Impact of COVID-19 Infection on Patients with Chronic Liver Disease

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Background and study aim: Elevation of liver chemistries in COVID19 infection has been documented worldwide. Our aim was to assess the impact of COVID19 on patients with chronic liver disease (CLD).

Patients and Methods: A total of 100 COVID19 patients (70 CLD patients and 30 non-CLD patients) were enrolled in a retrospective study to evaluate baseline and follow-up clinical and laboratory characteristics during 2020-2022.

Results: CLD patients had higher frequency of severe disease, ICU admission, non-invasive and mechanical ventilation and prolonged ICU stay. No significant differences between both groups regarding baseline and follow-up and clinical and laboratory data. Each group showed mild raised baseline liver enzymes and serum bilirubin levels with post-recovery improvement without statistical significance.

Conclusion: Severe infection, and prolonged hospital/ICU stay were higher in COVID19 patients with underling CLD. Monitoring of those high risk patients is a matter of worry increasing their diagnostic and therapeutic burden.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative agent of Coronavirus Disease 19 (COVID-19), a highly contagious and dangerous virus that originated in Wuhan, China and rapidly expanded globally [1]. Regardless of the viral state, the term "long COVID" refers to the manifestation of several symptoms even weeks or months after contracting a SARS-CoV-2 infection. Another name for it is post-COVID syndrome. It may be on-going or exhibit intermittent or relapsing patterns [2]. One or more of the acute COVID symptoms may remain, or new symptoms may emerge. The majority of COVID-19 patients had negative PCR results, which suggests microbiological recovery. Thus, the interval between microbiological and clinical healing is known as post-COVID syndrome [3]. Post-acute COVID, which occurs when symptoms last longer than three weeks but less than twelve weeks, and chronic COVID, which occurs when symptoms last longer than twelve weeks, are the two phases of post-COVID, also known as long COVID [4].

Patients with COVID-19 may have unusually elevated liver enzyme values, suggesting at least transient damage. It's unclear, however, whether this is directly connected to the illness or to other variables. Furthermore, further study may be required to confirm the fair assumption that COVID-19 individuals who already have chronic liver disorders (CLD), such as cirrhosis or chronic hepatitis, would be at increased risk of significant liver damage [5]. As the number of COVID-19 patients rises, several studies Zu et al., [6], Mao et al., [7], Guan et al., [8] revealed that after lung disease, the liver is the organ most often impacted. Between 14.8 and 53.1% of infected individuals showed atypical levels of the transaminases aspartate aminotransferase (AST) and alanine

aminotransferase (ALT). The majority of the rise in serum bilirubin was minor [9]. Research on COVID-19 infection and CLD patients is lacking in our area. Thus, our goal was to evaluate how COVID19 affected CLD patients [10].

PATIENTS/MATERIALS AND METHODS

Study design

Between 2020 and 2022, a retrospective cohort study centered in a hospital was carried out in the Post-COVID Outpatients Clinic at Assiut University Hospitals in Egypt.

The research was carried out in compliance with the guidelines of the Declaration of Helsinki and was authorized by the ethical committee of the Faculty of Medicine, Assiut University, Assiut, Egypt (IBR number 17101541). Patients gave their written, informed permission to participate in the trial.

Study population

Adult patients (with and without CLD) with history of COVID19 infection and recovery since more than one month before the recruitment in the study were eligible for the study. COVID19 infection was clinically, and laboratory suspected and confirmed by polymerase chain reaction (PCR). Chronic liver disease (CLD) was diagnosed by clinical, biochemical, and ultrasonography findings Patient were less than 18 years old, with concurrent COVID19 infection that wasn't completely recovered were excluded from the study.

Sample size calculation

Based on expected frequency of hepatic affection among recovered COVID19 patients that was 15.8% with assumption of 5% alpha error, 90% power and 95% confidence interval p value was significant if <0.05. A minimum of 65 patients was required. During the course of the trial, 100 patients in all were enrolled.

Participants and study tools

The current study enrolled a total of 100 patients; 70 CLD patients and 30 non-CLD patients, who had a history of COVID19 infection and recovery since more than one month before the recruitment in the study. Only patients with CLD who were admitted to hospital, others not admitted. The medical records of those patients (during the course of COVID 19 disease and follow-up after recovery) were reviewed and the following data were gathered; thorough history taking including age, sex, comorbidities, duration of the infection, duration of hospital stay, admission to intensive care unit (ICU), fever, diarrhea, dyspnea, cough, jaundice, and other clinical data. Laboratory data included liver transaminases, serum bilirubin, albumin, creatinine, complete blood count (hemoglobin, leucocytes, lymphocytes, and platelet), and international randomized ratio (INR). Different regimens used for management of COVID19 infection (antibiotics, oxygen therapy, vitamins and/or supportive treatment) were recorded.

Chronic liver disease (CLD) included: Chronic hepatitis B, C, and D infections are the most common causes of chronic liver disease, autoimmune liver disease (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis), drug induced liver injury, vascular: (Budd-Chiari syndrome), genetic: (Hereditary hemochromatosis and Wilson disease) and idiopathic/cryptogenic.

Statistical analysis

The statistical software for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA), was utilized to analyze the recorded data. Quantitative data were compared utilizing the Student or paired t test, and reported as mean ± Standard Deviation (SD). The Chi2 test was utilized to compare the frequency and proportion of qualitative data. Since there was a 95% level of confidence, a P value of less than 0.05 was considered significant.

RESULTS

This cohort study was performed on 100 COVID19 patients (70 patients with CLD and 30 without CLD). Their baseline demographic and clinical data were summarized in Table (1) where COVID19 patients with CLD were older and had more severe infection, lower hemoglobin level and platelets compared to those without CLD ($P < 0.001$, for all). In addition, patients with CLD showed higher frequency of symptomology including anosmia, fever, dyspnea and cough but without statistical

significance. Moreover, patients with CLD had significant higher frequency of ICU admissions, non-invasive ventilation (P< 0.001) and mechanical ventilation (P< 0.001) with longer stay at ICU (P< 0.001) compared to patients without CLD (Table 2). At follow-up after recovery, a part of significant lower Hemoglobin and platelets in CLD patients, no substantial variations were found between both groups as regard laboratory variables (Table 3).

In the current research, we found that among those patients without CLD, 6 (20%) patients developed raised liver transaminases and another 3 (10%) patients developed jaundice during COVID 19 infection. At follow-up after recovery, all those 9 (30%) patients were completely improved without any hepatic sequel.

Table 1. Baseline clinical and demographic information for the participants under study

	Patients with chronic liver disease		P
	No (n=30)	Yes (n=70)	
Age(years)	30.30 ± 5.11	55.13 ± 13.98	**< 0.001**
Sex (M/F)	20/10 (66.7/33.3)	40/30 (71.4/28.6)	0.90
Comorbid diseases*	17 (56.7)	19 (27.1)	0.005
Duration of symptoms(days)	8.11 ± 2.22	8.90 ± 3.11	0.90
Severe disease	2 (6.7%)	40 (57.1%)	**< 0.001**
Anosmia	10 (33.3%)	30 (42.8%)	0.34
Diarrhea	5 (16.7%)	10 (14.3%)	0.19
Fever	25 (83.3%)	60 (85.7%)	0.09
Dyspnea	21 (70%)	56 (80%)	0.07
Cough	23 (76.7%)	60 (85.7%)	0.32
Pulse oximetry saturation	93.39 ± 13.11	93.63 ± 15.71	0.89
Leucocytes (10^3/ul)	9.11 ± 5.11	8.80 ± 2.55	0.10
Lymphocytes (10^3/ul)	1.31 ± 0.71	0.81 ± 0.34	0.11
Hemoglobin (g/dl)	12.70 ± 2.56	9.98 ± 2.11	**< 0.001**
Platelets (10^3/ul)	267.09 ± 112.22	101.34 ± 24.99	**< 0.001**
Creatinine (mmol/l)	101.87 ± 24.66	105.55 ± 33.87	0.46
CRP (mg/dl)	70.98 ± 34.56	70.98 ± 34.04	0.45

*Comorbid diseases included diabetes mellitus, ischemic heart disease, systemic hypertension, chronic kidney disease.
CRP: C reactive protein.

Table 2. Lines of therapy and length of ICU stay among the studied COVID 19 patients.

	Patients with chronic liver disease		P
	No (n= 30)	Yes (n= 70)	
Admission to ICU	6 (20%)	56 (80%)	< 0.001
ICU duration (days)	4.40 ± 2.11	12.81 ± 3.11	< 0.001
Steroid therapy	24 (80%)	56 (80%)	0.69
Steroid dose (mg)	150.98 ± 12.6	149.11 ± 34.45	0.10
Hydroquine	6 (20%)	14 (20%)	0.69
Tamflu	8 (26.7%)	14 (20%)	0.10
Remdisvir	4 (13.3%)	10 (14.3%)	0.23
Actemera	6 (20%)	15 (21.4%)	0.39
High flow nasal cannula	3 (10%)	14 (20%)	0.10
NIV	5 (16.7%)	28 (40%)	< 0.001
MV	3 (10%)	28 (40%)	< 0.001

*NIV: Noninvasive ventilation, MV : mechanical ventilation

Table 3: Follow-up laboratory data of the studied COVID19 patients

	PATIENTS WITH CHRONIC LIVER DISEASE		P
	NO (N= 30)	NO (N= 30)	
LEUCOCYTES (10^3/UL)	*5.22 ± 1.09*	*5.14 ± 2.22*	*0.19*
LYMPHOCYTES (10^3/UL)	*1.56 ± 0.16*	*1.60 ± 0.87*	*0.98*
HEMOGLOBIN (G/DL)	*11.99 ± 2.31*	*11.01 ± 2.23*	*< 0.001*
PLATELETS (10^3/UL)	*245.99 ± 51.19*	*89.11 ± 12.87*	*< 0.001*
CREATININE(MMOL/L)	*99.35 ± 8.99*	*101.45 ± 21.87*	*0.11*
CRP(MG/DL)	*6.78 ± 2.01*	*7.88 ± 1.09*	*0.25*

CRP: C-REACTIVE PROTEIN

DISCUSSION

In this study, we aimed to assess the impact of COVID 19 on CLD patients and to evaluate the hepatic manifestations in post-COVID19 patients. We found that patients with CLD were older and had significant higher frequency of severe infection, ICU admissions, non-invasive ventilation, mechanical ventilation and prolonged ICU stay that non-CLD patients.

Consistent with the findings of the present research, Oyelade et al., [11] revealed that Patients having a history of hepatic illness were more likely to die (17.65%) and have a severe COVID-19 infection (57.33%)[11]. This may be connected to those individuals' low lymphocyte and platelet counts (14). Moreover, Cai et al., [12] revealed that A nine-fold increased risk of severe infection was linked to the development of liver damage during COVID-19 infection. In such group of patients, severe measures against SARS-CoV-2 infection should be taken since this might be the result of immunological failure linked to cirrhosis. Conversely, pooled analysis by Lippi et al., [13] revealed that There may be no correlation between the severity or mortality of chronic liver disease.

Patients with circulatory problems may be more susceptible to severe illness, hepatic decompensation, and SARS-CoV-2 infection. Significant cytokine activation associated with COVID-19 causes hepatocyte apoptosis and necrosis, which may result in hepatic decompensation given the reduced liver reserve [14].

In the present work, the studied patients in both groups showed raised baseline liver enzymes and serum bilirubin levels with post-recovery improvement without statistical significance. We found that, among non-CLD patients, 6 (20%) patients developed raised liver enzyme levels and another 3 (10%) patients developed jaundice. Our findings concurred with those of Cai et al., [12] revealed that Almost half of the patients had aberrant liver blood tests at some point during the SARS-CoV-2 infection.

Our findings were consistent with those of Wang et al., [15] that showed mild elevations in ALT and AST during COVID-19 disease course and during treatment, with most patients discharged with normal liver markers.

Richardson et al., [16] documented that During COVID-19 illness, AST and ALT were often increased (58.4% and 39.0% of patients, respectively).

Furthermore, Ji et al., [17] stated that AST and ALP levels increased progressively with increasing infection severity however, ALT and total bilirubin were not increased suggesting that AST and ALP values were indicative of disease severity.

Increased numbers of patients requiring ICU care, longer hospital stays, and elevated liver enzyme and bilirubin levels have all been linked to the severity of COVID-19 infection. These findings highlight the critical role that immune-mediated systemic inflammation plays in liver impairment associated with severe cases of COVID-19 infection [8, 18-22]

The main limitations in the current study included a small relatively sample size, no long-term follow, conducted in single center and we didn't perform survival analysis of the studied groups. And yet, this is the first study that discussed such issue in our locality.

CONCLUSION

Severe infection, and prolonged hospital/ICU stay were higher in COVID19 patients with underling CLD. Monitoring of those high risk

patients and tailoring of their therapeutic approaches is a matter of worry increasing their diagnostic and therapeutic burden. Patients with underlying comorbidity may have serious outcome and hepatic comorbidity is an important one of these comorbidities and this representing the outcome of this study.

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Author contribution: We declare that all listed authors have made substantial contributions to all of the following three parts of the manuscript:

- Research design, or acquisition, analysis or interpretation of data;

- drafting the paper or revising it critically;

- approving the submitted version.

We also declare that no-one who qualifies for authorship has been excluded from the list of authors.

Ethical approval: by the ethical committee of the Faculty of Medicine, Assiut University, Assiut, Egypt (IBR number 17101541).

HIGHLIGHTS

- COVID19 is a serious problem pandemic since 2020.
- Patient with underlying comorbidity may have serious outcome.
- Hepatic comorbidity is one of the comorbidities that may have serious outcome.

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