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Outcome of Elevated Liver Enzymes in Patients with COVID-19 Infection

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is an infectious pandemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In December 2019, in Wuhan city, China, the first case was discovered, and then it spread all over the world . On 12th of March 2020, the World Health Organization (WHO) officially announced COVID-19 as a global pandemic disease. In addition, patients with severe COVID-19 may be more likely to have liver injury than patients with less severe disease or asymptomatic carriers. Hypoalbuminemia is emerging as a consistent risk factor for severe disease, even among patients without chronic illness.

Aim of Study: In this study, we aimed at evaluating liver enzymes among COVID-19 patients and analyzing the relationship between the liver enzymes elevations and severity of COVID-19 infection.

Patients and Methods: A retrospective study on data collected from patients who presented between February 2021, and June 2021. The study included 200 patients that had confirmed SARS-CoV-2 infection based on positive results on RT-PCR testing. All patients were subjected to full history taking including history of previous liver disease, general examination, and laboratory investigations including: Liver function tests, hepatitis viral markers , RT-PCR for nasopharyngeal swab, and CT chest. The participants were categorized into two groups, if abnormal value of LFT > twice the normal ranges (group 1). The group 2, other participants who had normal LFTs. The length of hospital staying, intensive care requirement, and mortality were considered as prognostic indicators.

Results: Group 1 (n=61) with elevated LFT and group 2 (n=139) with normal LFT. When investigating basic characteristics, the mean age was 55.8 ± 22.1 and 59.3 ± 18.6 among group 1 and group 2 respectively. The ALT, AST, and TB were significantly higher among group 1 than group 2. There was no statistically significant difference between both groups regarding Hg, and WBCs. The mean hospital staying was statistically significantly higher among group 1. The intensive care requirement was statistically significantly higher among group 1. There was a statistically significant difference between both groups regarding mortality.

Key Words: *COVID-19 – SARS – CoV-2 – Liver enzyme – Intensive care – Aspartate aminotransferase – Alanine aminotransferase.*

Introduction

CORONAVIRUS disease 2019 (COVID-19) is an infectious pandemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In December 2019, in Wuhan city, China, the first case was discovered, and then it spread all over the world and after few months it became a global pandemic **[1]**.

SARS-CoV-2 is an enveloped RNA virus that attacks primarily the respiratory system, but also can affect multiple organs, especially the GIT, CVS, and CNS. The incubation period of COVID-19 infection ranges between one to fourteen days after exposure. The main mode of transmission occurs mainly through droplet infection as coughing, sneezing, or speaking **[2]**.

Most infected people are asymptomatic, some will develop mild to moderate symptoms and do not need hospitalization. But also, some infected people may develop acute respiratory distress syndrome (ARDS), and multi organ failure. The most common typical symptoms are fever, dry cough, difficult breathing, fatigue, headache and impaired taste and smell **[3]**.

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Abbreviations:

LFT : Liver function test.
RT-PCR : Reverse transcriptase - polymerase chain reaction.
CT : Computerized tomography.

In patients with COVID-19 pneumonia, the most common radiological finding is GGO (ground glass opacity), which is usually described as patchy, peripheral, bilateral, and sub pleural [1,4].

On the other hand, COVID-19 infection may present with atypical symptoms such as, gastrointestinal symptoms nausea, diarrhea, vomiting, abdominal pain, and gastrointestinal bleeding, and also acute onset of hepatitis causing elevated liver enzymes may occur [4].

Many studies are trying to identify the possible risk factors and prognostic indices for assessment of severity of COVID-19 infection [3-5]. Until now no definite curable treatment for COVID-19 infection, only symptomatic and supportive treatment is available. Vaccination for COVID-19 was recently discovered, and now spread all over the world [5].

Although the impact of COVID-19 on the liver remains poorly clarified, a significant proportion of patients with liver enzymes elevation had been reported. Elevations in transaminases are most often mild (1-2) times the upper limit of normal [ULN] , and severe liver injury (SLI) also had been reported [6].

In addition, patients with severe COVID-19 infection may be more likely to have liver injury than patients with mild or moderate disease or asymptomatic carriers. Hypoalbuminemia is considered an emergency and a consistent risk factor for severe disease [7].

Emerging data suggest that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations are common among patients with COVID-19 in the United States, with AST and ALT elevations found in 38%-63% and 29%-39% of patients, respectively [8].

The most reported common causes of deaths in COVID-19 infection were respiratory failure, septic shock and multi organ failure, neurogenic stroke either embolic or hemorrhagic, pulmonary embolism and cardiac arrest. Also the underlying comorbidities may be the cause of death as, Diabetes, hypertension, chronic chest diseases, and liver or cardiac diseases [2,3].

In this study, we aimed at evaluating liver enzymes among COVID-19 patients and analyzing the relationship between the liver enzymes elevations and severity of COVID-19 infection.

Patients and Methods

We performed a retrospective study on data collected from patients who presented between February 2021, and June 2021 at (El Sayed Galal) Al-Azhar University Hospital, isolation department. The study included 200 patients that had confirmed SARS-CoV-2 infection based on positive resulst on RT-PCR testing. In addition to the symptoms reported by the patients at presentation, demographic, clinical, and laboratory data were evaluated. Informed written consents were obtained by patients who agreed to participate in this study. All the studied patients were under the following:

Inclusion criteria:

- Age >18 years.
- Patients with confirmed SARS-CoV-2 infection by RT-PCR.

Exclusion criteria:

- Pregnancy.
- Known patients with chronic liver disease.

All the studied patients were subjected to full history taking including history of previous liver disease, general examination, and laboratory investigations including: CBC, Liver function tests, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TB), hepatitis viral markers as HCV AB and HBsAg by ELISA, RT-PCR for nasopharyngeal swab, and pregnancy test in females, and CT chest for detecting pulmonary consolidation. The normal ranges of hepatic enzymes were 5-40U/L for ALT, 5-37 U/L for AST, and 0.2-1mg/dl for TB.

Nasopharyngeal swab (NP) should be performed by a trained healthcare provider, only synthetic fiber swabs with thin plastic or wire shafts should be used, numerous swab samples have been taken for SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) testing.

For healthcare providers must be within 6 feet from patients suspected to be infected with SARS-CoV-2, maintain proper infection control and use recommended personal protective equipment (PPE), like N95 or face mask, eye protection, gloves, and a gown. Nasopharyngeal specimen (NP) collection was performed as following:

- Tilt patient's head back 70 degrees.
- Gently insert a minitip swab with a flexible shaft (wire or plastic) through the nostril parallel to the palate (not upwards) until resistance is occured or the distance is equivalent to that from

the ear to the nostril of the patient, indicating contact with the nasopharynx.

- Gently rub and roll the swab.
- Leave swab in place for several seconds to absorb secretions.
- Slowly remove swab while rotating it. Specimens can be collected from both sides using the same swab.
- Place swab, tip first, into the transport tube provided.

The swab samples become ready for SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) testing.

Statistical analysis:

Data was coded, entered, and processed on a computer using statistical packaged for the social science (version 26, IBM SPSS, IBM Software. Package for Statistical analysis, SPSS). *p*-value less than to 0.05 indicates significance. Continuous variables were expressed as mean and standard deviation, qualitative variables were expressed as frequencies and percentages.

Results

A total sample of 200 COVID-19 patients. They were categorized into two groups: Group 1 (n=61) with elevated LFT and group 2 (n=139) with normal LFT. The mean age was 55.8±22.1 and 59.3± 18.6 among group 1 and group 2 respectively. There was no statistically significant difference between both groups regarding age. There were 54% and 65% males and 46% and 35% females among group 1 and group 2 respectively. There was no statistically significant difference between both groups regarding gender. (Table 1).

The mean BMI was 28.5 ±2.4 and 26.1 ±3.6 among group 1 and group 2 respectively. There was no statistically significant difference between both groups regarding BMI. There were 34% and 32% smokers among group 1 and group 2 respectively. There was no statistically significant difference between both groups regarding smoking. (Table 1).

Table (1): Basic characteristics of the studied patients (N=200).

Variable	Group 1 n=61	Group 2 n=139	*p*-value
Age, Mean ± SD	55.8±22.1	59.3± 18.6	0.511
Male, n (%)	33 (54.1%)	90 (64.7%)	
Female, n (%)	28 (45.9%)	49 (35.3%)	0.102
BMI, Mean± SD	28.5±2.4	26.1±3.6	0.709
Smokers, n (%)	21 (34.4%)	45 (32.3%)	0.822

Student *t*-test. Fisher Exact test.
Chi square test. **p* is significant at <0.05.

As regard symptoms of the studied patients, there were 80% and 73% had fever among group 1 and 2 respectively. There were 69% and 64% had cough among group 1 and 2. There were 90% and 83% had dyspnea among group 1 and 2 respectively. There were 31% had diarrhea and, 15% had abdominal pain among both groups. There were 13% and 14% had nausea among group 1 and 2. There were 12% and 14% had vomiting among group 1 and 2 respectively. There was no statistically significant difference between both groups regarding clinical manifestations (Table 2).

Table (2): Clinical manifestations of the studied patients (N=200).

Variable	Group 1 n=61	Group 2 n=139	*p*-value
Fever, n (%)	49 (80.3)	102 (73.4)	0.802
Cough, n (%)	42 (68.9)	89 (64.0)	0.709
Dyspnea, n (%)	55 (90.2)	115 (82.7)	0.415
Diarrhea, n (%)	19 (31.1)	44 (31.7)	>0.999
Abd. Pain, n (%)	9 (14.8)	21 (15.1)	0.690
Nausea, n (%)	8 (13.1)	20 (14.4)	0.711
Vomiting, n (%)	7 (11.5)	19 (13.7)	0.312

Chi square test. **p* is significant at <0.05.

When past medical history was evaluated. In group I There were 39% had diabetes, 31% had hypertension, 16% had cardiac diseases, and 32% had chest diseases. In group II There were 32% had diabetes, 35% had hypertension, 15% had cardiac diseases, and 28% had chest diseases. There was no statistically significant difference between both groups as regard diabetes, hypertension, cardiac and chest diseases.

Table (3): Medical history of the studied patients (N=200).

Variable	Group 1 n=61	Group 2 n=139	*p*-value
Diabetes, n (%)	24 (39.3)	45 (32.4)	0.155
Hypertension, n (%)	19 (31.1)	48 (34.5)	0.220
Cardiac diseases, n (%)	10 (16.39)	21 (15.10)	0.21
Chest diseases, n (%)	20 (32.78)	39 (28.05)	0.147

Chi square test. **p* is significant at <0.05.

As regard results of laboratory investigations, the platelet count was statistically significantly lower among group 1 than group 2. The ALT, AST, and TB, were significantly higher at group 1 than group 2. There was no statistically significant difference between both groups regarding Hg, and WBCs (Table 4).

Table (4): Laboratory parameters of the studied patients (N=200).

Variable	Group 1	Group 2	*p*-value
Hg (g/L), Mean ± SD	12.4±3.2	13.3±2.6	0.409
WBCs (X10^3/L), Mean±SD	7.3±1.1	7.5±1.3	0.811
Platelet (X10^3/L), Mean±SD	218±30.7	230±35.5	0.022*
ALT (U/L), Mean±SD	120±10.5	35.5±4.3	<0.001*
AST (U/L), Mean±SD	98.6±20.4	37.7±9.3	<0.001*
TB (mg/dl), Mean±SD	0.82±0.2	0.45±0.1	<0.001*

Student *t*-test. **p* is significant at <0.05.

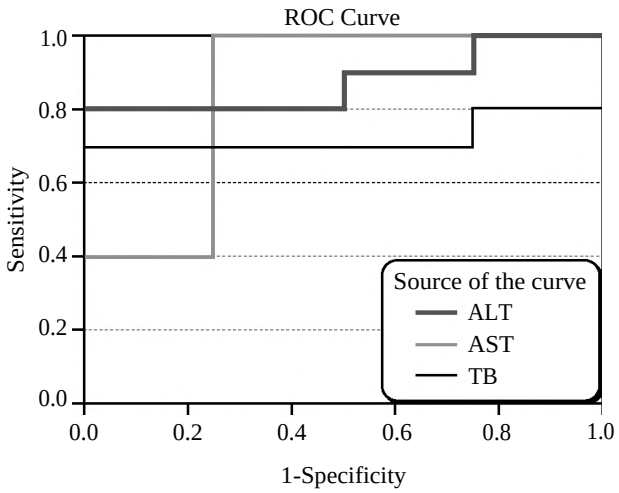

Fig. (1): ROC curve for ALT, AST, and TB of the studied patients.

The ROC curve was also plotted where the area under the curve was 0.875 (95% CI: 0.70-1.00, p=0.008) for ALT, the area under the curve was 0.85 (95% CI: 0.64-1.00, p=0.013) for AST, the area under the curve was 0.73 (95% CI: 0.45-0.99, p=0.010) for TB (Fig. 1).

The mean hospital staying was statistically significantly higher among group I. The intensive care requirement was statistically significantly higher among group I. There was statistically significant difference between both groups regarding mortality (Table 5).

Table (5): Prognosis of the studied patients (N=200).

Variable	Group 1	Group 2	*p*-value
Hospital staying, Mean±SD	12±3	7±2	0.042*
Intensive care, n (%)	15 (24.6)	19 (13.7)	0.022*
Mortality, n (%)	8 (13.11)	15 (10.79)	0.017*

Student *t*-test. Chi square test. **p* is significant at <0.05.

Discussion

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic now includes more than five million confirmed cases worldwide, with an average mortality rate approaching 6.5%. In the United States, New York City has >195,000 cases and >21,000 confirmed or suspected deaths [8].

COVID-19, the clinical syndrome caused by SARS-CoV-2, is primarily a respiratory disease that may lead to respiratory failure. However, COVID-19 also has significant systemic manifestations, including acute kidney injury, myocarditis, thrombosis, and acute liver injury (ALI) [9].

The virus known as SARS-CoV-2, which causes the disease COVID-19, had been caused a global pandemic in a few short months. As of March, 2020, there had been over 634,885 confirmed cases globally, and over 29,997 reported deaths worldwide. Although the virus primarily presents as a lower respiratory tract infection and is transmitted via respiratory droplets, there are many gastrointestinal and hepatic manifestations of the disease [10]. This brief study summarizes the available limited data on hepatic manifestations of COVID-19.

Multiple previous studies were reported that liver function test abnormalities seen with COVID-19 infection had been occured in about a third of patients. The most common abnormalities seen are elevations in the serum aminotransferases such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [11,12,13].

In our study, we aimed at evaluating liver enzymes among COVID-19 patients and analyzing the relationship between the liver enzymes elevations and severity of COVID-19 infection.

In the current study, we found that 30.5% [61] had elevated liver enzymes among (200) COVID-19 patients.

Similarly, Omrani-Nava et al., had been conducted a study aimed to analyze the laboratory investigations of COVID-19 patients including liver enzymes and association with outcomes. They found that 31.9% of COVID-19 patients had elevated liver enzymes [12].

To add to that, Balderramo and his colleagues found that 29.2% had elevated liver enzymes among COVID-19 patients [13].

In our study, The ROC curve was also plotted where the area under the curve was 0.875 (95% CI: 0.70-1.00, p=0.008) for ALT, the area under the curve was 0.85 (95% CI: 0.64-1.00, p=0.013) for AST, the area under the curve was 0.73 (95% CI: 0.45-0.99, p=0.010) for TB.

Similarly, Phipps and his colleagues found that a higher peak ALT values were significantly associated with overall disease severity and measured clinical outcomes **[8]**.

And also, a lot of Patients with SLI were more likely to have respiratory failure that require ICU admission and may need mechanical ventilation . Moreover, these patients were more likely to have died in the hospital **[8]**.

The results of our study support the findings, in which the mean hospital staying was statistically significantly higher among group with elevated liver enzymes.

In contrast, Omrani-Nava had found there was no association between elevated liver enzymes and length of hospital stay **[12]**.

In our study, the intensive care requirement was statistically significantly higher among group 1 and there was a statistically significant difference between both groups with and without elevated liver enzymes regarding mortality.

Additionally, Ngiam and his colleagues conducted a study to assess the prevalence and characteristics of the patients with COVID-19 related liver dysfunction in hospitalized patients with confirmed COVID-19 in Singapore. They reported that elevated liver enzymes had been seen in association with the need for mechanical ventilation and intensive care but did not show this association with mortality **[15]**.

To add to that, Omrani-Nava found also that elevated levels of liver enzymes and bilirubin in patients with COVID-19 infection in association with the need for intensive care unit and mortality rate **[12]**.

The possible mechanisms by which SARS-CoV-2 affects the liver is not fully understood but it is suggested to be a multi factorial: Direct hepato toxicity by the virus, and the immune-mediated inflammatory response especially cytokine storms which can lead to the damage of the liver cells **[14,16]**.

Also one of the possible mechanisms is that, in cases of respiratory failure, ischemic hepatitis may occur. Moreover, vascular changes due to coagulopathy and COVID-19 drug-induced liver injury cannot be ruled out **[17]**.

The SARS-CoV-2 cellular receptor, the angiotensin converting enzyme 2 (ACE2) receptor, is present in biliary and hepatic endothelial cells, providing an accepted explanation for the observed liver injury **[18]**.

Limitations exist in our research. This study was retrospective, and some cases did not have sufficient history of illness. Observational studies demonstrate association, not causation. Whether abnormal liver function is caused by SARS-CoV-2 or inflammation needs to be further investigated by direct clinical evidence.

Conclusion:

According to the results of this study, we first conclude that comorbid illness with elevated liver enzymes, associates with disease severity and worse clinical features. Second, we found that elevated liver enzymes associated with ICU admission, and length of hospital stay.

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تأثير ارتفاع انزيمات الكبد فى المرضى المصابين بمرض كوفيد ٢٠١٩

لقد أعلنت منظمة الصحة العالمية فى شهر مارس الماضى عن ظهور جائحة جديدة تسمى مرض فيروس كورونا ٢٠١٩ (كوفيد ٢٠١٩) نتيجة الإصابة بفيروس يسمى فيروس المتلازمة التنفسية الحادة الوخيمة كورونا ٢.

من أهم أعراض الإصابة بالكورونا (الحمى، السعال، الإرهاق، فقدان حاسة التذوق أو الشم، الصداع، صعوبة فى التنفس).

الهدف من هذه الدراسة: هو تقييم ارتفاع انزيمات الكبد فى المرضى المصابين بفيروس (كوفيد ٢٠١٩).

هذه الدراسة تم إجرائها على ٢٠٠ مريض مصرى مصابين بفيروس كوفيد ٢٠١٩ تم تشخيصهم عن طريق أخذ عينة من الأنف وتحليلها بجهاز البى سى ار.

وقد أظهرت النتائج ما يلى: أن نسبة حوالى ٦١٪ (٦١) مريض كوفيد ٢٠١٩ يعانون من ارتفاع انزيمات الكبد، كما وجد أن هؤلاء النوع من المصابين يحتاجون الحجز داخل مستشفيات العزل الصحى بفترة أطول من غيرهم ممن لديهم نسبة انزيمات الكبد طبيعية، كما أظهرت هذه الدراسة أن هؤلاء النوع من المصابين يعنون من مضاعفات شديدة تنفسية قد تحتاج بنسبة كبيرة إلى دخول العناية المركزة وقد يصل الأمر إلى استعمال التنفس الصناعى.

لقد أظهرت النتائج أيضاً أن نسبة الوفيات جراء الإصابة بمرض كوفيد ٢٠١٩ تزداد فى المرضى الذين يصاحبهم ارتفاع فى وظائف الكبد.