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Assessing hepatic Fibrotic and steatotic Changes in COVID-19 Patients

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Abstract

Background: COVID-19 is a respiratory infection that may affect other organs, including the liver.

Aim of work: We investigated hepatic involvement in COVID-19 patients to identify the risk factors and consequences of COVID-19-related hepatitis. We also assessed the association of hepatic steatosis with disease severity and outcomes, as well as the risk factors and consequences of hepatitis during the infection.

Methods: This prospective cohort study included 246 Egyptian patients with COVID-19 infection, divided into two groups: Group A (n=119) had normal transaminases, and Group B (n=127) had elevated levels of at least one transaminase at diagnosis. We collected data at baseline and after six months. We used vibration-controlled transient elastography (VCTE) and controlled attenuated parameter (CAP) to measure liver fibrosis and steatosis scores.

Results: We found that older males, smokers, and patients with diabetes, hypertension, and obesity were more likely to have elevated liver enzymes. Patients with elevated liver enzymes had higher levels of inflammatory markers and lower levels of platelets and albumin. They also had more severe COVID-19 symptoms, such as dyspnea, hypoxia, and chest pain, and required more intensive care and oxygen therapy. Patients with transaminitis had higher fibrosis and steatosis scores and more radiological abnormalities. After six months, we observed that some patients had persistent elevation of liver enzymes. We found that patients with a "bright liver" were associated with transaminase progression, while those with splenomegaly and hepatomegaly were associated with transaminase regression.

Conclusion: Our study demonstrates that COVID-19 infection can affect the liver and increase the risk of chronic hepatitis.

Introduction

The unimagined rise of COVID-19, first identified in Wuhan, China, in December 2019, has rapidly evolved into a global health conundrum. The primary mode of transmission of this virus is through respiratory droplets, facilitating its rapid global spread and resulting in countless infections. While the respiratory effects of SARS-CoV-2, the causative agent, are

more renowned, its multi-systemic manifestations cannot be ignored. Among these, COVID-19-related hepatitis, an associated liver disorder, has increasingly come under investigation.

COVID-19 hepatitis refers to liver involvement in COVID-19 patients, which can range from mild to severe insult and can lead to acute or chronic consequences. COVID-19 hepatitis can manifest with various clinical signs, such as fatigue, abdominal pain, nausea, vomiting, and jaundice [1]. However, some patients may remain asymptomatic or have nonspecific symptoms, making the diagnosis challenging. The diagnosis of COVID-19 hepatitis depends on the detection of viral RNA or specific antibodies in blood or liver samples, as well as the measurement of liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin. The treatment of COVID-19 hepatitis is mainly supportive, aiming to manage the symptoms and prevent complications such as liver failure. The exact mechanisms and risk factors of COVID-19 hepatitis are not fully understood, but they may involve direct viral infection of liver cells, immune-mediated damage, hypoxia, coagulopathy, and vascular inflammation. COVID-19 hepatitis may also have long-term implications, such as chronic hepatitis, fibrosis, or cirrhosis [1].

COVID-19 patients with pre-existing chronic liver diseases are at higher risk of poor outcomes, and those with liver cirrhosis have a higher mortality rate [2]. Hepatic tropism of SARS-CoV-2 and direct cytopathic effects could be considered possible mechanisms for COVID-19-related liver damage, even though a classic hepatitis picture has not been reported [3]. One of the main determinants of a virus's preference for a certain tissue is whether it has receptors on the surface of the host cell [4]. SARS-CoV-2 enters cells through its S protein, which interacts with Angiotensin-Converting Enzyme 2 (ACE2) and Transmembrane Protease Serine 2 (TMPRSS2) on the host cell [5].

ACE's catalytic function generates angiotensin II, which activates hepatic stellate cells, the major cause of fibrosis in chronic liver disease [6]. ACE2 produces anti-inflammatory and anti-fibrotic angiotensin, reducing the angiotensin II/angiotensin ratio and counteracting ACE action [6]. SARS-CoV-2 binding inhibits ACE2, increasing the angiotensin II/angiotensin ratio and ANG-II levels. This enhances ANG-II signaling and tissue injury. Reduced ACE2 activity also impairs ANG-II degradation, causing inflammation and damage [7].

Patients and Methods

Study design and setting

This prospective cohort study included 246 Egyptian COVID-19 patients, recruited from the National Hepatology and Tropical Medicine Research Institute (NHTMRI), Cairo, between December 2020 and October 2022. The study was approved by the NHTMRI ethical committee, and all participants provided informed written consent.

Study population and inclusion criteria

The study included adult patients (aged 18 years or older) of both sexes, who had a confirmed COVID-19 diagnosis by reverse transcription polymerase chain reaction (RT-PCR) using nasopharyngeal swab specimens. We excluded pregnant or lactating females, individuals with a history of consuming drugs known to affect transaminases in the past six months, those who had uncontrolled diabetes mellitus (DM) with glycated hemoglobin (HbA1c) greater than

8.5%, patients with a history of parenteral nutrition, immunocompromised patients, and those with a history of alcohol abuse.

Study groups and classification

Patients were stratified into two groups based on their liver enzyme levels at the time of diagnosis. Group A (n=119) had normal liver enzymes, defined as alanine aminotransferase (ALT) ≤ 40 U/L and aspartate aminotransferase (AST) ≤ 37 U/L. Group B (n=127) had elevated liver enzymes, defined as ALT > 40 U/L and/or AST > 37 U/L. We classified the patients according to the Ministry of Health (MOH) management protocol for confirmed COVID-19 infection [8].

Data collection and assessment

Comprehensive data were collected from each patient at baseline and after six months of follow-up. The data included sociodemographic information (age, sex, residence, marital status, and profession), lifestyle factors (smoking or alcohol consumption), comorbidities, and surgical history. We also measured weight and height and calculated body mass index (BMI). We performed a clinical examination and verified the presence of SARS-CoV-2 RNA by RT-PCR using the SARS-CoV-2 qualitative assay on the cobas® 6800 Systems. We conducted laboratory tests at baseline and after six months, covering inflammation markers, D-dimer, lactate dehydrogenase (LDH), complete blood count, liver profile, creatinine and estimated glomerular filtration rate (eGFR), as well as tests for hepatitis markers. Imaging techniques, such as chest computed tomography (CT) without contrast and abdominal ultrasound, were used to evaluate the patients at baseline. We also used vibration-controlled transient elastography (VCTE) and controlled attenuation parameter (CAP) to measure liver stiffness and steatosis, respectively, at baseline and after six months. We used the FibroScan® to measure liver stiffness and hepatic steatosis, following the standard protocol and criteria for valid and reliable results. We used the FibroScan® fibrosis and steatosis scores to classify the patients according to their liver condition.

Study endpoints

Primary endpoint: The change in liver enzyme levels (ALT and AST) at baseline and six months after COVID-19 diagnosis.

Secondary endpoints: The change in liver fibrosis and steatosis scores, the change in other liver function markers (bilirubin, albumin, prothrombin time), the incidence of chronic hepatitis, and the mortality rate from baseline to six months after COVID-19 diagnosis.

Statistical analysis

We used the Statistical Package for Social Sciences (SPSS) vs. 28 for data analysis. We explored the data for normality and used appropriate tests, such as Chi-square, Fisher's test, Student's t-test, Mann-Whitney test, and logistic regression, to draw comparisons and conclusions. We set the significance level at a p-value of ≤ 0.05.

Results

This cohort study included 246 Egyptian patients diagnosed with COVID-19, highlighting the significance of liver affection among the affected populations. Group A included 119 patients with normal transaminase levels, representing 48% of the cohort. Group B included 127

patients with elevated transaminase levels, accounting for 52% of the cohort. Notably, 6% (N=15) of the entire cohort succumbed to the disease, all of whom were from Group B. Additionally, 11 patients (4%) were lost to follow-up (7 from Group A and 4 from Group B), while 235 completed their follow-up visits and were included in the follow-up statistical analysis.

Sociodemographic and clinical characteristics

Table 1 summarizes the sociodemographic and clinical characteristics of the two groups. Females made up 62.2% of Group A, while their representation dwindled to 44.9% in Group B, a statistically significant variation (p=0.007). Group B members showed a heightened history of smoking and prevalent hypertension, and 1.6% had a history of coronary heart disease, a condition absent in Group A. Patients in Group B had a higher median age than those in Group A (p=0.008). The median age of Group B was 50 years, with a standard deviation (SD) of 16 years. The median age of Group A was 45 years, with an SD of 15 years.

Table 1. Sociodemographic and clinical characteristics of the two groups

Variable	**Group A (n=119)**	**Group B (n=127)**	**p-value**
Sex			0.007
Male	45 (37.8%)	70 (55.1%)	
Female	74 (62.2%)	57 (44.9%)	
Smoking	15 (12.6%)	27 (21.3%)	0,071
DM	12 (10.1%)	21 (16.5%)	0.135
HTN	12 (10.1%)	25 (19.7%)	0.035
CHD	0 (0%)	2 (1.6%)	<0.001
	Median ±SD	**Median ±SD**	
Mean Age	45 (±15) years	50 (±16) years	0.008

Note: Data are presented as n (%) or median (SD).

Anthropometric measurements

The comparison of the median weight and BMI of the two groups showed that Group B had a higher median weight than Group A ($p < 0.001$). The median weight of Group B was 92.9 kg, with SD) of 15.7 kg. The median weight of Group A was 80.7 kg, with an SD of 15 kg. Group B also had a higher median BMI than Group A ($p < 0.001$). The median BMI of Group B was 32.7 kg/m², with an SD of 7.1 kg/m². The median BMI of Group A was 28.4 kg/m², with an SD of 5.4 kg/m². There was no significant difference in the median height between the groups ($p = 0.598$). The median height of both groups was 1.7 m, with an SD of 0.1 m.

Laboratory results

AST levels

Table 2 summarizes the AST levels over time for the two groups. Group B consistently had a higher median AST level than Group A, both initially and at the 6-month mark (50 vs. 24 initially and 31 vs. 21 after 6 months, $p < 0.001$). Group B showed a significant decrease in their AST level over the 6-month period ($p < 0.001$).

Table 2. AST levels over time for the two groups

AST (U/L)	Group A (n=119)	Group B (n=127)	p-value
Initial	24 ± 6 U/L	50 ±47 U/L	<0.001
After 6 m	21 ±5 U/L	31 ±19 U/L	<0.001

Note: Data are presented as median (SD) in U/L.

The variation in AST elevation is based on the upper limit of normal (ULN) for AST, which is 37 U/L. Group B had a dominant AST level within a certain range (<2 ULN) initially ($p < 0.001$). Severe AST elevation (>5 ULN) was more frequent than severe ALT elevation, but still rare, occurring in 4 patients in Group B.

ALT levels

Table 3 summarizes the ALT levels over time for the two groups. Group B consistently had a higher median ALT level than Group A at both the initial point and after 6 months (46 vs. 21 initially and 41 vs. 21 after 6 months, $p < 0.001$). The changes in ALT levels within each group over time also had different significance ($p < 0.05$). Group B had a significant decrease in their ALT level over the 6-month period ($p = 0.004$), while Group A did not have a significant change in their ALT level over the 6-month period ($p = 0.215$).

Table 3. ALT levels over time for the two groups

Time	Group A (n=119)	Group B (n=127)	p-value

Initial	21 ±7 U/L	46 ±45 U/L	<0.001
After 6 m	21 ±18 U/L	41 ±36 U/L	<0.001

Note: Data are presented as median (SD) in U/L.

The changes in ALT and AST levels over time for the two groups are summarized as follows. Group B consistently had a higher median ALT level than Group A at both the initial point and after 6 months (46 vs. 21 initially and 41 vs. 21 after 6 months, $p < 0.001$). The changes in ALT levels within each group over time also had different significance ($p < 0.05$). Group B had a significant decrease in their ALT level over the 6-month period ($p = 0.004$), while Group A did not have a significant change in their ALT level over the 6-month period ($p = 0.215$). Similarly, Group B consistently had a higher median AST level than Group A, both initially and at the 6-month mark (50 vs. 24 initially and 31 vs. 21 after 6 months, $p < 0.001$). Group B showed a significant decrease in their AST level over the 6-month period ($p < 0.001$).

Transaminase levels

Table 4 The subset of patients devoid of steatosis (S0) presented in Table 4 shows that from Group A, 65.9% consistently exhibited normal transaminase levels, with only a marginal 7.4% seeing elevation. Contrarily, within Group B, 17% revealed a regression in their liver enzymes, but 9.5% remained persistently elevated. Although, after removing the most common factor for liver enzyme elevation (hepatic steatosis), approximately 17% of patients developed elevated transaminases, none of these patients had severe pulmonary affection initially.

Table 4. Transaminase change after 6 months in patients without steatosis (S0)

Change in liver enzymes (ALT and/or AST) in patients without steatosis (S0) initially and after 6 months of follow up	**94 patients (69 from group A and 25 from group B)**
	n (%)
Persistent normal from group A	62 (65.9)
Persistent elevated from group B	9 (9.5)
Normalization in group B (Regression)	16 (17)
Elevation in group A (Progression)	7 (7.4)

Note: Data are presented as n (%).

Creatinine and bilirubin levels

The comparison of the creatinine and bilirubin levels of the two groups shows that Group B had higher median creatinine and bilirubin levels than Group A, both initially and after 6 months ($p < 0.001$). Group B also had a significant increase in their creatinine and bilirubin

levels over the 6-month period ($p < 0.001$), while Group A did not have a significant change in their levels ($p > 0.05$).

FIB 4 score trends over time

The FIB-4 score is a non-invasive indicator of liver fibrosis, calculated from age, platelet count, and liver enzyme levels. Regarding the median and range of the FIB-4 scores in both groups at baseline and after six months, we found that there was no significant difference in the FIB-4 scores between the two groups at either time point ($p > 0.05$). However, both groups showed a significant decrease in the FIB-4 scores over time ($p < 0.001$), indicating an improvement in liver fibrosis.

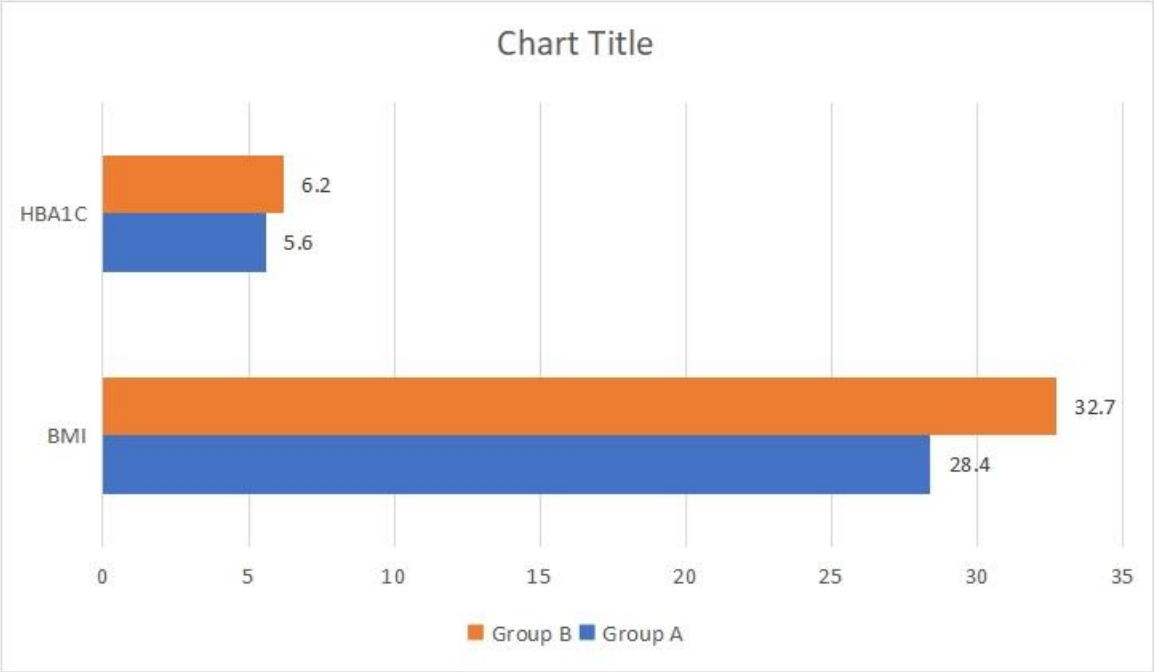
HbA1c levels

The comparison of the HbA1c levels of the two groups shows that Group B had a higher median HbA1c level than Group A ($p < 0.001$). The median HbA1c level of Group B was 6.2%, with a standard deviation (SD) of 1.2%. The median HbA1c level of Group A was 5.6%, with an SD of 0.9%. The majority of Group B surpassed the HbA1c threshold of 5.8%, indicating poor long-term blood sugar control.

BMI and HbA1c levels

Figure 1 shows the relationship between BMI and HbA1c levels for the two groups. BMI is a measure of body fat based on height and weight, and HbA1c is a marker of long-term blood sugar control. A BMI of 30 or higher is considered obese, and an HbA1c level of 5.8% or higher indicates poor control. Group B had a higher median BMI and HbA1c level than Group A ($p < 0.001$). The median BMI of Group B was 32.7 kg/m², with a standard deviation (SD) of 7.1 kg/m². The median BMI of Group A was 28.4 kg/m², with an SD of 5.4 kg/m². The median HbA1c level of Group B was 6.2%, with an SD of 1.2%. The median HbA1c level of Group A was 5.6%, with an SD of 0.9%. The majority of Group B surpassed the BMI and HbA1c thresholds of 30 and 5.8%, respectively. There was a positive correlation between BMI and HbA1c levels for both groups ($p < 0.001$).

Figure 1. Relationship between BMI and HbA1c levels for the two groups



Radiological and ultrasound findings

Table 5 summarizes the radiological and ultrasound findings of the two groups. Group A largely showed standard results, whereas Group B, already diagnosed with heightened transaminase levels, demonstrated conditions like splenomegaly and hepatomegaly more prevalently. Group B's chest CT scans also revealed significant anomalies, such as ground glass opacities, consolidation, and pleural effusion.

Table 5. Radiological and ultrasound findings of the two groups

Variable	**Group A (n=119)**	**Group B (n=127)**	**p-value**
Chest CT findings			<0.001
Normal Ct chest findings	44 (37)	27 (21.3)	0.007
Mild lung affection	39 (32.8)	38 (29.9)	0.63
Moderate lung affection	35 (29.4)	47 (37)	0.207
Severe lung affection	1 (0.8)	15 (11.8)	<0.001
US findings			<0.001

Normal	74 (62.2)	22 (17.3)	<0.001
Splenomegaly	2 (0.8)	24 (8.7)	<0.001
Bright liver	35 (29.4)	46 (36.2)	0.256
Hepatomegaly	9 (6.7)	48 (27.6)	<0.001

Steatosis and fibrosis assessment

Steatosis score trends over time

The steatosis score (S) indicates the degree of liver fat accumulation, ranging from 0 (no steatosis) to 3 (severe steatosis). Table 6 shows the mean and standard deviation of the FibroScan® steatosis scores (CAP) in both groups at baseline and after six months. We found that Group B had significantly higher steatosis scores than Group A at both time points ($p < 0.001$), indicating more liver fat accumulation. Moreover, Group B showed a significant increase in the steatosis scores over time ($p = 0.025$), while Group A did not ($p = 0.296$).

Table 6: Steatosis score (CAP) by fibroscan within 2 groups (Initially and after 6 months follow up)

	Group A	**Group B**	**P value**
	Mean ±SD	Mean ±SD	
Fibroscan steatosis (initial)	232.4 ±63.1	296.6 ±72.7	<0.001
Fibroscan steatosis (After 6 months)	228.1 ±65.2	308.8 ±66.6	<0.001
P value (within group)	0.296	0.025	

SD: Standard deviation, P value <0.05 is considered significant

The distribution of the steatosis scores in both groups at baseline and after six months showed a significant difference between the two groups at both time points ($p < 0.001$). Most of the patients in Group B had severe steatosis (S3) at both time points (59.8% and 63.9%, respectively), while most of the patients in Group A had no steatosis (S0) at both time points (62.2% and 66.1%, respectively).

Regarding the changes in the steatosis scores within each group over time, we found that most of the patients in Group A maintained their initial steatosis scores after six months. In

contrast, some patients in Group B showed significant changes in their steatosis scores, with some patients moving to lower or higher steatosis categories over time. For example, 11.1% of the patients who had no steatosis (S0) at baseline in Group B developed mild (S1) or severe (S3) steatosis after six months.

Fibrosis score trends over time

The fibrosis score (F) indicates the degree of liver scarring, ranging from 0 (no fibrosis) to 4 (cirrhosis). Table 7 shows the mean and standard deviation of the FibroScan® fibrosis scores in both groups at baseline and after six months. We found that Group B had significantly higher fibrosis scores than Group A at both time points ($p < 0.001$), indicating more liver damage. However, there was no significant change in the fibrosis scores within each group over time ($p > 0.05$).

Table 7: `

	Group A	**Group B**	**P value**
	Mean ±SD	Mean ±SD	
Fibroscan fibrosis (initial)	5 ±1.7	6.3 ±1.7	<0.001
Fibroscan fibrosis (After 6 months)	4.9 ±1.1	6.3 ±1.9	<0.001
P value (within group)	0.200	0.169	

SD: Standard deviation, P value <0.05 is considered significant

The changes in the fibrosis score within each group over time indicate that most patients in both groups maintained their initial fibrosis scores after six months. However, some patients in both groups showed improvement or worsening of their fibrosis scores over time. For example, in Group A, 14 patients who had no fibrosis (F0) at baseline developed mild fibrosis (F1) after six months. In Group B, 10 patients who had mild fibrosis (F1) at baseline developed moderate fibrosis (F2) after six months.

Multivariate analysis

Table 8 summarizes the results of the multivariate analysis for the predictors of hepatitis onset and mortality in the context of COVID-19. The effects of age, hypertension, HbA1c, sex, and BMI on the risk of hepatitis and mortality were examined using logistic regression. The results showed that older age, hypertension, and higher HbA1c levels were associated with an increased risk of mortality, while male sex, higher HbA1c levels, and higher BMI categories were associated with an increased risk of hepatitis. All these variables had significant effects on the respective outcomes, except for BMI over 35, which had a marginally significant effect on hepatitis.

Table 8: Variables Increasing the Risk of Hepatitis and Mortality (Significant in Stepwise Logistic Regression)

Variable	**B**	**S.E.**	**OR**	**95% C.I. for OR**	**P value**	**Outcome**
Age (> 50 year)	2.1	1.1	8.3	1.1-68.1	0.049	Mortality
HTN	1.9	0.6	6.9	2.1-23	0.002	Mortality
HBA1c (> 5.8)	1.8	0.8	6	1.2-28.7	0.026	Mortality
Sex (male)	1.2	0.3	3.2	1.7-6.1	<0.001	Hepatitis
HBA1c >5.8	1	0.3	2.7	1.5-4.8	0.001	Hepatitis
BMI (BMI 25 to <30 vs BMI <25)	0.8	0.4	2.2	0.9-5.2	0.075	Hepatitis
BMI (BMI 30-35 vs BMI <25)	1.3	0.4	3.5	1.5-8.5	0.005	Hepatitis
BMI (BMI >35 vs BMI <25)	2.4	0.6	10.7	3.6-31.8	<0.001	Hepatitis

DM: Diabetes mellitus, HTN: Hypertension, BMI: Body mass index, B: regression coefficient, SE: standard error, OR: odds ratio, CI: confidence interval. A p-value < 0.05 is considered significant.

Discussions

Background and rationale

The novel coronavirus pandemic, which primarily manifests as a respiratory ailment, has been linked to a variety of extrapulmonary effects, with hepatic involvement attracting significant interest from the medical community. The complexity of the COVID-19-liver nexus stems from both direct viral-induced hepatic damage and indirect consequences through systemic inflammatory response, exacerbated by pre-existing conditions or drugs. Therefore, it is of principal importance to understand the intricate relationship between COVID-19 and the liver and its implications for disease progression and outcomes.

We embarked on a comprehensive cohort study aimed at deciphering the myriad ways COVID-19 affects hepatic functions and the subsequent implications on disease progression. We segregated 246 confirmed COVID-19 cases into two different groups: Group A, which encompassed patients exhibiting normal transaminase levels, and Group B, which comprised patients displaying elevated transaminases (both ALT and/or AST) upon diagnosis. A focal point of our investigation revolved around evaluating the potential of the virus to cause hepatitis during its course and the subsequent morbidity and mortality outcomes. One of the pivotal questions that arose during this inquiry was: Could patients possibly evolve into a state of chronic hepatitis post their bout with COVID-19?

Main findings and interpretations

Our study revealed several key findings that may shed light on the COVID-19-liver nexus. First, we found a correlation between advancing age and exacerbation of liver disease, echoing broader epidemiological patterns of COVID-19. Age-related physiological changes predispose individuals to a higher vulnerability spectrum, which, when compared against inherent liver pathologies and the virulence of SARS-CoV-2, correlates with findings from [9]. Older patients in our study had higher levels of creatinine and bilirubin than younger patients. Moreover, older patients had higher mortality rates than younger patients, and all the deceased patients were from Group B, which had elevated liver enzymes.

Second, we found that Body Mass Index (BMI) emerged as a pivotal determinant of transaminase trajectories and liver complications. The ‘obese class II’ and higher strata showcased an accentuated susceptibility to severe liver disorders, a conclusion echoed by previous studies like [10, 11]. These trends accentuate the multifaceted role BMI plays in orchestrating metabolic health, liver functionality, and disease outcomes in a COVID-19 setting. This accentuated risk in obesity stems from a latent inflammatory state that modulates immunity, potentially escalating disease progression as elucidated by [12]. Obese patients in our study had higher levels of HbA1c than non-obese patients. Moreover, obese patients had higher levels of steatosis and fibrosis than non-obese patients.

Third, we found that the virus had the potential to prompt hepatitis during its course and that this had significant implications for morbidity and mortality. We observed that some patients in Group B had persistently elevated transaminase levels, even after excluding steatosis, which is a common cause of transaminase elevation. Moreover, some patients in Group B had severe hepatitis, as indicated by ALT or AST levels greater than five times the upper limit of normal. These patients had worse outcomes than those with mild or moderate hepatitis, as they had higher levels of inflammatory markers, such as CRP, D-dimer, and ferritin, and

higher mortality rates. These findings suggest that COVID-19 can directly or indirectly cause liver injury and inflammation and that this can affect the prognosis and survival of the patients.

The impact of smoking on liver damage

One aspect that demands acknowledgment is the pronounced presence of smokers within moderate to severe disease spectra. This observation recalls the harmful impact of smoking on the liver, an effect further amplified when coupled with the onslaught of SARS-CoV-2. The harmony between smoking and liver pathologies gains acceptance through the lens of systemic inflammation engendered by smoking. As [13] reported, "smoking was associated with higher levels of ALT, AST, and GGT, and lower levels of albumin and platelets in COVID-19 patients." Therefore, smoking may be a modifiable risk factor for liver damage in COVID-19 patients.

The domino effect of comorbidities

A noticeable feature of our study spotlighted the domino effect of comorbidities. Conditions like diabetes and hypertension had an inherent potential to mediate hepatic affection, their compounded presence, coupled with SARS-CoV-2 infection, escalated the deleterious outcomes. This finding is consistent with the observations by [14], who found that "COVID-19 patients with comorbidities had higher rates of liver injury and mortality than those without comorbidities." This suggests that comorbidities may exacerbate the inflammatory response and the oxidative stress induced by COVID-19, leading to more severe liver damage and dysfunction.

The role of inflammatory markers

Furthermore, harnessing the potency of inflammatory markers like CRP, ferritin, and D-dimer, elevated markers, as evidenced in our study cohort, bore a strong concurrence with intensified liver fibrosis severity. The ensuing hepatic inflammation, a byproduct of the virus's blockade of hepatic cells, together with inflammatory cascades, was strongly analogous to patterns observed by [13]. They found that "COVID-19 patients with liver injury had higher levels of CRP, ferritin, and D-dimer than those without liver injury, and these markers were positively correlated with the degree of liver injury." This indicates that inflammatory markers may reflect the extent and progression of liver damage in COVID-19 patients and may also be involved in the pathogenesis of liver injury. Therefore, inflammatory markers may be useful biomarkers for liver damage and potential therapeutic targets for liver protection in COVID-19 patients.

The utility of Fibroscan® and ultrasound imaging

The FibroScan® application served as a technological vanguard to quantify liver health. Measuring liver stiffness, which directly correlates with fibrosis, bestowed crucial insights into the virus's hepatic ramifications. Interestingly, while fibrosis scores were consistent across the cohort, steatosis scores revealed intriguing patterns. A significant divergence between the two groups was observed. While Group A largely retained its initial readings, Group B demonstrated a notable augmentation over six months. This implies that COVID-19 may have a differential impact on liver steatosis and liver fibrosis and that steatosis may be a more dynamic and reversible process than fibrosis. Therefore, FibroScan® may be a valuable

tool to assess and monitor liver damage and recovery in COVID-19 patients and to identify patients at risk of developing chronic liver disease.

The ultrasound imaging insights, both from our investigation and auxiliary studies like [9] and [15], chronicled discernible hepatic structural alterations post-COVID-19. For example, [9] reported that "COVID-19 patients had higher rates of liver enlargement, fatty infiltration, and portal vein dilation than non-COVID-19 patients." These findings suggest that COVID-19 may cause morphological changes in the liver. Therefore, ultrasound imaging may be a useful modality to detect and evaluate liver abnormalities in COVID-19 patients and to provide visual evidence of liver damage and recovery.

The importance of other liver markers

We didn't just limit our inquiry to transaminase dynamics. We delved into a more nuanced interrogation, encapsulating other pivotal liver markers. Serum bilirubin, albumin, and prothrombin time were actively monitored, acting as sentinels to liver health and function. The longitudinal follow-up revealed intriguing dynamics. Patients in Group A, despite their initial tendency to normalcy, started exhibiting marginal deviations in some of these parameters. However, the Group B cohort, while primarily showcasing elevated readings, demonstrated intriguing trajectories. While a significant subset evidenced stabilization or even regression, a minority, especially those with elevated BMI, bore witness to deteriorating hepatic markers. These results indicate that COVID-19 may have a variable and unpredictable effect on liver function and metabolism and that some liver markers may be more sensitive and responsive to COVID-19 than others.

The determinants of mortality

The terminality of the disease, albeit a grim reality, was an imperative dimension of our research. Our analysis revealed critical factors that modulate outcomes. Age emerged as a dominant determinant. However, other parameters like BMI, ALT, AST, CRP, bilirubin levels, and albumin had significant influence. Among the unfortunate fatalities, Group B patients were predominant, emphasizing the prognostic potency of liver health in the COVID-19 paradigm. These findings demonstrate that COVID-19 mortality is associated with multiple factors and that liver damage is a major contributor to poor outcomes. These findings are consistent with those of [16], who found that "COVID-19 patients with liver injury had higher mortality rates than those without liver injury, and that liver injury was an independent risk factor for mortality." This suggests that liver damage may impair the immune response and the organ function of COVID-19 patients and may increase the risk of complications and death. Therefore, liver damage may be a predictor and a potential modifier of mortality in COVID-19 patients.

Limitations

First, all the patients were from the same ethnicity and from one center, which may limit the generalizability of the findings to other populations and settings. Second, there was no previous data regarding the hepatic conditions of the patients, such as laboratory and radiological data, which could have influenced the results of the transaminase levels. Third, other latent infections that may cause transaminitis, such as cytomegalovirus (CMV) and

Epstein-Barr virus (EBV), were not excluded during the COVID-19 infection, which could have confounded the association between COVID-19 and liver injury. Fourth, liver biopsy, which remains the cornerstone to evaluate the histopathological changes that occur during the infection, was not performed in this study. Therefore, future studies with larger and more diverse samples and histological confirmation of liver injury are needed to validate and extend our findings.

Summary and Conclusion

Our study delved into the impact of COVID-19 on the liver and its correlation with disease severity and outcomes. We conducted a prospective cohort study involving 246 Egyptian COVID-19 patients, categorized into two groups based on their liver enzyme levels at diagnosis: Group A with normal enzymes and Group B with elevated enzymes. Comprehensive data, including sociodemographic, clinical, laboratory, and radiological information, were collected at baseline and six months later. FibroScan® and CAP were utilized to assess liver fibrosis and steatosis scores.

Our findings indicate that COVID-19 infection is associated with liver involvement and an increased risk of chronic hepatitis. We identified several risk factors and markers predictive of liver damage and disease severity. Specifically, older males, smokers, and patients with diabetes, hypertension, or obesity were more prone to elevated liver enzymes. Those with elevated enzymes exhibited higher inflammation markers (such as D-dimer and LDH), lower platelet and albumin levels, and more severe COVID-19 symptoms. They also showed higher fibrosis and steatosis scores, alongside more frequent radiological abnormalities like hepatomegaly and splenomegaly compared to patients with normal liver enzymes. Over six months, some patients developed chronic hepatitis, evident from persistently elevated enzymes and fibrosis scores.

In conclusion, our study highlights the intricate connections between individual characteristics, lifestyle choices, underlying health conditions, and the impact of COVID-19 on liver health. These findings underscore the necessity for tailored clinical strategies and attentive patient management, advocating for lifestyle modifications and diligent management of existing health issues. We propose the use of FibroScan® and CAP as valuable non-invasive tools for early detection and ongoing monitoring of liver conditions in COVID-19 patients.

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