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ORIGINAL ARTICLE

# Evaluation of Liver Damage in COVID-19 Patients Followed in The Intensive Care Unit

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## Abstract

**Introduction:** In coronavirus disease 2019 (COVID-19), liver injury has been associated with the direct cytopathic effect on cholangiocytes, an uncontrolled immune response, sepsis, or drug-induced liver injury. This study aimed to evaluate liver damage in COVID-19 patients in the intensive care unit.

**Methods:** Between January 1, 2021, and June 1, 2021, medications, mortality rates, length of stay in the intensive care unit, liver function tests, and acute phase reactants, during admission to the unit and on the 3rd, 7th, and 15th days of follow-up were analyzed retrospectively.

**Results:** A total of 92 patients were included in the study. In a mean follow-up of 2 weeks, ALT levels increased by 62%, AST levels increased by 78.3%, GGT levels increased by 65.2%, ALP levels increased by 43.5%, and total bilirubin levels increased by 20.7% of the patients were observed. In repeated measurements of the patients, significant increases were observed in ALP (p=0.013), GGT (p=0.001), and bilirubin levels (p=0.012). Thirty-six patients resulted in mortality, and in patients who died, AST (p=0.02), day 15 AST (p=0.02), GGT (p=0.02), and ALP (p=0.009) values were observed to be significantly high. There was no relationship between CRP and IL-6 levels, transaminases, and cholestasis enzymes. When the patients who received and did not receive favipiravir treatment were compared, there was no difference other than the 3rd day AST (p=0.043) value.

**Discussion and Conclusion:** Increases in cholestasis enzymes were detected in the 15-day follow-up of patients admitted to the intensive care unit due to severe COVID-19. Furthermore, it was observed that the transaminase and cholestasis enzymes of the patients who ended in mortality were higher. In addition, liver enzymes were at similar levels between patients who received and did not receive favipiravir treatment.

**Keywords:** Cholestase enzymes; COVID-19; Favipiravir; Liver injury; Transaminases.

The SARS-CoV-2 virus, which caused the coronavirus disease 2019 (COVID-19), launched a global pandemic in a relatively short time and is continuously generating new mutations. Although COVID-19 is most commonly associated with a lower respiratory tract infection, it can also appear in the gastrointestinal and hepatic systems[1]. The host cell receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2), located in alveolar cells, the gastrointestinal system, and the liver[2]. The ACE2 cell surface receptor was more abundant in cholangiocytes than in hepatocytes. ACE2 expression in cholangiocytes was comparable to that in type 2 alveolar cells in the lungs, suggesting that SARS-CoV-2 could target the liver[3,4]. Hepatobiliary damage can be caused by cholangiocyte dysfunction, and higher gamma-glutamyl transferase (GGT) levels have been identified in part of the COVID-19 case series[5,6]. However, in the pathological analysis of postmortem liver tissue during the COVID-19 pandemic, viral inclusions in the liver could not be demonstrated[7]. The liver is a critical organ for drug detoxification and is the target for the metabolism of drugs used during the treatment of COVID-19. The cause of liver damage in

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COVID-19 may be related to drug-induced liver injury, the direct cytopathic effect of the virus on cholangiocytes, an uncontrolled immune response, and sepsis[8].

Impaired liver function tests in hospitalized COVID-19 patients range from 14% to 83%[6,9-11]. In severe cases of COVID-19, liver damage is more common than in mild cases[5,10-12]. At the beginning of the primary disease process, there were transaminase levels 1-2 times the upper reference limit of normal, and substantially high total bilirubin levels[10,11]. Elevated levels of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) have been shown in COVID-19 patients[13]. Age, male gender, obesity, diabetes, medications, and inflammatory markers have all been implicated as predictors of increased abnormal liver tests[10,11]. Although the ACE2 level is highly observed in the biliary epithelium, the evaluation of liver damage by transaminase elevations in the literature has led to the need for a more detailed assessment of the relationship between cholestasis enzymes (ALP/GGT) and COVID-19.

Patients with COVID-19 have abnormal levels of acute-phase reactants, and in some case series, these markers have been shown to be risk factors for liver injury[5,14,15]. Considering the severe clinic of the patients in intensive care patients, it is thought that the correlation of inflammatory parameters with liver damage may be stronger, and studies are needed on this subject.

The pooled incidence of drug-induced liver injury in COVID-19 patients was 25.4% and was associated with lopinavir/ritonavir and remdesivir[13]. In our country, primarily favipiravir-based regimens have been used as an antiviral for COVID-19. Data on favipiravir and hepatotoxicity are very limited. It can cause elevations of transaminases, and there have been recently published case reports of it rarely causing cholestatic hepatitis[16].

This study aimed to assess liver damage in COVID-19 patients who were followed in the intensive care unit.

## Materials and Methods

Our study was conducted between January 1, 2021, and June 1, 2021. We retrospectively included critically ill patients over 18 with laboratory-confirmed newly diagnosed SARS-CoV-2 infection in the Anesthesia and Reanimation Intensive Care Unit (ICU) who were not followed up in an external center before. Demographic data (age, gender), liver function tests (ALT, AST, GGT, ALP, total bilirubin), acute phase reactants (C-reactive protein, IL-6, procalcitonin, and ferritin), and drugs the patients were using were recorded. Patients' death, discharge, hospitalization, hospital stay, and clinical conditions due to SARS-CoV-2 infection were also examined. Excluded from the study were children (under 18 years of age), patients not followed up in the intensive care unit due to COVID-19, patients who were previously treated for COVID-19 in an external center and referred, those with chronic heart failure, chronic hepatitis B and C, chronic liver disease, regular alcohol use, and pregnant women.

IBM SPSS 22.0 (Armonk, NY, USA) was used for data analysis. The Chi-Square test was used to determine statistical correlations between categorical data. For non-normally distributed variables, the Mann-Whitney U test was utilized. Two independent group ratio tests were used to compare ratios between the two groups. Related samples - the Friedman test was used to compare the values on days 0, 3, 7, and 15. The correlation between numeric variables evaluated with Spearman correlation analysis.

Approval was received from the Ethics Committee for Non-Interventional Clinical Research of the Faculty of Medicine of Pamukkale University (protocol no:10.150.1.90/106832, date of approval: 24.06.2021). The study protocol complies with the ethical criteria of the 1964 Declaration of Helsinki.

## Results

A total of 92 patients were included in the study. Sixty patients were male, and 32 were female. The median age of the patients was 69. When the data of all patients were analyzed retrospectively, it was observed that 56 patients were discharged from the intensive care unit, and 36 patients died. The distribution of patients by age, gender, favipiravir use, and mortality is shown in Table 1.

In the mean follow-up period of 2 weeks (minimum seven days, maximum 30 days) of all patients in our intensive care unit; an

**Table 1.** General characteristics of the patients

| | n | % |
|---|---|---|
| Gender | | |
| Female | 32 | 34.8 |
| Male | 60 | 65.2 |
| Age | | |
| <69 | 47 | 51 |
| >69 | 45 | 49 |
| Favipiravir | | |
| Received | 70 | 76.1 |
| Not Received | 22 | 23.9 |
| Mortality | | |
| Exitus | 36 | 39.1 |
| Alive | 56 | 60.9 |

ALT increase was observed in 62% (57 patients), AST increase in 78.3% (72 patients), GGT increase in 65.2% (60 patients), ALP increase in 43.5% (40 patients), and total bilirubin increase in 20.7% (19 patients). Non-parametric Spearman correlation of ALT, AST, GGT, ALP, bilirubin, and CRP values were examined on the same days. Transaminases and cholestasis enzymes were significantly correlated, and the CRP value was not correlated with these values at any time (Table 2).

**Table 2.** Correlation analysis of liver enzymes, bilirubin and CRP values determined on the same day

| | ALT | AST | GGT | ALP | BIL |
|---|---|---|---|---|---|
| 0th day | | | | | |
| AST | **r=0.596** | | | | |
| | **p<0.001** | | | | |
| GGT | **r=0.484** | **r=0.230** | | | |
| | **p<0.001** | **p=0.027** | | | |
| ALP | **r=0.430** | r=0.085 | **r=0.556** | | |
| | **p<0.001** | p=0.422 | **p<0.001** | | |
| BIL | r=0.200 | r=0.038 | **r=0.255** | r=0.009 | |
| | p=0.056 | p=0.716 | **p=0.014** | p=0.934 | |
| CRP | r=-0.002 | r=0.188 | r=-0.065 | r=-0.096 | r=-0.003 |
| | p=0.984 | p=0.072 | p=0.536 | p=0.363 | p=0.975 |
| 3rd day | | | | | |
| AST | **r=0.649** | | | | |
| | **p<0.001** | | | | |
| GGT | **r=0.540** | **r=0.367** | | | |
| | **p<0.001** | **p<0.001** | | | |
| ALP | **r=0.277** | r=0.083 | **r=0.473** | | |
| | **p=0.007** | p=0.432 | **p<0.001** | | |
| BIL | **r=0.350** | **r=0.327** | **r=0.223** | r=0.189 | |
| | **p=0.001** | **p=0.001** | **p=0.032** | p=0.071 | |
| CRP | r=-0.192 | r=0.034 | r=-0.016 | r=0.17 | r=0.128 |
| | p=0.067 | p=0.748 | p=0.88 | p=0.104 | p=0.224 |
| 7th day | | | | | |
| AST | **r=0.686** | | | | |
| | **p<0.001** | | | | |
| GGT | **r=0.521** | **r=0.452** | | | |
| | **p<0.001** | **p<0.001** | | | |
| ALP | **r=0.299** | **r=0.222** | **r=0.418** | | |
| | **p=0.004** | **p=0.033** | **p<0.001** | | |
| BIL | **r=0.270** | **r=0.339** | r=0.171 | r=0.053 | |
| | **p=0.009** | **p=0.001** | p=0.103 | p=0.616 | |
| CRP | r=-0.175 | r=0.18 | r=0.054 | r=0.168 | r=-0.006 |
| | p=0.096 | p=0.086 | p=0.609 | p=0.108 | p=0.953 |
| 15th day | | | | | |
| AST | **r=0.598** | | | | |
| | **p<0.001** | | | | |
| GGT | **r=0.551** | **r=0.380** | | | |
| | **p<0.001** | **p=0.002** | | | |
| ALP | **r=0.262** | **r=0.344** | **r=0.440** | | |
| | **p=0.04** | **p=0.006** | **p<0.001** | | |
| BIL | **r=0.451** | **r=0.273** | **r=0.337** | r=0.177 | |
| | **p<0.001** | **p=0.032** | **p=0.007** | p=0.168 | |
| CRP | r=-0.246 | r=0.227 | r=-0.064 | r=0.074 | r=0.028 |
| | p=0.054 | p=0.076 | p=0.622 | p=0.57 | p=0.832 |

Correlation analyzes were performed with Spearman test; Statistically significant values (p<0.05) are shown in bold; ALT: Alanine Aminotransferase. AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase. ALP: Alkaline Phosphatase. BIL: Total Bilirubin.

When hepatobiliary enzymes were compared on days 0, 3, 7, and 15 of the patients, no difference was found in ALT between days (p=0.116). The measurement in which AST was determined the highest was the 0th-day measurement, and a decrease was observed in the following days (p=0.04). GGT levels increased significantly in every measurement (p=0.001). ALP levels were close to each other in the 0th and 3rd-day measurements, and a significant increase was detected on the 15th day (p=0.013). A significant increase was observed in bilirubin levels between days 3 and 7 (p=0.012), and there was no significant difference between the other days (Fig. 1).

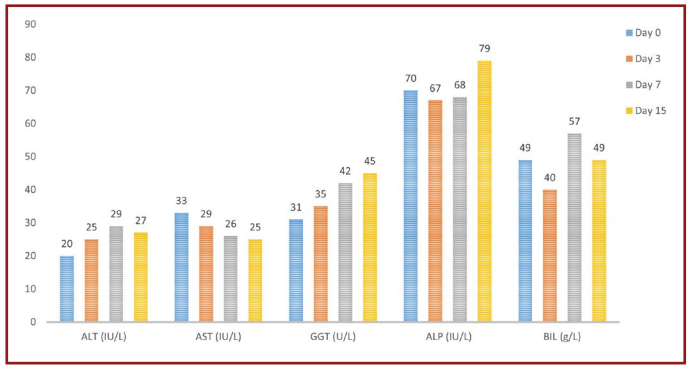


**Figure 1.** Mean liver function tests in all patients. (Bilirubin levels are shown as g/L for visual adaptation).

No correlation was found between IL-6 level and transaminases and cholestasis enzymes. ALT and AST values were significantly higher on days 0 and 3 in those with high ferritin levels at admission to the ICU (ALT p=0.003, 0.018; AST p=0.048, 0.032, respectively).

Seventy patients were divided into the group that received favipiravir treatment, and 22 patients were divided into those that did not receive favipiravir treatment. When the transaminases and cholestasis enzymes of the patients who received and did not receive favipiravir treatment were compared, no significant difference was found in the follow-up except for the AST measured on day 3 (p=0.043). Median liver function test values according to gender, mortality, and favipiravir use are summarized in Table 3.

When the relationship between ICU mortality and liver enzymes was examined, it was observed that 7th day AST

**Table 3.** Median Liver function test values by gender, mortality, and Favipiravir use.

| | Gender | | | Mortality | | | Favipiravir | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Female Median (Min-Max)** | **Male Median (Min-Max)** | **p level** | **Exitus Median (Min-Max)** | **Living Median (Min-Max)** | **p level** | **Not-Received Median (Min-Max)** | **Received Median (Min-Max)** | **p level** |
| ALT 0th day (IU/L) | **17.5 (2-403)** | **23.5 (5-165)** | **0.031** | 21.5 (2-403) | 19 (5-165) | 0.971 | 18 (5-105) | 22 (2-403) | 0.492 |
| AST 0th day (IU/L) | **23.5 (6-676)** | **35 (6-105)** | **0.015** | 33 (9-676) | 32.5 (6-98) | 0.282 | 28.5 (6-96) | 33 (9-676) | 0.341 |
| GGT 0th day (IU/L) | 34.5 (5-149) | 29.5 (10-307) | 0.787 | 34 (5-282) | 27.5 (7-307) | 0.792 | 35 (10-279) | 31.5 (5-307) | 0.392 |
| ALP 0th day (IU/L) | 75.5 (40-152) | 67.5 (25-954) | 0.210 | 66.5 (25-954) | 70.5 (30-301) | 0.584 | 71 (34-301) | 69.5 (25-954) | 0.498 |
| BIL 0th day (mg/dL) | 0.38 (0.1-2.22) | 0.5 (0.04-2.85) | 0.118 | 0.51 (0.04-2.22) | 0.47 (0.1-2.85) | 0.936 | 0.49 (0.11-1.92) | 0.49 (0.04-2.85) | 0.848 |
| ALT 3rd day (IU/L) | 20 (2-788) | 26.5 (6-176) | 0.134 | 23 (2-788) | 27 (4-176) | 0.666 | 19.5 (4-100) | 26 (2-788) | 0.163 |
| AST 3rd day (IU/L) | 26.5 (6-1516) | 31 (9-686) | 0.465 | 35.5 (6-1516) | 28 (7-236) | 0.062 | **23 (9-46)** | **31 (6-1516)** | **0.043** |
| GGT 3rd day (U/L) | 46 (9-261) | 33 (9-338) | 0.673 | 40.5 (10-261) | 33 (9-338) | 0.212 | 34.5 (13-282) | 37.5 (9-338) | 0.909 |
| ALP 3rd day (IU/L) | 75 (42-221) | 63.5 (29-820) | 0.114 | 69 (46-820) | 67.5 (29-150) | 0.205 | 72.5 (29-131) | 65 (35-820) | 0.586 |
| BIL 3rd day (mg/dL) | 0.37 (0.07-3.1) | 0.47 (0.14-2.84) | 0.285 | 0.42 (0.14-3.1) | 0.39 (0.07-2.84) | 0.452 | 0.42 (0.15-1.79) | 0.4 (0.07-3.1) | 0.967 |
| ALT 7th day (IU/L) | 25.5 (5-145) | 33.5 (7-244) | 0.090 | 31 (7-244) | 28.5 (5-195) | 0.845 | 27 (5-117) | 33 (5-244) | 0.239 |
| AST 7th day (IU/L) | 25.5 (8-106) | 26.5 (7-524) | 0.380 | **34.5 (8-524)** | **23.5 (7-120)** | **0.002** | 23.5 (8-45) | 27 (7-524) | 0.090 |
| GGT 7th day (U/L) | 47.5 (7-263) | 41 (16-286) | 0.768 | 61 (7-286) | 41 (12-263) | 0.059 | 34.5 (12-275) | 47.5 (7-286) | 0.355 |
| ALP 7th day (IU/L) | 69 (34-170) | 67.5 (29-756) | 0.812 | 73 (42-756) | 67 (29-149) | 0.241 | 71 (39-149) | 66 (29-756) | 0.808 |
| BIL 7th day (mg/dL) | **0.46 (0.07-6.67)** | **0.6 (0.16-2.27)** | **0.045** | 0.58 (0.16-6.67) | 0.57 (0.07-1.65) | 0.496 | 0.49 (0.16-2.27) | 0.57 (0.07-6.67) | 0.848 |
| ALT 15th day (IU/L) | **14 (3-73)** | **30 (3-251)** | **0.008** | 30 (3-86) | 26.5 (3-251) | 0.994 | 30.5 (8-251) | 26 (3-242) | 0.791 |
| AST 15th day (IU/L) | 18 (8-152) | 31 (9-107) | 0.088 | **38.5 (8-152)** | **18 (8-91)** | **0.020** | 32.5 (9-74) | 24 (8-152) | 0.681 |
| GGT -15th day (U/L) | 44 (10-282) | 46 (11-464) | 0.776 | **68.5 (21-464)** | **35 (10-399)** | **0.024** | 25 (11-399) | 48 (10-464) | 0.363 |
| ALP 15th day (IU/L) | 87 (38-215) | 78 (25-245) | 0.336 | **92 (51-245)** | **71 (25-161)** | **0.009** | 92 (25-161) | 75 (38-245) | 0.135 |
| BIL 15th day (mg/dL) | 0.51 (0.1-1.94) | 0.49 (0.13-4.27) | 0.965 | 0.48 (0.16-4.27) | 0.52 (0.1-1.94) | 0.958 | 0.41 (0.13-4.27) | 0.51 (0.1-1.94) | 0.224 |

All comparisons were made with the Mann-Whitney U test; Statistically significant values (p<0.05) are shown in bold; ALT: Alanine Aminotransferase. AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase. ALP: Alkaline Phosphatase. BIL: Total Bilirubin.

(p=0.02), 15th day AST (p=0.02), GGT (p=0.02), and ALP (p=0.009) values were higher in patients who died. No significant difference was observed in other liver enzyme tests between the mortality and discharge groups.

At admission to the intensive care unit, patients with high procalcitonin levels had significantly higher ALP levels on the 0, 3, 7, and 15th days (p=0.03, p=0.006, p=0.01, p=0.013).

## Discussion

Liver damage, manifested by elevated transaminases and cholestasis, is a clinically significant impact of COVID-19 and may indicate severe disease progression. The present study found elevated transaminase and cholestasis enzymes were associated with mortality in newly diagnosed severe COVID-19 patients who had not received any COVID-19 treatment before. Similarly, it was shown in the literature that COVID-19 severity and mortality are associated with elevated transaminase levels and cholestasis[17].

Rates of liver dysfunction appear to be higher in patients with severe COVID-19. ALT elevation was observed during this follow-up period in 62% of all patients in our study, and AST increase was observed in 78.3%. Similarly, in a study by Huang et al.,[14] AST elevation was observed in 62% of patients requiring ICU, while AST elevation was observed in 25% of patients who did not require ICU. In the first data from China, transaminase levels were mildly elevated in 14-53 percent of patients. In contrast, greater enzyme levels were seen in patients with severe infections who needed to be admitted to the intensive care unit[18].

In the study of Xu et al.,[17] progressively higher liver function parameters were observed in severe COVID-19 patients at follow-up from baseline to day 30 post-hospitalization. In the study of Zeng et al.,[19] it was suggested that SARS-CoV-2 did not cause an increase in ALT and AST at baseline on the 3rd and 7th days, but it could cause an increase in GGT and T. Bilirubin, thus impairing bile secretion. The absence of an increase in transaminases in our study but a significant decrease in AST levels contradicts Xu et al.'s study and supports the results of Zeng et al.'s study. Again, the gradual increase in GGT levels and the increase in bilirubin detected on the 7th day are consistent with the findings of Zeng et al.

In the literature, there is increasing evidence of liver damage with increased transaminase levels due to hepatocellular injury in people presenting with COVID-19[20]. While there are publications that argue SARS-CoV-2 does not directly cause elevations in ALT and AST but may cause elevations in GGT and T. Bilirubin levels[19], hepatocellular damage causes serum transaminase levels to increase in early-onset disease, and higher ALP, GGT, and bilirubin levels have been detected due to the cholestatic pattern that develops as the disease progresses[21]. In our study, AST level was high in the early period, and GGT and ALP levels, which are indicators of cholestasis, increased in the follow-up. The high level of ACE2, which is the cell entry receptor of SARS-CoV-2, is observed in the biliary epithelium at a high rate, which is in line with our results in which cholestatic hepatitis is kept in the foreground.

The fact that CRP value is not correlated with hepatobiliary enzyme increase at any time suggests the direct hepatotropic effect of SARS-CoV-2. However, in the study of Li et al.,[15] it was thought that CRP might be a risk factor associated with inflammatory cytokine storm in liver damage in COVID-19 patients. The correlation of procalcitonin value, which is suggested as evidence of bacterial infection, with elevated ALP in our study indicates the presence of intrahepatic cholestasis due to sepsis.

In the present study, the inability to detect a relationship between IL-6 level, which is a precursor of cytokine storm, and transaminases and cholestasis enzymes led to the failure to establish a relationship between elevated liver enzymes and uncontrolled immune response. Transaminase values were significantly higher in the early period of intensive care admission in patients with high ferritin levels. In the study of Phipps et al.,[10] severe acute liver injury in a COVID-19 patient was significantly associated with elevated inflammatory markers such as ferritin and IL-6, and patients with severe liver injury had a more severe clinical course, including higher rates of intensive care unit admission, intubation, and mortality (42%).

When the transaminases and cholestasis enzymes of patients who received and did not receive favipiravir treatment were compared, no significant difference was found in the follow-up, suggesting that favipiravir treatment did not contribute significantly to hepatocellular damage in COVID-19 patients. Data on favipiravir and hepatotoxicity are limited in the literature. It can cause ALT/AST elevations, and there are rare cases stating that it can cause cholestatic hepatitis[16,22].

This study has some limitations, one of which is that it only represents the inpatient population in the ICU. Therefore, this information may not apply to outpatients or those with mild illnesses. Additionally, the study's other limitations include the inability to identify all possible additional causes of liver injury, including comorbidities, non-alcoholic fatty liver disease, and hepatotoxic drugs.

## Conclusion

In conclusion, in the 15-day follow-up of the patients admitted to the intensive care unit due to severe COVID-19, it was observed that the cholestasis enzymes of the patients increased gradually, and the patients that ended in mortality had higher transaminase levels and cholestasis enzymes. The lack of a relationship between this enzyme elevation and inflammatory parameters and favipiravir treatment supports the notion that the SARS-CoV-2 virus causes cholestatic hepatitis through the biliary epithelium.

**Ethics Committee Approval:** Approval was received from the Ethics Committee for Non-Interventional Clinical Research of the Faculty of Medicine of Pamukkale University (protocol no:10.150.1.90/106832, date of approval: 24.06.2021). The study protocol complies with the ethical criteria of the 1964 Declaration of Helsinki.

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**Conflict of Interest:** None declared.

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