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ORIGINAL ARTICLE

Transient Aggravating Effect of COVID-19 Disease on Liver Function Parameters of Patients Hospitalized in the Intensive Care Unit

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Abstract

Introduction: In late December 2019, China's local office of the World Health Organization (WHO) reported a case of pneumonia of unknown cause in Wuhan City. In January 2020, the disease caused by 2019-nCoV was defined as COVID-19. Some reports stated that more than half of COVID-19 patients have liver disease of varying degrees. We hypothesized that liver injury might be common in Intensive Care Unit (ICU) patients. The current study scrutinized the changes in the liver function tests alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin in patients with and without COVID-19 admitted to the ICU at University Hospital.

Methods: There were 100 patients diagnosed with COVID-19 and 80 non-COVID-19 patients who were admitted to the ICU in this retrospective study. The study was conducted between March 15, 2020, and November 15, 2021 (20 months). Inclusion criteria for the control (n=80) and study groups (n=100) were to be older than 18 years of age and not have any liver disease. In addition, another inclusion criterion for the study group was having a diagnosis of COVID-19. AST, ALT, and total bilirubin results were obtained from a data recording system named "Pusula" used in Medipol Mega University Hospital. Data was analyzed by GraphPad Prism v. 5.0 statistical program, and $p<0.05$ was considered statistically significant.

Results: Findings demonstrated that ALT and AST levels were significantly higher in patients with COVID-19 when compared with patients without COVID-19 ($p<0.05$). Total bilirubin was also observed as elevated in patients with COVID-19. However, this elevation was not significant ($p>0.05$).

Discussion and Conclusion: In conclusion, it can be stated that COVID-19 may cause hepatosteatosis resulting in liver damage. However, further studies are needed to elucidate possible mechanisms of liver injury in COVID-19 patients and their significance for clinical prognosis.

Keywords: ALT; AST; COVID-19; Intensive Care Unit; Liver Function Tests; Total Bilirubin.

COVID-19 disease is caused by SARS-CoV-2, and the main cause of mortality and morbidity in this disease is acute viral pneumonia resulting in acute respiratory distress syndrome (ARDS)[1]. Respiratory symptoms are the most commonly reported manifestation of COVID-19; however, SARS-CoV-2 can also affect the gastrointestinal tract and liver[2]. Binding of SARS-CoV-2 to the ACE-2 receptor is hypothesized to be the primary mechanism of hepatic injury. The ACE-2 receptor is mostly expressed in cholangiocytes[3]. It was reported that the SARS-CoV-2

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virus can cause cholangiocyte dysfunction by binding to ACE-2 on cholangiocytes and triggering an inflammatory response systemically that causes hepatic damage[4].

Elevated liver enzymes were found in 16.1% to 53.1% of patients infected with SARS-CoV-2[5]. Most cases of COVID-19 have been described as mild, but more serious diagnoses have resulted in respiratory insufficiency, septic shock, and/or multi-organ failure[6]. COVID-19 may exacerbate underlying chronic liver illness and cause acute and chronic liver damage[7]. While many cases of COVID-19 recovered acutely and rapidly, they also had a mortality rate of about 3%. In addition, about a third of patients infected with SARS-CoV-2 became seriously ill and required intensive care[8]. Patients with critical ailments, especially those requiring admission to the intensive care unit (ICU), tend to have higher transaminase elevations[9,10].

The current study scrutinized to compare the liver function tests like transaminases (ALT, AST) and total bilirubin in patients with and without COVID-19 hospitalized in the ICU.

Materials and Methods

Study Design

The current study was designed retrospectively and performed in the ICU of the Mega Medipol University Hospital. In this study, liver function test results of patients with and without COVID-19 hospitalized in the ICU of the hospital between 15 March 2020 and 15 November 2021 (20 months) were examined only on the hospitalization day. Inclusion criteria for the study group (n=100) were being over 18 years old, diagnosed with COVID-19, and having no liver disease. In addition, inclusion criteria for the control group (n=80) were being over 18 years old, not diagnosed with COVID-19, and having no liver illness. This study was conducted in accordance with the Helsinki Declaration.

Data Collection

This retrospective study was approved by the local ethics committee of Istanbul Medipol University on 25 November 2021 (1161/2021) after obtaining permission from the Republic of Türkiye Ministry of Health on 16 November 2021. Data collection was done after obtaining the required permission and approval. Demographic characteristics were determined. Aspartate transaminase (AST), alanine transaminase (ALT), and total bilirubin levels of 180 patients were analyzed with a Roche Cobas C503 (Argen) device, a fully automated photometric analyzer for a large array of quantitative and qualitative *in vitro* tests. The device can analyze parameters related to fields of cardiology, endocrinology, gastroenterology, neurology, urology, hepatology, hematology, pulmonology, and oncology. Obtained data was stored in the data recording system named "Pusula" used in Medipol Mega University Hospital.

Statistical Analysis

GraphPad Prism v 5.03 (GraphPad Software Inc., La Jolla, CA) was used for the statistical analysis. Because there were two groups in this study, data were analyzed by the Student's t-test in order to compare them. In addition, correlation tests were done between the liver function tests in patients with COVID-19. $P<0.05$ was considered statistically significant, and exact p values were presented.

Results

Demographic Data

There were 100 and 80 patients in the ICU with and without COVID-19 diagnosis, respectively. The findings showed that the majority of all patients were between the ages of 60-69 and 70-79. Of the 180 patients included in the current study, 43.3% were women and 56.7% were men. Findings are shown in Table 1.

Liver Function Tests

While evaluating the hepatic parameters of the patients with and without COVID-19, significant changes were determined. Findings demonstrated that ALT and AST levels were found essentially elevated in patients with COVID-19 than those in patients without COVID-19, p=0.006 and p=0.0121, respectively. However, the total bilirubin level increased in patients with COVID-19 compared to patients without COVID-19, but this increase was not significant

Table 1. Age and sex demographics of patients

	Number	%
Age		
19-29	9	5
30-39	9	5
40-49	15	8.33
50-59	24	13.33
60-69	44	24.44
70-79	49	27.22
80-89	24	13.33
90-99	6	3.33
Sex		
Female	78	56.7
Male	102	43.3

Table 2. Liver function tests of patients

	AST	ALT	T. Bilirubin
COVID-19 (mean)	341.5	240.1	1.618
NON-COVID-19 (mean)	45.6	36.85	1.134
Difference between means±SEM	550.9±130.1	203.3±73.02	0.4842±0.5363
p value	0.0121	0.006	0.3678

AST: Aspartate transaminase; ALT: Alanine transaminase; T. Bilirubin: Total Bilirubin; SEM: Standard Error of Mean.

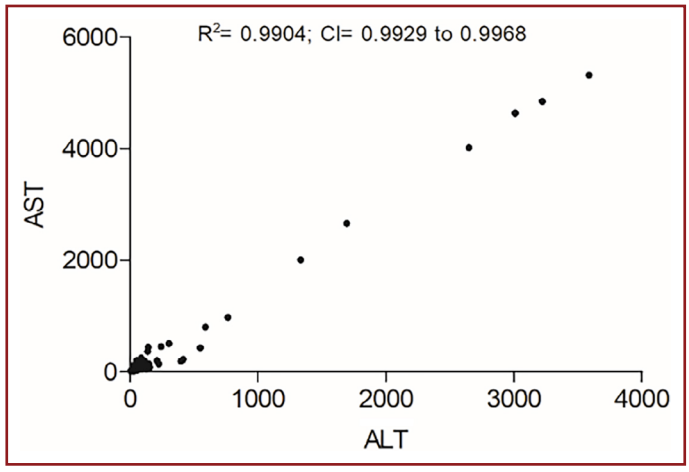

Figure 1. Correlation between ALT and AST.

R^2: Determination coefficient; CI: Confidence interval; AST: Aspartate transaminase; ALT: Alanine transaminase.

(p=0.3678). Results are given in Table 2.

In addition, correlation analyses were performed between AST, ALT, and total bilirubin levels in COVID-19 patients with a confidence interval (CI) of 95%. The findings showed that there was a positive correlation between ALT and AST (R^2=0.9904; CI=0.9929 to 0.9968), as given in Figure 1. However, there were no correlations between AST and total bilirubin or ALT and total bilirubin, respectively.

Discussion

The broad distribution of ACE-2 facilitates its outcome, SARS-CoV-2, as a systemic illness that can affect almost all vital organs. ACE-2 has been identified as a functional receptor for the entry of the SARS-CoV-2 virus into host target cells, and it has a direct cytopathic effect. Although ACE-2 mRNA is known to be present in almost all organs, its protein expression is unknown[11].

It is well known that steroids, antivirals, and antibiotics were used in the treatment of SARS and MERS. Similarly, these drugs are preferred to treat COVID-19 infection. While it is known that these drugs can cause liver damage, there is currently little evidence that they impair liver function in COVID-19 patients. In fact, a recent study demonstrated that antiviral drugs such as lopinavir/ritonavir used to treat COVID-19 patients may cause a loss of hepatic function[12].

Most infected patients with COVID-19 are asymptomatic, or a small proportion of patients with mild to moderate disease develop severe symptoms with shortness of breath. To confirm lung damage, pulmonary tests are suggested[13]. It shows significant abnormalities in the involvement of other organs, including heart and liver damage. In a different study, it was reported that liver function test abnormalities occur in 14% to 53% of COVID-19 patients, and these abnormalities are more common in ICU patients[14].

In a previous study, Wang et al.[15] suggested that ACE-2 localization did not fully explain SARS-CoV-2 hepatotropism. They stated that further studies were needed on how and to what extent SARS-CoV-2 infection contributes to liver enzyme abnormalities in different COVID-19 populations. It is well known that there are various mechanisms of liver injury. Hepatic injury may mainly occur as a result of viral hepatitis[16], changes in the gut barrier and microbiome[17], intensive care therapy[18], or drug toxicity[19].

In a study, it was observed that the prevalence of loss of liver function was crucially high in hospitalized COVID-19 patients. In addition, most of the patients had hepatic dysfunction at presentation and required intensive care and mechanical ventilation[20]. In a different previous cross-sectional study, Kaushik et al.[21] indicated the prevalence of liver function test disorders as 59.04%. In general, the incidence of increased serum liver function tests, particularly elevated transaminase levels, and mildly increased bilirubin levels in hospitalized COVID-19 patients ranges from 14% to 53%[22]. In a previous study, SARS infection was reported to cause hepatic damage resulting in mild to moderate elevations in ALT and/or AST levels. It has been shown that ACE-2 acts as a membrane surface receptor for SARS-CoV cell entry. In different studies, ACE-2 was noted to be mostly expressed in various cell types, including lung type II alveolar cells (AT-2), as well as monocytes and vascular endothelial cells[14,23].

The incidence of liver damage, as evaluated by serum analysis (AST, ALT, total bilirubin, and albumin levels), appears to be elevated in COVID-19 patients. While aminotransferase levels may be normal or slightly raised in mild cases of the virus, higher elevations were demonstrated in more serious cases[24]. In a previous study, it was reported that hepatocyte damage in the early stages of the disease increases serum AST and ALT levels. However, it was determined that ALP, GGT, direct and total bilirubin levels increased more in cholestatic-type liver damage due to the faster progression of the disease[25]. In addition, liver abnormalities with elevated AST, ALT, and GGT levels were prominent in COVID-19, whereas changes in ALP and bilirubin levels have been shown to be relatively rare[26].

The most important limitation of this study was the study population. The current study was conducted in a hospital with limited intensive care capacity for COVID-19 patients. In addition, the requirement to have no previous liver disease was the most restrictive inclusion criterion. Therefore, even if the study period appeared long, the number of patients meeting the study criteria was not as high as expected.

Conclusion

The observed findings of the current study, consistent with the findings of previous studies, suggest that deterioration in liver function tests in patients with COVID-19 infection depends on the severity of hepatic injury. While transaminase levels were slightly elevated in mild to moderate patients, liver function tests were crucially elevated, especially in patients with severe prognosis hospitalized in the ICU. In this view, this study reveals that it is vital to monitor patients' liver function tests frequently and regularly throughout their treatment in the ICU.

Ethics Committee Approval: The study was approved by the Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (no: 1161, date: 25/11/2021).

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Conflict of Interest: None declared.

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