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Effect of COVID-19 on Liver Enzymes in Hospitalized COVID-19 Patients in the Gaza Strip: A Retrospective Study

Mohammed Taha[1]*, Ismail Mansour[2]

[1] Department of Pharmacology and Medical Sciences, Faculty of Pharmacy, Al-Azhar University of Gaza, Palestine.
[2] The European Gaza Hospital, Palestinian Ministry of Heath, Palestine.

ABSTRACT

In severe cases, the novel coronavirus disease 2019 (COVID-19) can cause respiratory failure and multiple organ dysfunction, including liver injury. This study assessed the COVID-19 effect on liver function among hospitalized COVID-19 patients. Three-hundred and seventy patients were recruited. Patients were distributed as the following: control group (n=100), intensive care unit (ICU) hospitalized COVID-19 patients (n=140), and non-ICU hospitalized COVID-19 group (n=130). Data about the levels of liver enzymes were collected from the hospital medical records of the participants. Our results showed a significant increase in alanine aminotransferase (ALT) levels among the ICU hospitalized COVID-19 patients compared with the non-ICU hospitalized COVID-19 patients (p-value <0.01) and the controls (p-value <0.001). Aspartate aminotransferase (AST) concentration significantly increased among the ICU-hospitalized COVID-19 group compared with the non-ICU hospitalized COVID-19 group (p-value <0.01) and the controls (p-value <0.05). The ICU-hospitalized COVID-19 patients had a higher increase in alkaline phosphatase (ALP) levels compared to the non-ICU hospitalized COVID-19 patients and controls (p values <0.001). Based on ALT, AST, and ALP levels, we found that 73 (52%), 77 (55%), and 38 (27%) of the ICU hospitalized COVID-19 patients developed a liver injury. Of those, 12 (8.5%) died compared to 5 (3.5%) patients with abnormal liver function. In conclusion, these findings suggest that COVID-19 disease is associated with abnormal liver function and liver injury.

Keywords: COVID-19, SARS-CoV-2, Liver enzymes, Liver damage.

INTRODUCTION

A rapid outbreak of acute respiratory illnesses was observed in Wuhan, China, in December 2019 [1–6]. The China Novel Coronavirus Investigating and Research Team succeeded in isolating and identifying the causative agent of these respiratory diseases, which was called a novel coronavirus (2019-nCoV). The international committee on taxonomy of viruses later renamed it severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [4,7]. On March 7, 2020, the World Health Organization (WHO) announced a new name for the epidemic disease caused by SARS-CoV-2: Coronavirus disease (COVID-19), which has been proclaimed as a global pandemic [8]. On January 03, 2022, WHO reported that there have been 291,413,610 confirmed cases of COVID-19 globally, including 5,461,241 deaths [9]. According to Palestinian Ministry of Health statistics on January 03, 2022, there were 470656 confirmed COVID-19 cases (190538 in Gaza Strip) and 4947 confirmed deaths (1709 in Gaza Strip).

SARS-CoV-2 is a single-stranded RNA virus that binds to angiotensin-converting enzyme 2 (ACE2) strongly expressed by epithelial cells of the mouth, lower respiratory tissues, as well as to a lesser extent by the epithelial cells of other organs such as the heart, liver,

[*] ***Corresponding author: Mohammed Taha***
m.taha@alazhar.edu.ps
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kidneys and intestines [10]. SARS-CoV-2 infection has a wide range of symptoms, from asymptomatic to life-threatening conditions such acute respiratory distress syndrome and multiple organ failure. The majority of COVID-19 cases are mild, with the most common symptoms being fever, fatigue, and a dry cough [1,2,11–13]. Severe cases, on the other hand, can lead to organ dysfunctions such as lung injury, heart injury, liver injury, and kidney injury [1,2,11,12,14–16]. Patients with COVID-19 have aberrant liver function, according to recent studies, with raised alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) [2,12,14,17]. Interestingly, a histological evaluation of liver biopsy specimens from a COVID-19 patient revealed significant microvesicular steatosis as well as modest lobular and portal activity, showing that SARS-CoV-2 may trigger liver damage [18]. Additionally, COVID-19 individuals with pre-existing liver disease have a greater mortality rate than those who do not have pre-existing liver disease [19]. Regrettably, the actual mechanism underlying the development of COVID-19-related liver damage remains unknown. ACE2 receptors found in liver tissues may play a role in the progression of liver damage. Cholangiocytes exhibit a high expression of ACE2 receptors, according to a recent study, indicating that the SARS-CoV-2 virus may bind to ACE2 on cholangiocytes, inducing cholangiocyte malfunction and liver injury [20]. Liver injury is defined by an increase of over two times the upper limit of normal range in serum ALT or conjugated bilirubin, or a combined increase of AST, ALP, and total bilirubin, provided one of them is above the upper limit of the normal range. COVID-19 also causes severe acute systemic inflammatory responses and cytokine storms, that result in a permanent multi-organ damage[1,2,11,12,14]. Drug-induced liver injury is another possibility, as some COVID-19 patients are taking hepatotoxic medicines such as remdesivir, ritonavir, lopinavir, and chloroquine[14,18]. Recent information about the COVID-19 outbreak has begun to provide light on the impact of the COVID-19 disease on the liver [9,11,14]. However, few studies have analyzed variations in liver function tests among COVID-19 patients. This study aimed to evaluate the effect of SARS-CoV-2 infection on liver function among hospitalized COVID-19 patients.

MATERIAL AND METHODS

This study is a single-center cross-sectional retrospective study which assessed the effect of COVID-19 on liver function among COVID-19 patients who were admitted to the European Gaza Hospital in the Gaza Strip. This study was approved from the Helsinki Committee for Ethical Approval, Palestinian Health Research Council, Gaza, Palestine. The ethical approval number: PHRC/HC/1104/21.

Study population

Patients were included in the study if they were admitted with SARS-CoV-2 infection confirmed by the real-time polymerase chain reaction (RT-PCR) of nasal swab samples. In this study, 270 COVID-19 patients of both genders who were admitted to the European Gaza Hospital in the Gaza Strip, as well as 100 non-ICU patients with negative COVID-19 RT-PCR tests, free of liver diseases and any condition elevating liver enzymes levels have participated (Figure 1). The participants were divided into three groups: control group (100 people with negative COVID-19 PCR tests); non-ICU hospitalized COVID-19 patients (130 COVID-19 hospitalized patients were not admitted to the ICU); ICU hospitalized COVID-19 patients (140 COVID-19 hospitalized patients were admitted to the ICU). COVID-19 hospitalized patients and control group participants with pre-existing liver such as hepatitis, liver cirrhosis, or liver cancer were excluded from the study. Patients with missing clinical data or died before completing the biological tests for the liver function were excluded. In addition, individuals on regular hepatotoxic medications were also excluded from the study.

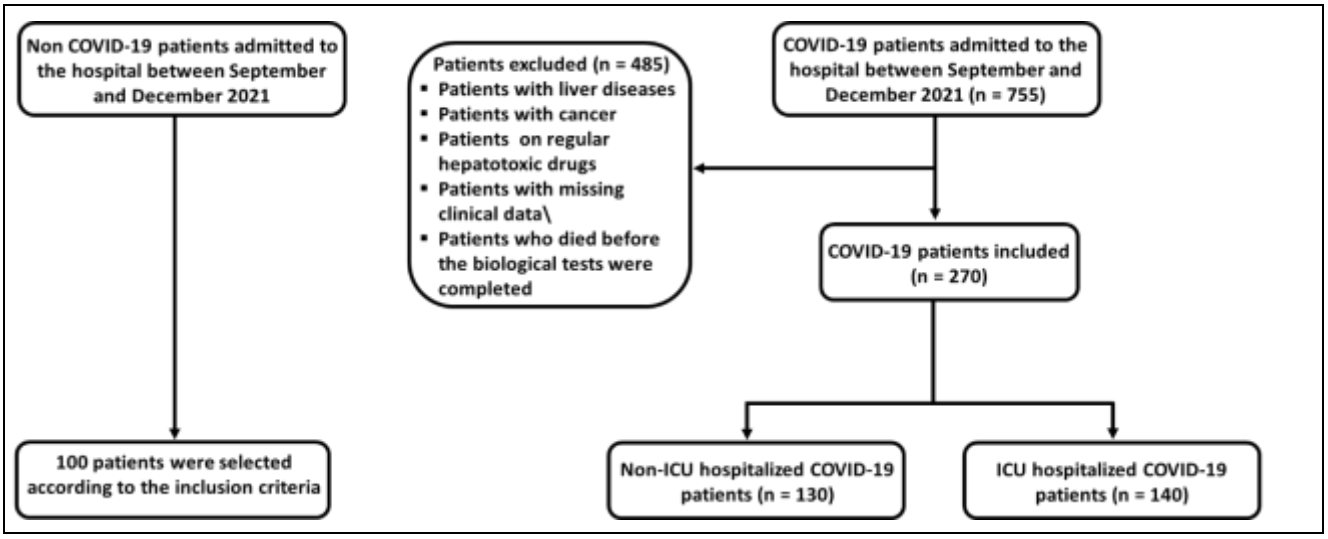

Figure 1: Patient flow chart.

Patient flow chart showing the total number of COVID-19 and non-COVID-19 patients admitted to the European Gaza Hospital in the Gaza Strip from September to December 2021. All participants were selected according to the inclusion criteria.

Data collection

During the study period, data was collected for each participant from the medical records at the European Gaza Hospital including patient demographics, and laboratory parameters of the liver function (ALT, AST and ALP). Clinical laboratory services at the European Gaza Hospital informed us that determination of serum levels of liver enzymes (ALT, AST and ALP) was performed using commercially available kits and according to manufacturer's instructions as the following: ALT kit (manufacturer: AMS – ITALY, Ref: GA492100, Lot: BB017CB); AST kit (manufacturer: AMS – ITALY, Ref: GA492100); ALP kit (manufacturer: Reactivos – SPAIN, Ref: EZ012LQ, Lot: LIQ-1148-M). Abnormal liver function tests were defined as: ALT >36 U/L, AST >35 U/L, ALP >120 U/L. Moreover, liver injury was defined in patients who had raised ALT, AST and/or ALP more than two times the upper limit unit of normal range[14].

Statistical analysis

Graphics and statistical analyses were performed using Graphpad Prism software (San Diego, CA, USA). Data was presented as mean ± SD. Comparisons between two different groups was performed using unpaired *t* test. For all tests, P values ≤ 0.05 were considered to be significant (* $p \leq 0.05$, ** $p < 0.01$, *** $p < 0.001$).

RESULTS

Characteristics of the Study Population

This study comprised a total of 370 participants divided into three groups. The data in Table 1 showed no statistically significant differences in age and BMI between the study population. The levels of ALT, AST, and ALP in the non-ICU hospitalized COVID-19 patients and ICU hospitalized COVID-19 patients were significantly different from those in controls. In addition, COVID-19 patients admitted to the ICU showed a significant increase in the levels of ALT, AST, and ALP compared with COVID-19 patients who were not admitted to the ICU. In the ICU hospitalized COVID-19 patients' group, we also observed that 5 (3.5%) of COVID-19 patients with abnormal liver function tests and 12 (8.5%) of patients with liver injury died during their hospitalization as a result of COVID-19-induced respiratory failure or multiple organ dysfunction.

Table 1: Characteristics of the study population

Variable		Control group	non-ICU hospitalized COVID-19 patients	ICU hospitalized COVID-19 patients	P values
		n=100	n=130	n=140	
Age (year)	Mean ± SD (range)	60.83 ± 0.87 (52 – 70)	62.70 ± 1.1 (54 – 71)	64.93 ± 0.96 (56 – 72)	0.14*, 0.28†, 0.11‡
BMI (kg/m2)	Mean ± SD	24.12 ± 1.3	23.82 ± 1.4	25.03 ± 0.9	0.53*, 0.84†, 0.72‡
ALT (U/L)	Mean ± SD	21.77 ± 0.37	28.92 ± 0.88	44.82 ± 2.28	< 0.05*, < 0.01†, < 0.001‡
	Normal (n, %)	100 (100%)	91 (70%)	12 (9%)	
	Abnormal (n, %)	0 (0%)	39 (30%)	55 (39%)	
	Liver injury (n, %)	0 (0%)	0 (0%)	73 (52%)	
AST (U/L)	Mean ± SD	19.85 ± 0.35	30.72 ± 0.98	42.41 ± 1.90	< 0.05*, < 0.01†, < 0.001‡
	Normal (n, %)	100 (100%)	87 (67%)	10 (7%)	
	Abnormal (n, %)	0 (0%)	43 (33%)	53 (38%)	
	Liver injury (n, %)	0 (0%)	0 (0%)	77 (55%)	
ALP(U/L)	Mean ± SD	50.79 ± 1.13	84.78 ± 2.98	145.30 ± 3.90	< 0.01*, < 0.001†, < 0.001‡
	Normal (n, %)	100 (100%)	85 (65%)	14 (10%)	
	Abnormal (n, %)	0 (0%)	45 (35%)	88 (63%)	
	Liver injury (n, %)	0 (0%)	0 (0%)	38 (27%)	
Death	Normal liver function tests (n, %)	0 (0%)	0 (0%)	0 (0%)	
	Abnormal liver function tests (n, %)	0 (0%)	0 (0%)	5 (3.5%)	
	Liver injury (n, %)	0 (0%)	0 (0%)	12 (8.5%)	

ICU: Intensive care unit; BMI: Body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase. *) p-values which represent the comparison between the means of control group and the non-ICU hospitalized COVID-19 patients' group. †) p-values which represent the comparison between the means of the non-ICU hospitalized COVID-19 patients' group and ICU hospitalized COVID-19 patients' group. ‡) p-values which represent the comparison between the means of control group and the ICU hospitalized COVID-19 patients' group. All p-values were calculated by unpaired Student's *t* test.

Severe cases of COVID-19 show an abnormality in liver functions

To evaluate the effect of COVID-19 disease on the liver function among hospitalized patients with COVID-19, we compared the levels of ALT (U/L), AST (U/L), and ALP (U/L) among the participants of each two groups separately. Our results showed a significant increase in the mean concentration of ALT (28.92 ± 0.88 U/L) in the non-ICU hospitalized COVID-19 patients compared with the controls (21.77 ± 0.37 U/L, p value < 0.05), (Figure 2A). The results also found that the ICU hospitalized COVID-19 patients showed a more pronounced increase in the levels of ALT (44.82 ± 2.28 U/L) compared with the non-ICU hospitalized COVID-19 patients (28.92 ± 0.88 U/L, p value < 0.05) and the control subjects (21.77 ± 0.37 U/L, p value < 0.05), (Figure 2A). We also found that the mean concentration of AST significantly increased among the ICU hospitalized COVID-19 group (42.41 ± 1.90 U/L) compared with the controls (19.85 ± 0.35 U/L, p value < 0.05) as well as the non-ICU hospitalized COVID-19 group (30.72 ± 0.98 U/L, p value < 0.05), (Figure 2B). Regarding the effect of COVID-19 on ALP levels, there was a significant increase in the concentrations of ALP among the non-ICU hospitalized COVID-19 patients (84.78 ± 2.98 U/L) compared with the controls (50.79 ± 1.13, p value < 0.05), (Figure 2C). Interestingly, our findings also revealed that ICU hospitalized COVID-19 patients had a higher increase in ALP levels (145.30 ± 3.90 U/L) compared to the non-ICU hospitalized COVID-19 patients (84.78 ± 2.98 U/L, p value <0.05) and control

individuals (50.79 ± 1.13, p value < 0.05), respectively (Figure 2C). These findings suggest that COVID-19 disease is associated with abnormal liver function tests and that abnormality increases during COVID-19 severity.

Patients with COVID-19 who are admitted to the ICU have more liver injury

We assessed whether COVID-19 disease may develop liver injury among the hospitalized patients with COVID-19. Liver injury was defined in patients who had raised ALT, AST and/or ALP more than two times the upper limit unit of normal [14]. Our results revealed that there was no patient with liver injury among the non-ICU hospitalized COVID-19 patients as well as the control group (Figure 3). Interestingly, the majority of COVID-19 patients who were admitted to the ICU had liver injury. Based on ALT, AST and ALP levels, we found that 73 (52%), 77 (55%) and 38 (27%) of the ICU hospitalized COVID-19 patients had liver injury, respectively (Figure 3A, B, C). In addition, the results showed that 12 (8.5%) of the ICU hospitalized COVID-19 patients who had liver injury died compared to 5 (3.5%) patients who had abnormal liver test results (Table 1). These findings propose that severe cases of COVID-19 may be associated with more liver injury, which may increase the risk of death.

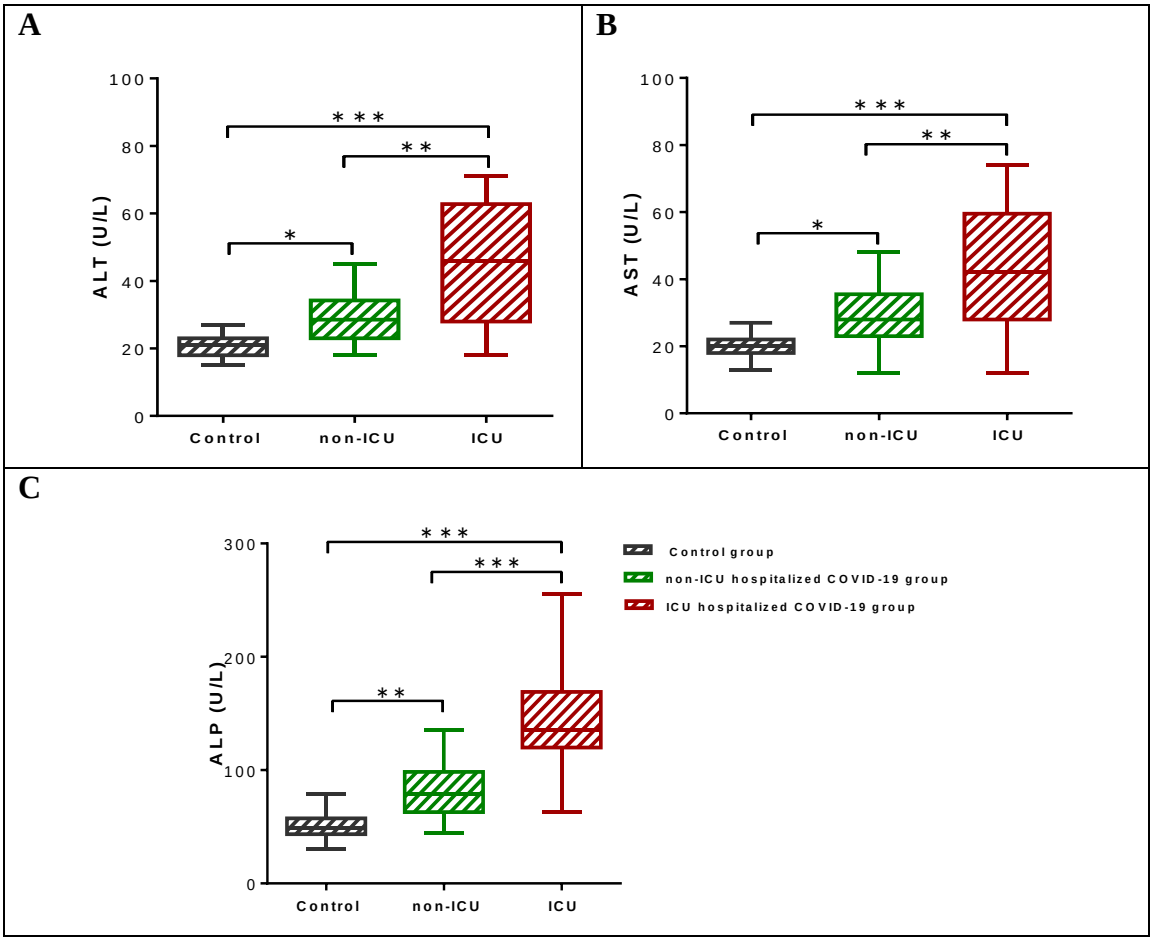

Figure 2: Severe cases of COVID-19 show an abnormality in liver functions.

The levels of ALT (U/L), AST (U/L), and ALP (U/L) were evaluated in the COVID-19 patients as well as controls. (A-C) Box and whisker graphs displaying the concentrations of ALT (U/L), AST (U/L), and ALP (U/L) in the peripheral blood of controls (n=100, black boxes), non-ICU hospitalized COVID-19 patients (n=130, green boxes), and ICU hospitalized COVID-19 patients (n= 140, brown boxes). Statistical analysis was performed using unpaired t-test (*p ≤ 0.05, ** p < 0.01, *** p < 0.001).

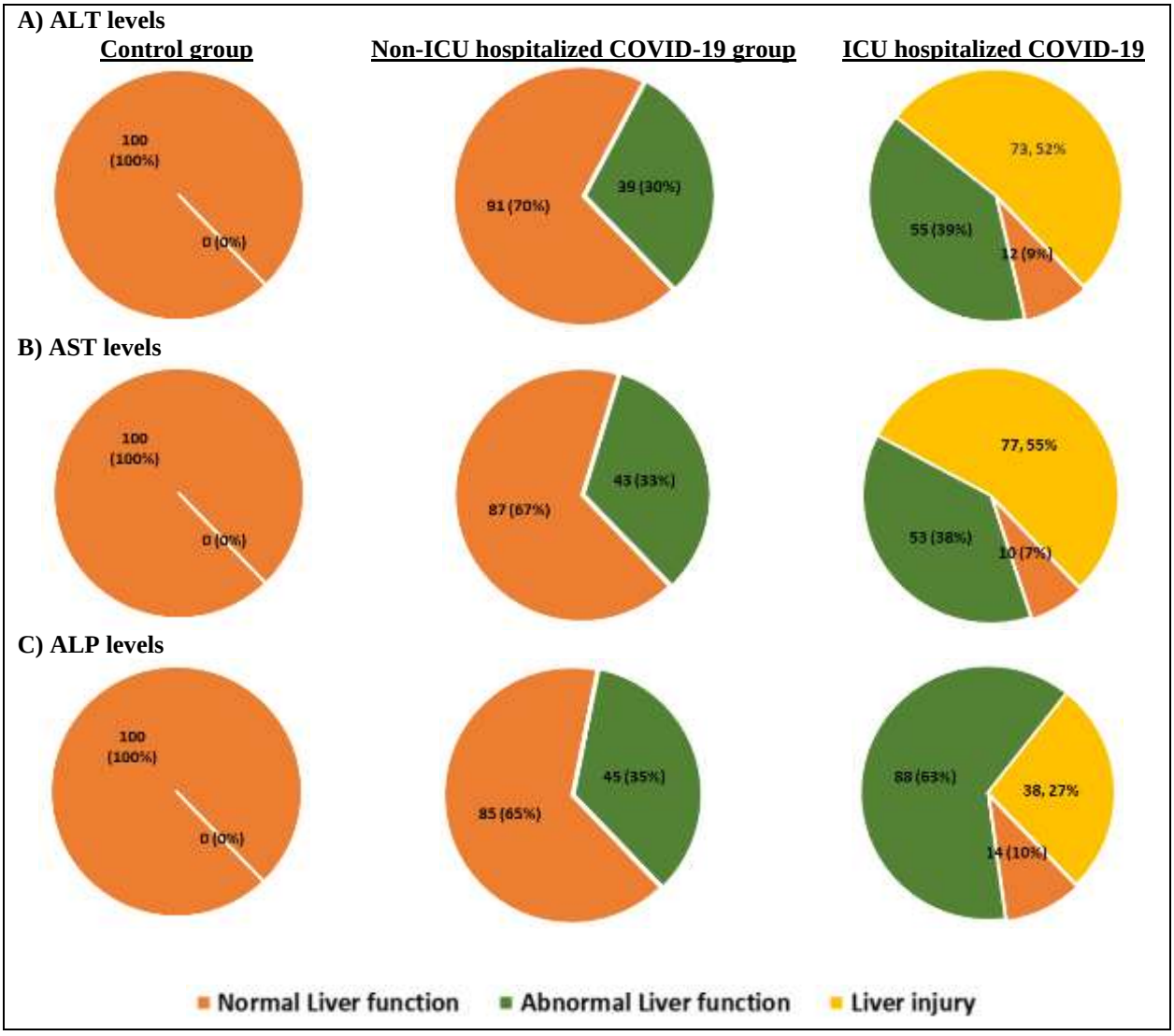

Figure 3: severe cases of COVID-19 are associated with more liver injury.

Liver injury is defined in patients who had raised ALT, AST and/or ALP more than two times the upper limit unit of normal range. (A-C) Pie chart illustrating the percentages of COVID-19 patients as well as the control subjects who had liver injury based on the levels of ALT, AST and ALP, respectively. Data represent the relative proportion (frequency) of the indicated responses measured.

DISCUSSION

In severe cases, COVID-19 patients develop severe lung disease and multi-organ dysfunction, which may increase the risk of death [1,2,15]. One of these organs which may affect by SARS-CoV-2 infection is the liver, causing liver dysfunction [21,22]. High percentage of patients with severe COVID-19 have an abnormal elevation in the liver enzymes as well as liver injury [22–25]. One study showed that 76.3% of the hospitalization COVID-19 patients had abnormal liver function and 21.5% of them with liver injury [14].

The present study was conducted to assess the effect of COVID-19 disease on the liver function among the hospitalized

COVID-19 patients by evaluation the liver enzymes levels (ALT, AST, ALP). Our results showed a significant increase in the levels of the liver enzymes among the hospitalized COVID-19 patients. Of note, we found that the majority of COVID-19 patients who were admitted to the ICU had liver injury. Supporting the findings of our study, several studies assessed the clinical features of COVID-19 patients and the factors that could possibly cause liver injury by SARS-CoV2 infection 26–31. The results of these studies found an increase in the levels of liver enzymes mainly ALT, AST and ALP as well as abnormal liver function tests among high percent of COVID-19 patients. A recent meta-analysis study of 47 studies showed that about 15 - 20% of the hospitalized patients with COVID-19 had abnormal elevations in the liver enzymes, including AST, ALT, and ALP 32. Another study carried out by Cholankeril and his colleagues found that 26 of 65 COVID-19 patients (40%) had abnormal liver enzymes, and 4 of them were noted to have liver injury due to a 2-fold elevation in liver enzymes during their SARS-CoV-2 infection 33. In the same perspective, Yao et al. conducted a study to evaluate the changes in liver function in hospitalized patients with COVID-19 30. Of the 40 cases, there were 21 cases (52.5%) with elevated ALT and 16 cases (40%) with both ALT and AST elevated, and liver damage occurred in 22 of the 40 confirmed patients (55%). Also, they found that the probability of liver injury in critically ill patients was significantly greater than that of non-critically ill patients. However, the results showed that liver injury was more likely to occur in patients who used drugs like lopinavir/ritonavir and methylprednisolone. This suggests that some drugs for COVID-19 may have hepatic toxicity in some patients. In the same context, 148 patients with confirmed COVID-19 were included in a study performed by Fan and his colleagues. At the time of admission to the hospital, 55 (37.2%) of the COVID-19 patients had abnormal liver function 34. According to their findings, a greater proportion of COVID-19 patients with abnormal liver function (57.8%) had received lopinavir/ritonavir treatment after admission 34. In the United States, another retrospective observational cohort study was conducted to investigate liver test abnormalities and their relationship to clinical outcomes in 1,827 hospitalized COVID-19 patients 24. The results showed that patients with COVID-19 had a pronounced increase in liver enzyme levels during hospitalization, and the drugs used for the treatment of COVID-19 (lopinavir/ritonavir, hydroxychloroquine, remdesivir, and tocilizumab) were linked to higher levels of liver enzymes and the development of liver injury. In our study, we did not assess the effect of COVID-19 medication on liver function because there was a missing data about the treatment protocol of COVID-19, and we excluded the patients using hepatotoxic drugs from the study.

Because our study is a retrospective study, we did not follow up the COVID-19 patients after their recovery. However, some studies assessed the longitudinal effects of SARS-CoV-2 infection on liver function [35,36]. In this context, Zhu et al. evaluated the liver function among COVID-19 patients immediately after hospitalization, before discharge and one year after discharge [36]. They found that 32.2% of the COVID-19 patients with abnormal liver function immediately after hospitalization, 45.8% before discharge and 28.8% after one year of discharge. Another study found that among 461 COVID-19 patients, 28.4% of them had liver dysfunction, and there was a marked improvement in liver function after 12 months of discharge where 13% of COVID-19 patients had liver dysfunction and most of them with pre-existing liver disease [35]. These findings suggest that long-term monitoring of liver function is essential mainly among COVID-19 patients with pre-existing liver disease.

This study had some limitations, including a retrospective single-center study design and limited access to laboratory, imaging, and medication variables, which may influence key clinical outcomes. In addition, as with other retrospective studies, there is a possibility of selection bias. Another drawback of our study was the challenge of evaluating overlapping drugs used for the treatment of COVID-19 patients while they are in the hospital. Future studies involving multiple centers with a larger sample size are required to confirm the findings of our study.

In conclusion, our findings added to a growing body of evidence indicating that SARS-CoV-2 infection is associated with a significant proportion of concomitant liver abnormalities that increase during COVID-19 severity, leading to liver injury and increasing the risk of COVID-19 mortality. As the etiology of liver abnormality noted in SARS-CoV-2 infection is not completely understood, further prospective studies are needed to clarify the exact mechanism by which SARS-CoV-2 infection can affect liver function and develop liver injury.

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تأثير كوفيد-19 على إنزيمات الكبد لدى مرضى كوفيد-19 في المستشفيات في قطاع غزة: دراسة بأثر رجعي

محمد طه[1]*، اسماعيل منصور[2]

[1] قسم علم الادوية والعلوم الطبية، كلية الصيدلة بجامعة الازهر، فلسطين.

[2] مستشفى غزة الأوروبي، وزارة الصحة الفلسطينية، فلسطين.

ملخص

في الحالات الشديدة، مرض فيروس كورونا الجديد 2019 (كوفيد-19) يمكن أن يتسبب في فشل الجهاز التنفسي وخلل في العديد من الأعضاء، بما في ذلك إصابة الكبد. قيمت هذه الدراسة تأثير كوفيد-19 على وظائف الكبد بين مرضى كوفيد-19 في المستشفى. تم تقسيم المشاركين (ن=370) إلى ثلاث مجموعات: المجموعة الضابطة (ن=100)، مجموعة كوفيد-19 التي لم تدخل وحدة العناية المركزة (ن=130) ومجموعة كوفيد-19 في وحدة العناية المركزة (ن=140). تم تقييم مستويات إنزيمات الكبد في عينات الدم لكل مشارك. أظهرت نتائجنا زيادة كبيرة في مستويات ALT بين مرضى كوفيد-19 في وحدة العناية المركزة مقارنة مع مرضى كوفيد-19 غير المعالجين بوحدة العناية المركزة (قيمة p اقل من 0.01) وعناصر التحكم (قيمة p اقل من.(0.001 أيضًا تركيز AST زاد بشكل كبير بين مجموعة كوفيد-19 في وحدة العناية المركزة مقارنةً بعناصر التحكم (قيمة p اقل من 0.05) ومجموعة كوفيد-19 غير المعالجة بوحدة العناية المركزة (قيمة p اقل من .(0.01 كان لدى مرضى كوفيد-19 في وحدة العناية المركزة زيادة أعلى في مستويات ALP مقارنة بمرضى كوفيد-19 غير المعالجين بوحدة العناية المركزة والضوابط (قيم p اقل من 0.001). استنادًا إلى مستويات ALT وAST وALP، وجدنا أن 73 (52٪) و77 (55٪) و38 (27٪) من مرضى كوفيد-19 يعانون من إصابة في الكبد. من هؤلاء 12 (8.5٪) ماتوا مقارنة بـ 5 (3.5٪) مرضى يعانون من خلل في وظائف الكبد. تشير هذه النتائج إلى أن مرض كوفيد-19 مرتبط بوظائف الكبد غير الطبيعية وإصابة الكبد.

الكلمات الدالة: كوفيد-19، فيروس كورونا 2 المرتبط بالمتلازمة التنفسية الحادة الشديدة، إنزيمات الكبد، تلف الكبد.

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* ***المؤلف المراسل: محمد طه***

m.taha@alazhar.edu.ps

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