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COVID-19-induced liver injury in adult patients: A brief overview

Martina Grando, Massimiliano Balbi, Marco Zeppieri

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Abstract

Coronavirus disease has spread worldwide since 2019, causing important pandemic issues and various social health problems to date. Little is known about the origin of this virus and the effects it has on extra-pulmonary organs. The different mechanisms of the virus and the influence it has on humans are still being studied, with hopes of finding a cure for the disease and the pathologies associated with the infection. Liver damage caused by coronavirus disease 2019 (COVID-19) is sometimes underestimated and has been of important clinical interest in the past few years. Hepatic dysfunctions can manifest in different forms which can sometimes be mild and without specific signs and symptoms or be severe with important clinical implications. There are several studies that have tried to explain the mechanism of entry (hepatotropism) of the virus into hepatocytes and the effects the virus has on this important organ. What clearly emerges from the current literature is that hepatic injury represents an important clinical aspect in the management of patients infected with COVID-19, especially in frail patients and those with comorbidities. The aim of our brief overview is to summarize the current literature regarding the forms of hepatic damage, complications, mechanisms of pathology, clinical features of liver injury, influence of comorbidities and clinical management in patients with COVID-19 infection.

Key Words: COVID-19; SARS-CoV-2; Hepatotropism; Hepatic injury; Cirrhosis; Cytokine storm; Angiotensin-converting enzyme 2

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Core Tip: Liver damage can occur in patients infected by coronavirus disease 2019 (COVID-19). The organ damage can be due to various mechanisms such as direct infection, immune injury, drug-induced damage, hypoxia or inflammation response. It is of clinical importance to manage hepatic damage in COVID-19-positive patients. Patient outcomes, the success of therapy, prevention of life-threatening complications and management of existing comorbidities depend on proper organ functioning.

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INTRODUCTION

In December 2019, a new ribonucleic acid (RNA) virus in humans was reported in China, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This viral infection has spread quickly throughout the world ever since the first outbreak. The virus causes coronavirus disease 2019 (COVID-19) which has had a great global impact[1]. SARS-CoV-2 started as a zoonotic infection but currently also affect humans. The disease propagates quickly between humans *via* air droplets, sneezing and coughing, especially amongst people that are in close contact with each other. Studies have also shown the possibility of fecal-oral transmission[2]. The majority of SARS-CoV-2 infected patients can be asymptomatic or can present with mild symptoms which range from coughing, fever, headache, anosmia, *etc.* About 15% of cases, however, can show severe pulmonary disease leading to respiratory dysfunction, which can progress to multiorgan failure, coagulopathy and even death[3-5]. Common risk factors for severe disease progression include male sex, advanced age and coexisting comorbidities (*i.e.* heart disease, tumors, diabetes, hypertension, *etc*) [6,7].

Possible hepatic involvement has been shown in two recent types of pathogenic Coronaviruses, which include SARS-CoV-2 and middle east respiratory syndrome coronavirus. These two viruses show striking genetic similarities, thus hepatic involvement is not entirely unexpected[8]. COVID-19 patients showing injury of the liver can present with abnormal liver biochemical indicators, such as elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin, in addition to low levels of albumin[9,10]. The possible mechanisms involved in viral infections include: a direct effect of the virus on hepatocytes or biliary epithelium; liver injury related to accentuated immune response (cytokine storm) and immune-mediated damage; drug toxicity; and ischemic hepatitis. These complications can be favored in patients having multiorgan dysfunction and hemodynamic instability [11]. COVID-19 can give rise to a worsening of existing chronic liver disease (CLD) which can lead to higher mortality due to acute-on-chronic liver failure and/or hepatic decompensation.

Our overview provides a brief summary based on the various forms of hepatic damage, complications, mechanisms, clinical features of liver injury, influence of comorbidities and clinical management in patients with infection of SARS-CoV-2.

SEARCHING OF THE LITERATURE

We conducted a search of the literature published between January 1, 2011 to June 1, 2022, using PubMed (<https://pubmed.ncbi.nlm.nih.gov>) and Reference Citation Analysis (<https://www.referencecitationanalysis.com>). The database was first searched using the key words "SARS-CoV-2 AND hepatic injury, hepatic damage AND therapy". We considered only studies in English and those referring to humans and with abstract, thus reducing the count to 350 papers. The reference lists of all retrieved articles were assessed to identify additional relevant studies. Only articles with abstracts were considered. Each study was independently assessed by at least two reviewers (Grando M and Balbi M), and rating decisions were based on the consensus of the reviewing authors. Our manuscript was based on the most relevant and pertinent studies which included 76 references listed in the paper.

Mechanism and hepatotropism of SARS-CoV-2

Angiotensin-converting enzyme 2 (ACE2) is expressed in about 80% of pulmonary alveolar cells, but also in other organs. It seems to be a susceptible receptor for SARS-CoV-2. In vitro studies during the SARS epidemic showed that ACE2 acts as the host receptor for viral entry[12]. Moreover, furin gene and transmembrane serine protease 2 (TMPRSS2) have also shown to play an important role in infection. Cells expressing these specific receptors can be indicative of putative hepatic permissive cells[13].

Hepatic distribution of ACE2 is particular. Single-cell RNA sequencing analyzed from livers from normal patients have shown higher levels of gene expression in cholangiocytes, sinusoidal endothelial cells and hepatocytes[14,15]. The ACE2 expression levels in cholangiocytes are like those found in pulmonary type 2 alveolar cells of the lungs, thus indicating that the liver could be a potential target for SARS-CoV-2[16]. In addition, studies have reported that furin and TMPRSS2 have shown a broad gene expression profile in many types of liver cells[14]. In three single-cell RNA combined analysis from sequencing obtained from healthy liver tissue, relatively few hepatocytes co-expressed ACE2 and TMPRSS2[17]. Zhao *et al*[18] conducted studies on liver ductal organoids that expressed ACE2 and TMPRSS2. These were shown to recapitulate infection of SARS-CoV-2, which could be indicative that the epithelium of the bile duct may support entry of pseudo particles[18]. The exact reasons to explain these findings are not known. It may be possible, however, that the virus may show low levels of replication in cholangiocytes *in vivo* in the absence of cell death.

The effects of coexisting liver disease and injury on SARS-CoV-2 hepatotropism is still not known. Studies performed before COVID-19 have reported an increase in liver ACE2 expression in patients with cirrhosis due to hepatitis virus C when compared with normal patients[19]. Moreover, liver mRNA TMPRSS2 and ACE2 expression have shown to be upregulated in non-infected obese individuals and non-alcoholic steatohepatitis patients[20]. Studies based on liver injury in animal models using ligation of the bile ducts have shown elevated expression and activity of hepatic ACE2 and the presence of hypoxia markers[19,21]. Inflammation and injury of the liver may potentially enhance hepatotropism of SARS-CoV-2 by influencing the expression of viral receptors, with ACE2 shown as an interferon-inducible gene in the epithelia of the respiratory system in humans[22,23]. While the tissue specific factors involved in the infection of SARS-CoV-2 are not completely known, the importance of accessory receptors like the receptor B type 1 high-density lipoprotein scavenger (SR-B1) can help better understand *in vitro* facilitated coronavirus attachment[24].

Clinical presentation

Liver biochemistries abnormalities are frequent in COVID-19 patients which has been reported to be seen in 15-65% of individuals infected with SARS-CoV-2[13]. Liver biochemistry abnormalities are generally characterized by mild to moderate elevated ALT and AST levels, accompanied by a slight increase in bilirubin levels and gamma-glutamyl transferase (GGT)[25]. Hypoalbuminemia, a typical manifestation of a hepatic synthetic dysfunction, has been reported to be associated with a worsening in COVID-19 outcomes[26-28]. Despite the presence of ACE2 in cholangiocytes, patients have shown to have elevated levels of transaminases. Several studies, however, have reported the development of cholangiopathy after severe COVID-19, which was characterized by marked elevation in serum alkaline phosphatase (ALP) accompanied by bile duct injury shown in imaging scans. ALP peaks can be seen in patients with worse prognosis. AST elevations can also be seen as a result of myositis[29]. Studies have showed that levels of AST at hospital admission tended to correlate with ferritin[30]. However, further studies are needed to determine whether COVID-19 aggravates cholestasis in individuals with primary sclerosing cholangitis and primary biliary cholangitis[31,32]. The clinical manifestation[10,13,28,32] of the disease can include gastrointestinal alterations like nausea, anorexia, vomiting, diarrhea, *etc.* Patients can also complain of abdominal pain, especially in the right upper quadrant region.

Prognosis

The prognostic significance of elevated liver enzymes in COVID-19 patients is currently debatable. Unpublished data from Wuhan, China showed increased GGT levels in severe cases of COVID-19[8]. Several reports have demonstrated that high levels of AST and ALT can be associated with negative outcomes including mechanical ventilation and management in an intensive care unit (ICU)[33-36]. A recent review showed that the pooled frequency of elevations of ALT and AST was similar in all COVID-19 cases, however, the prevalence of AST elevations was more than ALT in patients with severe COVID-19 disease[37]. Increased liver enzymes are commonly seen in patients needing severe critical care. Studies have reported raised AST in 62% of patients in the ICU compared to 25% in a non-ICU setting[38]. The current literature in this field can potentially be prone to bias considering that infected individuals with severe health issues tend to undergo more laboratory testing than patients with mild symptoms.

The influence of liver enzymes on mortality is debatable. Several studies have stated that there are no apparent associations between mortality rates and elevations in levels of liver enzymes[33,39]. Other studies, however, have reported elevated levels of liver enzymes (*i.e.* AST and ALT elevations higher than five times the normal ranges) in patients with greater risk of mortality[27,40]. Some authors have suggested that indicators based on liver biochemical levels can be useful predictors of prognosis and severity in COVID-19 individuals, however, it is important to note that the prognostic significance could also be due to enhanced host response and active treatments that could be more aggressive in patients with important signs and symptoms[41].

Hepatic damage

The complex mechanisms of liver injury during SARS-CoV-2 infection are of important clinical

importance but are still not all completely known. Hepatic damage could be related to the direct cytopathic effect of the virus. Huang *et al*[42] found that liver injury as the first clinical manifestation in COVID-19 patients was very rare and that hepatic damage in COVID-19 patients appeared mostly due to secondary liver injury. Numerous studies have speculated that in addition to the virus itself causing initial liver injury, other factors involved could cause secondary liver injury. These mechanisms include: an uncontrolled immune reaction; systemic inflammatory response syndrome (SIRS); ischemia and reperfusion; cytokine storm injury; and liver injury induced by drugs[38,41,43].

Direct damage: Liver injury in patients with COVID-19 could be partially caused by direct SARS-CoV-2 viral invasion and hepatocyte destruction. Several studies have reported hepatic necrosis foci located near peri-portal areas and terminal hepatic veins, without signs of surrounding inflammatory cellular infiltration (consistent with acute liver injury patterns)[43,44]. Amongst hospitalized patients with COVID-19, elevations of serum AST levels have been shown to be positively correlated with levels of ALT, which have not been seen with markers of systemic inflammation like ferritin and C-reactive protein (CRP)[30]. Increased liver enzyme levels in COVID-19 patients could possibly be due to direct hepatic injury. Bile duct epithelium shows ACE2 expression which tends to be much greater than that seen in hepatocytes. Compensatory proliferation in parenchymal cells of the liver arising from cells of the bile duct may lead to the upregulation of ACE2 expression in the liver. This could be an important mechanism involved in SARS-CoV-2 induced liver injury.

The direct hepatic damage caused by the virus is still a hypothesis, especially considering the low number of autopsies performed in COVID-19 patients and the relatively low ACE2 expression in the liver. The direct toxic attack of SARS-CoV-2 on the liver is still questionable and remains debatable. Moreover, biomarkers for cholangiocyte injury, such as GGT and ALP have also been seen in some patients, which tends to be consistent with injury to biliary epithelial cells[39]. COVID-19 patients can show elevated total bilirubin levels. These results could be indicative that SARS-CoV-2 can directly bind to cholangiocytes expressing ACE2, thus giving rise to cholangiocyte injury. Further clinical and histopathological studies are needed to confirm these hypothetical mechanisms.

SIRS and cytokine storm: Like numerous other diseases, SARS-CoV-2 is associated with systemic inflammation, which could cause elevations in biochemistries in the liver due to the release of cytokine [45]. Individuals with relatively high serum ALT levels tend to show elevated levels of CRP, D-dimer, ferritin and IL6[46]. Studies have shown elevated serum levels of interleukin (IL) IL2 receptor and IL6 in COVID-19 individuals which tend to correlate with the severity of the disease[47]. Moreover, other cytokines such as tumor necrosis factor IL18, IL4 and IL 10 have shown to be increased, as do peripheral blood pro-inflammatory CCR4+, CCR6+ and Th17 cells[48]. After being infected, a large number of immune cells may be overactivated and induced to secrete excessive cytokines and chemokines. This can lead to acute respiratory syndrome and SIRS which can give rise to cell damage and necrosis.

Ischemia and reperfusion injury: Individuals with COVID-19 tend to show different degrees of hypoxemia. Systemic hypoxia might also have a contributory role. Studies have shown raised AST levels with other viral pneumonias including influenza A (H1N1) infection[49]. With hypoxia and ischemia, glycogen consumption, lipid accumulation and adenosine triphosphate depletion of hepatocytes can inhibit cell survival signal transduction which can lead to hepatocyte death. It is important to note that hepatic ischemia-reperfusion injury (HIRI) is considered as a normal pathophysiological process. The mechanisms behind this injury are closely related to neutrophils, Kupffer cells, reactive oxygen species and calcium overload. HIRI can induce neutrophils, Kupffer cells and platelets which induce destructive cellular processes that can cause inflammation and injury to cells [11]. Ischemia and hypoxia could surely be involved in the mechanisms of liver damage in patients with severe and critical COVID-19 disease.

Histological studies have showed altered intrahepatic blood vessel derangement, coagulopathy, antiphospholipid antibodies and abnormal hepatic perfusion which could be indicative of micro thrombotic disease[50,51].

Antibody-dependent enhancement: Antibody-dependent enhancement (ADE) involves the interaction between the Fc receptor and/or complement receptor with the virus-specific antibody to enhance the virus' ability to enter granulocytes, macrophages and monocytes. Studies have shown that antibodies against the SARS-CoV-2 spike protein trigger ADE causing the virus to enter immune cells that do not express ACE2[52-54]. The liver has numerous immune-response cells. ADE could also mediate SARS-CoV-2 in immune cell infection by a pathway not dependent on ACE2 and be involved in injury to the liver.

Drug induced injury: Drug-induced liver injury may have been more common during the initial periods of the pandemic which could have been favored by the use of experimental therapies[53]. It is also important to note that the common symptom in COVID-19 patients tends to be fever which may lead to the abundant use of antipyretic agents that contain acetaminophen, which is known to cause liver damage when excessively used without prescription in certain patients.

Antiviral drugs that are currently available have not proven to be very effective in controlling the disease. During the outbreak, patients were given ritonavir, lopinavir, oseltamivir, *etc.* Raised hepatic enzyme levels have been reported in patients receiving lopinavir/ritonavir therapy (56.1% vs 25%) [54, 55]. Remdesivir is another antiviral drug that is used to inhibit the replication of SARS-CoV-2 virus and studies have shown increased levels of blood creatinine, acute kidney injury and higher levels of liver enzymes in patients using the drug [56]. A study published in 2019 showed that CYP3A4 may have an important role in hepatotoxicity mediated by ritonavir and that oxygen free radical can be produced by the CYP3A4 metabolic pathways [56]. Covalent binding could occur with substances found in the cells of the liver which can cause peroxidation of membrane lipid, damage the integrity and Ca²⁺-ATPase pathway of the membrane, influence the homeostasis of external and internal cell levels of Ca²⁺ and impair the function of critical organelles within the liver cells. This can eventually lead to tissue damage and cell death. In addition, the overuse of ritonavir and lopinavir could activate the endoplasmic reticulum stress pathway, induce apoptosis, inhibit the replication of hepatocytes, induce inflammatory reactions and accelerate liver injury by aggravating oxidative stress [11]. Drug-induced damage needs to be included in the differential diagnosis. This requires a thorough and accurate medical history in addition to pertinent examinations and testing to exclude other forms of liver injury and diseases.

Other mechanisms: There are several other potential contributors that can help provide a better understanding of abnormal liver biochemistries in COVID-19. Current literature has also described COVID-19 as a vascular disease, in which endothelial cells can be infected and cause endothelitis. Subsequent microvascular dysfunction can lead to hypercoagulability, tissue edema and organ ischemia [57,58]. Moreover, some studies have shown that AST levels can exceed ALT during the disease which is not typical in classic hepatocellular patterns of liver injury. This is commonly seen in alcohol-related liver disease and cirrhosis. These alternative factors that may play a role in hepatic damage in COVID-19 patients remain unknown and require future clinical and histological studies. The mechanisms may include mitochondrial dysfunction related to COVID-19 and hepatic steatosis induced by SARS-CoV-2 [59].

Aggravation or recurrence of existing liver disease

Patients with pre-existing CLD can get COVID-19. Whether or not CLD patients tend to be more susceptible to infection of SARS-CoV-2 is still not known. Data from large case series based on health records do not suggest that these patients are over-represented [60]. CLD patients tend to have immune dysfunction due to the disease and/or to long-term immunosuppressants treatments (as in immune hepatitis). These chronic patients have been reported to have worse clinical outcomes when compared to patients without underlying liver diseases. Preliminary studies have reported a potentially higher mortality rate and a more severe disease course in these patients, however, further studies with large cohorts are needed [61-63].

Cirrhosis: Acute hepatic decompensation (AHD) is typical in individuals with COVID-19 and cirrhosis. Studies have reported that about 50% of patients with cirrhosis and COVID-19 [62] show AHD which typically manifests as worsening ascites and encephalopathy. Amongst COVID-19 infected patients with cirrhosis, studies have shown an increase in mortality and morbidity with increasing disease severity based on the Child-Pugh class. The number of hospitalized individuals reported in COVID-Hep the SECURE-Cirrhosis registries have showed no significant differences amongst patients with CLD and CP classes A, B and C [63]. Studies however, have reported an increase in: ICU admissions; patients needing renal replacement therapy; individuals using mechanical ventilation; and mortality rates.

SARS-CoV-2 infection does not seem to cause the progression of liver disease beyond the natural clinical course of cirrhosis. The composition of the gut microbiota may play an important role in regulating disease severity and host immune responses. Considering that cirrhosis can induce changes in the function and composition of the gut microbiota, in addition to influencing the intestinal permeability, gut-liver axis alterations may play a role in the clinical severity in COVID-19 patients [13].

Non-alcoholic fatty liver disease: The influence of non-alcoholic fatty liver disease (NAFLD) on COVID-19 infected individuals is debatable. Studies have reported that it may be difficult to identify the effects of NAFLD from other metabolic conditions and viral-induced steatosis. A retrospective series based on about 200 SARS-CoV-2 patients showed NAFLD to be a risk factor in: COVID-19 infection severity; elevated levels of liver enzyme; and longer shedding times of the virus [13].

Immune hepatitis, viral chronic hepatitis: Studies have reported that individuals with autoimmune hepatitis tend to show COVID-19-related mortality rates similar to normal matched-individuals of the population [64]. Immunosuppression use does not seem to be an independent mortality risk factor. With regards to chronic hepatitis B individuals in the phase of immune tolerance, studies still need to be performed to show if these individuals have persistent liver injury after infection. Studied based on guidelines from the Chinese Medical Association reported that for hepatitis-B individuals using antiviral drugs, discontinuation of anti-HBV therapy could favor replication and reactivation of HBV after high-dose hormone therapy (*i.e.* estrogens, estradiol, progesterone, ethisterone, medroxyprogesterone, norethindrone, cyproterone, norgestrel, clomiphene, *etc.*) during SARS-CoV-2 infection [65].

Clinicians that deal with autoimmune liver disease know that an unspecific infection may induce a flare of these diseases. It could be possible that SARS-CoV2 favors the onset of several types of autoimmune disease and/or induces an autoimmune phenomena.

Liver transplant: It is not yet clear if liver transplant (LT) recipients are more susceptible to COVID-19. A prospective study based on more than 100 individuals showed that patients that underwent liver transplantation had an increased risk of SARS-CoV-2 infection which could probably be due to the chronic immunosuppression therapy[66]. Moreover, data from the United Kingdom and Spain have shown that SARS-CoV-2 diagnoses tend to be greater in LT patients when compared to normal individuals. Biases in the data could be present, however, considering the increased testing and intense management in LT patients[67,68]. Studies have reported that LT recipients tended to be more likely to present gastrointestinal symptoms when compared to non-LT patients[69]. Clinical data incorporating adjustments for concurrent comorbidity suggest that LT individuals do not seem to be at greater risk of COVID-19 severity or mortality when compared to normal individuals[67,68].

Treatment

In the presence of acute liver injury, clinicians should first assess the probable causes of injury before taking on applicable measures. Although liver injury is a normal complication of COVID-19 infection, most infected individuals show mild abnormalities in liver function that are not permanent and tend to resolve without therapy[38]. COVID-19 individuals showing liver damage can be treated with anti-jaundice, hepatoprotective or anti-inflammatory drugs (*i.e.* glycyrrhizic acid, polyene phosphatidylcholine, adenosylmethionine and ursodeoxycholic acid)[70]. Hepatoprotective drugs should be administered prudently. It is preferable to avoid administering more than 2 types of these drugs at the same time. For individuals with critical and severe COVID-19 disease with liver injury, the clinician should consider carefully managing the respiratory and circulatory support systems. Xu *et al*[71] showed that an artificial liver blood purification system may be beneficial in severe patients. This could be due to the rapid removal of inflammatory mediators, thus limiting cytokine storms, and enhancing the balance of water-electrolytes. In COVID-19 individuals with suspected liver damage caused by drugs, clinicians should consider dose reduction or suspension. Acetaminophen (paracetamol) can be useful in patients with COVID-19, however, dosing (preferably not exceeding 2000 mg in a 24 h period) must be carefully monitored[72]. Future studies in large cohorts having long-follow-ups are needed in determining the long-term effects of COVID-19 induced liver injury.

CONCLUSION

Liver damage caused by COVID-19 is very common, especially in individuals with severe or critical disease. This aspect is also more relevant in patients with pre-existing CLD. The damage can be caused by various mechanisms such as direct infection, immune injury, drug induced, hypoxia or inflammation response. Further studies, however, are needed to understand the pathogenic mechanisms that lead to this damage and the hepatotropic mechanism of the virus. It is of utmost importance to monitor and manage abnormal liver function in COVID-19 positive patients, considering that the success of therapy, prevention of life-threatening complications and worsening of comorbidities also depends on proper hepatic functioning in the global management of these patients.

FOOTNOTES

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REFERENCES

- 1 **COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE).** [cited 20 July 2022]. Available from: <https://coronavirus.jhu.edu/map.html> (2021)
- 2 **Leung WK,** To KF, Chan PK, Chan HL, Wu AK, Lee N, Yuen KY, Sung JJ. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. *Gastroenterology* 2003; **125**: 1011-1017 [PMID: [14517783](#) DOI: [10.1016/s0016-5085\(03\)01215-0](#)]
- 3 **Berlin DA,** Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med* 2020; **383**: 2451-2460 [PMID: [32412710](#) DOI: [10.1056/NEJMc2009575](#)]
- 4 **Tay MZ,** Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; **20**: 363-374 [PMID: [32346093](#) DOI: [10.1038/s41577-020-0311-8](#)]
- 5 **World Health Organization.** Clinical Management of COVID-19: Interim Guidance (2020)
- 6 **Williamson EJ,** Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AYS, Grieve R, Harrison D, Forbes H, Schultze A, Croker R, Parry J, Hester F, Harper S, Perera R, Evans SJW, Smeeth L, Goldacre B. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584**: 430-436 [PMID: [32640463](#) DOI: [10.1038/s41586-020-2521-4](#)]
- 7 **Ioannou GN,** Locke E, Green P, Berry K, O'Hare AM, Shah JA, Crothers K, Eastment MC, Dominitz JA, Fan VS. Risk Factors for Hospitalization, Mechanical Ventilation, or Death Among 10 131 US Veterans With SARS-CoV-2 Infection. *JAMA Netw Open* 2020; **3**: e2022310 [PMID: [32965502](#) DOI: [10.1001/jamanetworkopen.2020.22310](#)]
- 8 **Xu L,** Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020; **40**: 998-1004 [PMID: [32170806](#) DOI: [10.1111/Liv.14435](#)]
- 9 **Guan WJ,** Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: [32109013](#) DOI: [10.1056/NEJMoa2002032](#)]
- 10 **Wang Q,** Zhao H, Liu LG, Wang YB, Zhang T, Li MH, Xu YL, Gao GJ, Xiong HF, Fan Y, Cao Y, Ding R, Wang JJ, Cheng C, Xie W. Pattern of liver injury in adult patients with COVID-19: a retrospective analysis of 105 patients. *Mil Med Res* 2020; **7**: 28 [PMID: [32507110](#) DOI: [10.1186/s40779-020-00256-6](#)]
- 11 **Tian D,** Ye Q. Hepatic complications of COVID-19 and its treatment. *J Med Virol* 2020; **92**: 1818-1824 [PMID: [32437004](#) DOI: [10.1002/jmv.26036](#)]
- 12 **Li W,** Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; **426**: 450-454 [PMID: [14647384](#) DOI: [10.1038/nature02145](#)]
- 13 **Marjot T,** Webb GJ, Barritt AS 4th, Moon AM, Stamatakis Z, Wong VW, Barnes E. COVID-19 and liver disease: mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 348-364 [PMID: [33692570](#) DOI: [10.1038/s41575-021-00426-4](#)]
- 14 **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**: 2038-2040 [DOI: [10.1111/Liv.14500](#)]
- 15 **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**: 135-140 [PMID: [32199615](#) DOI: [10.1016/j.bbrc.2020.03.044](#)]
- 16 **Chai X,** Hu L, Zhang Y, Han W, Lu Z, Ke A. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. *BioRxiv*, 2020 [DOI: [10.1101/2020.02.03.931766](#)]
- 17 **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**: 993-995 [PMID: [32473193](#) DOI: [10.1016/j.jhep.2020.05.030](#)]
- 18 **Zhao B,** Ni C, Gao R, Wang Y, Yang L, Wei J, Lv T, Liang J, Zhang Q, Xu W, Xie Y, Wang X, Yuan Z, Zhang R, Lin X. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. *Protein Cell* 2020; **11**: 771-775 [PMID: [32303993](#) DOI: [10.1007/s13238-020-00718-6](#)]
- 19 **Paizis G,** Tikellis C, Cooper ME, Schembri JM, Lew RA, Smith AI, Shaw T, Warner FJ, Zuilli A, Burrell LM, Angus PW. Chronic liver injury in rats and humans upregulates the novel enzyme angiotensin converting enzyme 2. *Gut* 2005; **54**: 1790-1796 [PMID: [16166274](#) DOI: [10.1136/gut.2004.062398](#)]
- 20 **Fondevila MF,** Mercado-Gómez M, Rodríguez A, Gonzalez-Rellán MJ, Iruzubieta P, Valentí V, Escalada J, Schwaninger M, Prevot V, Dieguez C, Crespo J, Frühbeck G, Martínez-Chantar ML, Nogueiras R. Obese patients with NASH have increased hepatic expression of SARS-CoV-2 critical entry points. *J Hepatol* 2021; **74**: 469-471 [PMID: [33096086](#) DOI: [10.1016/j.jhep.2020.09.027](#)]
- 21 **Herath CB,** Warner FJ, Lubel JS, Dean RG, Jia Z, Lew RA, Smith AI, Burrell LM, Angus PW. Upregulation of hepatic angiotensin-converting enzyme 2 (ACE2) and angiotensin-(1-7) levels in experimental biliary fibrosis. *J Hepatol* 2007; **47**: 387-395 [PMID: [17532087](#) DOI: [10.1016/j.jhep.2007.03.008](#)]
- 22 **Chua RL,** Lukassen S, Trump S, Hennig BP, Wendisch D, Pott F, Debnath O, Thürmann L, Kurth F, Völker MT, Kazmierski J, Timmermann B, Twardziok S, Schneider S, Machleidt F, Müller-Redetzky H, Maier M, Krannich A,

- Schmidt S, Balzer F, Liebig J, Loske J, Suttorp N, Eils J, Ishaque N, Liebert UG, von Kalle C, Hocke A, Witzernath M, Goffinet C, Drosten C, Laudi S, Lehmann I, Conrad C, Sander LE, Eils R. COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis. *Nat Biotechnol* 2020; **38**: 970-979 [PMID: 32591762 DOI: 10.1038/s41587-020-0602-4]
- 23 **Ziegler CGK**, Allon SJ, Nyquist SK, Mbanjo IM, Miao VN, Tzouanas CN, Cao Y, Yousif AS, Bals J, Hauser BM, Feldman J, Muus C, Wadsworth MH 2nd, Kazer SW, Hughes TK, Doran B, Gatter GJ, Vukovic M, Taliaferro F, Mead BE, Guo Z, Wang JP, Gras D, Plaisant M, Ansari M, Angelidis I, Adler H, Sucre JMS, Taylor CJ, Lin B, Waghray A, Mitsialis V, Dwyer DF, Buchheit KM, Boyce JA, Barrett NA, Laidlaw TM, Carroll SL, Colonna L, Tkachev V, Peterson CW, Yu A, Zheng HB, Gideon HP, Winchell CG, Lin PL, Bingle CD, Snapper SB, Kropski JA, Theis FJ, Schiller HB, Zaragosi LE, Barbry P, Leslie A, Kiem HP, Flynn JL, Fortune SM, Berger B, Finberg RW, Kean LS, Garber M, Schmidt AG, Lingwood D, Shalek AK, Ordovas-Montanes J; HCA Lung Biological Network. Electronic address: lung-network@humancellatlas.org; HCA Lung Biological Network. SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. *Cell* 2020; **181**: 1016-1035.e19 [PMID: 32413319 DOI: 10.1016/j.cell.2020.04.035]
- 24 **Wei C**, Wan L, Yan Q, Wang X, Zhang J, Yang X, Zhang Y, Fan C, Li D, Deng Y, Sun J, Gong J, Wang Y, Li J, Yang H, Li H, Zhang Z, Wang R, Du P, Zong Y, Yin F, Zhang W, Wang N, Peng Y, Lin H, Feng J, Qin C, Chen W, Gao Q, Zhang R, Cao Y, Zhong H. HDL-scavenger receptor B type 1 facilitates SARS-CoV-2 entry. *Nat Metab* 2020; **2**: 1391-1400 [PMID: 33244168 DOI: 10.1038/s42255-020-00324-0]
- 25 **Zhong P**, Xu J, Yang D, Shen Y, Wang L, Feng Y, Du C, Song Y, Wu C, Hu X, Sun Y. COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms. *Signal Transduct Target Ther* 2020; **5**: 256 [PMID: 33139693 DOI: 10.1038/s41392-020-00373-7]
- 26 **Elmunzer BJ**, Spitzer RL, Foster LD, Merchant AA, Howard EF, Patel VA, West MK, Qayed E, Nustas R, Zakaria A, Piper MS, Taylor JR, Jaza L, Forbes N, Chau M, Lara LF, Papachristou GI, Volk ML, Hilson LG, Zhou S, Kushnir VM, Lenyo AM, McLeod CG, Amin S, Kufnec GN, Yadav D, Fox C, Kolb JM, Pawa S, Pawa R, Canakis A, Huang C, Jamil LH, Aneese AM, Glamour BK, Smith ZL, Hanley KA, Wood J, Patel HK, Shah JN, Agarunov E, Sethi A, Fogel EL, McNulty G, Haseeb A, Trieu JA, Dixon RE, Yang JY, Mendelsohn RB, Calo D, Aroniadis OC, LaComb JF, Scheiman JM, Sauer BG, Dang DT, Piraka CR, Shah ED, Pohl H, Tierney WM, Mitchell S, Condon A, Lenhart A, Dua KS, Kanagala VS, Kamal A, Singh VK, Pinto-Sanchez MI, Hutchinson JM, Kwon RS, Korsnes SJ, Singh H, Solati Z, Willingham FF, Yachinski PS, Conwell DL, Mosier E, Azab M, Patel A, Buxbaum J, Wani S, Chak A, Hosmer AE, Keswani RN, DiMaio CJ, Bronze MS, Muthusamy R, Canto MI, Gjeorgijevski VM, Imam Z, Odish F, Edhi AI, Orosey M, Tiwari A, Patwardhan S, Brown NG, Patel AA, Ordiah CO, Sloan IP, Cruz L, Koza CL, Okafor U, Hollander T, Furey N, Reykhart O, Zbib NH, Damianos JA, Esteban J, Hajidiacos N, Saul M, Mays M, Anderson G, Wood K, Mathews L, Diakova G, Caisse M, Wakefield L, Nitchie H, Waljee AK, Tang W, Zhang Y, Zhu J, Deshpande AR, Rockey DC, Alford TB, Durkalski V; North American Alliance for the Study of Digestive Manifestations of COVID-19. Digestive Manifestations in Patients Hospitalized With Coronavirus Disease 2019. *Clin Gastroenterol Hepatol* 2021; **19**: 1355-1365.e4 [PMID: 33010411 DOI: 10.1016/j.cgh.2020.09.041]
- 27 **Fu Y**, Zhu R, Bai T, Han P, He Q, Jing M, Xiong X, Zhao X, Quan R, Chen C, Zhang Y, Tao M, Yi J, Tian D, Yan W. Clinical Features of Patients Infected With Coronavirus Disease 2019 With Elevated Liver Biochemistries: A Multicenter, Retrospective Study. *Hepatology* 2021; **73**: 1509-1520 [PMID: 32602604 DOI: 10.1002/hep.31446]
- 28 **Fix OK**, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, Pratt DS, Russo MW, Schilsky ML, Verna EC, Loomba R, Cohen DE, Bezerra JA, Reddy KR, Chung RT. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. *Hepatology* 2020; **72**: 287-304 [PMID: 32298473 DOI: 10.1002/hep.31281]
- 29 **Panteghini M**. Aspartate aminotransferase isoenzymes. *Clin Biochem* 1990; **23**: 311-319 [PMID: 2225456 DOI: 10.1016/0009-9120(90)80062-n]
- 30 **Bloom PP**, Meyerowitz EA, Reinus Z, Daidone M, Gustafson J, Kim AY, Schaefer E, Chung RT. Liver Biochemistries in Hospitalized Patients With COVID-19. *Hepatology* 2021; **73**: 890-900 [PMID: 32415860 DOI: 10.1002/hep.31326]
- 31 **Meersseman P**, Blondeel J, De Vlioger G, van der Merwe S, Monbaliu D; Collaborators Leuven Liver Transplant program. Secondary sclerosing cholangitis: an emerging complication in critically ill COVID-19 patients. *Intensive Care Med* 2021; **47**: 1037-1040 [PMID: 34185115 DOI: 10.1007/s00134-021-06445-8]
- 32 **Tafreshi S**, Whiteside I, Levine I, D'Agostino C. A case of secondary sclerosing cholangitis due to COVID-19. *Clin Imaging* 2021; **80**: 239-242 [PMID: 34364072 DOI: 10.1016/j.clinimag.2021.07.017]
- 33 **Ponziani FR**, Del Zompo F, Nesci A, Santopaolo F, Ianiro G, Pompili M, Gasbarrini A; "Gemelli against COVID-19" group. Liver involvement is not associated with mortality: results from a large cohort of SARS-CoV-2-positive patients. *Aliment Pharmacol Ther* 2020; **52**: 1060-1068 [PMID: 32628793 DOI: 10.1111/apt.15996]
- 34 **Yip TC**, Lui GC, Wong VW, Chow VC, Ho TH, Li TC, Tse YK, Hui DS, Chan HL, Wong GL. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. *Gut* 2021; **70**: 733-742 [PMID: 32641471 DOI: 10.1136/gutjnl-2020-321726]
- 35 **Weber S**, Hellmuth JC, Scherer C, Muenchhoff M, Mayerle J, Gerbes AL. Liver function test abnormalities at hospital admission are associated with severe course of SARS-CoV-2 infection: a prospective cohort study. *Gut* 2021; **70**: 1925-1932 [PMID: 33514597 DOI: 10.1136/gutjnl-2020-323800]
- 36 **Ding ZY**, Li GX, Chen L, Shu C, Song J, Wang W, Wang YW, Chen Q, Jin GN, Liu TT, Liang JN, Zhu P, Zhu W, Li Y, Zhang BH, Feng H, Zhang WG, Yin ZY, Yu WK, Yang Y, Zhang HQ, Tang ZP, Wang H, Hu JB, Liu JH, Yin P, Chen XP, Zhang B; Tongji Multidisciplinary Team for Treating COVID-19 (TTTC). Association of liver abnormalities with in-hospital mortality in patients with COVID-19. *J Hepatol* 2021; **74**: 1295-1302 [PMID: 33347952 DOI: 10.1016/j.jhep.2020.12.012]
- 37 **Kumar-M P**, Mishra S, Jha DK, Shukla J, Choudhury A, Mohindra R, Mandavdhare HS, Dutta U, Sharma V. Coronavirus disease (COVID-19) and the liver: a comprehensive systematic review and meta-analysis. *Hepatol Int* 2020; **14**: 711-722 [PMID: 32623633 DOI: 10.1007/s12072-020-10071-9]

- 38 **Zhang C**, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; **5**: 428-430 [PMID: 32145190 DOI: 10.1016/S2468-1253(20)30057-1]
- 39 **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**: 2095-2103 [PMID: 32239796 DOI: 10.1111/Liv.14455]
- 40 **Lei F**, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, Zhang XJ, Cai J, Lin L, Ouyang S, Wang X, Yang C, Cheng X, Liu W, Li H, Xie J, Wu B, Luo H, Xiao F, Chen J, Tao L, Cheng G, She ZG, Zhou J, Wang H, Lin J, Luo P, Fu S, Ye P, Xiao B, Mao W, Liu L, Yan Y, Chen G, Huang X, Zhang BH, Yuan Y. Longitudinal Association Between Markers of Liver Injury and Mortality in COVID-19 in China. *Hepatology* 2020; **72**: 389-398 [PMID: 32359177 DOI: 10.1002/hep.31301]
- 41 **Bangash MN**, Patel JM, Parekh D, Murphy N, Brown RM, Elsharkawy AM, Mehta G, Armstrong MJ, Neil D. SARS-CoV-2: Is the liver merely a bystander to severe disease? *J Hepatol* 2020; **73**: 995-996 [PMID: 32502510 DOI: 10.1016/j.jhep.2020.05.035]
- 42 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]
- 43 **Li Y**, Xiao SY. Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical implications. *J Med Virol* 2020; **92**: 1491-1494 [PMID: 32369204 DOI: 10.1002/jmv.25973]
- 44 **Tian S**, Xiong Y, Liu H, Niu L, Guo J, Liao M, Xiao SY. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod Pathol* 2020; **33**: 1007-1014 [PMID: 32291399 DOI: 10.1038/s41379-020-0536-x]
- 45 **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0]
- 46 **Phipps MM**, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, Fox AN, Zucker J, Verna EC. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. *Hepatology* 2020; **72**: 807-817 [PMID: 32473607 DOI: 10.1002/hep.31404]
- 47 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]
- 48 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]
- 49 **Papic N**, Pangercic A, Vargovic M, Barsic B, Vince A, Kuzman I. Liver involvement during influenza infection: perspective on the 2009 influenza pandemic. *Influenza Other Respir Viruses* 2012; **6**: e2-e5 [PMID: 21951624 DOI: 10.1111/j.1750-2659.2011.00287.x]
- 50 **Sonzogni A**, Previtali G, Seghezzi M, Grazia Alessio M, Gianatti A, Licini L, Morotti D, Zerbi P, Carsana L, Rossi R, Lauri E, Pellegrinelli A, Nebuloni M. Liver histopathology in severe COVID 19 respiratory failure is suggestive of vascular alterations. *Liver Int* 2020; **40**: 2110-2116 [PMID: 32654359 DOI: 10.1111/Liv.14601]
- 51 **Zhang Y**, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C, Zhao J, Sun X, Tian R, Wu W, Wu D, Ma J, Chen Y, Zhang D, Xie J, Yan X, Zhou X, Liu Z, Wang J, Du B, Qin Y, Gao P, Qin X, Xu Y, Zhang W, Li T, Zhang F, Zhao Y, Li Y. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. *N Engl J Med* 2020; **382**: e38 [PMID: 32268022 DOI: 10.1056/NEJMc2007575]
- 52 **Wang SF**, Tseng SP, Yen CH, Yang JY, Tsao CH, Shen CW, Chen KH, Liu FT, Liu WT, Chen YM, Huang JC. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. *Biochem Biophys Res Commun* 2014; **451**: 208-214 [PMID: 25073113 DOI: 10.1016/j.bbrc.2014.07.090]
- 53 **Olry A**, Meunier L, Délire B, Larrey D, Horsmans Y, Le Louët H. Drug-Induced Liver Injury and COVID-19 Infection: The Rules Remain the Same. *Drug Saf* 2020; **43**: 615-617 [PMID: 32514859 DOI: 10.1007/s40264-020-00954-z]
- 54 **Karthik K**, Senthilkumar TMA, Udhayavel S, Raj GD. Role of antibody-dependent enhancement (ADE) in the virulence of SARS-CoV-2 and its mitigation strategies for the development of vaccines and immunotherapies to counter COVID-19. *Hum Vaccin Immunother* 2020; **16**: 3055-3060 [PMID: 32845733 DOI: 10.1080/21645515.2020.1796425]
- 55 **Dawood DRM**, Salum GM, El-Meguid MA. The Impact of COVID-19 on Liver Injury. *Am J Med Sci* 2022; **363**: 94-103 [PMID: 34752738 DOI: 10.1016/j.amjms.2021.11.001]
- 56 **Singh A**, Kamath A. Assessment of adverse events associated with remdesivir use for coronavirus disease 2019 using real-world data. *Expert Opin Drug Saf* 2021; **20**: 1559-1564 [PMID: 34328807 DOI: 10.1080/14740338.2021.1962846]
- 57 **Shehu AI**, Lu J, Wang P, Zhu J, Wang Y, Yang D, McMahon D, Xie W, Gonzalez FJ, Ma X. Pregnane X receptor activation potentiates ritonavir hepatotoxicity. *J Clin Invest* 2019; **129**: 2898-2903 [PMID: 31039134 DOI: 10.1172/JCI128274]
- 58 **Varga Z**, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417-1418 [PMID: 32325026 DOI: 10.1016/S0140-6736(20)30937-5]
- 59 **Fraser J**, Mousley J, Testro A, Smibert OC, Koshy AN. Clinical Presentation, Treatment, and Mortality Rate in Liver Transplant Recipients With Coronavirus Disease 2019: A Systematic Review and Quantitative Analysis. *Transplant Proc* 2020; **52**: 2676-2683 [PMID: 32891405 DOI: 10.1016/j.transproceed.2020.07.012]
- 60 **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, Koziel 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**: 2052-2059 [PMID: 32320003 DOI: 10.1001/jama.2020.10177]

- 10.1001/jama.2020.6775]
- 61 **Mohammed A**, Paranji N, Chen PH, Niu B. COVID-19 in Chronic Liver Disease and Liver Transplantation: A Clinical Review. *J Clin Gastroenterol* 2021; **55**: 187-194 [PMID: 33394628 DOI: 10.1097/MCG.0000000000001481]
 - 62 **Del Zompo F**, De Siena M, Ianiro G, Gasbarrini A, Pompili M, Ponziani FR. Prevalence of liver injury and correlation with clinical outcomes in patients with COVID-19: systematic review with meta-analysis. *Eur Rev Med Pharmacol Sci* 2020; **24**: 13072-13088 [PMID: 33378061 DOI: 10.26355/eurrev_202012_24215]
 - 63 **Elnaggar M**, Abomhaya A, Elkhattib I, Dawoud N, Doshi R. COVID-19 and liver diseases, what we know so far. *World J Clin Cases* 2022; **10**: 3969-3980 [PMID: 35665122 DOI: 10.12998/wjcc.v10.i13.3969]
 - 64 **Marjot T**, Buescher G, Sebode M, Barnes E, Barritt AS 4th, Armstrong MJ, Baldelli L, Kennedy J, Mercer C, Ozga AK, Casar C, Schramm C; contributing Members and Collaborators of ERN RARE-LIVER/COVID-Hep/SECURE-Cirrhosis, Moon AM, Webb GJ, Lohse AW. SARS-CoV-2 infection in patients with autoimmune hepatitis. *J Hepatol* 2021; **74**: 1335-1343 [PMID: 33508378 DOI: 10.1016/j.jhep.2021.01.021]
 - 65 **Wei L**. The protocol for prevention, diagnosis and treatment of corona virus infective disease 2019. *J Clin Exp Hepatol* 2020; **28**: E004
 - 66 **Hashemi N**, Viveiros K, Redd WD, Zhou JC, McCarty TR, Bazarbashi AN, Hathorn KE, Wong D, Njie C, Shen L, Chan WW. Impact of chronic liver disease on outcomes of hospitalized patients with COVID-19: A multicentre United States experience. *Liver Int* 2020; **40**: 2515-2521 [PMID: 32585065 DOI: 10.1111/Liv.14583]
 - 67 **Colmenero J**, Rodríguez-Perálvarez M, Salcedo M, Arias-Milla A, Muñoz-Serrano A, Graus J, Nuño J, Gastaca M, Bustamante-Schneider J, Cachero A, Lladó L, Caballero A, Fernández-Yunquera A, Loinaz C, Fernández I, Fondevila C, Navasa M, Iñarrairaegui M, Castells L, Pascual S, Ramírez P, Vinaixa C, González-Dieguez ML, González-Grande R, Hierro L, Nogueras F, Otero A, Álamo JM, Blanco-Fernández G, Fábrega E, García-Pajares F, Montero JL, Tomé S, De la Rosa G, Pons JA. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. *J Hepatol* 2021; **74**: 148-155 [PMID: 32750442 DOI: 10.1016/j.jhep.2020.07.040]
 - 68 **Ravanan R**, Callaghan CJ, Mumford L, Ushiro-Lumb I, Thorburn D, Casey J, Friend P, Parameshwar J, Currie I, Burnapp L, Baker R, Dudley J, Oniscu GC, Berman M, Asher J, Harvey D, Manara A, Manas D, Gardiner D, Forsythe JLR. SARS-CoV-2 infection and early mortality of waitlisted and solid organ transplant recipients in England: A national cohort study. *Am J Transplant* 2020; **20**: 3008-3018 [PMID: 32780493 DOI: 10.1111/ajt.16247]
 - 69 **Gordon DE**, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, O'Meara MJ, Rezelj VV, Guo JZ, Swaney DL, Tummino TA, Hüttenhain R, Kaake RM, Richards AL, Tutuncuoglu B, Foussard H, Batra J, Haas K, Modak M, Kim M, Haas P, Polacco BJ, Braberg H, Fabius JM, Eckhardt M, Soucheray M, Bennett MJ, Cakir M, McGregor MJ, Li Q, Meyer B, Roesch F, Vallet T, Mac Kain A, Miorin L, Moreno E, Naing ZZC, Zhou Y, Peng S, Shi Y, Zhang Z, Shen W, Kirby IT, Melnyk JE, Chorba JS, Lou K, Dai SA, Barrio-Hernandez I, Memon D, Hernandez-Armenta C, Lyu J, Mathy CJP, Perica T, Pilla KB, Ganesan SJ, Saltzberg DJ, Rakesh R, Liu X, Rosenthal SB, Calviello L, Venkataramanan S, Liboy-Lugo J, Lin Y, Huang XP, Liu Y, Wankowicz SA, Bohn M, Safari M, Ugur FS, Koh C, Savar NS, Tran QD, Shengjuler D, Fletcher SJ, O'Neal MC, Cai Y, Chang JCJ, Broadhurst DJ, Klippsten S, Sharp PP, Wenzell NA, Kuzuoglu-Ozturk D, Wang HY, Trenker R, Young JM, Cavero DA, Hiatt J, Roth TL, Rathore U, Subramanian A, Noack J, Hubert M, Stroud RM, Frankel AD, Rosenberg OS, Verba KA, Agard DA, Ott M, Emerman M, Jura N, von Zastrow M, Verdin E, Ashworth A, Schwartz O, d'Enfert C, Mukherjee S, Jacobson M, Malik HS, Fujimori DG, Ideker T, Craik CS, Floor SN, Fraser JS, Gross JD, Sali A, Roth BL, Ruggero D, Taunton J, Kortemme T, Beltrao P, Vignuzzi M, García-Sastre A, Shokat KM, Shoichet BK, Krogan NJ. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020; **583**: 459-468 [PMID: 32353859 DOI: 10.1038/s41586-020-2286-9]
 - 70 **Cai Y**, Ye LP, Song YQ, Mao XL, Wang L, Jiang YZ, Que WT, Li SW. Liver injury in COVID-19: Detection, pathogenesis, and treatment. *World J Gastroenterol* 2021; **27**: 3022-3036 [PMID: 34168405 DOI: 10.3748/wjg.v27.i22.3022]
 - 71 **Xu K**, Cai H, Shen Y, Ni Q, Chen Y, Hu S, Li J, Wang H, Yu L, Huang H, Qiu Y, Wei G, Fang Q, Zhou J, Sheng J, Liang T, Li L. [Management of COVID-19: the Zhejiang experience]. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2020; **49**: 147-157 [PMID: 32391658 DOI: 10.3785/j.issn.1008-9292.2020.02.02]
 - 72 **Pergolizzi JV Jr**, Varrassi G, Magnusson P, LeQuang JA, Paladini A, Taylor R, Wollmuth C, Breve F, Christo P. COVID-19 and NSAIDS: A Narrative Review of Knowns and Unknowns. *Pain Ther* 2020; **9**: 353-358 [PMID: 32447629 DOI: 10.1007/s40122-020-00173-5]



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