/cmm)		12 ± 10	9 ± 5	0.31
Serum creatinine (mg/dL)		1.58 ± 1.89	1.21 ± 0.76	0.59
Total bilirubin (mg/dL)		3 ± 4	3 ± 5	0.79
Serum albumin (g/dL)		3.3 ± 0.7	3.1 ± 0.6	0.36
Alanine transaminase (U/L)		67 ± 67	50 ± 40	0.21
Aspartate transaminase (U/L)		60 ± 37	101 ± 137	0.89
CT pattern	Consolidations and ground-glass opacities	4 (6.55%)	28 (43.75%)	< 0.001
	Ground-glass opacities	57 (93.45%)	36 (56.25%)	
Lesion distribution on CT	Bilateral	58 (95.1%)	64 (100.0%)	0.11
	Unilateral	3 (4.9%)	0	
COVID-19 severity	Moderate	50 (81.96%)	35 (54.69%)	0.003
	Severe	11 (18.04%)	29 (45.31%)	
Azithromycin		33 (54.1%)	39 (60.9%)	0.47
Paracetamol		16 (26.2%)	29 (45.3%)	0.04
Supplementary vitamin C		37 (60.7%)	48 (75.0%)	0.12
Supplementary zinc		33 (54.1%)	36 (56.3%)	0.85
Lactoferrin		3 (4.9%)	15 (23.4%)	0.004
Other antibiotics		28 (45.9%)	43 (67.2%)	0.019
Anticoagulants	LMWH	28 (45.9%)	28 (43.8%)	1
	Warfarin	1 (1.6%)	2 (3.1%)	1
Steroids		16 (26.2%)	22 (34.4%)	0.339
Alive (discharged)		52 (85.25%)	31 (48.44%)	< 0.001
Died at the hospital		9 (14.75%)	33 (51.56%)	

TLC: Thin layer chromatography; CT: Computed tomography; COVID-19: Coronavirus disease 2019.

Table 6 Multivariate regression analysis of factors affecting mortality

	B	S.E.	*P* value	Odds ratio	95%CI	
					Lower	Upper
Male	1.969	0.606	0.001	7.166	2.185	23.506
Diabetes mellitus	1.393	0.508	0.006	4.029	1.488	10.906
Liver cirrhosis	2.274	0.515	0.0001	1.103	1.037	1.282
Constant	-1.879	0.604	0.002	0.153		

patients with COVID-19 and hepatitis B virus-related liver cirrhosis (Child-Pugh classes A, B, and C in 16, 3, and 2 cases, respectively), mortalities occurred in patients assigned to class A (3; 60.0%) and C (2; 40.0%)[10]. In another multinational cohort study of 745 patients from 29 countries, Marjot *et al*[28] found that liver cirrhosis was present in 386 patients: 171 (44%) in Child-Pugh class A, 124 (32%) in class B, and 91 (24%) in class C. Mortality rates significantly increased with worsening scores: 33 (19%) in class A, 44 (35%) in class B, and 46 (51%) in class C died. Age, Child-Pugh

Table 7 Comparison between patients with COVID-19 who received or did not receive previous direct-acting antiviral therapy

		Did not receive previous DAA (*n* = 108)	Received previous DAA (*n* = 17)	*P* value
COVID-19 severity	**Moderate**	72 (66.7%)	14 (82.4%)	0.26
	Severe	36 (33.3%)	3 (17.6%)	
Admission zone	**ICU**	22 (20.4%)	2 (11.8%)	0.52
	Intermediate care	6 (5.6%)	0 (0.0%)	
	Ward	80 (74.1%)	15 (88.2%)	
Vital status	**Alive**	73 (67.6%)	12 (70.6%)	1
	Dead	35 (32.4%)	5 (29.4%)	
Total bilirubin (mg/dL)		1.00 (1-20)	1.30 (1-6)	0.84
Direct bilirubin (mg/dL)		0.9 (0.2-15.6)	0.9 (0.1-2.7)	0.93
Serum albumin (g/dL)		3.1 (1.7-5)	3.15 (2.4-3.8)	0.45
Alanine transaminase (U/L)		41.5 (13-324)	49 (18-175)	0.54
Aspartate transaminase (U/L)		46.5 (10- 549)	53 (16-415)	0.42

DAA: Direct-acting antiviral; COVID-19: coronavirus disease 2019; ICU: Intensive care unit.

class, and alcoholic liver disease were the independent factors affecting mortality in their study, and hepatic encephalopathy occurred in 104 (27%) of their patients[28]. Another study from 13 Asian countries studied 43 patients with liver cirrhosis and reported worsening liver disease and increased hepatic complications in patients with COVID-19 infection (P value < 0.05); they found that a baseline Child-Pugh score ≥ 9 was associated with higher mortality (area under the ROC 0.94, hazard ratio 19.2, 95%CI: 2.3–163.3; P value < 0.001). The independent factors affecting mortality in their study were increased serum bilirubin and AST/ALT ratio[29].

The exact mechanism causing poor outcomes among patients with COVID-19 and preexisting liver disease remains unknown; however, interactions between local liver injury and systemic disturbances seem likely culprits, especially in patients with cirrhosis. Patients with liver cirrhosis are theoretically more susceptible to poor outcomes from COVID-19-related liver injury. Moreover, patients with advanced liver disease exhibit immune deficiency and systemic inflammation, as reflected by activated circulating immune cells and increased serum levels of pro-inflammatory cytokines. These factors can predispose this population to cytokine storms[26]. Furthermore, some cirrhotic patients may have an underlying hepato-pulmonary syndrome, portopulmonary hypertension, or hydrothorax, which can increase the risk of respiratory failure, as indicated in a study by Oyelade *et al*[30].

Sun *et al*[31] suggested SARS-CoV-2-related direct cytotoxicity (*i.e.*, severe inflammatory response leading to immune-mediated liver damage), hypoxic hepatitis due to anoxia (particularly in patients with severe COVID-19), drug□induced liver injury (especially related to the use of antiviral agents such as lopinavir, ritonavir, remdesivir, chloroquine, tocilizumab, umifenovir, and traditional Chinese preparations), and reactivation of pre-existing chronic liver disease as possible mechanisms of hepatic injury. They also found that liver biopsy specimens from deceased patients with severe COVID-19 showed moderate microvascular steatosis and mild lobular and portal activity, indicating that liver injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury[31].

A limitation to our study is its retrospective nature and the limited number of patients. It remains unknown whether liver injuries and mortalities among patients with chronic hepatitis C and COVID-19 co-infection are due to patients' pre-existing chronic conditions or the impact of SARS-CoV-2 infection. We found that patients with decompensated hepatitis C-related cirrhosis were at higher risk of COVID-19-related mortality. Hepatic encephalopathy could be the presentation of underlying SARS-CoV-2 infection in patients with liver cirrhosis. The underlying etiology of chronic liver disease also could impact COVID-19 disease course and outcome. Further studies comparing outcomes and prognostic factors in patients with isolated underlying etiologies of chronic liver disease are therefore encouraged, rather than combining them into one group, which could obscure relevant risk factors for disease severity and

outcomes.

CONCLUSION

In Egypt, among patients with chronic hepatitis C who also were infected with COVID-19, those with cirrhosis had higher rates of pneumonia, severe COVID-19, and mortality, though cirrhotic mortality occurred among decompensated patients only. Male gender, diabetes mellitus, and liver cirrhosis were the independent factors affecting mortality in these patients.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) disease severity and outcomes are affected by pre-existing chronic liver disease, particularly cirrhosis. Patients with decompensated liver cirrhosis (Child-Pugh classes B and C) are severely affected, with higher mortality rates than patients with compensated disease.

Research motivation

Comprehensive research on the outcome of COVID-19 in patients with isolated etiology of pre-existing chronic liver disease is needed to understand the clinical presentations and outcomes.

Research objectives

This study aimed to demonstrate the impact of COVID-19 factors affecting mortality among patients with pre-existing hepatitis C with or without liver cirrhosis during the first peak of the pandemic in Egypt.

Research methods

This multicenter retrospective cohort study included 125 patients with COVID-19 at six quarantine hospitals in Egypt from May 1, 2020, to July 31, 2020. Clinical, laboratory features, COVID-19 severity, and outcomes were recorded. A regression analysis was performed to detect factors affecting mortality.

Research results

Fever, cough, dyspnea, and fatigue were the most frequent symptoms in patients with liver cirrhosis. Cough, sore throat, fatigue, myalgia, and diarrhea were significantly more common in patients with liver cirrhosis than in non-cirrhotic patients. Fifteen (23.4%) patients with liver cirrhosis presented with hepatic encephalopathy. Patients with liver cirrhosis were more likely to exhibit combined ground-glass opacities and consolidations in their chest CT scans and more likely to present with severe COVID-19 infection, compared to patients without liver cirrhosis. Mortality was higher among patients with liver cirrhosis: 33 (51.56%) *vs* 9 (14.75%), respectively (P value < 0.001. All patients in Child-Pugh class A recovered and were discharged, and mortalities occurred among patients in Child-Pugh classes B and C. A multivariate logistic regression revealed that male gender, diabetes mellitus, and liver cirrhosis were independent factors affecting mortality. Regarding liver function, COVID-19 disease severity, and outcomes, we found no difference between patients who previously received direct acting antiviral therapy (and achieved sustained virological response) and patients who did not receive such therapy.

Research conclusions

Patients with decompensated hepatitis C virus-related liver cirrhosis are at higher risk of severe COVID-19 disease and mortality. Male gender, diabetes mellitus, and liver cirrhosis are the independent factors affecting mortality.

Research perspectives

Male gender, diabetes mellitus, and liver cirrhosis significantly increased mortality in patients with COVID-19 and isolated hepatitis C virus-related chronic liver disease. Previous achievement of sustained virological response after direct acting antiviral therapy for chronic hepatitis C does not impact COVID-19 disease severity, outcome,

or the results of liver function tests.

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