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Original Article

Comparison of liver elastography results in COVID-19 patients with and without increased liver enzymes

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Abstract

Introduction: The coronavirus disease 20149 (COVID-19) may be associated with the elevated liver enzymes including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in which the disease has been associated with more severity. Liver stiffness (LS) is associated with the increased liver enzymes. Liver elastography is a non-invasive technique that is used to evaluate LS. This study aimed to evaluate the functional status of liver and its relationship with liver elastography results in the patients with COVID-19.

Methods: In this cross-sectional study, 90 patients with COVID-19, whose diagnosis was confirmed by polymerase chain reaction (PCR) test, were included. Levels of liver enzymes were measured and the patients underwent liver elastography. Liver size and interquartile range-median (IQR/M) of LS were also measured. Six months later, the patients underwent another liver elastography and measurement of liver enzymes.

Results: The frequency of fatty liver in the case group was significantly higher compared to the control group but no significant difference was observed in the frequency of liver fibrosis between two groups. In patients with COVID-19, the LS and IQR/M values at the beginning and six months after recovery were significantly higher in the group with the increased liver enzymes (case) compared to the group without the increased enzymes (control). *P* value was 0.001.

Conclusion: The use of elastography to evaluate LS in the patients with COVID-19 can be significantly effective in assessing the status of liver damage and inflammation of liver tissue. Since elastography is an inexpensive and non-invasive available tool, it can be used mainly in most medical centers.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has raised many challenges to global health.[1] Although the lungs are the main organ involved, other organs including the heart, skin, liver, pancreas, kidneys, and gastrointestinal tract have also been affected in this disease.[2] Studies show that as the Severe acute respiratory syndrome *coronavirus 2* (*SARS-CoV-2*) can cause changes in circulating lymphocytes and immune system, it can influence the liver and pancreas.[3] A large cohort study in China demonstrated that 2.1% of 1099 people with COVID-19 affected previous hepatitis B.[4] Up to 60% of liver impairment has been reported in patients with the severe acute respiratory syndrome (SARS). The findings suggest that SARS-coronavirus-induced liver damage is mainly due to the apoptosis as a result of hyperproliferative state and cell cycle arrest in cells infected with the virus. Another explanation for the liver impairment is the hepatotoxicity induced by using antiviral drugs in SARS patients.[5] Studies have shown an increase in liver enzymes including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in some patients with SARS, in which the disease has been associated with more severity.[2]

Liver Elastography is a non-invasive technique that is widely used to evaluate liver stiffness (LS). Measurement of LS is a sensitive method for determining liver damage and an increase in LS level has been observed in patients with cirrhosis and acute hepatitis.[6] In a study carried out by Effenberger et al, liver tests, spleen ultrasound, and liver elastography of 32 patients suffering from COVID-19 were studied. Twelve patients had elevated liver enzymes and LS. The LS degree was consistent with the gamma-glutamyl transferase level, and there was a significant relationship between the degree of LS and patients' condition.[7]

Therefore, some studies in patients with COVID-19 have reported an increase in liver function enzymes and liver impairment. Since liver elastography is a non-invasive, inexpensive, and available method that has a high sensitivity in the evaluation of LS, this study aimed to evaluate the functional status of the liver and its relationship with liver elastography results in patients with COVID-19.

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Methods

In this cross-sectional study, 90 patients with COVID-19 whose diagnosis was confirmed by PCR test were included. Patients with chronic liver disease, chronic renal failure, diabetes, and obese patients (with a body mass index above 28 kg/m^2) were excluded from the study. Levels of liver function enzymes (including AST, ALT, total bilirubin, and alkaline phosphatase) were measured two weeks after patients' polymerase chain reaction (PCR) was positive and patients underwent liver elastography. Liver size, LS (expressed in kilopascal), interquartile range-median value (IQR/M) of LS were also measured. Six months later, the patients underwent another liver elastography and measurement of liver function enzymes. The sample size was divided into two groups of 45 patients including case (patients with increased liver enzymes) and control (patients without increased liver enzymes) groups. Afterward, the effect of COVID-19 disease on fatty liver and liver fibrosis in patients with and without increased liver enzymes was investigated.

Statistical analysis

The collected data were statistically analyzed using SPSS version 21 statistical analysis software (Microsoft LTD, Chicago, USA). Data were reported as descriptive statistics (frequency and percentage) and mean ± standard deviation. Student t-test and Mann-Whitney U test were used to compare quantitative variables and a chi-square test and Fisher exact test were used to compare qualitative variables. The *P* value for statistical significance was considered lesser than 0.05.

Results

In this study, 90 patients were divided into two groups of 45 patients including case (patients with increased liver enzymes) and control (patients without increased liver enzymes) groups. In the case group, the average age of patients was 35.75 ± 10.44 years, including 23 (51.1%) females and 22 (48.9%) males. In the control group average age of patients was 34.40 ± 8.36 years, including 18 (40%) males and 27 (60%) females. The *P* value of the age difference between the two groups was 0.499, and the *P* value of sex difference between the two groups was 0.199.

Frequency of patients' risk factors and their *P* value are summarized in Table 1.

In the case group 17 (37.8%) patients had fatty liver while in the control group 8 (17.8%) patients had fatty liver ($P = 0.029$).

In case group 14 (31.1%) patients had liver fibrosis while in the control group 7 (15.6%) patients had liver fibrosis ($P = 0.067$).

The results of patients' Para clinical tests are given in Table 2.

Elastography results of patients at the beginning and six months after the examination are shown in Table 3.

Table 1. Patients' risk factors

Variable	Case (n = 45)	Control (n = 45)	*P* value
Smoking	15 (33.3%)	19 (42.2%)	0.257
Hypertension	12 (26.7%)	15 (33.3%)	0.594
Diabetes	10 (22.2%)	8 (17.8%)	0.396
Chronic heart failure	4 (8.9%)	5 (11.1%)	0.643
Fever	27 (60%)	7 (15.5%)	0.001
Nausea and vomiting	20 (44.4%)	6 (13.3%)	0.001
Diarrhea	22 (48.9%)	3 (6.7%)	0.001

Note: The results are expressed as number (percent).

Table 2. Patients' paraclinical tests

Variable	Case (n = 45)	Control (n = 45)	*P* value
ALT (U/L)	72.88 ± 16.77	30.00 ± 4.81	0.001
AST (U/L)	65.33 ± 18.29	18.95 ± 2.95	0.001
Bilirubin total (U/L)	0.44 ± 0.13	0.44 ± 0.13	0.578
ALP (U/L)	303.08 ± 63.25	228.55 ± 34.19	0.001

Note: The results are presented are expressed as mean ± standard deviation. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

Table 3. Elastography results of patients

Variable	Case (n = 45)	Control (n = 45)	*P* value
Liver span (cm)	7.31 ± 1.54	5.02 ± 1.33	0.001
Primary IQR/M	1.54 ± 0.26	0.43 ± 0.20	0.001
Primary liver stiffness (kPa)	7.63 ± 1.05	3.39 ± 0.79	0.001
IQR/M 6 months later	1.14 ± 0.19	0.33 ± 0.14	0.001
Liver stiffness 6 months later (kPa)	5.72 ± 0.89	2.68 ± 0.71	0.001

Note: The results are presented are expressed as mean ± standard deviation. Abbreviation: IQR/M, interquartile range-median.

Comparison of IQR/M of elastography values between the two study groups at the beginning and 6 months later is shown in Figures 1 and 2.

Comparison of LS between the two study groups at the beginning and 6 months later is shown in Figures 3 and 4.

Discussion

The COVID-19 disease may be associated with the elevated liver enzymes. Elevated AST and ALT enzymes have been reported in 16%-53% of patients with COVID-19, which was usually associated with the increased disease severity.[8] In a large study in China, the increase in AST and ALT in patients with mild disease were 18.2% and 19.8% respectively, while in patients with a severe disease that were 39.4% and 28.1% respectively.[9] Liver impairment has been reported in 60% of patients with SARS.[5]

This study aimed to evaluate the functional status of liver and its relationship with the results of liver elastography in 90 patients with the COVID-19 disease. Patients were divided into two groups and examined.

The results of the present study showed that the frequency of fever (60% vs. 15.5%, $P = 0.001$), nausea and

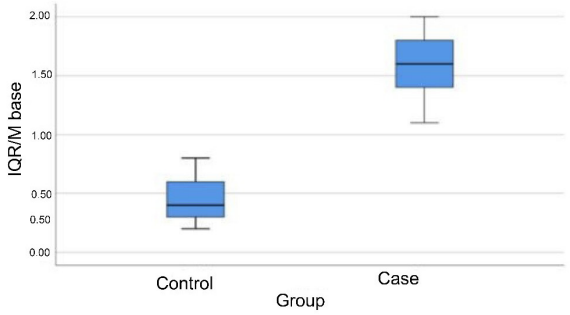

Figure 1. Comparison of IQR/M of elastography values between the two studied groups at the beginning

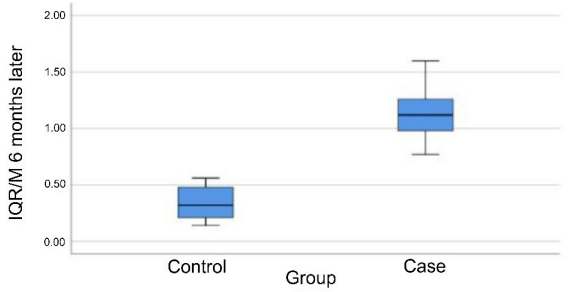

Figure 2. Comparison of IQR/M of elastography values between the two studied groups after 6 months

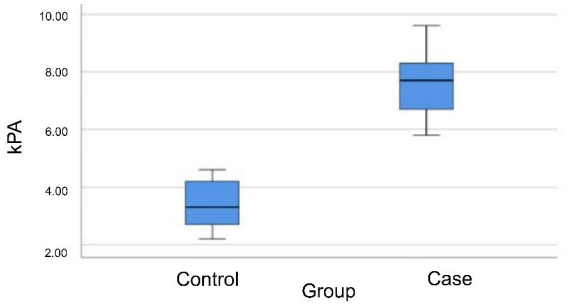

Figure 3. Comparison of liver stiffness between the two studied groups at the beginning

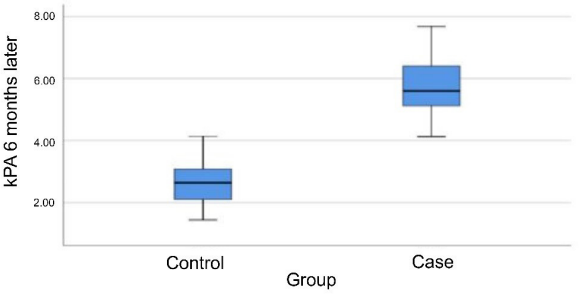

Figure 4. Comparison of liver stiffness between the two studied groups after 6 months

vomiting (44.4% vs. 13.3%, $P=0.001$) and diarrhea (48.9% vs. 6.7%, $P=0.001$) were significantly higher in patients in the case group.

The frequency of fatty liver in the case group was significantly higher compared to the control group (37.8% vs. 17.8%, $P=0.029$), but no significant difference was observed in the frequency of liver fibrosis between the two groups (31.1% vs. 15.6%, $P=0.067$).

Elastography was used as a non-invasive tool to measure LS. The results of the present study showed that in patients with COVID-19, the LS and IQR/M measurements at the beginning and six months after recovery were significantly higher in the group with the increased liver enzymes (case) compared to the group without the increased enzymes (control) ($P=0.001$).

Studies have shown that in liver fibrosis and acute hepatitis, the degree of LS increases.[10-12] One study showed that the degree of LS increased with the elevated aminotransferases from their cut-off point, and during the follow-up period, LS decreased as a result of decreased aminotransferases. Moreover, a significant correlation was found between aminotransferases and LS at the onset of acute viral hepatitis.[10]

A study done by Degous et al concluded that in non-alcoholic fatty liver disease transient elastography is an accurate test with a high negative predictive value and modest positive predictive value for excluding advanced fibrosis.[13] LS evaluation by elastography is now widely being used in several countries for the assessment of LS in chronic liver diseases.[14] Measurement of LS using transient elastography has high accuracy for exposure of hepatic fibrosis and cirrhosis. According to Wong et al, the higher LS value (> 12.0 kPa), the worse post-hepatectomy outcomes.[15] Pang et al stated that transient elastography is a valid and non-invasive method for the measurement of LS and staging of liver fibrosis. LS can independently predict mortality and liver complications in patients with chronic liver disease. It can improve physicians' information to estimate patients' prognoses and help them manage patients' conditions more carefully.[16]

As mentioned, COVID-19 disease has been reported to cause liver impairment, which is associated with severe cases and can affect the outcome of the disease, so it is important to be diagnosed and treated on time. Evaluation of LS can be a good predictor to predict the outcome of the disease. Liver elastography is an accurate method for measuring LS and can be helpful in this regard.

Conclusion

According to the results obtained in this study, it can be concluded that the use of elastography to evaluate LS in patients with COVID-19 can be significantly effective in assessing the status of liver damage and inflammation of liver tissue. Faster identification of patients can provide the appropriate treatment process and improve patient outcomes. Since elastography is an inexpensive, non-invasive tool available, it can be used mainly in most medical centers.

Authors' Contribution
Conceptualization: Masood Faghieh Dinevari.
Data curation: Masoud Hejazi.
Formal Analysis: Samaneh Abbasian.

Study Highlights

What is current knowledge?

- Some studies in patients with COVID-19 have reported an increase in liver function enzymes and liver impairment.

What is new here?

- The use of elastography to evaluate LS in the patients with COVID-19 can be significantly effective in assessing the status of liver damage and inflammation of liver tissue.

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Resources: Ali Riazi.
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Validation: Ali Riazi.
Visualization: Ali Riazi.
Writing – original draft: Masoud Hejazi.
Writing – review & editing: Ali Riazi.

Competing Interests
The authors declare that there is not any conflict of interest.

Ethical Approval
This research was approved by the regional ethics committee of Tabriz University of Medical Science's emergency department with registry no IR.TBZMED.REC (1399.857). All patients' information was kept confidential. Consent was obtained from patients.

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