Article published online: 2022-12-21

Effect of COVID-19 on Serum Activity of Liver Enzymes: Is This Associated with Severity and Mortality Rate?

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Ibnosina J Med Biomed Sci 2022;14:86–93.

Abstract

Introduction Coronavirus disease 2019 (COVID-19) is a viral infection caused by a novel coronavirus known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease raises an enormous public health challenge for the international community. Liver enzymes have been reported to be frequently elevated in hospitalized patients with severe COVID-19 disease.

Materials and Methods This article is a narrative review of abnormal liver tests and liver injury as a manifestation of progression to severe pneumonia. We collected data from the PubMed database (National Library of Medicine, Bethesda, Maryland, United States). We used the search term "abnormal liver test" and relevant records were measured. The review article was organized thematically.

Results This narrative review aims to summarize the available clinical data on abnormal liver enzymes in coronavirus infection and its association with the risk of mortality, severer pneumonia, and systemic inflammation. Some clinical studies refer to abnormal liver tests and liver injury as a manifestation of progression to severe pneumonia. Recent research verified the relationship between hepatic liver enzyme activities and liver damage in patients with COVID-19, which suggested that it might reflect the infection severity and the mortality risk. Thus, this review investigated the correlation between liver serum enzymes level and the severity of COVID-19 patients, by reviewing investigating the relationship between the illness severity in COVID-19 patients with abnormal liver tests, liver pathology, and markers of inflammation.

Conclusion In the current pandemic of SARS-CoV-2, abnormalities of liver enzyme tests were commonly observed in patients with COVID-19. However, because of multiorgan damages that observed in COVID-19 patients, various issues should be considered such as the pathology and pathophysiology of the liver tissue, especially on the activation process of the immune response and cytokine storm to prevent the severity of the disease.

Keywords
- COVID-19
- liver enzyme
- coronavirus
- liver injury
- mortality

DOI https://doi.org/10.1055/s-0042-1759739.
ISSN 1947-489X.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Coronavirus disease 2019 (COVID-19) causes a highly infectious disease. It started as a fast pneumonia epidemic in Wuhan, China, in December 2019. Since then, the virus has spread rapidly worldwide.[1,2] The upper respiratory system presented as a predominant site of infection. The disease usually causes severe respiratory tract infections and systemic symptoms such as fatigue, fever, cough, and chest pain.[3] However, the virus can affect other organs such as the heart, spleen, kidney, liver, and intestine, especially in critically ill patients that elicit severe symptoms of acute kidney and liver damage.[4–6] As supposed by perturbations of liver enzymes in COVID-19 patients, liver involvement was observed in one-third to half of the patients.[7] In the current pandemic of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), abnormalities of liver function tests (LFTs) are commonly observed in patients with COVID-19, indicating a strong link between COVID-19-associated liver injury and the mortality risk.[8] Thus, we reviewed the available clinical data on the altered LFTs in COVID-19 patients and the relationship between the illness severity in COVID-19 patients with abnormal LFTs.

COVID-19 and Liver Enzymes

Although COVID-19 patients suffer from respiratory symptoms, liver dysfunction has been reported in some patients.[7] Recent studies indicated the relationship between hepatic liver enzyme activities and liver damage in patients with COVID-19 suggesting that it may reflect the infection severity and the mortality risk.[1,8] Mechanistically, SARS-CoV-2 might directly bind to angiotensin-converting enzyme 2 (ACE2)-positive cholangiocytes, resulting in liver damage and elevated liver functions (►**Fig. 1**).[9]

Serum Enzymes Level and Severity of COVID-19 Patients

Recently, Liao et al investigated a retrospective study of 147 patients with COVID-19, focusing on the relationship between hepatic enzymes test and the illness severity and analyzed the diammonium glycyrrhizinate (DG) treatment on liver enzymes activity. On admission, 56 (38.1%) patients had abnormal alkaline phosphatase (ALP) activity, while 80 (54.4%) had abnormal aspartate aminotransferase (AST) activity. However, the superoxide dismutase (SOD) level was decreased to 40 (27.2%) in severe and critical patients compared with mild cases, suggesting that abnormal serum hepatic enzyme tests in severe COVID-19 cases probably reflect the illness severity. Moreover, ALP level was not statistically different between mild, severe, and critical COVID-19 patients and the control group. On the other hand, the utilization of the salt form of glycyrrhizin has shown improvement in abnormal liver enzymes in mild and severe cases after admission, but not in critically-ill cases. The authors concluded that abnormal AST combined with LDH and SOD might be related to the disease severity during hospitalization, and glycyrrhizin treatment alleviated the abnormal liver in mild to severe COVID-19 patients.[1] In another study of 63 patients with COVID-19 in Beijing. Liver tests abnormality was pronounced as alanine aminotransferase (ALT) in 16 patients (25.4%), AST levels were increased in 14 severe ill patients (22.2%), ALP was elevated in 3 patients (4.8%), and (gamma-glutamyltransferase [GGT]) was elevated in 21 patients (33.3%), while albumin level was decreased in 11 patients (17.5%), and lactate dehydrogenase (LDH) levels were elevated in 26 patients (41.3%). Moreover, creatine phosphokinase was significantly higher in critically ill COVID-19 patients compared with patients with moderate or mild symptoms.[10]

Clinical Features of Abnormal Liver Enzymes in COVID-19-Related Liver Injury

According to a recent study, the SARS-CoV-2 virus can bind to ACE2 on cholangiocytes, leading to cholangiocyte dysfunction and evolving a systemic inflammatory response into liver injury. In line with this finding, Cai and Chen evaluated the clinical characteristics of 417 laboratory-confirmed COVID-19 patients admitted to the referral hospital in Shenzhen, China, with abnormal liver test results. This study

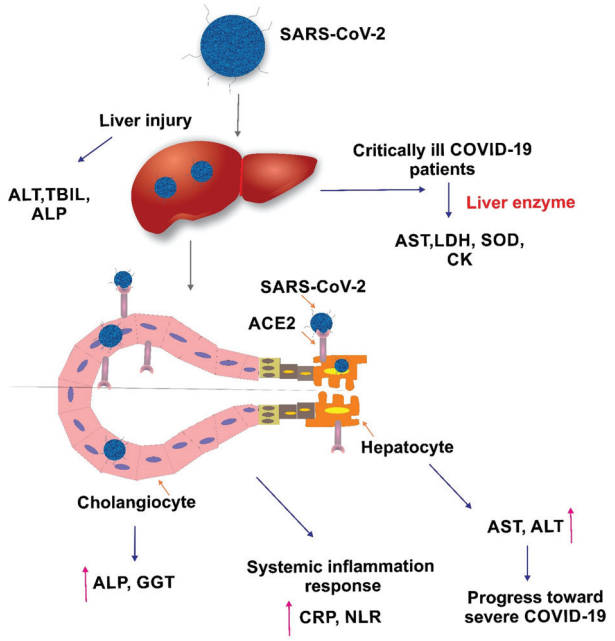

Fig. 1 Schematic diagram showing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly binding to angiotensin-converting enzyme 2 (ACE2)-positive cholangiocytes and hepatocytes, leading to cholangiocytes dysfunction and evolving a systemic inflammatory response into liver injury. Liver injury related to the coronavirus disease 2019 (COVID-19) disease differed in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBIL). Patients with twice elevated levels of ALP and gamma-glutamyltransferase (GGT) are classified as cholangiocyte type hepatocyte groups comprising patients with levels increased in ALT and/or AST more than three times the upper limit unit of ordinary (ULN). Patients associated with hepatocyte type revealed more intentions to progress toward severe COVID-19. In severe cases of COVID-19, C-reactive protein (CRP) and neutrophil to lymphocyte ratio (NLR) showed significant elevation.

showed that abnormal liver test results recognized 318 (76.3%) patients, and the rest of 90 (21.5%) showed liver injury within 2 weeks of hospitalization. Liver test abnormalities were defined and measured as ALT more than 40 U/L, AST more than 40 U/L, GGT more than 49 U/L, ALP more than 135 U/L, and total bilirubin (TBIL) more than 17.1 mmol/L. Moreover, the authors accordingly classified the liver abnormalities into hepatocellular, cholestatic, or mixed. Hepatocyte groups comprised patients who had levels increased in ALT and/or AST more than three times the upper limit unit of normal (ULN), while patients with twice elevated levels of ALP and GGT classified as cholangiocyte type, which constituted 20.75 and 29.25% of the total, respectively. Finally, 43.4% of patients recognized by a combination of three times increased levels of ALT/AST and twice elevated levels of ALP/GGT belonged to the mixed group. According to categories, patients with hepatocyte type or a mixed type showed more intentions to progress toward severe COVID-19 at admission or during hospitalization. After admission, the administration of drugs including lopinavir and ritonavir exhibited the most critical risk factor for liver injury, thus suggesting monitoring patients who received these medications. Thus, the authors concluded that abnormal liver tests might be a risk factor for developing severe COVID-19.[11] In addition, drug-induced liver injury has been reported in patients treated with Chinese herbal medicine, which warrants careful monitoring and evaluation for these patients.[12] In the same context, researchers from the Institutional Review Board of Henry Ford Hospital included in a retrospective study 348 laboratory-confirmed COVID-19 patients from March 10 to March 27, 2020 were divided into two cohorts as "cohort 1," defined as presenting liver injury or absence of liver injury known as "cohort 2."[13] The classification was based on elevations of AST more than 35 IU/L and/or ALT more than 52 IU/L. The study aimed to determine the outcome of liver damage and a consequent liver enzyme impairment in COVID-19 confirmed cases. Their assessment revealed that patients who had a severe liver injury on admission showed an initial elevated AST level of 44 IU/L (laboratory cutoff values: $>$ 35 IU/L) in "cohort 1" was associated with increased severity of illness, requiring mechanical ventilation, and heightened risk of mortality. In addition, mortality rates in patients included two groups showed that patients with liver injury died significantly compared with those without liver injury (28.9 vs. 17.9%; $p = 0.018$). In an attempt to determine the correlation, logistic regression analysis indicated that an increase in AST level, peak AST, peak ALT, TIBIL levels, and declined levels of albumin were individually related to increased risk of mortality. The authors explained that the degree of higher liver enzyme levels during hospitalization predisposed patients with liver injury to bacterial infections and to develop septic shock, partly due to elevation cytokine-induced inflammatory. Hence, 41.3% of patients with liver injury ($p = 0.001$) in this study showed bacterial infection more probability of developing septic shock. The results of this study have not shown any correlation between liver injury and comorbid conditions, the usage of ACE inhibitor, or baseline liver function and confirmed that liver injury in COVID-19 was associated with virus-induced inflammation.[13]

Serum Level of Aspartate Aminotransferase and Alanine Aminotransferase

The dynamic patterns of liver injury related to the COVID-19 disease differed in ALT, AST,[14] and ALP, and TBIL. Despite the acceptance of the minimal increase in AST due to sepsis in COVID-19 patients, the elevation of AST at least twice the ULN level has shown to be strongly associated with the highest mortality risk compared with other liver injury indicators during hospitalization.[8,15] Numerous studies have reported clinical features of liver injury in COVID-19 patients that presented increased levels of ALT and AST,[3,16] suggesting an indicator for severe pneumonia.[11,17] However, in a retrospective study performed by Ramachandran et al to evaluate the clinical outcome in hospitalized COVID-19 patients with an increased ratio of AST/ALT, of whom AST was defined as more than two times the ULN and compared with COVID-19 patients without an elevation in AST. Among patients with COVID-19, 13.7% revealed (AST/ALT) elevation. Although the increasing rates of mechanical ventilation were significantly pronounced among patients with increased AST compared with those without increased AST level (50 vs. 24%, $p = 0.028$), there was no significant difference in rates of mortality (50 vs. 36.8%, $p = 0.32$) and median length of hospital stay (7 vs. 7 days, $p = 0.78$) between two groups.[15]

Recent studies on COVID-19 have indicated the proportion of elevated AST[14] levels from initial symptoms to death in COVID-19 patients. Zhang et al studied the clinical characteristics of 82 cases who died from COVID-19 in a single-center local hospital in Wuhan. Although most patients with comorbidities (76.8%) succumb to COVID-19, there was shown a significant association between AST ($p = 0.002$) and ALT ($p = 0.037$) and time from initial symptoms to death.[18] In a single-center study that included 36 nonsurvivors with COVID-19 in the fifth hospital of Wuhan, elevated levels of AST (18, 58.06%) or ALT (4, 13.33%) were recorded in patients with COVID-19.[19] In a multicenter retrospective cohort study of 5,771 patients with COVID-19, Lei et al investigated the distribution patterns of liver damage indicators in these patients and analyzed its correlation with the risk factor and death.[8] Among patients classified as severe (1,186, 20.6%), 81 (1.4%) patients were recognized with chronic liver disease, four reported fatty liver diseases, and 77 viral hepatitis. These patients developed an acute liver injury, which is defined as (ALT $>$3 ULN) approximately 17 days after symptom onset. Moreover, there was shown an association between all-cause mortality risk and increased levels of AST (between 40 and 120 U/L, 4.81-fold; 95% confidence interval [CI], 3.38–6.86; $p < 0.001$) and AST ($>$120 U/L, 14.87-fold (95% CI, 9.64–22.93; $p < 0.001$) compared with elevated ALT and other liver enzymes such as ALP and TBIL. Indeed, the study concluded that AST elevated significantly among severe cases upon admission and remained at a high level compared with nonsevere cases.[8] However, in a study by Li et al, a significant increase in ALT level was shown in patients with a higher C-reactive protein

(CRP) index, suggesting that cytokine storm syndrome might cause COVID-19-related hepatic damage.[16] However, the underlying mechanism of COVID-19-related liver injury is still unclear.[20] Apart from a retrospective study performed by Lei et al of 279 patients with confirmed COVID-19 recruited to Imam-Reza teaching and treatment hospital, Tabriz, Iran, determined abnormal liver enzymes related to COVID-19 infection in patients who had not any historical record of liver diseases and chronic hepatitis viral infection and identified their liver disease was due to COVID-19 disease. This study shows that 41 (14.70%) patients revealed an elevation level of ALT in all cases. However, only 75% (4 of 41) of patients experience high ALT accompanied by high-level AST (~89 U/L and 105 U/L vs. 21 U/L and 33 U/L, respectively; p-value < 0.001). Moreover, seven patients (17.07%) who were recruited from the intensive care unit had increased ALT levels compared with 22 patients (9.24%) with normal ALT, and the majority of them were male in comparison with normal ALT patients (p-value $= 0.017$). In the context of elevated ALT levels, the authors classified the patients into four groups; 1X ALT, 1.5X ALT, 2X ALT, 3X ALT, and more than 3X ALT, and found that AST values were significantly different between groups ($p < 0.001$). Also, rge AST was significantly increased in groups belonged to 3X ALT and greater than 3X ALT (p¼0.033 and $p<0.001$, respectively).[20] In a single-center study in Erbil city/Kurdistan region of Iraq that comprised 74 patients with confirmed COVID-19 with no history of liver disease, elevated both ALT and AST were recorded in 25 patients (34.7%) and 28 (40%), respectively, and most of them were male (74.3%) compared with female (54.2%).[21] Another single retrospective study of 115 COVID-19 patients at Zhongnan Hospital of Wuhan University from January 18, 2020 to February 22, 2020 determined liver function indexes concerning disease progression.[7] To evaluate the effect of COVID-19 on liver injury, the authors excluded patients with chronic hepatitis B, chronic hepatitis B, cirrhosis, and other known liver diseases. Although ALT and AST levels were increased in 11 (11/115, 9.57%) and 17 (17/115, 14.78) patients, respectively, the majority of cases presented mild abnormalities, and only one patient presented elevation of more than $3 \times$ the ULN at baseline. Moreover, there was no significant difference in the levels of ALT and AST ($p > 0.05$) in those patients compared with those with community-acquired pneumonia. This study revealed that liver function indexes such as ALT, AST, TBIL, albumin (ALB), globulin (GLB), international normalized ratio (INR), LDH, and CRP did not show an independent association with severity in patients with COVID-19.

Liver Enzymes in Pediatric Patients with COVID-19

Despite previous studies on predisposing adults to SARS-CoV-2 infection, recent studies confirmed that COVID-19 affects pediatric patients.[14,22] In a cohort study that included 44,672 patients from China with laboratory-confirmed COVID-19, 1 to 2% were pediatric patients. However, the clinical course of more than 90% of pediatric patients admitted to Wuhan Children's Hospital was much milder compared with adults with COVID-19 disease.[23] Another retrospective study was published in which 157 pediatric patients were admitted to Wuhan Children's Hospital with laboratory-confirmed SARS-CoV-2 infection. In this retrospective study, the immune-associated biomarkers such as NLR (the neutrophil to lymphocyte ratio and biochemical indexes including ALT, AST, creatine-kinase-MB (CK-MB) activity, and LDH abnormal liver test) were determined. The study showed a striking contrast between the results obtained from adult and pediatric patients. In pediatric patients, NLR was negatively associated with ALT, AST, CK-MB activity, and LDH levels that were not seen in adult patients, suggesting that age-related neutrophil recruitment is responsible for worsening disease. Moreover, the children with moderate disease (median age 18–123 months, and 59.5% were girls) revealed liver and myocardial injuries documented by elevated levels of ALT, AST, CK-MB, and LDH.[2]

Abnormal Liver Enzymes Correlated with Inflammation in COVID-19 Patients

Liver damage could result from invading the host by the virus and the immune responses evolved by releasing inflammatory mediators like chemokines and cytokines.[24,25] In severe cases of COVID-19, CRP and NLR showed significant elevation. To assess correlations between CRP and NLR and liver enzymes, including ALT, AST, ALP, GGT, LDH, GLB, and INR by logistic regression analysis, the study reported by Zhang et al showed a positive correlation between liver enzymes with CRP. However, CRP revealed no correlation with TBIL and a negative correlation with ALB ($p < 0.001$). Similar to CRP, ALB showed a negative correlation with NLR ($p < 0.001$), and no correlation was observed between GLB and NLR ($P > 0.05$). This study concluded that abnormalities of liver function indexes did not have severe clinical consequences.[7]

A recent study reported significantly higher levels of CRP (231.1 ± 35.7 pg/mL) and IL-6 (4.9 ± 1.0 mg/dL) in COVID-19 patients with abnormal liver tests than those who had normal liver tests (p-value < 0.05). The authors found revealed that there were no significant differences in the increase in levels of CRP and IL-6 between males and females (for CRP: males (3.43±1.38), versus females (1.450.73); p:=0.626' and for IL-6: males (371.45±36.181) versus females (384.01±51.567); p=0.167). It has been suggested that abnormal liver tests in patients with COVID-19 could originate from high levels of CRP and IL-6 and consequent severity of inflammation. Thus, the serum level of inflammatory biomarkers could effectively determine disease severity.[21] In line with this study, Effenberger et al studied the relationship between systemic inflammation reflected in elevated interleukin-6 (IL-6) and liver injury in 655 hospitalized COVID-19 patients. They found that elevated AST (≥ 50 units/L) was reported in 41 (42%) COVID-19 patients of whom patients with higher AST exhibited serum concentrations of IL-6 significantly ($p < 0.001$), CRP ($p < 0.05$) compared with patients with normal AST. The result of this study highlighted that the origin of liver injury could be associated

with systemic inflammation, which was noted as an increase in IL-6 and acute phase proteins.[26]

Another study by Sun et al classified COVID-19 patients into four groups: mild, moderate, severe, and critically ill, and measured liver enzymes among them. Although higher levels of liver enzymes such as ALT, ALP, and GGT were pronounced, only AST was significantly higher among the four groups ($p = 0.034$). However, the serum levels of CRP, ESR, ferritin, and IL-6 were significantly higher in severe and critically ill groups. Notably, serum ferritin levels positively correlated with AST, ALT, and LDH, confirming that the hyperimmune inflammation condition is thought to play a crucial factor in predicting morbidity and mortality.[10] A summary of published studies is shown in ►**Table 1**.

Abnormal Liver Enzymes Related to Liver Histopathology

Recent studies indicated that approximately 44% of COVID-19 patients suffered deranged LFTs,[3,27] which the histopathological changes in these cases may explain. Vishwajeet et al evaluated the morphological changes in the liver of COVID-19 patients. This study was performed at a tertiary care center from May 2020 to March 2021 in western India. Core biopsies of the liver were taken at 40 cases that reported macrovesicular steatosis, vascular alterations, and lobular necroinflammation. Lobular necroinflammation was documented in one-fourth of patients, while no statistical significance of the correlation between deranged LTF and any specific changes in pathological findings was not

Table 1 Studies of COVID-19 and liver injury

Patients (*n*)	Study	Objective of the study	Main outcome	Special outcome	References
191	A retrospective, multicenter cohort study	The risk factors associated with in-hospital death in adult inpatients with COVID-19	-Older age -Higher Sequential Organ Failure Assessment (SOFA) score (5·65, 2·61–12·23; $p < 0·0001$). -D-dimer greater than 1 μg/mL (18·42, 2·64–128·55; $p = 0·0033$)	Prolonged viral shedding provides the rationale for a strategy of isolation of infected patients and optimal antiviral interventions in the future	Zhou et al
147	A retrospective study	Investigated the serum hepatic enzyme activities in different phenotypes of COVID-19 patients	Increase in serum levels of AST and LDH Decrease in serum level of SOD in severe and critical patients, compared with mild cases	DG treatment may alleviate the abnormal liver enzyme activities in noncritical COVID-19 patients	Liao et al[1]
82	Case report	Characteristics cases of death from COVID-19	The bulk of the patients who died had comorbidities (76.8%) including: -Hypertension (56.1%) -Heart disease (20.7%) -Diabetes (18.3%) -Cerebrovascular disease (12.2%) -cancer (7.3%). Respiratory failure remained the leading cause of death (69.5%), followed by sepsis/MOF (28.0%). Cardiac failure (14.6%) Hemorrhage (6.1%) Renal failure (3.7%) Most patients had: High neutrophil-to-lymphocyte ratio of >5 (94.5%) High systemic immune-inflammation index of >500 (89.2%) Increased C-reactive protein (100%) LDH (93.2%) D-dimer (97.1%) levels A high level of IL-6 (>10 pg/mL)	-Older males with comorbidities are more likely to develop severe disease and even die from SARS-CoV-2 infect Respiratory failure is the main cause of COVID-19. Cytokine release syndrome-mediated damage to other organs, including: cardiac, renal, hepatic, and hemorrhagic damage	Zhang et al[18]
417	Clinical records and laboratory results	Evaluating clinical characteristics of COVID-19 in patients with abnormal liver test results	Abnormal liver test results during hospitalization in 318 (76.3%) that was elevated to more than 3× the upper limit of normal, including: ALT, 49 (23.4%). AST 31 (14.8%), total bilirubin, 24 (11.5%). Liver injury during hospitalization in 90 patients (21.5%) The application of lopinavir/ritonavir was also found to lead to increased odds of liver injury	Patients with abnormal liver tests were at higher risk of progressing to severe disease. Certain medications during hospitalization leads to detrimental effects on liver injury	Cai and Chen[17]

Table 1 (*Continued*)

Patients (*n*)	Study	Objective of the study	Main outcome	Special outcome	References
348	A retrospective cohort study	Investigating liver injury as a predictive outcome in COVID-19 patients	The presence of new onset liver enzyme elevation was associated with increased severity of illness. Presence of liver injury increased the chance of acute hypoxic respiratory failure requiring. The degree and timeline of liver enzyme elevation during hospitalization corresponded with increase in other inflammatory markers	Liver injury correlated with the inflammatory syndrome caused by COVID-19. The degree of liver injury corresponding with severity of inflammation	Mishra et al[13]
5,771	A multicenter retrospective cohort study	Longitudinal liver function correlated with the risk factors and death in COVID-19 patients	AST elevated first, followed by ALT in severe patients ALP modestly increased during hospitalization and largely remained in the normal range. The fluctuation in TBIL levels was mild in the nonsevere and the severe group. Common factors related with increased injury indicators were decrease in lymphocyte count. Increase in neutrophil count male gender	AST abnormality was associated with the highest mortality risk compared with other indicators of liver injury during hospitalization	Lei et al[8]
63	A binary logistic regression model	Investigated prognostic factors of disease severity in patients with COVID-19	General symptoms: Fever (84.1%). Cough was present in only slightly over half of the patients. Decrease in lymphocyte and eosinophils count In severe and critically ill patients: Increase in eosinopenia Decrease in CD4+, CD8+ T lymphocytes, and B lymphocytes. Elevated liver function tests including AST, ALT, GGT and LDH. Decrease in albumin. Increase in inflammatory markers CRP, ESR and ferritin and IL-6	The presence of a hyperimmune inflammatory state indicated higher morbidity and mortality. Independent predictors of disease severity including: C-reactive protein level CD8 T lymphocyte counts D-dimer	Sun et al[10]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DG, diammonium glycyrrhizinate; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyltransferase; IL-6, interleukin-6; LDH, lactate dehydrogenase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOD, superoxide dismutase; TIBIL, total bilirubin.

determined.[28] The vascular alteration in portal tracts observed in COVID-19 patients could thus be related to a systemic hypercoagulable state induced by the viral infection that resulted in the derangement of hepatic vasculature.[28] Indeed, pathological examination of liver tissues obtained from COVID-19 patients confirmed liver involvement by characterizing microvesicular steatosis, focal necrosis with infiltration of lymphocytes, and microthrombosis.[29,30] Zhao et al evaluated liver histopathology from 17 COVID-19 patients who underwent liver autopsy. This study displayed a spectrum of impairments that may affect the severity of the disease. The prominent features were extensive platelet-fibrin microthrombi, steatosis, histiocytic hyperplasia in the portal tract, mild lobular inflammation, ischemic-type hepatic necrosis, and hemorrhage in zone 3 suggestive of systemic damage that evolved from platelet microthrombi and megakaryocytes in the microvasculature of the liver.[31]

Schmit et al examined liver histopathology from 14 autopsies of deceased COVID-19 confirmed patients. Only three patients showed elevated levels of liver enzymes such as AST, ALT, and GGT at the precious moment of death. Further histopathological evaluation of 14 deceased patients due to COVID-19 infection revealed severe central lobular necrosis in one case, steatosis in eight cases (57%), and lobular and portal inflammation in twelve cases (86%). In addition, two cases were reported with a mixed infiltration with neutrophils, and one had a predominantly eosinophilic infiltrate in the portal area. However, based on autopsy evaluation, central lobular necrosis (zone 3, and in some instances, zone 2) associated with moderate lobular and portal inflammation indicated the most frequently observed histopathological change. It was hypothesized that changes in liver pathology were not due to direct damage caused by the SARS-CoV-2 infection, while it might raise a probability

of a combination of hypoxia caused by severe pulmonary disease and drug toxicity in liver damage in deceased COVID-19 patients.[32]

Liver Enzymes May Be Associated with a Higher Mortality Rate in the COVID-19-Associated Liver Injury

Although various studies reported elevated liver enzymes, especially aminotransferase, among severe COVID-19, the relationship between liver chemistries and in-hospital deaths is unclear.[33–35] In this context, a large retrospective cohort study at three centers conducted by Ding et al evaluated the association between in-hospital outcomes of patients with COVID-19 and liver abnormalities and liver diseases such as hepatitis B. This study included 2,073 patients with COVID-19 to analyze LFT abnormalities. The authors compared liver abnormalities in deceased and discharged patients at admission and during hospitalization. On admission, 73.0% (146/200) of deceased patients had abnormal liver tests, and this incidence of liver abnormalities was higher compared with discharged patients (73.0 vs. 43.4%, $p < 0.001$). Further in comparison to discharged patients, deceased patients had more liver tests abnormalities (58.6 vs. 92.5%, $p < 0.001$), and liver injury (3.6 vs. 31.5%, $p < 0.001$). The value of abnormal admission levels of liver chemistries was explored to predict in-hospital mortality. Liver injury in patients with COVID-19 was associated with in-hospital death (hazard ratio [HR]: 2.08; 95% CI, 1.25–3.44; $p = 0.005$). Moreover, COVID-19 patients with abnormal AST and direct bilirubin levels at admission showed predictive potential for in-hospital death, with HRs of 1.61 (95% CI, 1.20–2.15, $p = 0.001$) and 1.57 (95% CI, 1.14–2.16, $p = 0.006$), respectively. Among patients with no severe pneumonia on admission, those with liver injury (5.9% versus 2.0%, $p = 0.002$) or abnormal AST (9.8% versus 2.0%, $p < 0.001$) showed increased mortality rate. In addition, patients with COVID-19 and hepatitis B virus showed 6.0% (8/134) in-hospital mortality.[30]

Conclusion and Future Views

In this review, we have highlighted liver test abnormalities in patients diagnosed with COVID-19 and summarized relatively recent papers. Although severe COVID-19 patients showed a higher percentage of liver abnormality tests than those with nonseverity patients, the underlying mechanism behind the chronic liver disease and consequent abnormal liver tests in COVID-19 patients require detailed evaluation.[17] Moreover, SARS-CoV-2 infection has a complicated mechanism. Despite the progressive respiratory failure, which is considered a leading cause of COVID-19, the virus and cytokine storm could damage other organs, including cardiac, renal, hepatic, and hemorrhagic injuries.[18] In this regard, elevated serum levels of liver enzymes have been reported to be contributed to the early severity of the disease.[10] Nevertheless, some research has suggested that COVID-19-related liver dysfunction may arise from secondary liver damage by respiratory distress syndrome-induced hypoxia, multiple organ failure, and the administration of potentially hepatotoxic drugs.[36,37] In addition, in a recently published paper, the positive correlation between increased level of transaminase liver enzyme and the level of inflammation in COVID-19 patients has suggested that abnormal liver tests might be associated with elevated CRP.

Thus, the histopathological character of patients with COVID-19 may overcome issues regarding distinguishing the effect of a viral infection such as hepatitis B virus, cytomegalovirus, and other treatment modalities, including antibiotics and antiviral drugs from abnormal liver associated with COVID-19.[31] There are only limited available data on the pathological findings in the liver of patients recognized by COVID-19.[31]

Another possible mechanism is due to the level expression of ACE2 receptors in cholangiocytes displayed as similar to that expressed in type 2 alveolar cells of the lungs; one may propose that the liver could be a potential target for COVID-19. In addition, the expression of ACE receptors expressed in liver cholangiocytes (59.7%) was higher than in hepatocytes (2.6%).[12,36] However, COVID-19 patients who were treated with the administration of ACE inhibitors showed to have liver-test abnormality at admission.[11]

In conclusion, from the point of view of the abnormal liver test associated with severity in COVID-19 patients, we presented recent data on the clinical characteristic of patients with abnormal liver enzymes. However, due to multiorgan damages in COVID-19 patients, various issues should be considered, including the pathology and pathophysiology of the liver tissue, especially on the activation process of the immune response and cytokine storm to avoid the severity of disease and requiring mechanical ventilation, and mortality. Moreover, certain medications received by COVID-19 patients during hospitalization are of paramount importance and need to be evaluated.

Authors' Contributions

All authors contributed to the review on effect of COVID-19 on serum activity of liver enzymes: Is this associated with severity and mortality rate? They have all assisted in writing, revision, and approval of its final version.

Funding Statement

This project received no specific funding.

Conflicts of Interest

None declared.

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