

## Original Article

# Hepatic Involvement and Association with Prognosis in COVID-19 Patients: A Single-Centre Report from Iran

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**Background:** There were no documents about the non-lung involvement of COVID-19, even in the absence of lung involvement. The present study aimed to report a single-centre experience of liver involvement caused by COVID-19 disease in Iran.

**Materials and Methods:** We recorded information of 120 patients who suffered COVID-19 disease, and they were admitted to the intensive care unit at Taleghani hospital in Tehran, Iran, between March and May 2020. Along with clinical and diagnostic parameters, the outcome of patients concerning improvement, disease progression or death was also assessed.

**Results:** In total, 68 patients (56.7%) had abnormal liver dysfunction. The most common changes in liver-related parameters were elevated international normalized ratio (INR) (mean serum level of 2.5) followed by elevated alkaline phosphatase (ALP) (mean serum level of 412 mg/dl). The mean level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased 4 and 9 times more than the standard limit. The overall death rate in COVID-19 patients was 38 patients (55.88%, n=68).

**Conclusion:** Liver injuries are common findings in patients suffering COVID-19 infection and leading to poorer outcomes. Serum bilirubin level of more than 3mg/dl was associated with higher mortality in patients with liver damage.

**Keywords:** COVID-19, Liver injury, Liver aminotransferase, SARS-COV-2

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## Introduction

In December 2019, a series of pneumonia patients were diagnosed with an unknown cause in Wuhan, China, and quickly spread around the world<sup>1</sup>. A new type of coronavirus, known as COVID-19, was identified by analyzing the genomic sequence responsible for pneumonia<sup>2</sup>. As of February 2020,

72,436 cases of coronavirus have been identified in 31 Chinese states, resulting in 1,688 deaths in that country<sup>3,4</sup>. After the first reports from Wuhan, China, other cases worldwide have been gradually identified and reported in the United States, Italy, Spain, Iran, Japan, and other parts of the world<sup>5-8</sup>. In January 2020, the World Health Organization identified COVID-19 as a global epidemic<sup>9</sup>. The virus has a high potential

for person-to-person transmission, leading to numerous reports of its spread worldwide<sup>10-16</sup>. In recent months, extensive efforts have been made to describe the epidemiology, clinical manifestations, and clinical features of COVID-19. What has recently attracted the attention of many researchers has been the out-of-lung involvement of the disease, even in the absence of lung involvement. In this regard, liver injuries have been much highlighted<sup>17</sup>. To date, the extensive studies on COVID-19 could reveal elevated serum levels of liver aminotransferases and Bilirubin in a majority of patients who are suffering COVID-19. Although significant liver dysfunction was not reported in some studies, some others have suggested the increased risk of liver dysfunction and even failure following COVID-19 infection<sup>18-20</sup>. Close inspection of the available data supports a higher prevalence of abnormal aminotransferase levels in severe COVID-19 disease, but these studies suggest that clinically significant liver injury is uncommon, even when data for the most severely ill patients are selected<sup>21,22</sup>. Some studies have hypothesized that hepatic congestion might be caused by increasing right atrial pressure and impeding venous return following mechanical ventilation, but others could show such liver injuries without mechanical ventilation<sup>23</sup>. Also, it seems that the applied therapeutic regimens for treating and controlling COVID-19 infection may be hepatotoxic, and thus it has been known as drug-induced liver injury<sup>24</sup>. Some studies hypothesized that liver injuries might be due to the direct invasion of the virus to liver tissue causing viral hepatitis<sup>25</sup>, but such suggestions have not been exclusively assessed. However, what is certain is that liver involvement, for whatever reason and pathogenesis, is associated with the adverse outcome of the disease and can lead to disease progression and even death. The present study aimed to report a single-center experience of liver involvement during COVID-19 infection in Iran.

## Methods

Approval of this study was obtained from The Medical Ethical Committee (Approval no: IR.SBMU.RIGLD.REC.1400.008) at Shahid Beheshti University of Medical Sciences, Tehran,

Iran. In the present report, the hospital recorded all patients who suffered COVID-19 infection and were admitted to the intensive care unit (ICU) at Taleghani hospital in Tehran between March and May 2020 were retrospectively assessed. In addition to collecting the baseline characteristics, including demographics, clinical manifestations and therapeutic regimens, all laboratory parameters recorded in the hospital files were assessed potentially in terms of the changes in liver function tests. Along with clinical and diagnostic parameters, the outcome of patients concerning improvement, disease progression, or death was also assessed. In this study, the patients with a history of hepatitis, hepatic cirrhosis, or related cancers were excluded from the final assessment. The results were presented as mean±standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Categorical variables were compared using the chi-square test or Fisher's exact test when more than 20% of cells with an expected count of less than five were observed. Quantitative variables were also compared with the t-test or Mann U test. The statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used for the statistical analysis. P values of 0.05 or less were considered statistically significant.

## Results

A total of 120 patients with a definitive diagnosis of COVID-19 were admitted to ICU. Almost 37.5% were women, and 62.5% were men. The average age of participants was 68.42±6.45 years in the male group and 61.31±5.79 years in the female group. Fifty-one patients (75%) had a history of smoking, and 65 (95.5%) showed respiratory symptoms, including shortness of breath or cough, and 57 (83.8%) patients had a typical chest CT scan.

Overall, 108 out of 120 evaluated patients (90.0%) had evidence of lung involvement, 68 patients (56.7%) had abnormal liver dysfunction, defined as increasing INR, ALT, AST, ALP or Bilirubin. Among the Patients with hepatic dysfunction, 29 (42.6%) were men, 39 (57.3%) were female, and 85.2% were over 50 years old. Of all 68 patients with liver involvement, 3 (4.4%) had no simultaneous lung involvement. Sixty-three patients (92.6%) with abnormal LFT had a

**Table 1:** Liver parameters in population with liver injury following COVID-19.

Parameter	Mean level	Lower limit	Higher limit
Serum ALT	140	60	220
Serum AST	308	50	465
Serum ALKp	412	320	2305
Serum bilirubin	2.8	1.5	14.5
Serum INR	2.5	1.5	5.0

**Table 2:** Comparison between patients with abnormal and normal liver function test.

	Abnormal Liver Function Test	Normal Liver Function Test
Male	42.6%	28.8%
Female	57.3%	71.1%
Age > 50 year	85.2%	88.4%
Smoking	75%	65.3%
respiratory symptoms	95.5%	92.3%
Typical Chest CT scan	83.8%	98.07%
Abdominal Pain	92.6%	34.6%
hospitalization > 15 days	17.6%	15.3%
Death	30.8%	32.6%
Septic Shock	26.4%	32.6%
AKI (↑Cr)	51.4%	40.3%
Ecmo	0	0
CRRT	1.4%	0
Invasive mechanical ventilation	69.11%	84.61%
Non-invasive mechanical ventilation	30.8%	15.3%
DM	14.7%	13.4%
Poor control DM (HbA1c>7)	13.2%	11.5%
↑ LDH	83%	69%
Blood group O+	39%	32%

history of abdominal pain, compared with 18 patients (15.3%) in the group with normal LFT.

The characteristics of liver parameters on admission in the patients with liver involvement are presented in

**Table 3:** Review of the papers aiming liver injuries following COVID-19 infection.

Author, year	Patients	ALT (range)	AST (range)	PT (range)	Bilirubin (range)	Raised LDH	Death (time)
Guan, 2020	67	Not known	Not known	Not known	Not known	Yes	22% (51 days)
Huang, 2020	13	49 (29-115)	44 (32-70)	12.2 (11.2-13.4)	14.0 (11.9-32.9)	Yes	38% (37 days)
Chen, 2020	99	39 (22-53)	34 (26-48)	11.3 (1.9-13.6)	15.1 (7.3-22.9)	Yes	11% (24 days)
Wang, 2020	36	35 (19-57)	52 (30-70)	13.2 (12.3-14.5)	11.5 (3.6-24.0)	Yes	17% (34 days)
Shi, 2020	81	46 (>30)	41 (>18)	10.7 (>0.9)	11.9 (>3.6)	Not known	5% (50 days)
Xu, 2020	62	22 (14-34)	26 (20-32)	Not known	Not known	Not known	0% (34 days)
Yang, 2020	52	Not known	Not known	12.9 (>2.9)	19.5 (>11.6)	Not known	62% (28 days)

Table 1. In this regard, the most common changes in liver-related parameters were elevated INR (mean serum level of 2.5) followed by elevated ALP (mean serum level of 412 mg/dl). The mean level of direct Bilirubin was 2.8 mg/dl, and the mean level of ALT was 140 mg/dl (four times more than the standard limit), and the mean level of AST was 308 mg/dl (nine times more than the standard limit). Elevated lactate dehydrogenase (LDH) was also seen in 74 patients (86.0%), that 57 of them were among patients with liver dysfunction. In those patients with injured liver, 27(39%) of patients with liver damage had blood group O, vs 17 (32%) of patients in the opposite group.

The mean admission day to ICU was also 11.2±2.26 in men and 8.50±2.12 in women, significantly higher in men than in women (P=0.002). Also, the disease severity requiring hospitalization in the ICU was higher in men than women (P=0.001). Thirty-five people with abnormal LFT spent more than 15 days

in ICU compared with 27 in the opposite group. The overall death rate in COVID-19 patients was 38 patients (27 men and 11 women), indicating a significant difference between the two genders (P=0.001). There were 21 deaths (30.8%) in patients with liver dysfunction and 17(32.6%) death in patients in the other group with regular liver function tests (Table 2).

In autopsies on four non-survived subjects, liver and gastrointestinal involvements were found in all of them. Also, liver biopsy on three dead subjects revealed positive PCR tests in all three cases.

Of 38 non-survived subjects, the D-dimer was checked in 8, which led to a positive result in 7 (87.5%). The blood group of O in 26 (68.4%), history of diabetes mellitus in 17 (25.0%) and elevated direct bilirubin in 10 (14.7%). In general, nine patients were readmitted to ICU after discharging from the hospital, that one of them died.

## Discussion

There are various hypotheses about liver dysfunction in patients with COVID-19. Like the first hypothesis, the liver impairment may result from direct invasion of the COVID-19 virus to the liver tissue. The virus is known to be one of the wild pathogens for viral hepatitis. Approximately 2–10% of patients with COVID-19 present with diarrhea and SARS-CoV-2 RNAs have been detected in stool and blood samples. This evidence implicates the possibility of viral exposure in the liver<sup>26</sup>. Second, the presence of angiotensin-converting enzyme 2 (ACE2) receptors in different organs such as the liver suggest that SARS-CoV-2 can enter the target cell by binding to the ACE2 receptor virus replicates and subsequently infects other cells in the lung, heart and liver tissues<sup>27,28</sup>. Moreover, it seems that the inflammatory reactions following exposure to virus antigen can also be another potential mechanism for injuring vital organs such as the liver. In this regard, increased inflammatory cytokines such as interleukin 6 and 10 are solid defendants for disease severity and vital organ involvement<sup>29</sup>.

The literature (Table 3) indicates various liver parameters and poor outcomes following liver involvement in patients with COVID-19. In this regard, the serum levels of liver enzymes, serum bilirubin and LDH widely varied in the affected patients. Moreover, the mortality rate in patients suffering liver injury varied widely, with a range of 0.0% to 62.0% in the follow-up from 24 to 51 days after admission<sup>30-36</sup>. The adverse effects of COVID-19 on liver function are very dependent on different underlying factors such as disease severity and progression, co-morbidities, and the presence of different confounders affecting liver function (that should be excluded in study planning) and also the difference in the follow-up time. However, it is necessary to mention a few points. First, severe pulmonary and renal involvement can be concurrent. Second, liver injuries leading to metabolic disturbances can deteriorate the patients' condition and even lead to death. As shown in a meta-analysis by Parohan et al. in 2020<sup>37</sup>, higher serum levels of AST, ALT, and Total Bilirubin and lower serum levels of Albumin were associated with a significant

increase in the severity of COVID-19 disease. In our study, elevated direct Bilirubin was also significantly associated with higher death rates and higher ICU hospitalization. Overall, a serum bilirubin level of more than 3mg/dl was associated with a higher likelihood of death in patients with liver dysfunction. Third, impairing liver functional parameters is a common finding in COVID-19 patients, significantly increasing Bilirubin, AST and ALT levels, and LDH. Guan et al.<sup>26</sup> showed elevated levels of AST in 18.2% of patients with the non-severe disease and 39.4% of patients with severe disease, while elevated levels of ALT in 19.8% and 28.1% of patients in Huang, et al. study<sup>32</sup> was seen, respectively. Patients with severe COVID-19 had an increased incidence of abnormal liver function so that elevated AST levels were found in 62% and 25% of patients with and without ICU admission, respectively. In our study, the most common changes in liver-related parameters were elevated INR followed by elevated ALP. In general, despite the limited evidence, some baseline parameters appear to be associated with an increased likelihood of liver involvement, such as male gender, blood group of O, increased serum bilirubin level, history of uncontrolled diabetes mellitus, and elevated LDH, which should be evaluated in further studies. Collecting this information helps to justify the common cause of liver involvement and its poor consequences in patients with COVID-19.

## Conclusion

We found that SARS-CoV-2 may infect the bile duct cells and cause abnormal liver function in patients with COVID-19 disease. Liver injuries are common findings in patients suffering COVID-19 infection and leading to poorer outcomes. Serum bilirubin level more than 3mg/dl was associated with higher mortality in patients with liver damage.

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