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Hepatotoxicity and Its Impact on Mortality in COVID-19 Patients*

Hepatotoxicty in COVID-19

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Abstract:

Objective: "COVID-19 related liver damage" can occur frequently in course of COVID-19 disease and cause significant problems. Our research aims to identify the risk factors for liver damage seen in COVID-19 cases and explore the connection between liver damage, illness course, and death.

Method: One hundred adult patients treated in the hospital between 01.08.2021-01.03.2022 were included in the study. Impaired liver function tests were identified as having alanine aminotransferase and aspartate aminotransferase levels exceeding upper laboratory limits.

Results: The mean age of patients included in study was 57.9 ± 14.9 years, with 49% of them being male. In our study, we had an 8% death rate and 37% of patients had abnormal liver function tests. The presence of severe disease ($p<0.001$), anorexia symptoms ($p=0.027$), and abdominal pain ($p=0.010$) were significant for mortality. A prolonged hospital stay was significantly associated with death ($p=0.029$), with the mean length of hospital stay being 11.8 ± 4.6 days. Favipiravir use for longer than five days was associated with a substantial risk of liver damage ($p=0.044$) and mortality ($p=0.020$), while use of antibiotics in carbapenem group was associated with a significant risk of death ($p=0.001$).

Conclusions: It should be noted that an increase in liver tests may be observed in a significant portion of COVID-19 patients, and in some of these patients, this may be a sign of disease progression and mortality.:

Keywords: COVID-19, liver function tests, mortality, alanine aminotransferase, aspartate aminotransferase

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INTRODUCTION

Coronavirus disease 2019 (COVID-19); It has become an epidemic that has spread rapidly around the world since the first months of 2020, causing disruption among human communities and significant economic instability, and has opened a new perspective on respiratory infections. Although the rate of spread of the disease has decreased under current conditions, the situation continues dynamically, especially in the winter months, and epidemiological data change from day to day. According to WHO data dated February 3, 2024, the total number of confirmed cases was approximately 773 million, while 6.98 million people died due to this disease (1). From the beginning of COVID-19 until the present, a number of research have demonstrated that the virus affects not only the respiratory system but also the neurological, cardiovascular, and gastrointestinal systems (2). Numerous people, particularly those with severe or critical illnesses, have been shown to have liver damage, or hepatotoxicity, according to studies (3). The majority of COVID-19 patients with liver dysfunction were found to be male, older, and to have a higher body mass index (4). According to reports, liver dysfunction lengthens hospital stays, worsens prognoses, and raises the likelihood of a severe COVID-19 infection. (3, 4). Our hypothesis for this study was that COVID-19-related inflammation and severe sickness damage numerous organs, including the liver, and have a direct impact on the disease's progression. It was believed that defining risk factors for liver injury in COVID-19, endorsing related research, and forging a shared understanding of the care and treatment of these patients could add something to the body of literature. Finding the risk factors for hepatotoxicity associated with COVID-19, investigating the association between hepatotoxicity and mortality, and investigating the relationship between COVID-19 and liver malfunction or hepatotoxicity were the main goals of the study.

METHODS

Study Design

Our single-center and descriptive study was conducted based on retrospective data. It was carried out between 01.08.2021 and 01.03.2022, based on the findings of patients hospitalized in the ward and intensive care unit (ICU) where COVID-19 patients were followed in a tertiary hospital. On March 4, 2022, Cukurova University's non-interventional clinical research ethics committee granted the study approval (No. 48/120). The hospital's ethical guidelines, the national research committee's guidelines, and the 1964 Declaration of Helsinki were followed in every procedure carried out during the study involving human subjects.

Participants

100 patients aged 18 and over, whose COVID-19 infection was confirmed by reverse transcription polymerase chain reaction (RT-PCR) results from nasal and pharyngeal swab samples, were included in the study. Patients were divided into those with and without liver damage. Initially, 164 patients were determined for the study, but later 64 patients (16 people with radiological COVID-19 RT-PCR negativity, 28 people with missing laboratory tests, 20 people who did not want to participate in the study) were excluded from the study. According to discharge status, they were divided into two different groups as survivors and deceased patients. The patients' sociodemographic and clinical data, laboratory parameters, radiological findings, and treatments they received during their stay (anticoagulant, antiviral, antibacterial, corticosteroid and anticytokine drugs) were recorded.

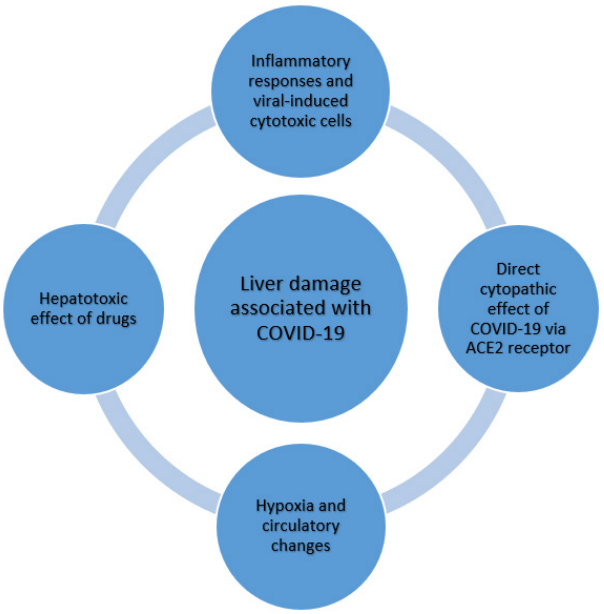

Figure 1. Liver Damage Mechanisms Associated with COVID-19

Variables

Comorbidities were categorized according to the Charlson Comorbidity Index as "0 points low, 1-2 points moderate, 3-4 points high, and 5 points and above very high risk". According to the clinical and radiological results of the patients at the time of admission, the severity of the COVID-19 disease was classified into three categories: Those with oxygen saturation above 94% on room air and radiological lung involvement below 25% have mild disease, those with oxygen saturation between 88-94% and radiological lung involvement between 25-49% have moderate disease, those with oxygen saturation below 88% and radiological lung involvement have moderate disease. Those with 50% and above were defined as severe disease. The laboratory range for alanine aminotransferase (ALT) was (10-40 IU/L) and the laboratory range for aspartate aminotransferase (AST) was (15-45 IU/L), and values above these values were recorded as liver damage (hepatotoxicity). Increases in gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) levels were not considered as primary liver dysfunction. Favipiravir was used as antiviral treatment in all patients (in line with the recommendations of the Ministry of Health COVID-19 monitoring and treatment application guide).

Statistical Analysis

The data were statistically analyzed using IBM SPSS Statistics Version 20.0 package program (Armonk, NY: IBM Corp.). In the investigations, categorical variables were compared using the chi-square test or the Fisher exact test, and the Kolmogorov-Smirnov method was employed to ascertain whether the distribution of the variables was within the normal range. A p-value of less than 0.05 indicated statistical significance.

RESULTS

The study's 49% of patients were men, with an average age of 57.85 ± 14.87 (min.24–max.95). Hepatotoxicity was detected in 37% of the patients, and 8 patients died. At admission, loss of appetite was the most prevalent gastrointestinal symptom (26%) and the most common comorbidities were diabetes mellitus (30%) and hypertension (38%). According to the charlson comorbidity index, 30% of the patients had mild risk, 46% had moderate risk, 20% had high risk

and 4% had very high risk. In terms of COVID-19 disease severity, 47% of our patients had mild, 38% moderate and 15% severe disease. Demographic findings, symptoms, comorbidities, Charlson comorbidity index and disease severity were not statistically significant in terms of hepatotoxicity. Among the symptoms, loss of appetite (p=0.027) and abdominal pain (p=0.010) and disease severity (p=0.000) were statistically significant for mortality. While the average total hospital stay was 11.8 ± 4.6 days (min.6-max.24), extended hospitalization time was found to be significant for mortality (p=0.029). Details of demographic data and clinical findings are presented in table 1.

Table 1. Effects of Demographic Data and Clinical Findings on Liver Toxicity and Mortality

Characteristics		Hepatotoxicity (-)	Hepatotoxicity (+)	p	Survived	Death	p
Age	<65 years	37	25	0.254	59	3	0.135
	≥65 years	26	12		33	5	
Sex	Male	28	21	0.163	45	4	0.620
	Female	35	16		47	4	
COVID-19 Disease Severity	Mild	31	16	0.846	47	0	**0.000**
	Moderate	23	15		38	0	
	Severe	9	6		7	8	
Lack of appetite		16	10	0.519	21	5	**0.027**
Nausea		5	2	0.484	6	1	0.453
Vomiting		1	1	0.605	2	0	0.846
Abdominal pain		5	2	0.484	4	3	**0.010**
Diarrhea		5	1	0.275	6	0	0.598
Charlson Comorbidity Index	Low	15	15	0.261	28	2	0.160
	Middle	33	13		44	2	
	High	13	7		16	4	
	Very high	2	2		4	0	
Hypertension		28	10	0.063	34	4	0.356
Diabetes Mellitus		22	8	0.119	27	3	0.450
Cardiovascular Diseases		11	6	0.552	15	2	0.409
Chronic Lung Diseases		12	3	0.115	15	0	0.259
Neurological Diseases		5	2	0.484	5	2	0.096
Cancer		12	6	0.472	16	2	0.441
Chronic Kidney Diseases		3	0	0.246	3	0	0.777
Chronic Liver Diseases		1	1	0.605	2	0	0.846
Day of hospitalization		11.3 ± 4.5	12.8 ± 4.7	0.700	11.6 ± 4.6	14.8 ± 3.6	**0.029**

Favipiravir was used as an antiviral drug in all our patients, and in 47% of the patients, favipiravir was used for longer than the 5th day. Low molecular weight heparin (LMWH) was used for anticoagulant treatment in 96% of our patients, and methyl-prednisolone was used for anti-inflammatory treatment in 38% of our patients. The most commonly used antibacterial agent is ceftriaxone with 19%. It was discovered that favipiravir use for longer than five days was associated with a substantial increase in mortality and hepatotoxicity (p = 0.044 and p = 0.020, respectively). Only the use of antibiotics belonging to the carbapenem group was revealed to be significant for death (p = 0.001) when compared to other medical therapies. According to laboratory

results, hepatotoxicity was shown to be significantly indicated by high LDH values on days 3, 5, and 7 (p = 0.008, p = 0.002, p = 0.015, respectively) and high ALP levels on days 5 and 7 (p = 0.002, p = 0.001, respectively). High ALP values (p=0.040, p=0.002, respectively) recorded on days 1 and 7 were found to be relevant with death. Furthermore, in 6 (75%) of the 8 individuals whose illness process resulted in death, hepatotoxicity was discovered; this finding was shown to be statistically significant (p = 0.028). Details of medical treatment and laboratory findings are presented in table 2.

Table 2. Effects of Medical Treatment and Laboratory Findings on Liver Toxicity and Mortality

Characteristics		Hepatotoxicity (-)	Hepatotoxicity (+)	p	Survived	Death	p
Favipiravir	≤5 day	38	15	**0.044**	52	1	**0.020**
	>5 day	25	22		40	7	
Low Molecular Weight Heparin		61	35	0.473	89	7	0.287
Methyl prednisolone		21	17	0.149	33	5	0.135
Ceftriaxone		9	10	0.097	17	2	0.472
Piperacillin-tazobactam		11	7	0.528	16	2	0.441
Carbapenems		9	4	0.433	8	5	**0.001**
Anakinra		12	11	0.164	19	4	0.079
Elevated Alanine Amino-transferases	1 day	2	17	**<0.001**	16	3	0.174
	3 day	1	22	**<0.001**	20	3	0.267
	5 day	2	25	**<0.001**	24	3	0.370
	7 day	9	29	**<0.001**	35	3	0.644
Elevated Aspartate Amino-transferases	1 day	4	16	**<0.001**	17	3	0.196
	3 day	5	17	**<0.001**	20	2	0.564
	5 day	3	19	**<0.001**	21	1	0.438
	7 day	8	22	**<0.001**	27	3	0.450
Elevated Lactate Dehydrogenase	1 day	23	14	0.075	4	4	0.150
	3 day	20	17	**0.008**	3	5	0.450
	5 day	14	23	**0.002**	6	2	0.056
	7 day	21	16	**0.015**	3	5	0.423
Elevated Alkaline Phosphatase	1 day	10	27	0.097	4	4	**0.040**
	3 day	11	26	0.084	4	4	0.058
	5 day	16	21	**0.002**	4	4	0.105
	7 day	16	21	**0.001**	2	6	**0.002**
Elevated Gamma Glutamyl Transferase	1 day	1	15	**<0.001**	12	4	**0.021**
	3 day	1	15	**<0.001**	14	2	0.376
	5 day	2	17	**<0.001**	16	3	0.174
	7 day	2	17	**<0.001**	16	3	0.174

DISCUSSION

During SARS-CoV-2 infection, abnormal liver blood tests can happen to nearly half of the patients. It was shown that both AST and ALT were frequently high during COVID-19 (58.4% and 39.0% of patients, respectively) in a large research with 5700 patients (5). Another study by Cai Q et al. found that 41% of patients had an abnormality in liver function tests.

It was found that GGT can increase up to 3-fold, especially in severe SARS-CoV-2 infections, but this was not accompanied by an increase in ALP (6). According to a systematic analysis, 25% of the 2541 COVID-19 patients had high AST and/or ALT, 20% had elevated LDH, 3% had elevated bilirubin, and nearly all of the patients had normal ALP (7). In our study, we found the rate of liver damage to be 37%.

Increased liver enzymes were found in 15,407 COVID-19 patients in a meta-analysis; these patients had increased liver enzymes 23.1% at the beginning of the disease and 24.4% over the course of the illness (8). The proportion of patients with increases in both ALT and AST ranged from 12.6% in mild instances to 46.2% in severe cases, according to another study detailing temporal changes along the course of COVID-19 disease. Most patients had an ALT increase between days 4 and 17 of hospital stay; in severe cases, this occurred on average after 7.3 days, whereas in moderate ones, it occurred on average after 10.7 days. The majority of patients had relatively modest, isolated increases in their ALT and AST levels during treatment, and the majority of them were released with normal liver marker values (9). In our study, in addition to the elevations of AST-ALT and GGT, the elevations of LDH on days 3, 5 and 7, and ALP on days 5 and 7 were found to be significant for liver damage.

Cai Q et al. it has been shown that more than 10% of COVID-19 patients have increased liver enzyme levels during hospitalization and this can be attributed to the medications used (6). Kulkarni et al. conducted a meta-analysis comprising 20,874 COVID-19 participants, revealing that the incidence of drug-induced liver injury was 25.4% (8). Of the 53 patients in a case study looking at the use of remdesivir to treat COVID-19, 23% experienced increases in liver enzymes that led to an early stop to therapy (10). Unlike our study, it was conducted with favipiravir and was found to be significant for both hepatotoxicity and mortality when used for more than 5 days.

More severe COVID-19 infections were linked to higher ALT, AST, and bilirubin levels, according to a meta-analysis that examined 3428 patients in total (11). A nine-fold increased risk of severe infection was estimated to be linked to liver damage after COVID-19 infection in another large-scale investigation (6). Increases in these parameters have been linked in other studies to worse lung CT scores, a higher number of patients needing ICU care, longer hospital stays, and mortality (12, 13). The prevalence of elevated liver markers in COVID-19-related deaths ranges from 58% to 78% (4). Our study found the liver damage rate of patients who died as a result of the COVID-19 process to be 75% and found that prolonged hospitalizations and liver damage had an impact on mortality.

Limitations of the study

The fact that the study was based on retrospective data was possibly its biggest drawback. Further limitations to our study include the non-uniform distribution of patients' ages, concurrent medical conditions, and medication use, as well as the absence of imaging methods like computed tomography and ultrasonography to rule out structural pathologies of the liver, pancreas, and biliary tract.

CONCLUSIONS

Our study concluded that liver damage due to any cause may occur in a significant portion of COVID-19 patients, especially those treated in hospital, and that these patients carry a serious risk of mortality. In such a situation, it is important to first rule out or confirm drug-induced liver injury and provide comprehensive evaluations, including regular liver tests, especially when treating and monitoring patients with risk factors. On the other hand, it is clear that more comprehensive, multi-center, prospective-observational studies with large participation are needed to fully understand this issue and especially to determine its relationship with drugs used in the treatment of COVID-19.

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Conflict of Interest

Authors declare no conflicts of interest

Support Resources

No financial support was used by authors during this study.

Ethical Declaration

Ethical permission was obtained from the Cukurova University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date March 4, 2022 and number 48/120, and Helsinki Declaration rules were followed to conduct this study.

Authors contributions

Concept: EG, Design: EG, Supervising: EG, Financing and equipment: EG, Data collection and entry: EG, Analysis and interpretation: EG, Literature search: EG, Writing:
EG, Critical review: OBT,KA.