



# Role of COVID-19 in Hepatic Damage and Its Cellular Entrance and Mechanism of Action: A Mini-Review

Ali Akbar Oroojan <sup>1,\*</sup>

<sup>1</sup>Department of Physiology, Faculty of Medicine, Student Research Committee, Dezful University of Medical Sciences, Dezful, Iran

\*Corresponding author: Department of Physiology, Faculty of Medicine, Student Research Committee, Dezful University of Medical Sciences, Dezful, Iran. Email: aliakbar\_oroosan@yahoo.com

Received 2021 February 08; Revised 2021 March 14; Accepted 2021 March 29.

## Abstract

**Context:** COVID-19 induces damage to the liver in addition to the pulmonary system. This event can alter hepatic biochemical and histological variables. Therefore, the present mini-review study investigated the effect of COVID-19 on hepatic damages and its cellular mechanism of action.

**Evidence Acquisition:** In this mini-review study, the effects of COVID-19 on liver cells were sought in PubMed without restriction. The related components were searched in the Me SH term system and also used in two groups of COVID-19 and hepatocytes in combination with each other. Then, the titles and abstracts of the selected articles were assessed, and unrelated articles were removed.

**Results and Conclusion:** COVID-19 leads to liver tissue damage and hepatocyte apoptosis by inducing increased cytokines, ischemia, and hepatic hypoxia following cardiorespiratory failure, coagulation disorders, and intracellular calcium. The SARS-CoV-2 virus exerts this effect through the ACE2 receptor and increasing its expression in cholangiocytes.

**Keywords:** COVID-19, SARS-CoV-2, Liver, Hepatocyte

## 1. Context

In addition to the respiratory system, COVID-19 induces damage to the gastrointestinal tract and liver. This damage is more severe in patients with a history of virus infection. In COVID-19 patients, the levels of liver enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), change abnormally in the stages of disease progression and acute hepatitis. In addition, hepatotoxicity is more pronounced in patients with severe COVID-19, which can be caused by systemic inflammation, liver damage from medications used to treat COVID-19, or pre-existing chronic liver disease. Previous studies suggest that liver damage associated with COVID-19 is usually rare, and damage to this tissue is secondary to pneumonia resulting from the disease and the length of hospitalization (1-4). Therefore, according to the mentioned explanations, the present mini-review study investigated the effect of COVID-19 on hepatic damages and its cellular mechanism of action.

## 2. Evidence Acquisition

In this mini-review study, initially, the effect of COVID-19 on liver cells was searched in PubMed without re-

striction. The language of the assessed articles was English. The related components were searched in the Me SH term system and also used in the two groups of COVID-19 and hepatocytes in combination with each other. Therefore, the search syntax was (“2019 novel coronavirus disease”[tiab] OR “COVID19”[tiab] OR “COVID-19 pandemic”[tiab] OR “SARS-CoV-2 infection”[tiab] OR “COVID-19 virus disease”[tiab] OR “2019 novel coronavirus infection”[tiab] OR “2019-nCoV infection”[tiab] OR “coronavirus disease 2019”[tiab] OR “coronavirus disease-19”[tiab] OR “2019-nCoV disease”[tiab] OR “COVID-19 virus infection”[tiab]) AND (Hepatocytes[tiab] OR Hepatocyte[tiab] OR “Hepatic Cells”[tiab] OR (Cell[tiab] AND Hepatic[tiab]) OR (Cells[tiab] AND Hepatic[tiab]) OR “Hepatic Cell”[tiab]). Ultimately, the selected articles were transferred to End-Note (x7) software and the titles and abstracts of them were assessed by the researcher to remove unrelated articles.

## 3. Results

### 3.1. Effect of COVID-19 on Liver Biochemical and Histological Variables

Some studies showed that hepatic AST levels increased in COVID-19 patients admitted to the intensive care unit

(ICU) of the hospital. Also, the levels of liver enzymes ALT and AST in patients with COVID-19 increased significantly when compared to the control group. Meanwhile, Alkaline Phosphatase (ALP) had a significant increase in patients with liver damage induced by COVID-19 in a cholestatic assessment study (2). In addition to the increase of these enzymes, some changes in biochemical factors of these individuals, including increased Alveolar-arterial Oxygen Gradient (A-aDO<sub>2</sub>) and ferritin, or decreased albumin, CD4 + T cells, lymphocytes B, leukopenia (decrease in white blood cells), and thrombocytopenia (decrease in platelets) can be caused by damage to the liver (5, 6). Histologic changes in hepatic tissue caused by COVID-19-induced ischemic injury consist of coagulation necrosis and lymphohistiocytic inflammation of the sinus vein and central vessel endothelium, mild microvesicular steatosis, and duct cholestasis. Activated histocytes, hepatocyte apoptosis, the presence of fibrin microbes in the hepatic sinusoids, extensive dilatation of the portal vein branches, duct thrombosis, port duct fibrosis, and deep vein thrombosis (7-9). Previous studies have shown COVID-19-induced mitochondrial swelling, endoplasmic reticulum dilation, cell membrane dysfunction, and dual or multinucleated cell apoptosis in hepatocytes (Figure 1)(10).

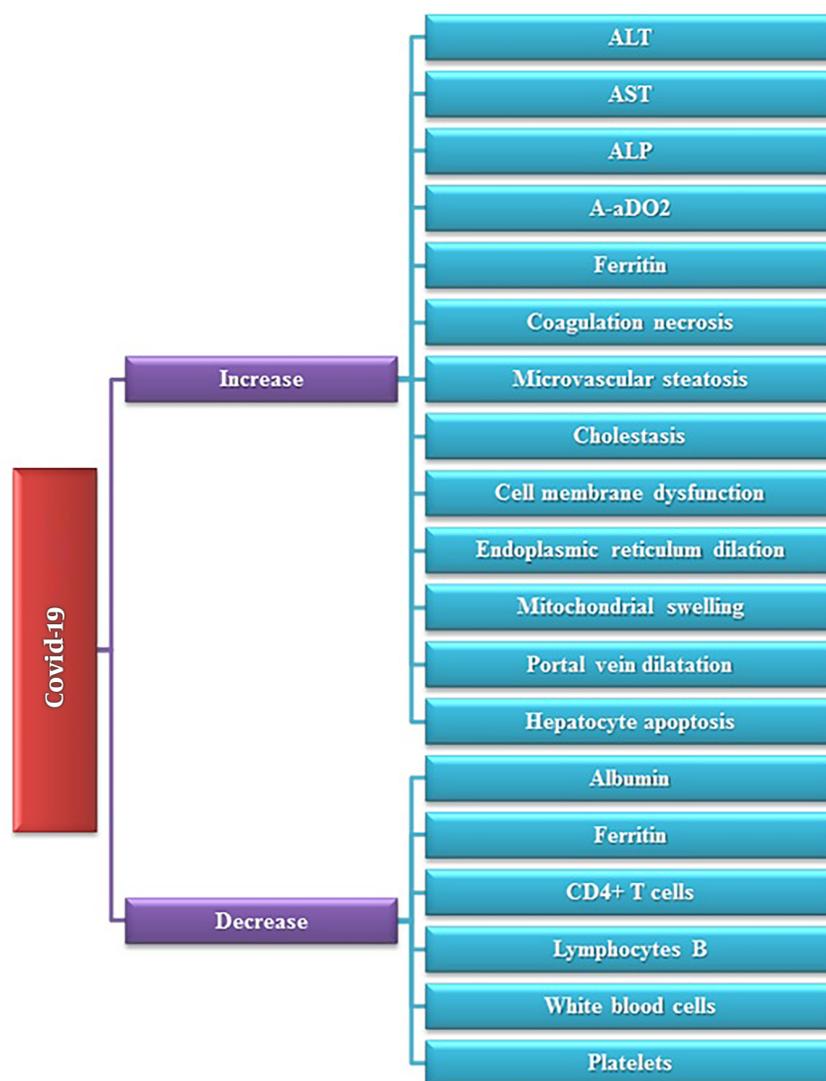
### 3.2. Factors Affecting Liver Damage Caused by COVID-19

One of the important factors affecting liver damage during COVID-19 is the abnormal coagulation and disruption of fibrinolytic pathways in the blood coagulation process. These disorders occur after the onset of a cytokine storm, inflammation, and toxicity caused by drugs used to treat this disease (1). Cytokine storm syndrome (CSS) is a process in which, pro-inflammatory cytokines increase uncontrollably following the entry of the virus into the cell. In this syndrome, an increase occurs in the levels of interleukins, including IL-6, IL-10, IL-2, and interferon-gamma (IFN- $\gamma$ ), which is directly related to the severity of the disease and the insufficiency of several organs, including the liver. Therefore, instead of protecting the immune system and clearing the body from the virus, this syndrome attacks the immune system uncontrollably, and increased cytokines lead to the exacerbation of infection, ischemia, hypoxia, and necrosis of liver tissue. These disorders are more severe and even more fatal in the elderly due to the greater weakness of the immune system. Moreover, CSS causes disseminated intravascular coagulation (DIC), which induces thrombotic microangiopathy in various organs such as the liver. Another study found that liver damage in COVID-19 could be triggered by a systemic immune response following inflammation, liver ischemia, or hypoxia of liver cells, which ultimately increases liver enzymes and hypoalbuminemia. On the other hand, hypoxia

in the liver causes the accumulation of lactic acid in this tissue, and as a result, large amounts of the acid are released into the blood, which upsets the acid-base balance of the body and leads to systemic acidosis in the whole body (3, 11, 12). Another cause of liver damage in COVID-19 is heart failure induced by this disease. In heart failure, systemic arterial pressure suddenly decreases, which leads to decreased hepatic arterial blood flow, hypoxia of liver cells, and increased aminotransferases in this organ. On the other hand, in heart failure, with increasing central venous pressure, hepatic venous congestion, and further predisposes the liver tissue to damage caused by hypoxia were occurred (11). In addition, the oversupply of Kupffer cells, the increase of oxidative stress following hypoxia in the liver, hypovolemia due to cardiopulmonary failure and shock, metabolic acidosis, increased intracellular calcium levels (the most important inducer of cellular apoptosis), changes in mitochondrial membrane permeability, intestinal endotoxemia, and activation of the sympathetic nervous system and adrenal system, which leads to decreased blood flow to the liver, can lead to liver damage during COVID-19 disease. Also, sepsis can be produced by an uncontrolled immune response to infection, cholestasis due to impaired bile metabolism, the toxicity of administered drugs, or inflammation followed by COVID-19-induced liver damage (Figure 2)(13).

### 3.3. Hepatocellular Mechanism of Action of SARS-CoV-2 in Liver Damage

The SARS-CoV-2 virus uses the angiotensin-converting enzyme (ACE2) receptor and membrane proteinase serum (TMPRSS2) to enter the cell (1). This receptor is expressed in bile endothelial cells of the liver, and the SARS-CoV-2 virus can enter these cells and cause damage to them through this receptor. Studies have also shown that the readjustment of ACE2 expression in liver tissue occurs by the compensatory proliferation of hepatocytes from bile duct epithelial cells, followed by hepatic tissue damage resulting from COVID-19 disease (3). Molecular studies have shown that ACE2 receptor expression in collagenocytes increases during infection with SARS-CoV-2. Meanwhile, TMPRSS2 mRNA expression in hepatocytes and cholangiocytes increases by 68% during COVID-19. Thus, ACE2 receptor expression in hepatic endothelial cells is still debated (11, 14, 15). In addition, an immunohistochemical study showed that ACE2 expression is increased in bile duct epithelial cells but not in Kupffer and hepatic endothelial cells. Animal studies also confirm that in mice with acute liver injury, ACE2 expression initially increases but returns to normal after seven days following the compensatory proliferation of bile duct-derived hepatocytes. Thus, SARS-CoV-2



**Figure 1.** Effect of COVID-19 on biochemical and histological variables of the liver (2, 5-8, 10)

may induce its damage to the liver via the ACE2 receptor on the cholangiocytes (Figure 3) (13).

#### 3.4. Limitation

One of the limitations of this review article is that not all articles were available and they were not free. Also, some articles were written in a language other than English, which required a native translator.

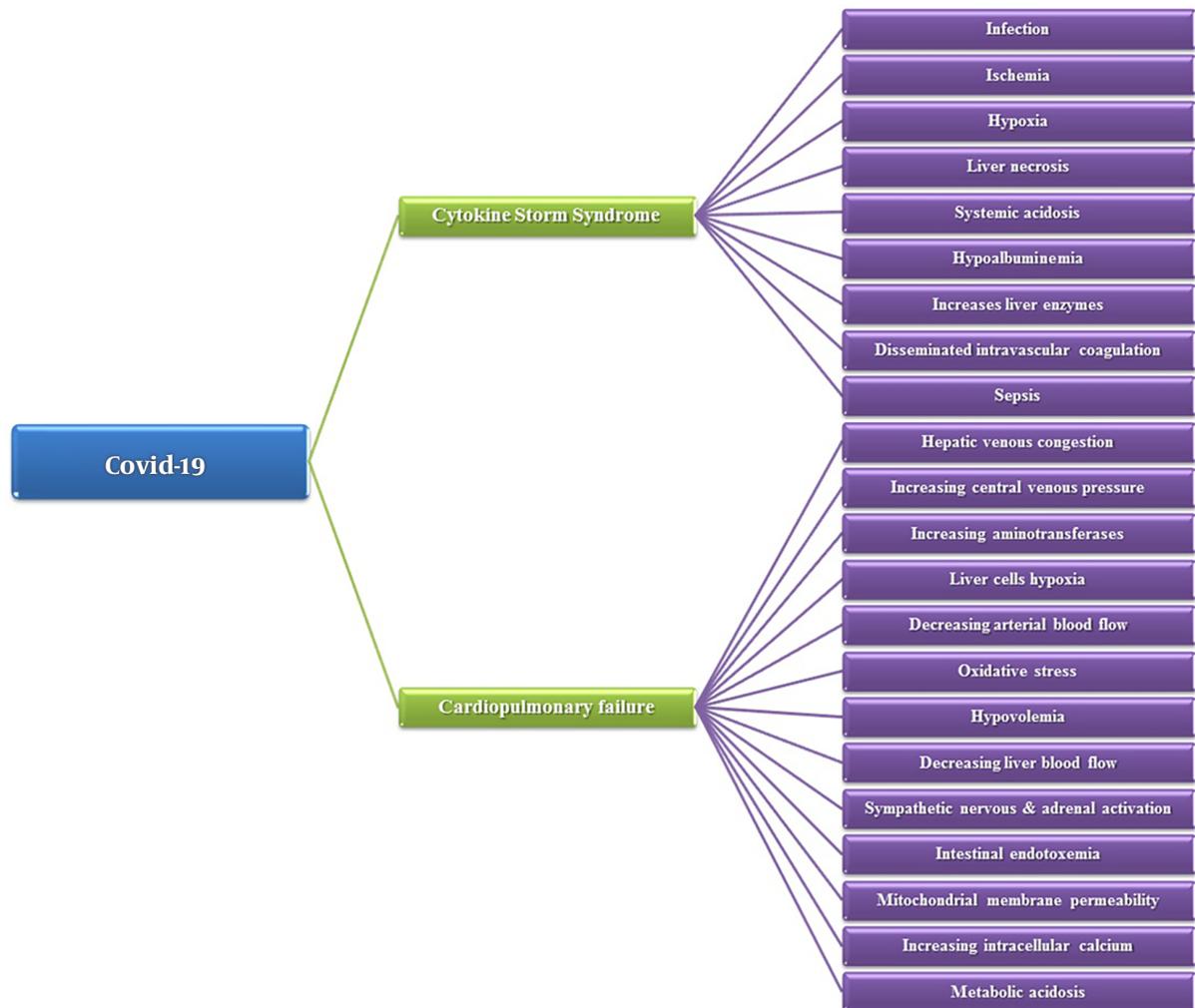
#### 3.5. Future Directions

According to what mentioned in the present study, it can be suggested that future studies focus on the liver and

shed light on the mechanisms and pathways of COVID-19 effects on this organ to select effective drugs for the treatment of this disease and use them in clinical studies.

#### 4. Conclusions

In conclusion, COVID-19 leads to liver tissue damage and hepatocyte apoptosis by inducing increased cytokines, ischemia, and hepatic hypoxia following cardiorespiratory failure, coagulation disorders, and intracellular calcium. Moreover, the SARS-CoV-2 virus exerts this effect by binding to and entering through the ACE2 receptor



**Figure 2.** Factors affecting liver damage caused by COVID-19 (1, 3, 11, 13)

and increasing its expression in cholangiocytes. Therefore, COVID-19 with damage to various parts of liver tissue, including liver sinusoids or Kupffer cells, etc. causes an increase in liver enzymes ALT, AST, ALP, and other factors associated with liver damage, which ultimately leads to hepatotoxicity.

### Acknowledgments

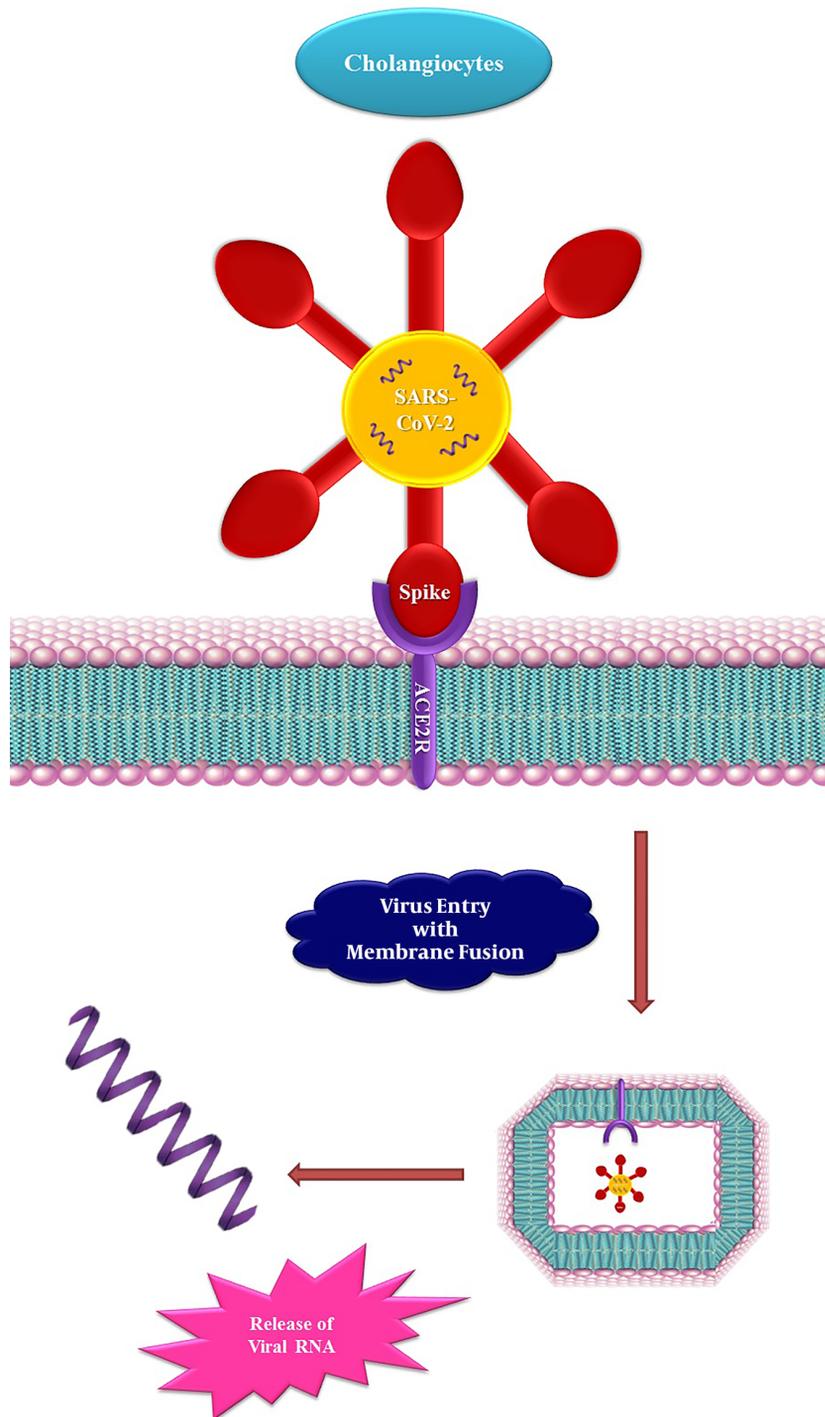
We would like to thank the vice-chancellor of Research Affairs of Dezful University of Medical Sciences, Dezful, Iran, for assistance in the production of this scoping mini-review research.

### Footnotes

**Authors' Contribution:** Study concept and design, acquisition of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and study supervision, A A. O.

**Conflict of Interests:** The author has no conflicts of interest to declare.

**Funding/Support:** There is no funding/support.



**Figure 3.** Cholangiocytes entrance mechanism of SARS-CoV-2 for inducing liver damage (1, 3, 11, 13)

## References

1. Saheb Sharif-Askari N, Saheb Sharif-Askari F, Mdkhana B, Al Heialy S, Ratemi E, Alghamdi M, et al. Effect of common medications on the expression of SARS-CoV-2 entry receptors in liver tissue. *Arch Toxicol.* 2020;**94**(12):4037–41. doi: [10.1007/s00204-020-02869-1](https://doi.org/10.1007/s00204-020-02869-1). [PubMed: [32808185](https://pubmed.ncbi.nlm.nih.gov/32808185/)]. [PubMed Central: [PMC7430937](https://pubmed.ncbi.nlm.nih.gov/PMC7430937/)].
2. Farshidpour M, Kim D, Junna S, Merchant J. A brief review of liver injury in patients with Corona Virus Disease-19 during the pandemic. *Indian J Gastroenterol.* 2020;**39**(3):232–5. doi: [10.1007/s12664-020-01068-1](https://doi.org/10.1007/s12664-020-01068-1). [PubMed: [32621206](https://pubmed.ncbi.nlm.nih.gov/32621206/)]. [PubMed Central: [PMC7333972](https://pubmed.ncbi.nlm.nih.gov/PMC7333972/)].
3. Li X, Zhang ZC, Zhang PL. Severe COVID-19 patients with liver injury: A seven-case series. *Eur Rev Med Pharmacol Sci.* 2020;**24**(14):785–60. doi: [10.26355/eurrev\\_202007\\_22290](https://doi.org/10.26355/eurrev_202007_22290). [PubMed: [32744713](https://pubmed.ncbi.nlm.nih.gov/32744713/)].
4. Tellez L, Martin Mateos RM. COVID-19 and liver disease: An update. *Gastroenterol Hepatol.* 2020;**43**(8):472–80. doi: [10.1016/j.gastrohep.2020.06.006](https://doi.org/10.1016/j.gastrohep.2020.06.006). [PubMed: [32727662](https://pubmed.ncbi.nlm.nih.gov/32727662/)]. [PubMed Central: [PMC7332955](https://pubmed.ncbi.nlm.nih.gov/PMC7332955/)].
5. Wang Y, Liu S, Liu H, Li W, Lin F, Jiang L, et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol.* 2020;**73**(4):807–16. doi: [10.1016/j.jhep.2020.05.002](https://doi.org/10.1016/j.jhep.2020.05.002). [PubMed: [32437830](https://pubmed.ncbi.nlm.nih.gov/32437830/)]. [PubMed Central: [PMC7211738](https://pubmed.ncbi.nlm.nih.gov/PMC7211738/)].
6. Cheong J, Bartell N, Peeraphatdit T, Mosli M, Al-Judaibi B. Gastrointestinal and liver manifestations of COVID-19. *Saudi J Gastroenterol.* 2020;**26**(5):226–32. doi: [10.4103/sjg.SJG\\_147\\_20](https://doi.org/10.4103/sjg.SJG_147_20). [PubMed: [32367837](https://pubmed.ncbi.nlm.nih.gov/32367837/)]. [PubMed Central: [PMC7739995](https://pubmed.ncbi.nlm.nih.gov/PMC7739995/)].
7. Wang XX, Shao C, Huang XJ, Sun L, Meng LJ, Liu H, et al. Histopathological features of multiorgan percutaneous tissue core biopsy in patients with COVID-19. *J Clin Pathol.* 2020. doi: [10.1136/jclinpath-2020-206623](https://doi.org/10.1136/jclinpath-2020-206623). [PubMed: [32848014](https://pubmed.ncbi.nlm.nih.gov/32848014/)].
8. Lagana SM, De Michele S, Lee MJ, Emond JC, Griesemer AD, Tulin-Silver SA, et al. COVID-19 associated hepatitis complicating recent living donor liver transplantation. *Arch Pathol Lab Med.* 2020. doi: [10.5858/arpa.2020-0186-SA](https://doi.org/10.5858/arpa.2020-0186-SA). [PubMed: [32302212](https://pubmed.ncbi.nlm.nih.gov/32302212/)].
9. Huang C, Li Q, Xu W, Chen L. Molecular and cellular mechanisms of liver dysfunction in COVID-19. *Discov Med.* 2020;**30**(160):107–12. [PubMed: [33382966](https://pubmed.ncbi.nlm.nih.gov/33382966/)].
10. Yang L, Han Y, Nilsson-Payant BE, Gupta V, Wang P, Duan X, et al. A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. *Cell Stem Cell.* 2020;**27**(1):125–136 e7. doi: [10.1016/j.stem.2020.06.015](https://doi.org/10.1016/j.stem.2020.06.015). [PubMed: [32579880](https://pubmed.ncbi.nlm.nih.gov/32579880/)]. [PubMed Central: [PMC7303620](https://pubmed.ncbi.nlm.nih.gov/PMC7303620/)].
11. Bertolini A, van de Peppel IP, Bodewes F, Moshage H, Fantin A, Fari-nati F, et al. Abnormal liver function tests in patients with COVID-19: Relevance and potential pathogenesis. *Hepatology.* 2020;**72**(5):1864–72. doi: [10.1002/hep.31480](https://doi.org/10.1002/hep.31480). [PubMed: [32702162](https://pubmed.ncbi.nlm.nih.gov/32702162/)]. [PubMed Central: [PMC7404414](https://pubmed.ncbi.nlm.nih.gov/PMC7404414/)].
12. Marjot T, Webb GJ, Barritt AS, Moon AM, Stamataki Z, Wong VW, et al. COVID-19 and liver disease: Mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol.* 2021. doi: [10.1038/s41575-021-00426-4](https://doi.org/10.1038/s41575-021-00426-4). [PubMed: [33692570](https://pubmed.ncbi.nlm.nih.gov/33692570/)]. [PubMed Central: [PMC7945972](https://pubmed.ncbi.nlm.nih.gov/PMC7945972/)].
13. Li J, Fan JG. Characteristics and mechanism of liver injury in 2019 Coronavirus disease. *J Clin Transl Hepatol.* 2020;**8**(1):13–7. doi: [10.14218/JCTH.2020.00019](https://doi.org/10.14218/JCTH.2020.00019). [PubMed: [32274341](https://pubmed.ncbi.nlm.nih.gov/32274341/)]. [PubMed Central: [PMC7132021](https://pubmed.ncbi.nlm.nih.gov/PMC7132021/)].
14. Nardo AD, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. *Liver Int.* 2021;**41**(1):20–32. doi: [10.1111/liv.14730](https://doi.org/10.1111/liv.14730). [PubMed: [33190346](https://pubmed.ncbi.nlm.nih.gov/33190346/)]. [PubMed Central: [PMC7753756](https://pubmed.ncbi.nlm.nih.gov/PMC7753756/)].
15. Lozano-Sepulveda SA, Galan-Huerta K, Martinez-Acuna N, Arellanos-Soto D, Rivas-Estilla AM. SARS-CoV-2 another kind of liver aggressor, how does it do that? *Ann Hepatol.* 2020;**19**(6):592–6. doi: [10.1016/j.aohep.2020.08.062](https://doi.org/10.1016/j.aohep.2020.08.062). [PubMed: [32858226](https://pubmed.ncbi.nlm.nih.gov/32858226/)]. [PubMed Central: [PMC7445466](https://pubmed.ncbi.nlm.nih.gov/PMC7445466/)].