

An overview of SARS-COV-2-related hepatic injury

Abdullah Tarık Aslan¹, Hatice Yasemin Balaban²

¹Department of Internal Medicine, Hacettepe University School of Medicine, Ankara, Turkey; ²Department of Gastroenterology, Hacettepe University School of Medicine, Ankara, Turkey

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen of coronavirus disease 2019 (COVID-19), is highly contagious and has a variety of clinical manifestations, including liver injury. There have been a few reports indicating acute-on chronic liver failure among COVID-19 patients, however, patients with COVID-19-related liver injury are generally asymptomatic and present with a mild to moderate elevation in serum hepatic enzymes. Severe COVID-19 patients have high rates of liver injury with poorer outcomes. The pattern of abnormalities in liver biochemical indicators may be hepatocellular, cholestatic, or mixed. Although the pathogenesis of hepatic injury is not yet completely understood, causes of liver damage include systemic inflammatory response syndrome, ischemia-reperfusion injury, side effects of medications, and underlying chronic liver disease. While viral RNA has been detected in hepatocytes, it remains unknown if the coronavirus has the capacity to cause cytopathic effects in hepatic tissue. Additionally, it is important to remember that the current upheaval to daily life and access to healthcare caused by the COVID-19 pandemic has had a significant and negative effect on other patients with chronic liver disease. The objective of this review was to summarize the current literature on COVID-19-related hepatic injury with an examination of clinical features, potential pathogenesis, and histopathological findings of this entity.

Keywords: COVID-19; drug-induced liver injury; hepatic injury; hepatotoxicity; liver; SARS-CoV-2.

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 led to a global pandemic and a significant medical crisis. As of January 25, 2021, the total number of cases of the disease caused by infection with SARS-CoV-2, coronavirus disease 2019 (COVID-19), was some 100 million worldwide, and the US led with approximately 25 million cases.^[1] While patients with COVID-19 typically present with a fever, cough, and shortness

of breath, mounting evidence shows that patients might also have extra-pulmonary involvement, including the liver. A growing body of evidence has shown that patients with COVID-19 may develop different degrees of liver dysfunction, primarily characterized by elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) accompanied by slightly increased bilirubin levels.^[2-6] Liver involvement was also reported with SARS-CoV^[7] and Middle East respiratory syndrome (MERS-CoV).^[8]

The reasons for liver injury in COVID-19 patients may be multifactorial and can be delineated according to several mechanisms. It has been established that SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE-2) receptor and the co-receptor (neuropilin-1) to enter host cells, and this entry is regulated by transmembrane protease serine 2 (TMPRSS2).^[9-11] ACE-2 expression occurs at different densities. Cholangiocytes, and to a lesser extent, hepatocytes, can express ACE-2 receptors on the cell surface.^[12,13] Therefore, theoretically, one mechanism for liver injury might be viral-induced cytopathic effects. Other potentially contributing effects are systemic inflammatory response syndrome,^[14] ischemia-reperfusion injury,^[15] drug-induced liver injury,^[6] or underlying chronic liver disease.^[16]

This review is based on a literature search of English-language articles published in the PubMed and MEDLINE databases as of December 2020.

Clinical Features of Hepatic Involvement in COVID-19

The prevalence of abnormal hepatic biochemical indicators in hospitalized patients with symptomatic COVID-19 ranges from 14% to 53%. The prevalence of hepatic injury among asymptomatic patients infected with SARS-CoV-2 is largely unknown. The most common abnormalities are mild elevation of transaminases, hypoalbuminemia, elevated gamma-glutamyltransferase (GGT), and hyperbilirubinemia.^[17-21] Many studies have demonstrated high rates of liver function test (LFT) abnormalities in severe COVID-19 patients, such as intensive care unit patients and those requiring mechanical ventilation.^[5,22] The pattern of LFT abnormality is generally hepatocellular, rather than cholestatic.^[23,24] A high bilirubin level and liver stiffness observed with transient elastography has been reported to be correlated with more severe outcomes.^[25,26] Although LFT abnormalities have been frequently encountered in COVID-19 patients, and may be associated with mortality, acute liver failure has been demonstrated in only a few patients with underlying chronic liver disease and multi-organ dysfunction.^[27,28]

Another important point is that the hepatic injury in COVID-19 patients is usually assessed with LFT abnormalities in the current literature; elevated ALT and AST levels are the most frequent biomarker measures of hepatic parenchymal injury. Based on the available data, patients infected with SARS-CoV-2 generally have mildly to moderately elevated aminotransferase levels in the early stages of the disease, accompanied

How to cite this article: Aslan AT, Balaban HY. An overview of SARS-COV-2-related hepatic injury. *Hepatology Forum* 2021; 2(3):122-127.

Received: May 06, 2021; **Accepted:** June 24, 2021; **Available online:** September 15, 2021

Corresponding author: Hatice Yasemin Balaban; Hacettepe Universitesi Tip Fakultesi, Gastroenteroloji Anabilim Dalı, Ankara, Turkey
Phone: +90 312 305 17 13; **e-mail:** yhbabalan@gmail.com



OPEN ACCESS
This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

© Copyright 2021 by Hepatology Forum - Available online at www.hepatologyforum.org

by a slight increase in bilirubin level.^[29-31] In a study of 5700 individuals with COVID-19, ALT and AST abnormalities were detected in 39.0% (n=2176) and 58.4% (n=3263), respectively.^[32] A meta-analysis of 108 studies encompassing 17,776 patients found abnormal aminotransferase levels in 24% of the patients (95% confidence interval [CI]: 17-31).^[33] Consistent with those findings, another meta-analysis reported that the AST level was elevated in 15% of 2514 individuals in 16 studies and the ALT level was higher than the accepted normal level in 15% of 2711 patients in 17 studies (95% CI: 13.6-16.5 and 13.6-16.4, respectively).^[34] Patients with high aminotransferase levels tended to have a higher body mass index and underlying chronic liver disease and were generally male and elderly.^[29] Additionally, the prevalence of elevated transaminase and bilirubin levels has been reported to be at least double in cases of severe COVID-19.^[35] However, myositis can produce elevated aminotransferases without the presence of a concomitant hepatic injury, and the level of creatinine kinase, a muscle damage marker, was reported to be elevated in 14% of patients with COVID-19 in a cohort from China.^[4] Evaluation of the albumin level and prothrombin time are standard tests to assess function of the liver. Zhang et al.^[36] reported hypoalbuminemia in 55% of hospitalized COVID-19 patients. It was also found to be a factor associated with greater disease severity and an independent predictor of mortality.^[37,38] Given the high inflammatory activity in COVID-19 patients, the level of albumin may decrease as a result of increased capillary permeability.^[39] Higher catabolic activity and malnutrition may be additional factors that could result in hypoalbuminemia in severe COVID-19 cases. Alkaline phosphatase (ALP) and GGT are markers for biliary injury and cholestasis. The bilirubin level also provides important clues regarding hepatic clearance and biliary secretion capacity. However, none of these markers are sufficiently specific for liver functions.

Potential Pathogenesis of Hepatic Injury in COVID-19

The ACE-2 receptor is not only expressed in type-2 alveolar cells; abundant expression of ACE-2 has been found in cholangiocytes.^[11] Hepatocytes can express ACE-2 receptors on the cell surface with less enrichment than cholangiocytes.^[40,41] In addition, TMPRSS2 mRNA expression has been demonstrated in a subset of hepatocytes and cholangiocytes.^[42]

There are 3 proposed mechanisms responsible for abnormality in LFTs among COVID-19 patients.

i. Viral Cytopathic Effects

Although SARS-CoV-2 particles and RNA have been identified in liver biopsy specimens of patients with COVID-19, productive infection of hepatocytes has yet to be demonstrated. Similarly, the low rate of clinically significant hepatic injury and ALP elevation in patients without pre-existing chronic liver disease or multi-organ failure suggests that direct infection of hepatocytes or cholangiocytes is not a main mechanism of hepatic injury. According to the available data, we may conclude that liver injury in COVID-19 most likely originates from systemic inflammation, underlying chronic liver disease, or multi-organ dysfunction, rather than a direct cytopathic effect of viral infection of liver cells.

ii. Immune-Mediated Hepatic Injury

As previously mentioned, COVID-19-related hepatic injury is more common in severe forms of COVID-19. It has been established that the antiviral response is mediated by joint action of the innate and adaptive immune systems. In brief, the immune system of human beings charac-

teristically recognizes pathogen-associated molecular patterns (PAMPs) along with special viral antigens and expresses inflammatory molecules, such as cytokines and chemokines, in response. These molecules stimulate macrophages and T-cells to kill the virus and virus-infected cells.^[43] Early elevation of several inflammatory cytokines (e.g., interleukin [IL] 6, IL-10, IL-2, interferon lambda [IFN λ]) have been found in the vast majority of COVID-19 patients.^[44,45] This excessive cytokine response against the virus remains high and becomes a cytokine storm over the course of the disease in severe COVID-19 cases.^[44,46] Patients with severe outcomes had increased levels of the inflammatory cytokines IFN λ , transforming growth factor alpha, thymic stromal lymphopoietin, IL-16, IL-23, IL-33, and coagulopathy-related mediators, such as thrombopoietin.^[44] This kind of overreaction is called "cytokine storm syndrome," which can be associated with multi-organ failure and disseminated intravascular coagulation due to a dysregulated release of pro-inflammatory cytokines.^[47,48] This uncontrolled inflammatory reaction can also result in endotheliitis, which has been identified in the hepatic tissue samples of the patients with COVID-19.^[48] In a study that assessed liver samples taken at autopsy, the authors reported massive dilation of portal vein branches, luminal thrombosis, portal tract fibrosis, and microthrombi in the sinusoids.^[49] Additionally, patients with severe COVID-19 have been found to have lower levels of stromal growth factors, such as epidermal growth factor, which mediate tissue healing and repair.^[44]

The available evidence suggests that an exaggerated systemic immune response can be considered a major contributory factor to liver injury in COVID-19 patients.

iii. Drug-Induced Liver Injury

Many drugs, such as acetaminophen, antivirals, antibiotics, corticosteroids, and immune-modulators, utilized for symptom relief, treatment of accompanied bacterial infections, or COVID-19 itself, are potentially hepatotoxic. A meta-analysis reported a pooled incidence of drug-induced hepatic injury in 25.4% of COVID-19 patients.^[19] Cai et al.^[50] found that lopinavir-ritonavir use was associated with a 7-times higher odds of LFT alterations during the course of treatment. In contrast, a clinical trial of 199 patients with severe COVID-19 reported that LFT abnormalities were not more frequent in patients treated with lopinavir-ritonavir compared with those who received standard care.^[51] It is necessary to note that a lopinavir-ritonavir regimen has now been almost abandoned in COVID-19 treatment, as has hydroxychloroquine.^[52]

Remdesivir was found to significantly shorten the recovery time of hospitalized patients with COVID-19 and has been used as a standard of care therapy in some countries.^[52,53] In a randomized controlled trial, the rate of abnormalities in aminotransferase levels among patients treated with remdesivir was 5% to 8% and 1% to 2% of all patients experienced significant increases in ALT/AST levels that would warrant discontinuation of therapy.^[54] In a smaller double-blinded placebo-controlled trial in China, 155 patients treated with remdesivir were compared with 78 patients who received a placebo. In this study, 15 patients (10%) had an increased total bilirubin level, and severe hyperbilirubinemia was seen in only 1 patient. Similar to other studies, an AST abnormality was detected in 5% of patients, and no patient had grade 3 or 4 level adverse events related to elevation in AST level. Remdesivir treatment was discontinued in 18 patients (12%) because of severe adverse events. However, hepatic toxicity was not the cause of the event in any of these cases.^[55] Furthermore, certain immunomodulator drugs, such as tocilizumab and dexamethasone, used to tame an uncontrolled immune response in severe COVID-19, can potentially lead to hepatic injury

by reactivating hepatitis B virus in patients with occult infections.^[56,57] Other drugs, including baricitinib^[58] and favipiravir,^[59] are notoriously known to have the potential to cause hepatic injury.

Acetaminophen is frequently used to relieve COVID-19 symptoms of fever and body ache. Acetaminophen is the most common cause of drug-induced liver failure worldwide. However, no studies have so far specifically addressed its role in observed LFT abnormalities among COVID-19 patients.

Histopathological Findings of COVID-19-Related Hepatic Injury

Histopathological examinations of liver biopsies taken from patients with COVID-19 revealed that the most common findings were moderate macrovacuolar steatosis, and mild lobular and portal inflammation.^[60,61] Findings suggesting acute hepatitis were detected in almost 50% of cases. The bile ducts were generally unaffected. However, changes may be related to baseline comorbidities and a variable degree of acute congestion may be seen. Additionally, SARS-CoV-2 RNA has been identified in up to 55% of biopsy specimens.^[61,62] Partial or complete sinusoidal thrombosis has been another important finding observed in histopathological examinations of postmortem wedge biopsies.^[49] Another report of postmortem whole-body autopsy and macroscopic inspection study of 22 patients (18 patients with comorbidities and 4 patients without any comorbidity) conducted in Italy noted that liver parenchymal congestion was typically observed. Similar to previous reports, microscopic changes seen included sinusoidal congestion, red blood cell extravasation into the space of Disse, congestion of small veins, hepatocyte necrosis, and macrovacuolar and microvacuolar steatosis.^[63] The available data suggest that most of pathological findings appear to originate from underlying co-morbidities and a systemic inflammatory response, rather than as direct SARS-CoV-2-related cytopathic effects.

The Impact of Underlying Chronic Liver Disease on Clinical Outcome in COVID-19 Patients

The prevalence rate of underlying chronic liver disease in patients with COVID-19 has been reported to range from 1% to 11%.^[64-66] The liver is a well-known regulator of immune homeostasis. Therefore, patients suffering from chronic liver diseases, especially those with cirrhosis, may be at higher risk of acquiring SARS-CoV-2 and COVID-19-related complications.^[67] However, the current evidence shows no tendency towards increased susceptibility to SARS-CoV-2 infection in patients with chronic liver disease.^[66] A large-scale study of 2780 COVID-19 patients reported that the patients with chronic liver disease had a 3-fold higher risk of mortality compared with patients without chronic liver disease, and this risk was substantially (~5-fold) higher in patients with cirrhosis.^[68] Similarly, Sarin et al.^[69] confirmed a higher rate of severe liver injury and death in patients with more advanced stages of liver disease following SARS-CoV-2 infection, particularly in patients with a Child-Pugh score of ≥ 9 . However, the current literature is inconsistent in this regard, since no association was observed between pre-existing liver disease and COVID-19 severity or mortality in another study.^[70] It should be kept in mind that chronic liver disease includes a spectrum of diseases that may have the potential to change outcomes. For instance, liver transplant recipients and patients with autoimmune liver disease who use immunosuppressive drugs merit special concern with regard to COVID-19-related outcomes. However, the current literature is not yet sufficient to indicate that these patients have a higher risk of infection or a higher likelihood of

serious complications compared with the general population.^[71-74]

The other important type of chronic liver disease that should be noted is non-alcoholic fatty liver disease (NAFLD). Patients with NAFLD have exhibited more rapid disease progression and a longer duration of viral shedding compared with those without NAFLD.^[16] Similarly, a higher risk of severe disease has been reported when NAFLD was found with co-existing obesity, in younger patients and in patients with high hepatic fibrosis scores.^[75-77] Given the profound immunological changes seen in obesity, such as low-grade inflammation and macrophage activation, it is likely that similar changes in the immune system of patients with NAFLD play an important role in the higher rate of severe COVID-19 in these patients.^[77,78] In addition, NAFLD significantly increases the hepatotoxic potential of some drugs, including acetaminophen, which may result in a higher incidence of the LFT abnormalities in NAFLD patients during the course of COVID-19.^[79] As most studies have not stratified patients with NAFLD according to the presence of non-alcoholic steatohepatitis (NASH), it is still unknown whether more severe outcomes stem from the presence of NASH rather than NAFLD.

In addition to patients with NAFLD, patients with alcohol-associated liver disease (ALD) may be at particular risk of severe COVID-19. Excessive alcohol use weakens the anti-infective defense mechanisms of the human body by disrupting both the innate and adaptive immune systems.^[80] Moreover, accompanying comorbidities, such as obesity and use of corticosteroid therapy for alcoholic hepatitis, may increase the risk of severe COVID-19. Likewise, concurrent smoking, which is frequent among patients with ALD, makes these patients vulnerable to COVID-19-related mortality and morbidity. At the time of writing, there are not enough data regarding the impact of COVID-19 on ALD. Nevertheless, SARS-CoV-2 infection, particularly a severe infection, can act as a significant decompensating factor in patients with ALD.

The current pandemic has created unbearable difficulties for healthcare services around the world. Limited access to healthcare centers and the deferral of all non-urgent diagnostic and screening tests or treatments have led to an unprecedented upheaval in the care of patients with chronic liver disease.^[81] For instance, postponement of prophylactic screening and treatment of esophageal varices, insufficient hepatocellular carcinoma screening in cirrhotic patients, and a significant decrease in organ donation and liver transplantation will have long-term adverse outcomes that cannot be compensated for with future interventions.^[82] In addition, measures to control the spread of the virus, including social distancing and curfews, have resulted in negative influences on the mental health of patients and provoked alcohol addiction relapse and abuse, which can aggravate ALD.^[83]

Conclusion

LFT abnormalities are commonly seen in COVID-19 patients on admission or during follow-up. Although the underlying pathogenesis of hepatic injury in COVID-19 is not fully understood, a direct viral cytopathic effect seems unlikely at this time. Hepatic injury associated with COVID-19 seems to correlate with the severity of inflammatory response and ensuing multi-organ dysfunction, the presence of pre-existing chronic liver disease, or exposure to hepatotoxic drugs. Additionally, patients with NAFLD and cirrhosis have an increased risk of severe disease independent of other concomitant comorbidities. Last, but not least, healthcare professionals should be aware that restrictions on access to healthcare can have serious short- and long-term effects on morbidity and mortality associated with chronic liver disease.

Peer-review: Externally peer-reviewed.

Author Contributions: Author contributions: Aslan AT and collected data and wrote the paper; Balaban HY edited the paper; Both authors read and approved the final manuscript.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

- Johns Hopkins University of Medicine. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University. 2021. Available at: <https://coronavirus.jhu.edu/map.html> Accessed on January 25, 2021.
- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382(18):1708-1720. [CrossRef]
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323(11):1061-1069. Erratum in: *JAMA* 2021;325(11):1113. [CrossRef]
- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395(10223):507-513.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497-506. [CrossRef]
- Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical features of COVID-19-related liver functional abnormality. *Clin Gastroenterol Hepatol* 2020;18(7):1561-1566. [CrossRef]
- Chau TN, Lee KC, Yao H, Tsang TY, Chow TC, Yeung YC, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. *Hepatology* 2004;39(2):302-310. [CrossRef]
- Alsaad KO, Hajeer AH, Al Balwi M, Al Moaiqel M, Al Oudah N, Al Ajlan A, et al. Histopathology of Middle East respiratory syndrome coronavirus (MERS-CoV) infection - clinico-pathological and ultrastructural study. *Histopathology* 2018;72(3):516-524. [CrossRef]
- Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell* 2020;183(6):1735. Erratum for: *Cell*. 2020 Apr 16;181(2):281-292.e6.
- Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181(2):271-280.e8. [CrossRef]
- Daly JL, Simonetti B, Klein K, Chen KE, Williamson MK, Antón-Plágaro C, et al. Neuro-pilin-1 is a host factor for SARS-CoV-2 infection. *Science* 2020;370(6518):861-865. [CrossRef]
- Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. *Gastroenterology* 2020;158(6):1831-1833.e3. [CrossRef]
- Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem Biophys Res Commun* 2020;526(1):135-140. [CrossRef]
- Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine* 2020;55:10276. [CrossRef]
- Kavaliuniene A, Vaitiekienė A, Cesnaite G. Congestive hepatopathy and hypoxic hepatitis in heart failure: a cardiologist's point of view. *Int J Cardiol* 2013;166(3):554-558. [CrossRef]
- Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020;73:451-453. [CrossRef]
- Fu Y, Zhu R, Bai T, Han P, He Q, Jing M, et al. Clinical features of patients infected with coronavirus disease 2019 with elevated liver biochemistries: a multicenter, retrospective study. *Hepatology* 2021;73(4):1509-1520. [CrossRef]
- Hao SR, Zhang SY, Lian JS, Jin X, Ye CY, Cai H, et al. Liver enzyme elevation in coronavirus disease 2019: a multicenter, retrospective, cross-sectional Study. *Am J Gastroenterol* 2020;115(7):1075-1083. [CrossRef]
- Kulkarni AV, Kumar P, Tevethia HV, Premkumar M, Arab JP, Candia R, et al. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. *Aliment Pharmacol Ther* 2020;52(4):584-599. [CrossRef]
- Yip TC, Lui GC, Wong VW, Chow VC, Ho TH, Li TC, et al. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. *Gut* 2021;70(4):733-742. [CrossRef]
- Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020;26(7):1017-1032. [CrossRef]
- Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, Fan Y, Zheng C. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020;20(4):425-434. [CrossRef]
- Wu Y, Li H, Guo X, Yoshida EM, Mendez-Sanchez N, Levi Sandri GB, et al. Incidence, risk factors, and prognosis of abnormal liver biochemical tests in COVID-19 patients: a systematic review and meta-analysis. *Hepatology* 2020;71(5):621-637. [CrossRef]
- Wijarnprecha K, Ungprasert P, Panjawan P, Harnois DM, Zaver HB, Ahmed A, et al. COVID-19 and liver injury: a meta-analysis. *Eur J Gastroenterol Hepatol* 2021;33(7):990-995. [CrossRef]
- Kovalic AJ, Huang G, Thuluvath PJ, Satapathy SK. Elevated liver biochemistries in hospitalized Chinese patients with severe COVID-19: systematic review and meta-analysis. *Hepatology* 2021;73(4):1521-1530. [CrossRef]
- Effenberger M, Grander C, Fritsche G, Bellmann-Weiler R, Hartig F, Wildner S, et al. Liver stiffness by transient elastography accompanies illness severity in COVID-19. *BMJ Open Gastroenterol* 2020;7(1):e000445. [CrossRef]
- Lenti MV, Borrelli de Andreis F, Pellegrino I, Klersy C, Merli S, Miceli E, et al; Internal Medicine Covid-19 Team. Impact of COVID-19 on liver function: results from an internal medicine unit in Northern Italy. *Intern Emerg Med*. 2020;15(8):1399-1407. [CrossRef]
- Schattenberg JM, Labenz C, Wörns MA, Menge P, Weinmann A, Galle PR, et al. Patterns of liver injury in COVID-19 - a German case series. *United European Gastroenterol J* 2020;8(7):814-819. [CrossRef]
- Ferm S, Fisher C, Pakala T, Tong M, Shah D, Schwarzbaum D, et al. Analysis of gastrointestinal and hepatic manifestations of SARS-CoV-2 infection in 892 patients in Queens, NY. *Clin Gastroenterol Hepatol* 2020;18(10):2378-2379.e1. [CrossRef]
- Wu H, Zhu H, Yuan C, Yao C, Luo W, Shen X, et al. Clinical and Immune Features of Hospitalized Pediatric Patients With Coronavirus Disease 2019 (COVID-19) in Wuhan, China. *JAMA Netw Open* 2020;3(6):e2010895.
- Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. *J Infect* 2020;80(4):388-393. [CrossRef]
- Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020;323(20):2052-2059. Erratum in: *JAMA* 2020;323(20):2098. [CrossRef]
- Dorrell RD, Dougherty MK, Barash EL, Lichtig AE, Clayton SB, Jensen ET. Gastrointestinal and hepatic manifestations of COVID-19: A systematic review and meta-analysis. *JGH Open* 2020;5(1):107-115. [CrossRef]
- Sultan S, Altayar O, Siddique SM, Davitkov P, Feuerstein JD, Lim JK, et

- al; AGA Insti-tute. AGA institute rapid review of the gastrointestinal and liver manifestations of COVID-19, meta-analysis of international data, and recommendations for the consultative management of Patients with COVID-19. *Gastroenterology* 2020;159(1):320-334.e27. [CrossRef]
35. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. *Lancet Gastroenterol Hepatol* 2020;5(6):529-530. [CrossRef]
 36. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: a retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver Int* 2020;40(9):2095-2103. [CrossRef]
 37. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. *Crit Care*. 2020;24(1):255. [CrossRef]
 38. Huang J, Cheng A, Kumar R, Fang Y, Chen G, Zhu Y, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. *J Med Virol* 2020;92:2152-2158. [CrossRef]
 39. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. *JPEN J Parenter Enteral Nutr* 2019;43(2):181-193.
 40. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med* 2020;14(2):185-192. [CrossRef]
 41. De Smet V, Verhulst S, van Grunsven LA. Single cell RNA sequencing analysis did not predict hepatocyte infection by SARS-CoV-2. *J Hepatol* 2020;73(4):993-995. [CrossRef]
 42. Pirola CJ, Sookoian S. SARS-CoV-2 virus and liver expression of host receptors: Putative mechanisms of liver involvement in COVID-19. *Liver Int* 2020;40(8):2038-2040. [CrossRef]
 43. Benani A, Ben Mkaddem S. Mechanisms underlying potential therapeutic approaches for COVID-19. *Front Immunol* 2020;11:1841. [CrossRef]
 44. Lucas C, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 2020;584(7821):463-469. [CrossRef]
 45. Zhou Z, Ren L, Zhang L, Zhong J, Xiao Y, Jia Z, et al. Heightened innate immune responses in the respiratory tract of COVID-19 patients. *Cell Host Microbe* 2020;27(6):883-890.e2 [CrossRef]
 46. Wang H, Ma S. The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction syndrome. *Am J Emerg Med* 2008;26(6):711-715. [CrossRef]
 47. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020;8:e46-e47. [CrossRef]
 48. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395(10234):1417-1418. [CrossRef]
 49. Sonzogni A, Previtali G, Seghezzi M, Grazia Alessio M, Gianatti A, Licini L, et al. Liver histopathology in severe COVID 19 respiratory failure is suggestive of vascular alterations. *Liver Int* 2020;40(9):2110-2116. [CrossRef]
 50. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: Abnormal liver function tests. *J Hepatol* 2020;73(3):566-574. [CrossRef]
 51. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020;382(19):1787-1799. [CrossRef]
 52. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Chi-Chung Cheng V, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID- 19. 2020. Available at: <https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt-v3.6.0.pdf> Accessed on January 8, 2021
 53. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020;383(19):1813-1826. [CrossRef]
 54. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al; GS-US-540-5773 Investigators. Remdesivir for 5 or 10 days in patients with Severe Covid-19. *N Engl J Med* 2020;383(19):1827-1837. [CrossRef]
 55. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020;395(10236):1569-1578. [CrossRef]
 56. Shiota G, Harada K, Oyama K, Udagawa A, Nomi T, Tanaka K, et al. Severe exacerbation of hepatitis after short-term corticosteroid therapy in a patient with "latent" chronic hepatitis B. *Liver* 2000;20(5):415-420. [CrossRef]
 57. Chen LF, Mo YQ, Jing J, Ma JD, Zheng DH, Dai L. Short-course tocilizumab increases risk of hepatitis B virus reactivation in patients with rheumatoid arthritis: a prospective clinical observation. *Int J Rheum Dis* 2017;20(7):859-869. [CrossRef]
 58. Jorgensen SCJ, Tse CLY, Burry L, Dresser LD. Baricitinib: a review of pharmacology, safety, and emerging clinical experience in COVID-19. *Pharmacotherapy* 2020;40(8):843-856. [CrossRef]
 59. Udawadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial. *Int J Infect Dis* 2021;103:62-71. [CrossRef]
 60. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;8(4):420-422. [CrossRef]
 61. Lagana SM, Kudose S, Iuga AC, Lee MJ, Fazlollahi L, Remotti HE, et al. Hepatic pathology in patients dying of COVID-19: a series of 40 cases including clinical, histologic, and virologic data. *Mod Pathol* 2020;33:2147-2155. [CrossRef]
 62. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. *Lancet* 2020;396(10247):320-332. [CrossRef]
 63. Falasca L, Nardacci R, Colombo D, Lalle E, Di Caro A, Nicastri E, et al. Postmortem findings in Italian patients with COVID-19: a descriptive full autopsy study of cases with and without comorbidities. *J Infect Dis* 2020;222(11):1807-1815. [CrossRef]
 64. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020;5(5):428-430. [CrossRef]
 65. Lei F, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. *Hepatology*. 2020;72(2):389-398. [CrossRef]
 66. Mantovani A, Beatrice G, Dalbeni A. Coronavirus disease 2019 and prevalence of chronic liver disease: A meta-analysis. *Liver Int* 2020;40(6):1316-1320. [CrossRef]
 67. Noor MT, Manoria P. Immune dysfunction in cirrhosis. *J Clin Transl Hepatol* 2017;5(1):50-58. [CrossRef]
 68. Singh S, Khan A. Clinical characteristics and outcomes of coronavirus disease 2019 among patients with preexisting liver disease in the United States: a Multicenter Research Network Study. *Gastroenterology* 2020;159(2):768-771.e3. [CrossRef]
 69. Sarin SK, Choudhury A, Lau GK, Zheng MH, Ji D, Abd-Elsalam S, et al; APASL COVID Task Force, APASL COVID Liver Injury Spectrum Study (APCOLIS Study-NCT 04345640). Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). *Hepatol Int* 2020;14(5):690-700. [CrossRef]
 70. Lippi G, de Oliveira MHS, Henry BM. Chronic liver disease is not associated with severity or mortality in Coronavirus disease 2019 (COVID-19): a pooled analysis. *Eur J Gastroenterol Hepatol* 2021;33(1):114-115. [CrossRef]
 71. D'Antiga L. Coronaviruses and immunosuppressed patients: the facts during the third epi-demic. *Liver Transpl* 2020;26(6):832-834. [CrossRef]
 72. Lleo A, Invernizzi P, Lohse AW, Aghemo A, Carbone M. Management of patients with autoimmune liver disease during COVID-19 pandemic. *J Hepatol* 2020;73(2):453-455. [CrossRef]
 73. Becchetti C, Zambelli MF, Pasulo L, Donato MF, Invernizzi F, Detry O, et al; COVID-LT group. COVID-19 in an international European liver trans-

- plant recipient cohort. *Gut* 2020;69(10):1832-1840. [\[CrossRef\]](#)
74. Colmenero J, Rodríguez-Perálvarez M, Salcedo M, Arias-Milla A, Muñoz-Serrano A, Graus J, et al. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver trans-plant patients. *J Hepatol* 2021;74(1):148-155. [\[CrossRef\]](#)
 75. Hussain A, Vasas P, El-Hasani S. Letter to the Editor: Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. *Metabolism* 2020;108:154256. [\[CrossRef\]](#)
 76. Zhou YJ, Zheng KI, Wang XB, Yan HD, Sun QF, Pan KH, et al. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: a multicenter preliminary analysis. *J Hepatol* 2020;73(3):719-721. [\[CrossRef\]](#)
 77. Targher G, Mantovani A, Byrne CD, Wang XB, Yan HD, Sun QF, et al. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. *Gut* 2020;69(8):1545-1547. [\[CrossRef\]](#)
 78. Michalakis K, Ilias I. SARS-CoV-2 infection and obesity: common inflammatory and metabolic aspects. *Diabetes Metab Syndr* 2020;14(4):469-471.
 79. Massart J, Begriche K, Moreau C, Fromenty B. Role of nonalcoholic fatty liver disease as risk factor for drug-induced hepatotoxicity. *J Clin Transl Res* 2017;3(Suppl 1):212-232.
 80. Szabo G, Saha B. Alcohol's effect on host defense. *Alcohol Res* 2015;37(2):159-170.
 81. Eshraghian A, Taghavi A, Nikeghbalian S, Malek-Hosseini SA. Reduced rate of hospital admissions for liver-related morbidities during the initial COVID-19 outbreak. *Lancet Gastro-enterol Hepatol* 2020;5(9):803-804 [\[CrossRef\]](#)
 82. Reddy MS, Hakeem AR, Klair T, Marcon F, Mathur A, Samstein B, et al. Trinational study exploring the early impact of the COVID-19 pandemic on organ donation and liver transplantation at national and unit levels. *Transplantation* 2020;104(11):2234-2243. [\[CrossRef\]](#)
 83. Da BL, Im GY, Schiano TD. Coronavirus disease 2019 hangover: a rising tide of alcohol use disorder and alcohol-associated liver disease. *Hepatology* 2020;72(3):1102-1108. [\[CrossRef\]](#)