Impact of COVID-19 on Liver Functions Tests in Egyptian Patients with or without Chronic Liver Disease

Mohamed Abdel-Samiee[1], Mostafa Shaldoum[2], Eman Abdelsameea[1],Samah Mohamed Awad[3], Nabil Abdelhamid Omar[1]

[1]*Department of Hepatology and Gastroenterology, National Liver Institute, Menoufia University, Shebin El-Kom, Egypt.*

[2]*Fever Hospital, Mansoura, Egypt*

[3]*Department of Clinical Microbiology and Immunology, National Liver Institute, Menoufia University, Shebin El-Kom, Egypt*

Corresponding Author
Mohamed Abdel-Samiee.
Mobile:
+2 01002415018
E mail:
Drmohammed100@yahoo.com

Receive date:18/1/2024
Revise date:27 /1/2024
Accept date:17/2/2024
Publish date:20/2/2024
.Key words

COVID-19; Liver Functions Tests; Egyptian Patients; Chronic Liver Disease

Background and aim: Impact of corona virus disease 2019 (COVID-19) on liver remains poorly characterized. Severe hepatic injury has been reported in COVID-19, even though the transaminases levels' elevation is usually mild. We aimed to evaluate the correlation between these abnormalities and severity of COVID-19.

Patients and Methods: This retrospective research was performed on COVID-19 cases. All studied cases were classified into: group 1 (n=100): cases without chronic liver disease (CLD) and group 2 (n=100): cases with CLD.

Results: The mean ± SD of age was 50.57 ± 11.78 in group 1 and 55.77 ± 7.87 in group 2. Liver tests were abnormal in 41% and 55% of the subjects in group 1 and 2 respectively. Group 2 had significantly more gastrointestinal tract symptoms than group 1 (p =0.033). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin and international normalized ratio (INR) after infection were significantly higher than before infection in both groups (p <0.001). Group 2 had significantly higher mortality rate (47%) than group 1 (32%) (P= 0.02). MELD score was significantly higher in died patients than recovered patients in group 2 (p <0.001). After COVID-19 infection, hepatic encephalopathy (HE) and aggravation of ascites was found in 34% and 36% of patients in group 2.

Conclusion: COVID-19 infection can cause liver function abnormalities in both cases with and without CLD with aggravation of ascites and HE development in cirrhotic patients.

INTRODUCTION

For the first time in Wuhan, China (December 2019), a pandemic of the novel coronavirus disease- 2019 (COVID-19) started as an outbreak of unexplained pneumonia. [1] 7 410 510 confirmed cases and 418 294 mortalities have been recorded as of 12 June 2020. Based on a report from the Chinese Center for Disease. Control and Prevention (CDC), the overall mortality rate was 2.3%.[2]

Multiple studies have detailed the clinical features of cases with COVID19, symptoms typically are similar to viral pneumonia including fatigue, dry cough, fever, headache and anosmia and the symptoms could evolve to respiratory failure.[3] The virus has now been named (SARS-CoV-2). Digestive system involvement such as nausea, vomiting and diarrhea has also been reported. [4]. Even though acute respiratory failure and diffuse alveolar damage are the hallmarks of COVID-19, other organs' impairment are also reported. [5].

Significant systemic signs of COVID-19 also include myocarditis, acute kidney injury, acute liver injury (LI) and thrombosis. [6] A significant proportion of COVID-19 cases have been reported to have elevated liver enzymes, even though its impact of

on the liver remains poorly understood. Severe LI has been reported in COVID-19, even though the transaminases levels' elevation is usually mild [one to two times the upper limit unit of normal (ULN)]. It is not entirely understood how SARS-CoV-2 affects the liver, although it is believed to be a mix of immune-mediated inflammatory response and direct virally-mediated injury [7, 8].

The presence of the angiotensin-converting enzyme 2 (ACE2) receptor, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) cellular receptor, in hepatic and biliary endothelial cells offers a potential mechanism for the observed injury in the liver. Other LI etiologies including congestion, shock, drug-induced LI, sepsis, and extrahepatic sources of aspartate aminotransferase (AST) must be considered [7]

Li et al. concluded that lymphopenia and raised C-reactive protein (CRP) are risk factors of liver injury in COVID-19 infected cases [9]

Our objective was to evaluate COVID-19 effect on liver functions tests in Egyptian subjects with or without chronic liver disease (CLD). Also, we aim to evaluate the correlation between these abnormalities and COVID-19 severity.

PATIENTS AND METHODS

This retrospective research was performed on COVID-19 cases who attended the outpatient clinic of National Liver Institute (NLI) and New Mansoura General hospital (International) in the period from April 2020 to January 2021. Real time reverse transcriptase polymerase chain reaction (RT-PCR) assay was used for the detection of SARS-CoV-2 using nasopharyngeal swabs, and also if there was one or more of these symptoms of COVID-19 symptoms are present such as: fever, cough, chills, shortness of breath, fatigue, red eyes, rash, drowsiness, confusion body aches, headache, congestion or runny nose, new loss of taste and/or smell, persistent chest pressure or pain, sore throat, gastrointestinal (GI) symptoms such as nausea or vomiting or diarrhea. All studied patients were classified into two groups: group 1 (n=100) included cases without CLD and group 2 (n=100) included cases with CLD. All studied cases underwent the following laboratory investigations: Liver tests such as gamma glutamyltranspeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total and direct bilirubin, alkaline phosphatase (ALP), international normalized ratio (INR), Viral markers as HBsAg and HCV Ab, complete blood count (CBC), ferritin, D-dimer, C reactive protein (CRP), abdominal ultrasound and computed tomography (CT) of the chest. The diagnosis of chronic liver disease was performed by determining the etiology (Chronic HCV infected patients were positive for HCV Ab and HCV RNA by real time PCR. Chronic HBV infected patients were positive for HBsAg and HBV DNA by real time PCR for more than 6 months) and complications of the disease (Ultrasound abdomen in case of CLD detects size and echogenicity nodularity of liver and absence or presence of ascites). Assessment of severity of liver disease was done according to Child Pugh classification and model for end stage liver disease (MELD).

Abnormalities of Liver test were defined as an increase in the serum levels of: total bilirubin (TBIL) >17.1 μmol/L, AST >40 U/L, alkaline phosphatase (ALP) >135 U/L, ALT >40 U/L, and gamma-glutamyltransferase (GGT) >49 U/L [10].

The classification of the pattern of these abnormalities was: cholestatic, hepatocellular, or mixed.

Cases with hepatocyte type had high AST and/or ALT levels > 3 times the ULN. Cases with cholangiocyte type had elevated ALP or GGT twice the ULN. Cases with mixed type [Abnormality type (1)] had an elevation in both ALT/AST > 3times the ULN and ALP/GGT twice the ULN [10].

The liver abnormality patterns were assessed based on another criterion: When the activity of AST/ALT was higher than the activity of ALP/GGT, with the calculation of liver enzyme activities by multiples of their ULN, respectively, cases were classified as hepatocyte type; and were classified as cholangiocyte type [Abnormality type (2)] when the opposite occurred [10].

COVID-19 severity: On the basis of chest radiography, symptoms, and clinical examination, all cases were categorized as severe or mild cases. Cases without abnormalities, and with mild symptoms (i.e., cough, expectoration,

fever, and other symptoms of the upper respiratory tract), or with mild changes on chest radiography will be classified as non-severe cases. The presence of any of the subsequent criteria defines severe pneumonia: i) hypoxia: oxygen saturation ≤93% (while resting); ii) significantly elevated respiration rate (RR): RR ≥30 breaths/minute; iii) respiratory or other organ failure that necessitates monitoring and treatment in the intensive care unit (ICU), or shock [10].

Statistical analysis

SPSS V26 was used to conduct the statistical analysis (IBM Inc., ARMONK, NY, USA). Categorical data were displayed as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. Continuous data were displayed as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test and compared between the three groups utilizing ANOVA (F) test with post hoc test (Tukey). Kaplan Meier curve was used to show the time of mortality. A two tailed $p< 0.05$ was deemed statistically significant.

RESULTS

The clinical features of the two studied groups were described. Group 2 had significantly higher age than group 1 ($p <0.001$) and males were significantly higher in group 2 than group 1 ($p= 0.048$). Many of patients complained from fever, cough and GIT symptoms. Fever and cough were insignificantly different between both groups while group 2 had significantly more GIT symptoms than group 1 ($p= 0.033$). The main medical history was diabetes mellitus (DM) and hypertension with insignificant difference between both groups as mentioned in table 1**.**

Many laboratory investigations were done during hospitalization. HCV antibody and HBs Ag were negative in all patients in group 1 while HCV antibody was positive in 90 (90%) patients in group 2 and HBs Ag was positive in 10 (10%) patients in group 2. The mean± SD of CRP in group 1 was 89.02 ± 54.46 mg/dl and it was 76.27 ± 35.62 mg/dl in group 2 with insignificant variation between the 2 studied groups ($p= 0.051$). D-dimer was high in 67 and 71 cases in group1 and group 2 respectively with insignificant difference between them. Serum ferritin was high in 44 and 42 cases in group1 and group 2 respectively with insignificant different between them as mentioned in table 2**.**

Abdominal ultrasound and CT chest were done for all cases. Abdominal ultrasound findings for liver were normal for all cases of group 1 while, in group 2 all patient had cirrhotic liver, 96 patients had splenomegaly and about 91 patients had variable degrees of ascites. CT chest for all patients varied from CO-RAD 3 to CO-RAD 5 with insignificant variation between both groups ($p= 0.91$).

During hospitalization, liver function tests (AST, ALT, ALP and GGT) were found to be abnormal in 41 and 55 individuals in group 1 and group 2 respectively. LI abnormality type 1 was hepatocyte type in 27 individuals in group 1 and in 32 individuals in group 2, mixed type in 1 individual in both groups with no cholangiocyte type in both groups. Abnormality type 2 was hepatocyte type in 35 individuals in group 1 and in 48 individuals in group 2 and cholangiocyte type in 3 individuals in group 1 and in 2 individuals in group 2. LI, abnormality type 1 and abnormality type 2 were insignificantly different between both groups ($p< 0.05$).

Direct bilirubin, TBIL, INR, AST, and ALT after infection were significantly elevated than before infection in both group 1 and group 2. GGT was insignificantly different between before and after infection and ALP and serum albumin levels after infection were significantly reduced than before infection in group 1. In group 2, GGT, ALP and serum albumin after infection were significantly lower than before infection. Group 2 had significantly increased delta change of TBIL and INR than group 1 ($p =0.007$ and <0.001 respectively). Group 2 had significantly lower delta change of serum albumin than group 1 ($p=0.002$). Delta change of ALT, AST, direct Bilirubin, GGT and ALP were insignificantly different between both groups as mentioned in tables 3&4.

At admission, MELD score and Child score were calculated for the cases of group 2 and result showed that MELD score range from7 to 18 with a mean value (± SD) of 11.9 (±2.45).

Due to complications and LI happened after covid-19 infection for both groups, 41(41%)

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DOI: 10.21608/AEJI.2024.262584.1350

patients had elevated Liver enzymes, 33 (33%) patients had hypoalbuminemia and 23 (23%) patients had elevated total bilirubin after infection in group 1,but aggravation of ascites and hepatic encephalopathy occurred in 36 (36%) patients and 34 (34%) patients respectively in group 2. Child score was significantly higher after covid-19 infection, it ranged from 4-8 but after infection it ranged from 5-13. Regarding Child-classification, class A was significantly lower after infection than before infection ($p < 0.001$), class B was insignificantly different between before and after infection and class C was significantly higher after infection than before infection ($p < 0.001$) as mentioned in table 5.

About 99 patients in each group were presented with sever pneumonia due to high respiratory rate (RR) ≥ 30, or oxygen saturation (resting state) ≤ 93%. PaO_2 and PaO_2/FiO_2 were insignificantly different between both groups. Oxygen therapy was mask in 35 (35%) individuals in group 1 and 25 (25%) individuals in group 2, CPAP in 20 (20%) individuals in group 1 and 22 (22%) individuals in group 2, BiPAP in 23 (23%) individuals in group 1 and 26 (26%) individuals in group 2, Vent-CPAP in 3 (3%) individuals in group 1 and 4 (4%) individuals in group 2, Vent-BiPAP in 8 (8%) individuals in group 1 and 14 (14%) individuals in group 2 and Vent-tube in 11 (11%) individuals in group 1 and 9 (9%) individuals in group 2. Oxygen therapy was insignificantly different between both groups**.**

Hospitals stay (in days) for patients were insignificant different between the two groups. Also, the two groups of patients received the same treatments (anti-viral, anti-biotic, anti-inflammatory, anti-coagulant) with insignificant difference between both groups except for anti-coagulant (Heparin/ Clexan) was significantly elevated in group 1 in comparison to group 2 ($p<0.001$). but about 47 cases in group 2 died and only 32 cases died at group 1 so, group 2 had significantly higher mortality rate than group 1 ($p =0.02$) and the causes of death were respiratory failure or multi-organ failure with insignificant difference between both groups as mentioned in table 6 and figure 1.

Our study showed that PaO_2/FiO_2 was significantly reduced in died cases in group 1 and group 2 than recovered cases. MELD score was significantly higher in died cases (median 14; range 9-18) than recovered cases (median 10; range 7-15) in group 2 ($p <0.001$), but as shown in table 7: age, direct bilirubin, TBIL, AST, ALT, GGT, ALP, serum albumin, INR, hemoglobin (HB) and platelets were insignificant predictors of mortality.

Table 1: Demographics of the studied groups.

		Group 1 (n=100)	Group 2 (n=100)	P value
Age (years)	**Mean ± SD**	50.57 ± 11.78	55.77 ± 7.87	**<0.001***
	Range	22 - 80	32 – 70	
Sex	**Male**	44 (44%)	58 (58%)	**0.048***
	Female	56 (56%)	42 (42%)	
Medical history	**Hypertension**	52 (52%)	53 (53%)	0.887
	DM	34 (34%)	31 (31%)	0.651
Symptoms	**Fever**	70 (70%)	74 (74%)	0.529
	Cough	75 (75%)	76 (76%)	0.869
	GIT symptoms	14 (14%)	26 (26%)	**0.033***

* Significant as p value < 0.05, DM: diabetes mellitus, GIT: Gastro-intestinal tract

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DOI: 10.21608/AEJI.2024.262584.1350

Table 2: Possible markers for Covid -19 infection of the studied groups.

		Group 1 (n=100)	Group 2 (n=100)	P value
CRP (mg/dL)	**Mean ± SD**	89.02 ± 54.46	76.27 ± 35.62	0.051
	Range	12 - 262	18 – 180	
D-dimer (mg/L)	**Mean ± SD**	717.65 ± 431.86	772.41 ± 408.94	0.358
	Range	110 - 2520	110 – 2300	
Ferritin (µg/L)	**Mean ± SD**	334 ± 157.34	321.74 ± 180.49	0.609
	Range	101 - 886	45 – 855	

CRP: C reactive protein

Table 3: Liver tests in each group before and after covid-19 infection.

`	Group 1		Group 2	
	Before	**After**	**Before**	**After**
ALT(U/L)	33 ±9.26	73.51 ±78.51	40.28 ±12.72	95.66 ±83.61
P value	**<0.001***		**<0.001***	
AST(U/L)	34.19 ±11.59	88.09 ±94.84	41.88 ±13	108.27 ±98.74
P value	**<0.001***		**<0.001***	
Total bilirubin (mg/dl)	1.16 ±0.25	1.2 ±0.49	1.51 ±0.57	1.71 ±0.92
P value	**<0.001***		**<0.001***	
Direct Bilirubin (mg/dl)	0.27 ±0.22	0.31 ±0.34	0.57 ±0.44	0.66 ±0.65
P value	**<0.001***		**<0.001***	
GGT (U/L)	57.67 ±16.01	36.06 ±13.97	57.54 ±13.95	42.67 ±13.73
P value	0.145		**0.002***	
ALP (U/L)	125.5 ±24.17	110.82 ±41.28	133.42 ±39.93	119.87 ±35.19
P value	**<0.001***		**<0.001***	
Serum albumin (g/dl)	4.67 ±0.39	4.53 ±0.42	3.32 ±0.39	3.1 ±0.37
P value	**<0.001***		**<0.001***	
INR	1.19 ±0.27	1.27 ±0.26	1.26 ±0.18	1.74 ±0.52
P value	**<0.001***		**<0.001***	

* Significant as p value < 0.05, Data presented as mean± SD, INR: international normalized ratio, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase,

Table 4: Delta change of Liver tests in each group between before and after infection.

		Group 1 (n=100)	Group 2 (n=100)	P value
ALT(U/L)	**Mean ± SD**	115.4 ± 83.03	115.7 ± 77.32	0.655
AST(U/L)	**Mean ± SD**	141.8 ± 101.63	135.3 ± 96.25	0.532
Total bilirubin (mg/dl)	**Mean ± SD**	0.9 ± 0.38	1.2 ± 0.86	**0.007***
Direct Bilirubin (mg/dl)	**Mean ± SD**	0.5 ± 0.43	0.5 ± 0.5	0.542
GGT (U/L)	**Mean ± SD**	34.3 ± 13.11	35.2 ± 12.09	0.625
ALP (U/L)	**Mean ± SD**	98.3 ± 35.85	94.5 ± 39.98	0.504
Serum albumin (g/dl)	**Mean ± SD**	-0.1 ± 0.2	-0.2 ± 0.17	**0.002***
INR	**Mean ± SD**	0.1 ± 0.18	0.6 ± 0.45	**<0.001***

* Significant as P value < 0.05, Data presented as mean± SD, AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio, GGT: gamma-glutamyl transferase, ALP: alkaline phosphatase.

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DOI: 10.21608/AEJI.2024.262584.1350

Table 5: Child-score and Child-classification before and after infection of the group 2

		Before infection	After infection	P value
Child-score	**Mean ± SD**	6.4 ± 1.08	8.5 ± 1.98	**<0.001***
	Range	4 - 8	5 - 13	
Child-Classification	**A**	49 (49%)	17 (17%)	**<0.001***
	B	51 (51%)	37 (37%)	0.064
	C	0 (0%)	46 (46%)	**< 0.001***

Table 6: Hospital stay, prognosis and cause of death of the two studied groups

			Group 1 (n=100)	Group 2 (n=100)	P value
Hospital stay (in days)		**Mean ± SD**	9.08 ± 3.35	9.59 ± 4.47	0.362
		Range	3 - 18	2 – 19	
Treatment	**Anti-viral**	**Remdesivir**	100 (100%)	100 (100%)	--
	Antibiotic	**Ceftriaxone**	38 (38%)	36 (36%)	0.883
		Azithromycin	78 (78%)	76 (76%)	0.866
		Levofloxacin	63 (63%)	64 (64%)	0.883
		Averozolid	65 (65%)	74 (74%)	0.219
	Anti-inflammatory	**Corticosteroid**	100 (100%)	100 (100%)	---
		ACTEMRA	11 (11%)	5 (5%)	0.192
	Anti-coagulant	**Heparin/Clexan**	100 (100%)	75 (75%)	**< 0.001***
Prognosis		**Recovery**	68 (68%)	53 (53%)	**0.03***
		Die	32 (32%)	47 (47%)	
Cause of death		**Respiratory failure**	11 (11%)	15 (15%)	0.819
		Multi organ failure	21 (21%)	32 (32%)	

Table 7: Relation between PaO2/FiO2, MELD score and prognosis

			Recovery	Die	P value
PaO_2/FiO_2	**Group1**	**Mean ± SD**	381.04 ± 22.21	296.25 ± 23.72	**<0.001***
		Range	329 - 424	257 - 343	
	Group2	**Mean ± SD**	387.77 ± 22.02	319 ± 31.46	**<0.001***
		Range	324 - 424	248 - 395	
	Total	**Mean ± SD**	383.99 ± 22.29	309.78 ± 30.56	**<0.001***
		Range	324 - 424	248 - 395	
MELD score		**Mean ± SD**	10.79 ± 2.12	13.15 ± 2.2	**<0.001***
		Range	7 - 15	9 - 18	
		Median	10	14	
		IQR	9 - 12	11 - 15	

* Significant as P value < 0.05

PaO2/FiO2 was significantly lower in die patients in group 1 and group 2 than recovery patients. MELD score was significantly higher in die patients than recovery patients in group 2 (P value <0.001).

https://aeji.journals.ekb.eg/
DOI: 10.21608/AEJI.2024.262584.1350

DISCUSSION

Based on multiple researches, the infection of SARS-CoV-2 results in abnormal hepatic tests, including elevated levels of prothrombin time (PT), ALT, AST, and total bilirubin [11].

In addition, lower levels of platelets, lymphocytes and albumin, advanced age, and elevation in ALT, lactate dehydrogenase, leucocytes, ferritin, creatinine and PT are associated with increased mortality [12].

Our objective was to evaluate COVID-19 effect on liver functions tests in Egyptian patients with or without CLD. Also, we aimed to assess the correlation between these abnormalities and COVID-19 severity.

In our study, oxygen saturation and respiration rate were insignificantly different between both groups.

The present research revealed that cases with CLD had a significant reduction in O_2 saturation, indicating that hospitalization was most likely necessitated with the decompensation of CLD.

In our work, TBIL, direct bilirubin, AST, ALT, and INR after infection were significantly elevated than before infection in both group 1 and group 2. GGT level was insignificantly different between before and after infection and ALP and serum albumin after infection were significantly reduced than before infection in group 1. GGT, ALP and serum albumin after infection were significantly reduced than before infection in group 2.

In an Egyptian multicenter cohort study that explored the GI and hepatic disturbances in COVID-19 cases, they reported more frequent elevation in AST (32.10%), compared to ALT (26%). Only 21 (4.91%) and 16 (3.70%) cases respectively, had a significant LI with an elevation in ALT or AST > 3-fold. Only 8 (1.86%) cases had the cholestatic pattern of elevated ALP >147 U/L, elevated bilirubin > 1.1 mg/dL, and GGT > 48 U/L. These data demonstrated a clear association between higher liver enzyme levels and COVID-19 disease activity **[13]**.

Similarly, the majority of previous investigations indicate a prevalent pattern of liver enzyme abnormalities in COVID-19 cases, especially elevated levels of ALT and AST **[14, 15]**.

Wu *et al*'s meta-analysis reported that the most prevalent abnormalities on admission were high GGT and low serum albumin, and that during hospitalization, elevation of ALT occurred most frequently, which they hypothesize that this might be attributable to including cases with pre-existing hepatic disease **[14]**.

Based on **Afify et al.** trial, which evaluated the outcomes of COVID-19 infection among cases with pre-existing hepatitis C with or without liver cirrhosis, they reported that ALT levels were normal in 58 (46.4%) subjects, elevated one to two times above the ULN in 40 (32%) subjects, elevated two to three times above the ULN in 7 (5.6%) subjects, three times above ULN in 20 (16%) subjects, and five times above the ULN in 1 subject only **[16]**.

Based on **Cai et al.** trial, 76.3% of COVID-19 cases had abnormal liver tests. 21.5% of COVID-19 cases during hospitalization had higher levels of total bilirubin, AST, and ALT > 3 times the ULN confirming their LI. **[10].**

In our study, the liver tests of 41% of COVID-19 cases in group 1 and 55% of COVID-19 cases group 2 of COVID-19 cases were abnormal. The higher levels of total bilirubin, AST, and ALT in 68% and 60% of these patient > 3 times the ULN indicated their LI. Our results agreed with **Samir et al.** who reported that the levels AST, ALT, bilirubin, and INR were significantly elevated in COVID-19 subjects. These results may assist in predicting bad outcomes for COVID-19 cases **[17]**.

However, **Phipps *et al.*,** found no significant relation between the type and severity of underlying CLD (*e.g.*, chronic hepatitis B or C and non-alcoholic fatty liver disease) and the liver disturbances related to COVID-19, this might be attributed to the minimal number of CLD subjects in their research. **[18].**

In the current work, prognosis was recovery in 68 (68%) patients in group1and 53 (53%) patients in group 2, die in 32 (32%) patients in group1 and 47 (47%) patients in group 2 with

significant variation between the two groups. Cause of death was insignificantly different between both groups.

This was in accordance with **Afify et al.** who reported that cases with liver cirrhosis, especially decompensated cirrhosis, had a significantly higher mortality rate **[16]**.

Also, **Singh et al.** reported a higher relative risk of hospitalization and mortality in cases with cirrhosis in comparison with cases without liver disease **[19]**.

Similarly, **Samir et al.** reported that their CLD cases had higher rates of mortality in comparison with cases without CLD **[17]**.

Moreover, **Iavarone et al.** reported that 29% of the cases who died suffered with end-stage liver disease, and 34% of the cases died after a median of 10 days post their COVID-19 diagnosis **[20]**. In contrary, **Shalimar et al.** reported no variation in the rate of mortality among cases with and without cirrhosis; however, they included a small number of cases **[21]**.

In our findings, serum albumin was insignificant predictors for mortality in our study. This agreed with **Shousha et al.** who found no variation between non-survivors and survivors in the levels of serum albumin **[13]**. While, **Liu *et al.*** and **Wu *et al.*** reported a significantly lower serum albumin levels in the non-survivors **[22, 14]**.

In our study, direct bilirubin, total bilirubin, ALT and AST were insignificant predictors of mortality. Twenty (20%) cases had acute decompensation with hepatic encephalopathy and 18 (18%) cases had developed worsening ascites and 13 (13%) cases had acute decompensation with both hepatic encephalopathy and worsening ascites after infection in group 2.

This was slightly in agreement with **Shousha et al.** who reported a significantly elevated AST in the non-survivors; however, they observed no significant variation in the levels of ALT between non-survivors and survivors **[13]**. In contrast, **Phipps *et al.*** found that peak ALT was independent predictors of mortality **[18]**.

In our study, age was insignificant predictor of mortality in our study. In contrast, **Phipps *et al.*** found that peak older age was independent predictor of mortality **[18]**. A research by **Mangia et al.** reported that older age and cirrhosis of metabolic origin were risk factors for mortality **[23]**.

In our study, platelet count was insignificant predictor for mortality in our study. **Váncsa et al's** meta-analysis which presented mainly researches of chronic hepatitis B in China, found that platelet count and liver failure were significant predictors with high specificity of in-hospital mortality, and lactate dehydrogenase was a significant predictor with moderate specificity **[24]**.

In our study, 41% of patients had elevated liver enzymes, 33% of patients had hypoalbuminemia and 23% of patients had elevated total bilirubin after infection in group 1. In our study, liver tests were normal in 59 subjects in group 1 and in 45 subjects in group 2 and abnormal in 41 subjects in group 1 and in 55 subjects in group 2. Abnormality type 1 was hepatocyte type in 27 subjects in group 1 and in 32 subjects in group 2 and mixed type was found in one subject in both groups. Abnormality type 2 was hepatocyte type in 35 (35%) subjects in group 1 and in 48 (48%) subjects in group 2 and cholangiocyte type in 3 (3%) subjects in group 1 and in 2 (2%) subjects in group 2. LI, abnormality type 1 and abnormality type 2 were significantly different between both groups. **Cai et al.** showed the results of abnormal liver test, from 318 patients, 43.4% had mixed type, 29.25% had cholestatic type, and 20.75% had hepatocyte type **[10]**.

Previous meta-analyses indicated that subjects with severe COVID-19 and those hospitalized to the ICU had higher levels of transaminases **[15, 25].**

Phipps *et al.*, reported a severe LI with ALT > 5 times above the ULN in 6.4% of their cases **[18]**.

Moreover, **Ponziani *et al.*** found that changes in the levels of transaminase in COVID-19 cases were mild to moderate, while a few cases had pure cholestatic injuries and significant LI with transaminases > 3 times the ULN **[26]**.

DOI: 10.21608/AEJI.2024.262584.1350

Ten percent of patients in group 1 and 15% of subjects in group 2 in our study had severe LI with ALT > 5 times above the ULN.

Furthermore, **El-Adly et al.** reported that severe COVID-19 cases show signs of liver dysfunction more frequently compared to the cases with milder infection. Many ICU cases had an elevation in the levels of AST, ALT, and TBIL **[27].Cai et al.** mentioned that cases with abnormal liver tests were more likely to have severe pneumonia **[10].Boettler et al.** discovered that the risk of a severe COVID-19 did not seem to be raised due to chronic viral hepatitis **[28]**.

Also, the APCOLIS trial reported that CLD cases infected with COVID-19 had an increased incidence of liver-related complications such as ascites, aggravation of jaundice, hematemesis, spontaneous bacterial peritonitis, and hepatic encephalopathy. These outcomes were more prevalent in cases with decompensated cirrhosis and diminished hepatic reserves at baseline. In the current research, aggravation of ascites and hepatic encephalopathy had happened in 36 (36%) patients and 34 (34%) patients respectively after infection in group 2 **[29].**

Our results ha some limitations such as its retrospective design, which may introduce selection bias and confounding factors. The relatively limited sample size may restrict the generalizability of the findings.

Conclusions

COVID-19 infection can cause abnormalities in the liver function in cases with and without CLD. Additionally; severe COVID-19 was associated with more liver dysfunction and complications, including lower serum albumin, higher bilirubin and more aggravation of ascites and HE development. However, liver function test abnormalities were not found to be significant predictors of mortality in this study.

Acknowledgement: • All authors in this study participated in a good selection of cases, instructive supervision, continuous guidance, valuable suggestions and good instructions.

Funding information: None. Author funded

Conflict of Interest: "The authors have no conflict of interest to report".

Ethical considerations: A written informed consent was obtained from all participants in the study.The work was done according to the declaration of Helsinki and the sound practices and was approved by the Ethical Committee of Faculty of Medicine , Zagazig university (Approval code).

RESEARCH HIGHLIGHTS

1. COVID-19 infection can cause liver function abnormalities in both cases with and without CLD with aggravation of ascites and HE development in cirrhotic patients.
2. Additionally; severe COVID-19 was associated with more liver dysfunction and complications, including lower serum albumin, higher bilirubin and more aggravation of ascites and HE development.
3. However, liver function test abnormalities were not found to be significant predictors of mortality.

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Site as: Abdel-Samiee, M., Shaldoum, M., Abdelsameea, E., Awad, S., Omar, N. Impact of COVID-19 on Liver Functions Tests in Egyptian Patients with or without Chronic Liver Disease. *Afro-Egyptian Journal of Infectious and Endemic Diseases*, 2024; 14(1): 75-84. doi: 10.21608/aeji.2024.262584.1350