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Does liver density change in computed tomography in COVID-19 patients?

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Abstract

Aim: Corona virus disease 2019 (COVID-19) mainly affects the lungs. However, other organs are affected as well. This article aimed to evaluate the effects of coronavirus infection on liver density in addition to the laboratory findings.

Materials and Methods: Biochemical parameters and non-contrast tomography images of the patients who presented to the pandemic clinic were studied retrospectively. Densities of the right and left lobes of the liver were measured. Patients were divided into two groups according to the results of polymerase chain reaction (PCR) tests.

Results: Our study included 117 PCR (+) and 66 PCR (-) patients. Statistical comparison of the two groups revealed a significant difference in age, densities of the right and left lobes of the liver, and aspartate aminotransferase, gammaglutamyl transferase, total bilirubin, and lactate dehydrogenase values ($p < 0.05$). According to the correlation test, there was a negative correlation between the densities of the right and left lobes of the liver and transaminases.

Conclusion: An inverse relationship emerged between liver density and transaminases. Therefore, liver functions should be monitored more closely in COVID-19 patients during treatment, and if it is at high levels, treatment should be started early.

Introduction

Coronavirus disease first appeared in the Wuhan region of China in December 2019 and has spread all over the world. A pandemic was declared in March 2020. Although the main clinical picture is acute respiratory failure in patients diagnosed with COVID-19, liver damage/dysfunction has also been reported. The cause of liver damage is not yet known. However, currently COVID-19-related liver injury/dysfunction can be attributed to viral infection, hypoxia, systemic inflammatory response, use of hepatotoxic drugs. Liver damage in patients infected with COVID-19 is usually manifested by mild or moderately elevated transaminase levels. Significantly increased enzyme levels have also been reported [1-4]. Radiological examinations are of great importance in the early diagnosis of COVID-19. Although the results of thin-section thoracic computed tomography (CT) reverse transcriptase polymerase chain reaction (RT-PCR) test are negative, it can be diagnosed with imaging findings. On tomography, liver density changes most in diseases that may affect the liver diffusely, such as fatty liver and acute viral infections [5, 6, 7]. To our knowledge, there are few articles in the literature evaluating changes in liver density after COVID-19 infection. Therefore, in this study, we aimed to compare CT findings, biochemical parameters and liver density measurements of patients diagnosed with COVID-19 with the control group.

Material and Methods

Patients who applied to our hospital's Pandemic Outpatient Clinic between March 2020 and June 2020 and underwent PCR test and thoracic CT due to suspected COVID-19 were included in the study. No antiviral treatment was applied to the patients. The tomography images taken at the first admission were reviewed retrospectively. There were 117 PCR positive (+) patients in Group 1 with or without CT findings, and 66 PCR and CT negative (-) control group patients in Group 2. The median age was 44(15-98) in group 1 and 40(23-67) in group 2. Of the patients in Group 1, 59 (50.4%) were female and 58 (49.6%) were male. In group 2, there were 26 (39.4%) women and 40 (60.6%) men. Patients with a

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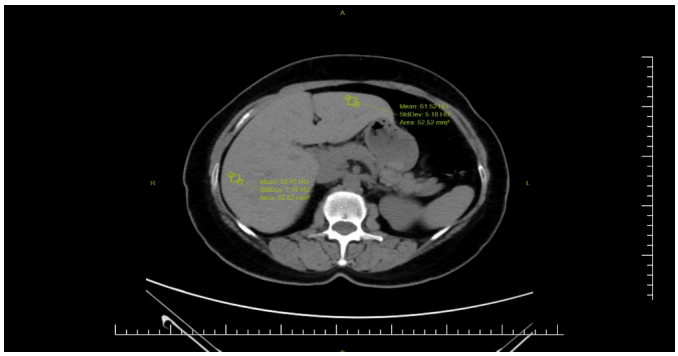

Figure 1. Measurement of liver density in a PCR (−) patient

history of liver disease, discordant PCR test and radiological findings, suspected COVID-19 diagnosis, and medical treatment with COVID-19 were excluded from the study. After obtaining the necessary legal permissions, radiological and laboratory data were obtained retrospectively through the patient information system (For this article Firat University Non-Interventional Research Ethics Committee Date: 12/06/2020 Issue: 2020/ 09-15). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gammaglutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin, direct bilirubin and lactate dehydrogenase (LDH) levels, as well as the densities of the right and left lobes of the liver were recorded in all patients. Imaging was performed using a single scanner (Philips Healthcare, Ingenuityelite, The Netherlands) with the patient in the supine position during inspiration without intravenous (IV) contrast material. The CT protocol is as follows: 120 kV; automatic tube current 100–200 mA; 128mm detector; slice thickness 2-5 mm. Image analysis was performed using an institutional digital database system. The densities of the right and left lobes of the liver were measured in Hounsfield Unit (HU) from the thoracic tomography images taken according to this protocol. Measurements were made by a single radiologist. Measurements were made by placing a 10 mm diameter ROI on the liver parenchyma corresponding to the rib level (shown in Figure 1, 2). Statistical analyzes were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc, Chicago, IL). The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk test. Data were compared statistically between groups using the Mann-Whitney U test. Descriptive data were presented as median (min-max). Spearman correlation coefficient method was used to evaluate the correlation. Qualitative data were analyzed using the Pearson chi-square test, while descriptive statistics were presented as frequency and percentage. The significance level for all tests was determined as 0.05.

Results

Group 1 included 59 (49.6%) female patients and 58 (50.4%) male patients and the Group 2 included 26 (39•4%) female patients and 40 (60.6%) male patients. There was no significant difference in terms of sex between the groups (p = 0•151). The mean age of the patients was 44 (15–98) in Group 1 and 40 (23–67) in Group 2. The statistical comparison of the two groups in terms of their age revealed a significant difference between them. Ad-

Table 1. Comparison of PCR (+) and (−) patient groups.

Variables median (min–max)	Group 1 (n = 117)	Group 2 (n = 66)	p* value
Age (years)	44 (15–98)	40 (23–67)	0.009
Right Lobes Densities (HU)	55 (26–80)	59 (37–81)	0.002
Left Lobes Densities (HU)	56 (9–88)	62 (39–85)	< 0.001
Aspartate Aminotransferase (U/L)	27 (14-107)	21 (10–46)	< 0.001
Alanine Aminotransferase (U/L)	22 (9–197)	19•5 (8–47)	0.288
Gammaglutamyl Transferase (U/L)	26•5 (9–303)	20 (8–140)	0.049
Alkaline Phosphatase (U/L)	75•5 (38-157)	80 (47-180)	0.285
Total Bilirubin (mg/dl)	0•45 (0•18-1•75)	0•52 (0•2–2•9)	0.049
Direct Bilirubin (mg / dl)	0•1 (0•04–0•4)	0•11 (0•04-0•43)	0.395
Lactate Dehydrogenase (U/L)	66 (144–420)	192•5 (127–365)	< 0.001

*: Mann-Whitney U test

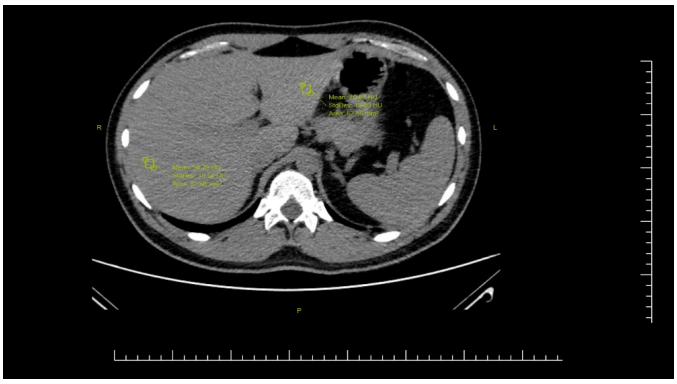

Figure 2. Measurement of liver density in a PCR (+) patient

Table 2. Correlation coefficients between liver density and transaminase levels.

	AST	ALT
Right Lobes Densities	r = −0.222 p = 0.016	r = −0.415 p = <0.001
Left Lobes Densities	r = −0.249 p = 0.007	r = −0.465 p = <0.001

ditionally, there was a significant difference between the groups in terms of the densities of the right and left lobes of the liver and values of AST, GGT, total bilirubin, and LDH (Table 1). The density of the right lobe of the liver was 55 (26–80) HU in Group 1 and 59 (37–81) HU in Group 2. The density of the left lobe of the liver was 56 (9–88) HU in Group 1 and 62 (39–85) HU in Group 2. Pearman's correlation test, which was used to evaluate the presence of correlation between the densities of the right and left lobe of the liver and transaminases, demonstrated the presence of a negative correlation between liver density and transaminases (Table 2).

Discussion

The newly emerged COVID-19 has become a global threat. This newly identified virus has a high level of genome sequence similarity with previously identified SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) viruses. All three of these coronaviruses are known to cause serious respiratory diseases. In addition, varying degrees of liver damage have been reported in the literature in patients infected with these three coronavirus families [3, 8]. In published articles, it is reported that 14-53% of COVID-19 patients develop liver damage during the course of the disease. As a result, abnormal AST and ALT levels are observed during clinical trials. Liver dysfunction is more common in males than females [9-11]. In our study, no statistically significant difference was observed in terms of gender. We think that the significant age difference between the two groups is due to the more severe course of COVID-19 in patients with advanced age and comorbidities. Huang et al. liver damage has been reported more frequently in patients with comorbidity and severe COVID-19 [1]. Another study showed that patients with severe COVID-19 had a higher rate of abnormal liver transaminase levels than patients with mild disease. In another study, COVID-19 patients diagnosed early by CT scan had less frequent transaminase disorders than those diagnosed after symptom onset [12]. Therefore, liver damage is observed more often in severe cases than in mild cases. In the patient population in our study, transaminase levels did not increase due to testing of radiological and laboratory parameters at the time of admission to the hospital. Therefore, an increase in this parameter exceeding five times the normal limit was not observed in any of the patients. The mechanism of liver dysfunction due to COVID-19 is not fully known. Like other SARS-CoV viruses, COVID-19 uses the ACE2 receptor as a cell entry receptor. Chai et al. found that both hepatocytes and cholangiocytes have ACE2 receptors. However, ACE2 expression in cholangiocytes is much higher than in hepatocytes [13, 14, 15]. The GGT showing cholangiocyte damage was significantly different in our study, as was the case in epidemiological studies of current COVID-19 cases. In the pathological examinations of the liver tissue of SARS-CoV patients, the virus was isolated but no inclusion bodies were detected. Virus could not be isolated in patients with MERS. However, pathological analysis of liver tissue from a patient who died from COVID-19 did not show the presence of viral inclusions in the liver [14, 16]. These results suggest that liver damage in COVID-19 patients may result from cholangiocyte damage due to virus infection. The significant difference in GGT and bilirubin levels detected in our study supports cholangiocyte damage in the liver. It is also possible for liver damage to result from drug hepatotoxicity. Therefore, our patients were selected from the first application. The patients did not receive any antiviral treatment. Therefore, drug toxicity is not important in our patients. In addition, immune-mediated inflammation that causes hypoxia may also contribute to liver damage and progression to liver failure in critically ill COVID-19 patients [17, 18]. However, none of our patients were in intensive care or experienced severe hypoxia, eliminating these possibilities. Liver density measurement with tomography is used especially in acute viral hepatitis and diseases that cause fatty liver that affects the liver diffusely. Although biopsy is the main diagnostic method for liver fat, inflammation and fibrosis, it is sometimes not applicable because it is not invasive and economical. In cases where biopsy cannot be performed, radiological and biochemical findings are helpful. In these diseases, elevation in transaminases and decrease in liver density are inversely proportional to each other and is the main indicator of damage. In a study evaluating the common CT findings of COVID-19 patients, the most common findings were liver hypodensity and pericholecystic fat streaking. Although these findings are also seen in fatty liver and acute hepatitis, other findings such as hepatomegaly, splenomegaly, gallbladder wall edema, periportal edema and lymphadenopathy, bile duct dilatation, ascites have not been encountered in COVID-19 patients [6]. These findings indicate that there is an inflammation and damage to the liver in patients with COVID-19. In a study that evaluated pathologically in COVID-19 patients, Xu et al. reported moderate microvascular lubrication and mild inflammation in the portal region. According to autopsy results, it has been shown that the virus does not have a direct lethal effect on liver cells [16]. The limitations of our article are that it is retrospective and the number of patients is small.

Conclucion

As a result, liver function tests should be checked in patients diagnosed with COVID-19. In mild cases of COVID-19, liver damage usually does not require treatment. However, it would be appropriate to start hepatoprotective treatment as soon as possible in patients with serious illness and in need of intensive care. Larger and molecular studies are needed to explain the cause of liver damage.

Ethics approval

Approval was obtained from Firat University Non-Interventional Research Ethics Committee for this article. Date: 12/06/2020 No: 2020/09-15

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