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What Happens with Liver in Critically ill COVID-19 Patients- Ultrasound and Elastography Findings

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ABSTRACT

The liver is the second potential target organ of COVID-19 after lungs. However, the COVID-19 induced liver injury's definition, clinical importance and even the real existence of a clinically important liver injury during the disease course is still unclear. Therefore, in seeking information about the existence of the liver injury we decided to evaluate sonographic findings and consecutive tissue stiffness alterations with shear wave elastography in critically ill COVİD-19 patients.

A total of 28 critically ill COVID-19 patients from ICU were randomly enrolled in this study between October 2020 and December 2020. US and SWE findings, age, gender, comorbidities, previous liver disease history, aspartate transaminase (AST), and alanine transaminase levels (ALT) were recorded.

A total of 28 participants were included in this study, data for the 19 participants were evaluated. Hepatomegaly was detected in 12 (63%) cases. 2 patients had periportal cuffing while 1 patient had hepatosplenomegaly. The mean liver stiffness value was 4.73 kPa with a reference range between 2.55 and 8.49 kPa. Only one patient's liver stiffness value exceeded normal limits.

The mild increase of liver function biomarkers, the lack of typical sonographic findings for virus-induced hepatitis and lack of any significant increase in tissue stiffness expected in acute hepatitis, are not supporting the previous hypotheses of direct virus-mediated liver damage due to COVID-19. On the contrary, a mild liver injury seen in these patients may be attributed to the collateral liver damage mainly from dysregulated and severe immune response.

Keywords: COVID-19, elastography, liver, spleen

Introduction

Coronavirus Disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has turned into a global public health and socioeconomic problem resulting in almost 6 million deaths worldwide (1–3). While most of the COVID-19 cases are usually presented by mild symptoms of acute respiratory tract infection, a part of infected individuals may become more severely ill, and require intensive medical care.

Besides the pulmonary system, SARS-CoV-2 may target the digestive tract, cardiovascular and even central nervous system. The liver, being the "chemical factory of the body" is second potential target organ of COVID-19 after the lungs. However, the COVID-19 induced liver injury's definition, clinical importance, mechanisms of damage and even the real existence of a clinically important liver injury during the disease course is still unclear.

The protein Spike (S) of SARS-CoV-2, which interacts with expressed ACE2 and TMPRSS2 receptors of a host cell, enables entry of a virus into a human cell. These receptors are expressed in many tissues as lung epithelium, hepatocytes, cholangiocytes, intestine, and endothelium while the expression rate widely varies between tissues (4,5). It has been reported that the expression rate of receptors in hepatocytes is very small compared to biliary system-cholangiocytes, raising the possibility of a tendency to biliary injury during the infection. But surprisingly, in the course of COVID-19, probably due to the up-regulation of hepatocyte receptors in metabolic stress conditions, the increase in hepatocytes markers as aspartate transaminase (AST), and alanine transaminase (ALT) is greater than compared to biliary system markers as gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP) (6,7).

Recently it has been postulated that severe cases of COVID-19 were more likely to have severe liver injury compared to mild cases and that the pre-existing liver disease, cirrhosis-associated

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immune dysfunction, and liver dysfunction have devastating effects on the COVID 19 course and prognosis (8–12). On the other side, liver biochemistry values-which are clinical representatives of liver damage were usually only mildly altered even in severely ill patients and the significance of these tiny alterations and their attribution to liver damage is still doubtful.

Therefore, in seeking additional supportive or exclusionary information about the existence of the liver injury we decided to evaluate sonographic findings and consecutive tissue stiffness alterations with shear wave elastography. It is well established that in chronic and acute liver disease; tissue stiffness may alter due to multiple conditions including inflammatory infiltration, tissue necrosis, edema, accumulation of extracellular matrix, and fibrosis. The recently introduced method of shear wave elastography enables rapid and noninvasively, even bedside, evaluation of tissue stiffness. Also, it has been estimated that liver stiffness shows a trend to increase with the degree of necro-inflammatory activity (13).Therefore, in this study we suggested that if there is liver damage in the course of COVID-19, it should be most pronounced in severe ill-intensive care unit (ICU) patients and the presence of sonographic findings of hepatitis and detection of alterations in tissue stiffness by shear wave elastography may be the evidence of the presence of clinically important liver damage or vice versa.

Material and Methods

Study Population: A total of 28 critically ill COVID-19 patients from our ICU were randomly enrolled in this study between October 2020 and December 2020. COVID-19 SARS-CoV-2 infection was diagnosed by the real-time PCR from nasopharyngeal specimens.

USG and SWE findings (on the 8-12 th days of ICU admission), age, gender, comorbidities, previous liver disease history, aspartate transaminase (AST), and alanine transaminase levels (ALT) (IU/L) (on the day of admission and on the day the USG-SWE imaging was performed) were recorded. The interval between biochemical tests and USG-SWE ranged between 3-12 hours.

Exclusion criterias were: a previous clinical history of liver disease, elevated liver markers on the day of admission (AST; ≥30U/L, ALT; ≥50U/L), and not sufficient SWE procedure.

USG and SWE technique: SWE studies were performed by two experienced abdominal imaging radiologists, each with more than 100 SWE imaging experience prior to the study. B mode US and SWE imaging were performed using a convex transducer probe (C1-6 MHz) with the GE Logiq P9 medical system ultrasound device (GE Healthcare, Chicago, IL, USA). All patients were in a fasting state.

The patients were examined in a supine position with the maximally abducted right arm. The liver was examined in transversal and longitudinal planes. Right hepatic lobe measurements were obtained by the intercostal approach. Liver length (a right lobe length >150mm was considered to be enlarged), parenchymal heterogeneity, periportal cuffing, gallbladder wall thickening, presence of free peritoneal fluid was evaluated.

Subsequently, after the B mode examination, real-time shear wave elastography was performed. SWE measurements were obtained during gentle normal respiration in the same position. Sampling for SWE was performed in the right liver lobe and was defined to be nearly 4-5cm in depth and excluding major vascular structures (Fig. 1). The region of interest (ROI) was considered 1 cm^2. The SWE measurement was considered to have failed when it was impossible to acquire 5 ROIs throughout the whole series of the SWE cine clip. Liver stiffness was given in kilopascal (kPa) and m/s. A value of >7 kPa was considered to be elevated and to reflect liver damage. SWE technical failure was defined as the failure to obtain a color-coded elasticity map with the appropriate stiffness value after at least six trials. To minimize confounding effects due to the operator variability, all US exams were performed by the same radiologist (EB) with over 15 years of experience. The mean examination time for liver imaging was 20±2 minutes.

Interobserver reproducibility: Before the examination of the study group, interobserver reproducibility of shear wave measurements were evaluated. Liver stiffness measurements were performed by both examiners in a healthy cohort consisting of 20 participants referred to our clinic for urinary tract infection or follow-up of a simple renal cyst. Radiologists were blinded to the results. The mean liver stiffness measurement performed by the first radiologist (EB) was 5.2 ± 1.2 kPa, and by the second radiologist was 5.3 ± 1.1 kPa. Inter-observer reliability among readers was very good (95%, CI: 0.816–0.924), with an intra-class correlation coefficient of 0.872 (ICC; two-way mixed-effects model, single measures, absolute agreement; before reassessment).

Statistical analysis: SPSS 26.0 (IBM Corporation, Armonk, New York, United States)

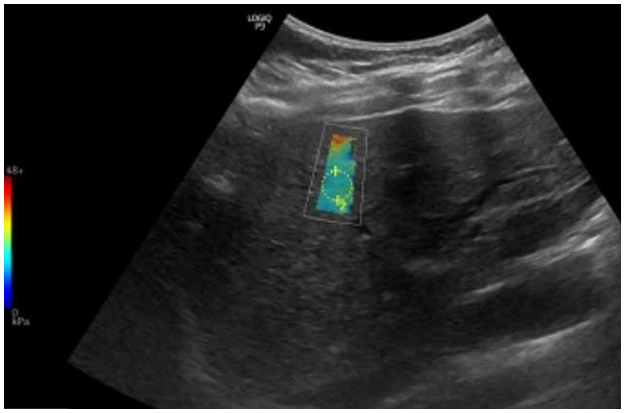

Fig. 1. Quantitative evaluation of liver tissue stiffness with SWE in a 55-year old female patient without underlying liver disease and with normal range of liver stiffness (patient number 8). Sampling was performed in the right lobe and was defined to be nearly 4-5cm in depth, excluding major vascular structures. The region of interest (ROI) was considered 1 cm^2

programs were used in the analysis of the variables. The reference ranges of normal hepatic elasticity were reported in the study to hold on by Petzold et al. (14) as 3.62 to 7.02 kPa; the liver stiffness >7 kPa was considered elevated. Intra-reader agreements were obtained for both imaging techniques using the Cohen-weighted kappa statistic and the intra-class correlation coefficient (ICC). Variables were analyzed at 95% confidence level, and p value less than 0.05 was considered significant.

Ethical Approval: The study was approved by the Regional Ethics Committee, informed consent was obtained from all patients.

Results

A total of 28 participants (M/F= 8/11; mean age 71.4±7.9 years) were included in this study. 9 patients (5 men and 4 women) were excluded from the analysis [three patients for the history of non-alcoholic steatohepatit (NASH), one patient for the history of Hepatitis B, and five patients because of an unsuccessful SWE procedure]. Data for the remaining 19 participants (15 men and 4 women) were evaluated.

At the time of enrolment, no patient showed clinical or biochemical features of fulminant hepatitis. The enlargement of liver size was detected in 12 (63%) cases. 2 patients had periportal cuffing while 1 patient had hepatosplenomegaly. None of the patients showed sonographic signs suggestive of acute hepatitis.

The mean liver stiffness value was 4.73 kPa with a reference range between 2.55 and 8.49 kPa while the mean shear wave velocity was 1.24 m/s. Only one patient's liver stiffness value exceeded normal limits (14). All the results and the demographics were expressed in Table 1.

Discussion

The liver being the "chemical factory of the body" is the very important and also second potential target organ of COVID-19 after lungs. The possible mechanisms of liver injury were proposed as: direct virus-mediated cell damage, virus-induced immune dysregulation leading to cytokine storm and systemic inflammatory response syndrome (SIRS), pneumonia-associated hypoxia, ischemic hepatitis, and drug-induced hepatotoxicity (15). However, the COVID-19 induced liver injury's definition and even the real existence of a clinically important liver injury during disease course is still unclear (16).

While some researchers define liver injury as the liver enzyme levels above the upper limit of normal, other researchers define it as liver enzymes two-three or even 5 times higher than the normal limits (17–20). Therefore, due to the differences in definition and study inclusion criteria, the incidence of liver injury due to the COVID-19 widely varies across studies from 14.8% to 53% (8,21), and in death cases might reach as high as 78% (22). However, there are also several studies stating that there is no difference in the incidence of liver injury between survivors and non-survivors and stating that the clinically significant liver injury is uncommon, even data were selected from the most severely ill patients (21).

The important finding leading to clinical debates about the existence of clinically important liver damage in COVID-19 patients lies in the fact that the alterations of liver biochemistry values were very diminutive in most of the published studies (23,24) which was also confirmed in our critically ill study group whom even in the second week of ICU stay, liver biochemistry values did not exceed 2 times from the normal limits. Do these tiny alterations truly represent direct liver damage or COVID induced viral hepatitis or are just findings of collateral liver damage is still very suspicious. Therefore, in seeking additional supportive or exclusionary information about the existence of the liver injury we decided to evaluate sonographic findings and consecutive tissue stiffness alterations with shear wave elastography in critically ill patients.

Table 1. Patient Characteristics, Biochemistry, Ultrasonography and Shear Wave Elastography Findings

Patient No	Demogaphics			Liver biomarkers*		Sonographic evaluation						Shear wave elastography		Outcome
	Gender	Age	Comorbidity	AST	ALT	Liver size	Starry sky appearance	Periportal cuffing	Gall bladder wall thickening	Enlarged periportal lymph nodes	Spleen size	Liver Elastography kPa	Velosity -m/s	
1	F	80	–	2x	2x	enlarged	–	–	–	–	normal	5,21	1,32	Death
2	F	66	HT,CAD	N	N	enlarged	–	–	–	–	normal	5,2	1,3	recovery
3	M	76	KOAH	2x	N	normal	–	present	–	–	normal	5,46	1,35	recovery
4	F	55	–	N	N	enlarged	–	–	–	–	normal	2,55	0,92	recovery
5	M	75	DM, CAD	2x	N	normal	–	–	–	–	normal	3,88	1,14	Death
6	M	81	–	N	N	enlarged	–	–	–	–	normal	4,44	1,22	Death
7	F	80	COPD, CVE	2x	N	normal	–	–	–	–	normal	5	1,29	Death
8	F	55	DM	N	N	normal	–	–	–	–	normal	5,36	1,34	recovery
9	F	70	CAD	N	N	enlarged	–	–	–	–	normal	4,32	1,2	death
10	F	81	DM	N	N	normal	–	–	–	–	normal	3,67	1,11	death
11	M	80	CAD	N	N	enlarged	–	–	–	–	enlarged	5,48	1,35	death
12	F	71	COPD,DM,HT	N	N	normal	–	present	–	–	normal	8,49	1,68	death
13	M	67	–	N	N	enlarged	–	–	–	–	normal	5,18	1,33	recovery
14	F	75	HT,	N	N	enlarged	–	–	–	–	normal	3,32	1,05	death
15	F	72	HT, DM, CAD	2x	2x	enlarged	–	–	–	–	normal	4,1	1,17	death
16	F	74	HT, CAD	N	N	enlarged	–	–	–	–	normal	6,56	1,48	death
17	M	68	–	N	N	normal	–	–	–	–	normal	5	1,29	death
18	M	60	HT	2x	x2	enlarged	–	–	–	–	normal	3	1	death
19	M	71	CAD, HT, CHF	N	N	enlarged	–	–	–	–	normal	3,79	1,12	death

HT, hypertension; CAD, coronary artery disease; CVE, cerebrovascular event; DM, diabetes mellitus type 2; CHF, congestive heart failure; COPD chronic obstructive pulmonary disease; N, normal; 2x, 2 times of the normal limits; * liver biomarkers on the same day of the US and SWE imaging performed

Despite the role of US in viral liver injury or hepatitis is mostly limited to ruling out surgical causes of jaundice, there are definite sonographic features, which point toward the diagnosis of viral hepatitis as hepatomegaly, gallbladder wall thickening, enlarged periportal lymph nodes, splenomegaly, and periportal cuffing. While the existence of one of these findings alone is non-specific; the presence of two or more strengthen the clinical diagnosis of viral liver injury or hepatitis.

On US imaging, hepatomegaly was detected in 12 (%63), periportal cuffing in two (%10.5), splenomegaly in one (%5.2) of 19 patients, while the other findings as gallbladder wall thickening, enlarged periportal lymph nodes were not detected in any of them. Just one patient (Patient No: 11) had hepatosplenomegaly. Nandi et al. reported the incidence of hepatomegaly during hepatitis as 70% (25) which is very close to our results (67%). On the other hand, liver enlargement as a single sonographic finding (which was detected in 11 patients) is not a specific condition attributable just to viral hepatitis, also being observed in many other diseases but still being the most common finding in cases of acute viral hepatitis. Furthermore, taking into consideration that our study population consists of patients with multiple comorbidities like diabetes mellitus, metabolic syndrome, and congestive heart failure. We think that high rates of liver enlargement reported in our study may be attributed mostly to the aforementioned conditions, not to hepatitis itself. While the incidence of splenomegaly in viral hepatitis, which is mostly attributed to immune complex-mediated conditions, was reported about 10%–20% in previous studies; in our study population the incidence was established as %5 only (26).

Arena et al. reported that in acute liver damage caused by acute hepatitis, the liver tissue stiffness is significantly increased, providing values that have been associated with advanced fibrosis and cirrhosis (>12kPa) also they stated that the level of necro-inflammatory activity has a serious contribution on liver stiffness measurements (27). Therefore, we suggested that if there is significant liver damage in critically ill COVID-19 patients, the stiffness values have to be increased as was reported in a previous study. Surprisingly, even though the study population consisted of critically ill patients, having comorbidities, severe infection, and high mortality rates (%78.9); except for one patient, all other patient's elastography values were within normal limits, not supporting the theory of direct virus-mediated damage leading to acute viral hepatitis.

Our final results demonstrate only the mild increase of liver function biomarkers even in critically ill COVID-19 patient; also the lack of typical sonographic findings for virus-induced hepatitis (hepatomegaly associated with other findings as gallbladder wall thickening, periportal cuffing, starry sky appearance, or enlarged periportal lymph nodes), lack of any significant increase in tissue stiffness expected in high grade of necro-inflammatory activity seen in acute hepatitis; are not supporting the hypothesis of virus-mediated damage leading to acute viral hepatitis in COVID-19. Therefore, we think that mild derangement in liver enzymes in COVİD-19 patients may be explained by the theory previously described by Bangash MN et al. (28) as "a combination of indirect liver injury pathways of collateral liver damage from virally induced cytotoxic T-cells, and a dysregulated and severe immune response leading to multiple organ dysfunction syndromes" (MODS).

Our study has several limitations. First; the study group is very small and heterogeneous. Second, the liver stiffness values were evaluated only once on the expected peak of aminotransferase levels relying on the assumption that the liver stiffness values should be within normal limits in patients without a previous history of liver disease and with normal liver biomarkers on the day of the admission, on the other side, because the estimated range of liver stiffness values in normal subjects is very wide; tiny alterations in liver stiffness values, or any small increase in tissue stiffens falling still within normal limits may be easily overlooked.

The real mechanisms of liver injury in COVID-19 still remain unclear and need further evaluation and studies. But our current findings suggest that liver injury or increase in liver enzymes in COVİD-19 are mostly a combination of indirect liver injury pathways resulting in collateral liver damage from probably virally induced cytotoxic T-cells and dysregulated severe immune response, sometimes leading to multiple organ dysfunction syndrome (MODS) and death.

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Ethical approval for this study was obtained from Hospital's ethics committee.

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