**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 79636

**Manuscript Type:** MINIREVIEWS

**Molecular mechanisms implicated in SARS-CoV-2 liver tropism**

Quarleri J *et al*. SARS-CoV-2 liver tropism

Jorge Quarleri, M. Victoria Delpino

**Jorge Quarleri, M. Victoria Delpino,** Institute for Biomedical Research on Retroviruses and AIDS, Faculty of Medical Sciences, National Scientific and Technical Research Council-University of Buenos Aires, Buenos Aires 1121, Argentina

**Author contributions:** Quarleri J and Delpino MV have contributed equally to conceptualization, methodology, writing, review, and editing.

**Corresponding author: M. Victoria Delpino, PhD,** Institute for Biomedical Research on Retroviruses and AIDS, Faculty of Medical Sciences, University of Buenos Aires, Paraguay 2155 Piso 11, Buenos Aires 1121, Argentina. mdelpino@ffyb.uba.ar

**Received:** September 5, 2022

**Revised:** November 7, 2022

**Accepted:** November 27, 2022

**Published online:**

**Abstract**

The coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Hepatic involvement is common in SARS-CoV-2-infected individuals. It is currently accepted that the direct and indirect hepatic effects of SARS-CoV-2 infection play a significant role in COVID-19. In individuals with pre-existing infectious and non-infectious liver disease, who are at a remarkably higher risk of developing severe COVID-19 and death, this pathology is most medically relevant. This review emphasizes the current pathways regarded as contributing to the gastrointestinal and hepatic ailments linked to COVID-19-infected patients due to an imbalanced interaction among the liver, systemic inflammation, disrupted coagulation, and the lung.

**Key Words:** SARS-CoV-2; Viral hepatitis; Non-infectious liver disease; Hyperinflammation; Coronavirus disease 2019

Quarleri J, Delpino MV. Molecular mechanisms implicated in SARS-CoV-2 liver tropism. *World J Gastroenterol* 2022; In press

**Core Tip:** Clinical manifestations of coronavirus disease 2019 (COVID-19) may be triggered by the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the liver. SARS-CoV-2 genomic RNA and its replicative intermediates were found in liver tissues. SARS-CoV-2 causes direct cholangiocyte damage. Systemic inflammation due to COVID-19 correlated with the degree of acute liver injury as revealed by the rise in aspartate aminotransferase levels. SARS-CoV-2 infection increased the risk of morbidity and mortality in patients with a history of advanced liver disease.

**INTRODUCTION**

The coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Globally, as of 5 August 2022, there have been 579119505 confirmed cases of COVID-19, including 6457101 deaths, as reported by the World Health Organization[[1](#_ENREF_1)].

Coronaviruses are enveloped with crown-shaped spike glycoprotein, positive-sense single-stranded RNA viruses that include three genera: alphacoronavirus, betacoronavirus, and gammacoronavirus, mainly related to respiratory infections. SARS-CoV-2 employs receptor recognition mechanisms comparable to those used by preceding virulent coronaviruses such as SARS-CoV, responsible for the SARS epidemic of 2003[2-5].

In addition to common respiratory symptoms, COVID-19 patients also present with gastrointestinal symptoms comprising diarrhea, nausea, and vomiting[6]. Anal swabs from COVID-19 patients test positive for genomic SARS-CoV-2 RNA, and the virus can be isolated from stool samples[[7](#_ENREF_7),[8](#_ENREF_8)]. However, the possibility of fecal-oral transmission cannot be completely ruled out[[9](#_ENREF_9" \o "Zhong, 2020 #4),10].

The entry of the virus into target cells is mediated by the coronavirus spike protein (S) that engages angiotensin-converting enzyme 2 (ACE2) expressed in multiple cell types allowing SARS-CoV-2 to infect different organs such as the nasopharynx, lungs, lymph nodes, kidney, stomach, small intestine, spleen, brain, and liver leading to multiple organ damage[[11](#_ENREF_11)]. Cell entry also requires the transmembrane serine protease 2 or other proteases[[12](#_ENREF_12)]. The binding efficiency of the virus to ACE2 is a key determinant of transmissibility[[13](#_ENREF_13)]. Different reports have revealed that SARS-CoV-2 has higher binding affinity to ACE2 than the previous SARS-CoV. This finding may in part explain the increased transmissibility of SARS-CoV-2, organ tropism, and ultimately multi-organ damage and mortality[14-16]. The mechanisms that could be involved in the multi-organ injury due to infection with SARS-CoV-2 comprise the damage of endothelial cells, dysregulation of the immune response, and an imbalance in the renin-angiotensin-aldosterone system (RAAS). The relative significance of these mechanisms in the pathophysiology of COVID-19 is at present not completely known. Although some of these mechanisms comprising ACE2-mediated viral entry and tissue injury with misbalance of the RAAS may be specific to COVID-19, immune pathogenesis produced by systemic delivery of cytokines and impaired microcirculatory function can also take place due to viral sepsis[17].

Hepatic involvement is common in SARS-CoV-2-infected patients. In cases with severe COVID-19 and to a lesser extent in mild/moderate COVID-19, some authors have reported a significant increase in alanine aminotransferase and aspartate aminotransferase (AST) indicating abnormal liver function[[18](#_ENREF_18" \o "Wu, 2020 #16)]. Likewise, albumin decreased while alkaline phosphatase, gamma-glutamyl transferase (GGT), C-reactive protein (CRP), procalcitonin, ferritin, lactate dehydrogenase (LDH) as well as bilirubin levels were also significantly higher in severe than in other cases[[19-21](#_ENREF_19)]. Patients without a history of liver illness were found to have abnormal liver test results[[20](#_ENREF_20)]. These data suggests a direct connection between SARS-CoV-2 infection and digestive tract impairment. This review emphasizes the pathways currently regarded as contributing to the gastrointestinal and hepatic ailments linked to COVID-19.

To recognize the relevant literature, we employed a search and screening strategy. This process consisted of an extensive search of the online scientific database on the PubMed webpage using the most frequent synonyms to detect all possibly pertinent studies. In the following steps, references were analyzed to eliminate papers that were not relevant, and the remaining references were organized into categories for additional evaluation.

**Molecular mechanisms implicated in SARS-CoV-2 Liver tropism** **Detection of SARS-CoV-2 in LIVER tissue**

The liver coordinates an essential role in the host-microbe defense by assembling the portal and systemic circulation. Changes in the liver such as ductular fibrosis, hepatic steatosis, cholestasis, acute liver necrosis, and central vein thrombosis with concomitant lymphocytic infiltrate were detected in autopsies from COVID-19 deceased patients[[22](#_ENREF_22),23].

In line with previous reports, ACE2 is mostly expressed in cholangiocytes and to a lesser extent in hepatocytes. Accordingly, formalin-embedded liver tissues contain the SARS-CoV-2 RNA genome[24]. Other studies have stated that 2 of 3 autopsy livers carry the infectious virus, and 31 of 45 postmortem liver tissues contain the SARS-CoV-2 RNA genome[25]. Such studies that demonstrate the presence of SARS-CoV-2 RNA and proteins in liver cells are significant, as these may be found in the vascular lumen of blood vessels feeding the liver but also in portal vein endothelial cells, suggesting that the virus can also invade the liver through the circulation[[26](#_ENREF_26)]. Postmortem liver biopsies have shown the presence of typical coronavirus particles in the cytoplasm of hepatocytes by electron microscopy[[27](#_ENREF_27)], while hepatic parenchymal cells have also shown the presence of SARS-CoV-2 RNA[25]. Furthermore, the viral nucleocapsid protein has been detected in hepatic stem cells, hepatocytes, and cholangiocytes[28]. The presence of the SARS-CoV-2 RNA genome and its replicative intermediates in liver tissues has also been reported[28]. Most importantly, the nucleocapsid and the spike protein have been found in the liver 6 mo after recovery from COVID-19[29].

There is some proof that COVID-19 may be triggered by the presence of SARS-CoV-2 infection in the liver. However, other histological examinations revealed non-detectable viral particles in the liver and signs of significant hepatic damage[23,[30](#_ENREF_30)]. This supports the notion that both direct and indirect pathways contribute to liver damage in the context of SARS-CoV-2 infection; more investigation is required to assess the importance of each pathway.

**Viral effect on the liver**

The concept that SARS-CoV-2 can reach the liver cells through the ACE2 receptor is supported by the fact that ACE2 is present in liver and bile duct cells[[11](#_ENREF_11)]. Furthermore, recent research found that 59.7% of cholangiocytes and 2.6% of hepatocytes express ACE2. Likely, SARS-CoV-2 might infect cholangiocytes and cause liver damage since the amount of ACE2 found in cholangiocytes is similar to that reported in type 2 alveolar cells of the lung[[31](#_ENREF_31" \o "Kumar, 2020 #30)]. SARS-CoV-2-associated liver damage may be related to the presence of ACE2 receptors in cholangiocytes rather than hepatocytes[[32](#_ENREF_32)]. Moreover, given the rich supply of blood to the liver from the small bowel, the SARS-CoV-2 virus can use the gut-liver way across the liver reticular system to reach the liver[[33](#_ENREF_33),[34](#_ENREF_34)]. Taking into account that ACE2 was regarded as an interferon-inducible gene in human epithelial cells from respiratory tissues, the hepatocyte permissiveness for SARS-CoV-2 might be also modified when the viral receptor expression is increased after liver injury[[35](#_ENREF_35)], but it would be because of the shortened isoform of ACE2, identified as deltaACE2, instead of the functional viral receptor[[36](#_ENREF_36)].

In homeostasis, the bile acid released by hepatocytes into bile ducts is transported by cholangiocytes. The tight junction between cholangiocytes conserves the barrier function of the bile ductal epithelial cells, allowing bile acid collection and excretion. Besides, cholangiocytes play an important function in liver renewal and immune response[[37](#_ENREF_37)]. Thus, the disruption of the cholangiocyte function can induce hepatobiliary injury. Previous reports have demonstrated that SARS-CoV-2 infection impairs the barrier through the modulation of tight junctions[[38](#_ENREF_38)]. This effect could be attributed to the direct viral cytopathic effect on cholangiocytes. Likewise, SARS-CoV-2 infection induces the expression of apoptotic factors, including cluster of differentiation 40 (CD40), caspase recruitment domain family member 8, and serine/threonine kinase 4 in cholangiocytes[[38](#_ENREF_38" \o "Zhao, 2020 #31)]. Thus, SARS-CoV-2 causes direct cholangiocyte damage with subsequent liver homeostasis disruption in COVID-19 patients.

Liver biopsies from SARS-CoV-2 infected patients have revealed fatty degeneration, cellular infiltration, hepatocellular necrosis, increased ballooned hepatocytes, and mitotic cells. These findings are in line with the idea that liver damage in COVID-19 patients is caused by an indirect effect as a result of direct viral cholangiocyte damage and subsequent bile acid accumulation. However, it remains uncertain whether hepatic involvement during SARS-CoV-2 infection reveals direct cytopathic effects of the virus, ischemia and hypoxic reperfusion-related injury, exacerbated immune response responsible for the systemic inflammatory response syndrome, or a combination of mechanisms that have not been completely elucidated until now[39].

**Effect of systemic hyperinflammation in the liver**

SARS-CoV-2 infection is related with an acute phase response characterized by the secretion of very high levels of proinflammatory cytokines in conjunction with CRP and ferritin[[40](#_ENREF_40)]. The mechanisms involved in this “cytokine storm” are not completely elucidated. The proinflammatory response appears to be associated with the ability of the SARS-CoV-2 spike protein to activate C-type lectins and 20 family member 2 on innate immune cells[[41](#_ENREF_41" \o "Lu, 2021 #33)]. A transcriptome analysis of 284 samples from 196 SARS-CoV-2-infected patients revealed that diverse peripheral immune alterations are associated with clinical characteristics comprising severity and disease phase of COVID-19. The increased expression and release of S100A8/A9 during inflammation exerts a critical role in controlling the inflammatory reaction by inducing leukocyte recruitment and stimulating cytokine release. These are calcium-binding proteins constitutively expressed as a heterodimer in neutrophils and monocytes, and they are the most important platelet-derived activators of endothelial cells. Additionally, SARS-CoV-2 RNA was detected in different epithelial and immune cells, followed by transcription alterations within virus-positive cells[[42](#_ENREF_42)].

One of the mechanisms that encourage platelet adhesion to inflamed vascular endothelium is the early adhesive events that stimulate platelets to “roll” along endothelium. Among them is the interaction between the main platelet membrane receptor, GP1b (CD42)-1X-V, and von Willebrand factor secreted by endothelial cells. This phenomenon is strengthened by interactions between upregulated CD62P expression, which is present in both cell types and its counter receptor, P selectin glycoprotein ligand-1, which is also present in both cell types, although weakly in platelets. In a similar manner, the SARS-CoV-2 spike protein bound to the CD42b receptor to activate platelets *via* two different signaling pathways and stimulated platelet-monocyte interaction by engaging P selectin glycoprotein ligand-1 (PGSL-1) and CD40 ligand (CD40L)/CD40, which causes monocytes to produce proinflammatory cytokines. These findings demonstrate the correlation between hypercoagulation, monocyte activation, and a cytokine storm in patients severely affected.

The contact between the spike protein of SARS-CoV-2 and CD42 activates platelets and stimulates platelet-monocyte interactions through CD40L/CD40 and P-selectin/PGSL-1, contributing to hypercytokine secretion by monocytes[43]. Additionally, systemic inflammation is evidenced by a complement activation induced by the interferon (IFN)-Janus Kinase 1/2 (JAK1/2)-signal transducer and activator of transcription 1 (STAT1) signaling pathway[44].

The significance of the IFN pathways has been revealed in postmortem analyses of deceased patients due to severe COVID-19, where the livers displayed a significant induction of type I and II IFN responses and their related-JAK-STAT signaling pathways[25].

Moreover, the inflammation and cytokine stimulation observed in SARS-CoV-2 disease can contribute to endothelial injury and vascular damage, revealed by hypercoagulation, and arterial and venous embolism with the activation of immune cells and platelets, leading to clot formation[[45](#_ENREF_45),46]. High levels of CRP, which are indicative of acute liver injury, are correlated with the degree of systemic inflammation[47,[48](#_ENREF_48)]. Increased levels of high-sensitive CRP, interleukin 6 (IL-6), and ferritin in COVID-19 patients are indicative of systemic inflammation, which correlates with the degree of acute liver injury as determined by the rise in AST levels[49]. Through the downregulation of hepatobiliary uptake and deficiencies in the excretory systems, the massive systemic inflammation contributes to hepatocellular cholestasis in the late stages of the disease[[50](#_ENREF_50)]. Thus, it can be conclusively stated that SARS-CoV-2 infection is accompanied by a “cytokine storm” with a high proinflammatory cytokine profile that causes hepatic injury. It is obvious that systemic inflammation may contribute to acute liver damage, but SARS-CoV-2 infection cannot be ruled out directly. This theory is supported by the observation that liver damage appears early in the course of infection, as indicated by an increase in AST levels.

**SARS-CoV-2 infection in patients with previous liver disease**

Since the onset of the COVID-19 pandemic, an increased risk of morbidity and mortality was observed among SARS-CoV-2-infected patients with a history of advanced liver disease[[51](#_ENREF_51)]. Data obtained from multicenter studies have revealed a higher possibility of hospitalization and risk of death compared to patients without chronic liver disease[[52](#_ENREF_52)]. To date, the mechanisms linking both pathologies are unknown. However, it has been proposed that the prothrombotic alteration caused by COVID-19 upsets the delicate homeostatic balance of cirrhotic patients, leading to venous microthrombosis and parenchymal dysfunction along with subsequent respiratory failures[[53](#_ENREF_53)] (Figure 1).

**Viral hepatitis**

Patients with viral hepatitis are more likely to experience liver damage, according to data from previous SARS-CoV infections. The severity of liver disease and a worse prognosis are associated with SARS-CoV-2 superinfection in patients with chronic hepatitis B virus (HBV) infection. According to a study of 105 patients with both chronic HBV infection and SARS-CoV-2, the risk of complications such as acute chronic liver failure, acute cardiac injury, and shock was higher in co-infected patients than in patients who only had the SARS-CoV-2 virus[[54](#_ENREF_54)]. Consequently, patients with liver damage had a higher mortality rate (28.6%) than patients without liver damage (3.3%), and the treatment of COVID-19 in co-infected individuals had a significant negative impact on liver function[[54](#_ENREF_54)]. A higher risk of abnormal liver function was found in inactive HBV carriers in a retrospective study that included 133 hospitalized patients with confirmed COVID-19, 116 of whom tested negative for serum hepatitis B antigen, and 17 were HBV inactive carriers. Hepatocytes and the immune response, as shown by the production of IL-6, D-dimer, and LDH are involved in the liver damage observed in SARS-CoV-2/HBV[[55](#_ENREF_55" \o "Lin, 2021 #62)]. Moreover, chronic HBV infection-induced immune dysfunction may be a key factor in the development of COVID-19. Due to persistent viral antigens, studies have shown that chronic HBV infection is linked to the depletion of virus-specific CD4+ and CD8+ T cells[[56](#_ENREF_56)]. IL-2) and tumor necrosis factor alpha (TNF-α) release are particularly hampered by HBV-specific exhausted T lymphocytes, resulting in progressively diminished antiviral function[[57](#_ENREF_57" \o "Brooks, 2005 #70)]. IL-2, IL-6, and TNF-α are among the proinflammatory cytokines overproduced as a result of the excessive immunological response to SARS-CoV-2 infection (cytokine storm), which is to our knowledge a significant factor associated with disease severity and mortality[[58](#_ENREF_58)]. In this situation, it is conceivable that immunosuppression and depletion of HBV-specific T lymphocytes might prevent an excessive immunological response to SARS-CoV-2 and lessen the cytokine storm, resulting in milder illness. Although HBV reactivation is a potential side result of SARS-CoV-2 infection, the overall risk is minimal. Reactivation is primarily described as an abrupt and quick rise in HBV DNA levels in individuals with a history of detectable HBV DNA or recurrence of HBV DNA viremia in those with previous undetectable viral DNA[[59](#_ENREF_59)]. Immunosuppressive therapy such as IL-6 receptor antagonists, IL-1 receptor antagonist, and high-dose corticosteroids are frequently used to treat HBV reactivation[[60](#_ENREF_60)]. These treatments may be utilized in severe COVID-19 patients to manage the cytokine storm and to lessen the immune-mediated multiorgan damage. The impaired balance between the host’s immune system and viral replication is the main cause of the progression to HBV reactivation after infection with SARS-CoV-2. The dosage of glucocorticoids or immunosuppressive medications is a major risk factor for the reactivation of HBV during the treatment of COVID-19, together with the host baseline virological markers[[61](#_ENREF_61)].

The COVID-19 pandemic may delay the global commitment to eradicate HBV infection for several years because of the decrease in chronic hepatitis B prevention, diagnosis, and treatment. According to estimates, during the COVID-19 pandemic, half of low- and middle-income families were unable to access healthcare facilities for the diagnosis, clinical evaluation, and treatment of HBV. This was primarily due to travel restrictions, job and income losses, and patients’ fear of contracting SARS-CoV-2[[62](#_ENREF_62)]. Only 18% of the patients with hepatocellular carcinoma (HCC) and 32% of those with decompensated cirrhosis had continuity of care, while 23% of the health centers postponed HBV infection therapy initiation[[63](#_ENREF_63)].

Regarding hepatitis C virus (HCV), some studies have revealed that corticosteroid-treated individuals might experience significant viral reactivation, which is mostly caused by immunosuppression[[64-66](#_ENREF_64)]. Steroid therapy can lead to HCV reactivation through two different mechanisms: first, they increase the capacity of the virus to replicate by upregulating two essential HCV entry factors: occludin and scavenger receptor class B type I; and second, they do so by inhibiting the immune response against the virus, including T lymphocytes and plasmacytoid dendritic cells[[67-69](#_ENREF_67)]. In individuals with persistent HCV infection, corticosteroid therapy can aggravate the course. Evidence suggests that HCV viremia rises in response to corticosteroids and falls back to normal levels in response to their cessation[[70](#_ENREF_70)]. Therefore, it is best to avoid using corticosteroids in individuals with HCV infection[[71](#_ENREF_71)].

However, the synergism between SARS-CoV-2 and chronic viral HBV and HCV has not been clearly elucidated. Hence, more widespread studies are required to evaluate the use of this therapy.

**COVID-19 in non-infectious chronic liver disease patients**

Currently, decompensated liver disease and HCC cause 2 million deaths annually as a result of liver cirrhosis, which affects 112 million people globally[[72](#_ENREF_72)]. High COVID-19 death rates in cirrhotic patients have been found in numerous recent reports[[73](#_ENREF_73),[74](#_ENREF_74)]. The baseline Child-Pugh score also showed to be substantially correlated with death. The most frequent cause of mortality in COVID-19 patients is lung damage. Liver dysfunction is a possible cause of persistent lung damage. Indeed, liver failure plays a significant role in individuals with bacterial chest sepsis[[75](#_ENREF_75)]. Cirrhosis and SARS-CoV-2 may have a fatal synergy because of alterations in the immune system caused by viral infection and coagulation. Dysregulation of pulmonary dynamics has been attributed to a number of factors, including ascites or deteriorating encephalopathy, immunological dysfunction in viral infection, a rise in the burden of venous thromboembolic illness, and concurrent lung disease. According to Marjot *et al*[[52](#_ENREF_52)], mortality rates in patients with cirrhosis was 32% compared to 8% in those without it, while the mortality rate rose in connection with the Child-Pugh class [A (19%), B (35%), and C (51%)] in patients with cirrhosis. The principal cause of decease was respiratory failure (71%).

***Alcohol-associated liver disease and COVID-19***

There is very little effect of COVID-19 on patients with alcoholic hepatitis or alcoholic liver disease[[74](#_ENREF_74),[76](#_ENREF_76)]. However, research on cirrhotic patients has revealed that, like other cirrhotic patients, those with alcohol-related cirrhosis have higher mortality rates[[74](#_ENREF_74),[76](#_ENREF_76)]. Chronic kidney disease, obesity, and diabetes are common comorbidities among patients with alcohol-related cirrhosis, leading to higher risks of COVID-19 complications[[77](#_ENREF_77)]. In a study involving 867 patients with COVID-19 and chronic liver disease, Kim *et al*[[78](#_ENREF_78)] found that alcohol-associated liver disease (ALD) was independently associated with a higher risk of poor survival and a higher COVID-19 mortality rate. ALD is connected to the inflammatory state prompted by danger-associated molecular patterns which trigger the secretion of pro-inflammatory cytokines by particular immune cells[[74](#_ENREF_74),[79](#_ENREF_79)]. It was hypothesized that the superimposed cytokine storm produced by SARS-CoV-2 in patients with ALD could exacerbate the heightened inflammatory process, leading to worse outcomes[[80](#_ENREF_80)].

***Non-alcoholic fatty liver disease***

Diabetes, hypertension, cardiovascular disease, and obesity are well-known risk factors for severe COVID-19[[81](#_ENREF_81)]. These metabolic comorbidities are closely related to non-alcoholic fatty liver disease (NAFLD).

Wide-ranging effects of the course of COVID-19 make distinguishing the independent effect on NAFLD a challenge. The difficulty is raised by a number of confounding cofactors, reverse causality from steatosis caused by SARS-CoV-2, as well as population heterogeneity and the diagnostic conditions studied. Consequently, results from clinical studies have been ambiguous. In a retrospective study of 202 SARS-CoV-2 infected patients, 35% were individuals with NAFLD. When compared to SARS-CoV-2 infected patients without NAFLD, patients with NAFLD displayed a higher risk of severe COVID-19, as evidenced by a higher probability of liver abnormalities in the hospitalized patient and long-term viral shedding[[33](#_ENREF_33)].

Seventy-one consecutive COVID-19 patients from a different case-control study were divided into groups based on whether or not they had NAFLD. After reviewing all medical records, including demographic, clinical, and laboratory data, this study concluded that NAFLD poses a significant risk for developing severe COVID-19[[82](#_ENREF_82)]. Patients with NAFLD were more probable to be admitted to the intensive care unit, according to a retrospective multicenter study with a cohort of hospitalized adults with COVID-19[[83](#_ENREF_83)]. These results were supported by two thorough systematic reviews, as well as a meta-analysis[[84](#_ENREF_84),[85](#_ENREF_85)].

On the other hand, NAFLD was not linked to severe COVID-19, as shown by a study conducted by Mushtaq *et al*[86] in a Middle Eastern cohort. The authors revealed that gene variants associated with NAFLD (transmembrane 6 superfamily 2 [TM6SF2], patatin-like phospholipase domain-containing protein 3 [PNPLA3], glucokinase regulator, and membrane-bound O-acyltransferase domain-containing protein 7 [MBOAT7]) and the severity of COVID-19 disease (TM6SF2, PNPLA3, and MBOAT7) is associated with genetic variation as a mechanism to establish a genetic risk score[[87](#_ENREF_87)]. Additionally, other studies have concluded that some PNPLA3 allelic variants may act protectively by lowering the risk of COVID-19 mortality[[88](#_ENREF_88)]. Finally, a study that used a Mendelian randomization approach to investigate the correlations between COVID-19 severity and NAFLD found scant evidence supporting such a relationship[[89](#_ENREF_89)].

**COVID-19 AND HCC**

At the beginning of the SARS-CoV-2 pandemic, serious measures were taken to preserve cancer patients from morbidity and mortality by restraining hospital presence and submitting anti-cancer therapy. The European Association for the Study of the liver recommended postponing treatments and evaluating the possibility of gradually removing anti-cancer immunological therapy[[90](#_ENREF_90)].

In the context of rapidly escalating viral transmission, a series of precautionary principles were dictated. These measures rested on the hypothesis that cancer and active anti-cancer therapy have an unfavorable effect on the consequences of SARS-CoV-2 infection. It is widely known that cancer patients are commonly immunosuppressed as a consequence of chemotherapy. Therefore, different studies indicated that patients with subjacent cancer were at major risk of acquiring SARS-CoV-2 infection and severe outcomes could eventually evolve[[91](#_ENREF_91),[92](#_ENREF_92)].

Recently, a multicenter retrospective revision including 250 non-vaccinated patients with liver cancer and COVID-19 infection showed that the mortality rate was 12.96% in patients with a diagnosis of HCC simultaneously with SARS-CoV-2 infection, and 20.25% in individuals with HCC history[[74](#_ENREF_74)].

However, the prevalence of SARS-CoV-2 infection did not display a real rise in patients with chronic liver disease or in HCC patients. Nevertheless, HCC cirrhotic patients with COVID-19 may have a worse prognosis than the general population regarding severe disease, complications of SARS-CoV-2 infection, and mortality. Hereafter, the significance of applying actions to decrease the possibility of infection in these patients[[93](#_ENREF_93)].

**COVID-19 among liver transplant recipients**

Managing liver transplantation in the curse of SARS-CoV-2 pandemic was difficult as numerous hospitals had to essentially stop or drastically scale back their transplantation operations owing to a sudden drop in donor numbers and were forced to convert several care facilities into COVID-19 units. Due to the limited information available and the necessity of continuing immunosuppressive medication in these patients, the medical staff faced difficult challenges to manage post-liver transplant receivers in the course of COVID-19 pandemic while patients were at risk for a more severe COVID-19 infection and possible continued viral shedding. Qin *et al*[[94](#_ENREF_94)] described the first instance of SARS-CoV-2 infection in a patient with hepatocellular cancer who had undergone liver transplantation, and discovered a higher viral load with an increasing immunosuppressive dosage. Immunosuppressive medications had no effect on the frequency of COVID-19 severity, according to Bhoori *et al*[[95](#_ENREF_95)]. Early studies from Italy claimed that transplant patients experienced low death rates of less than 5%[[96](#_ENREF_96)]. However, later assessments revealed that liver recipients and other solid organ transplants experienced mortality rates of over 25%[[97](#_ENREF_97),[98](#_ENREF_98)]. Recently, findings from a prospective European trial comprising 57 liver transplant patients with proven SARS-CoV-2 infection and 19 transplant facilities were released. These results are consistent with is consistent with the projected mortality rate because patients with severe COVID-19 infection had overall and in-hospital case fatality rates of 12% and 17%, respectively. Five of the seven patients who passed away had a cancer history at the time of their deaths[[99](#_ENREF_99)]. The evidence currently available does not support the idea that transplantation or certain immunosuppressive therapies have a significant impact on the likelihood of disease severity. Nevertheless, patients with underlying malignancies may need special care[[97](#_ENREF_97)]. A number of COVID-19 vaccines have lately approved and have demonstrated effectiveness in healthy individuals. However, careful assessment and immunization of immunocompetent individuals are still required due to the potential immunological imbalance brought on by their illness or immunosuppressive medication. According to Boyarsky *et al*[[100](#_ENREF_100)], solid organ transplant recipients who were fully vaccinated with the mRNA vaccine showed an appropriate humoral response, while the subpar response was linked to the use of antimetabolite immunosuppression.

**CONCLUSION**

It is widely acknowledged that the effects of SARS-CoV-2 infection on the liver have played a significant role during the COVID-19 pandemic. In patients with pre-existing infectious and non-infectious liver disease, who are at an extra high risk of developing severe COVID-19 and death, this feature is most medically relevant. This review aims to provide an overview of the current research on the molecular mediators responsible for inflammatory liver injury during SARS-CoV-2 infection. To fully comprehend the pathogenic pathways that cause clinical deterioration of patients with COVID-19 due to an imbalanced interaction between the liver, systemic inflammation, disrupted coagulation, and the lung, further research should be conducted.

**REFERENCES**

1 **World Health Organization**. WHO Coronavirus (COVID-19) Dashboard. 2022. [cited 25 August 2022]. Available from: https://covid19.who.int/

2 **Lan J**, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L, Wang X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature* 2020; **581**: 215-220 [PMID: 32225176 DOI: 10.1038/s41586-020-2180-5]

3 **Shang J**, Ye G, Shi K, Wan Y, Luo C, Aihara H, Geng Q, Auerbach A, Li F. Structural basis of receptor recognition by SARS-CoV-2. *Nature* 2020; **581**: 221-224 [PMID: 32225175 DOI: 10.1038/s41586-020-2179-y]

4 **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**: 1735 [PMID: 33306958 DOI: 10.1016/j.cell.2020.11.032]

5 **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]

6 **Parasa S**, Desai M, Thoguluva Chandrasekar V, Patel HK, Kennedy KF, Roesch T, Spadaccini M, Colombo M, Gabbiadini R, Artifon ELA, Repici A, Sharma P. Prevalence of Gastrointestinal Symptoms and Fecal Viral Shedding in Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2020; **3**: e2011335 [PMID: 32525549 DOI: 10.1001/jamanetworkopen.2020.11335]

7 **Holshue ML**, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber SI, Kim L, Tong S, Lu X, Lindstrom S, Pallansch MA, Weldon WC, Biggs HM, Uyeki TM, Pillai SK; Washington State 2019-nCoV Case Investigation Team. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med* 2020; **382**: 929-936 [PMID: 32004427 DOI: 10.1056/NEJMoa2001191]

8 **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]

9 **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]

10 **Ning T**, Liu S, Xu J, Yang Y, Zhang N, Xie S, Min L, Zhang S, Zhu S, Wang Y. Potential intestinal infection and faecal-oral transmission of human coronaviruses. *Rev Med Virol* 2022; **32**: e2363 [PMID: 35584273 DOI: 10.1002/rmv.2363]

11 **Hamming I**, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]

12 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280.e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]

13 **Li F**, Li W, Farzan M, Harrison SC. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science* 2005; **309**: 1864-1868 [PMID: 16166518 DOI: 10.1126/science.1116480]

14 **Wrapp D**, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020; **367**: 1260-1263 [PMID: 32075877 DOI: 10.1126/science.abb2507]

15 **Wang Q**, Zhang Y, Wu L, Niu S, Song C, Zhang Z, Lu G, Qiao C, Hu Y, Yuen KY, Wang Q, Zhou H, Yan J, Qi J. Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2. *Cell* 2020; **181**: 894-904.e9 [PMID: 32275855 DOI: 10.1016/j.cell.2020.03.045]

16 **Lei C**, Qian K, Li T, Zhang S, Fu W, Ding M, Hu S. Neutralization of SARS-CoV-2 spike pseudotyped virus by recombinant ACE2-Ig. *Nat Commun* 2020; **11**: 2070 [PMID: 32332765 DOI: 10.1038/s41467-020-16048-4]

17 **Li H**, Liu L, Zhang D, Xu J, Dai H, Tang N, Su X, Cao B. SARS-CoV-2 and viral sepsis: observations and hypotheses. *Lancet* 2020; **395**: 1517-1520 [PMID: 32311318 DOI: 10.1016/S0140-6736(20)30920-X]

18 **Wu C**, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020; **180**: 934-943 [PMID: 32167524 DOI: 10.1001/jamainternmed.2020.0994]

19 **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]

20 **Fan Z**, Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang S, Liu Z, Cheng J. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol* 2020; **18**: 1561-1566 [PMID: 32283325 DOI: 10.1016/j.cgh.2020.04.002]

21 **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**: 425-434 [PMID: 32105637 DOI: 10.1016/S1473-3099(20)30086-4]

22 **Lax SF**, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, Vander K, Bargfrieder U, Trauner M. Pulmonary Arterial Thrombosis in COVID-19 With Fatal Outcome : Results From a Prospective, Single-Center, Clinicopathologic Case Series. *Ann Intern Med* 2020; **173**: 350-361 [PMID: 32422076 DOI: 10.7326/M20-2566]

23 **Peiris S**, Mesa H, Aysola A, Manivel J, Toledo J, Borges-Sa M, Aldighieri S, Reveiz L. Pathological findings in organs and tissues of patients with COVID-19: A systematic review. *PLoS One* 2021; **16**: e0250708 [PMID: 33909679 DOI: 10.1371/journal.pone.0250708]

24 **Chornenkyy Y**, Mejia-Bautista M, Brucal M, Blanke T, Dittmann D, Yeldandi A, Boike JR, Lomasney JW, Nayar R, Jennings LJ, Pezhouh MK. Liver Pathology and SARS-CoV-2 Detection in Formalin-Fixed Tissue of Patients With COVID-19. *Am J Clin Pathol* 2021; **155**: 802-814 [PMID: 33914058 DOI: 10.1093/ajcp/aqab009]

25 **Wanner N**, Andrieux G, Badia-I-Mompel P, Edler C, Pfefferle S, Lindenmeyer MT, Schmidt-Lauber C, Czogalla J, Wong MN, Okabayashi Y, Braun F, Lütgehetmann M, Meister E, Lu S, Noriega MLM, Günther T, Grundhoff A, Fischer N, Bräuninger H, Lindner D, Westermann D, Haas F, Roedl K, Kluge S, Addo MM, Huber S, Lohse AW, Reiser J, Ondruschka B, Sperhake JP, Saez-Rodriguez J, Boerries M, Hayek SS, Aepfelbacher M, Scaturro P, Puelles VG, Huber TB. Molecular consequences of SARS-CoV-2 liver tropism. *Nat Metab* 2022; **4**: 310-319 [PMID: 35347318 DOI: 10.1038/s42255-022-00552-6]

26 **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]

27 **Wang Y**, Liu S, Liu H, Li W, Lin F, Jiang L, Li X, Xu P, Zhang L, Zhao L, Cao Y, Kang J, Yang J, Li L, Liu X, Li Y, Nie R, Mu J, Lu F, Zhao S, Lu J, Zhao J. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol* 2020; **73**: 807-816 [PMID: 32437830 DOI: 10.1016/j.jhep.2020.05.002]

28 **Kaltschmidt B**, Fitzek ADE, Schaedler J, Förster C, Kaltschmidt C, Hansen T, Steinfurth F, Windmöller BA, Pilger C, Kong C, Singh K, Nierhaus A, Wichmann D, Sperhake J, Püschel K, Huser T, Krüger M, Robson SC, Wilkens L, Schulte Am Esch J. Hepatic Vasculopathy and Regenerative Responses of the Liver in Fatal Cases of COVID-19. *Clin Gastroenterol Hepatol* 2021; **19**: 1726-1729.e3 [PMID: 33516952 DOI: 10.1016/j.cgh.2021.01.044]

29 **Cheung CCL**, Goh D, Lim X, Tien TZ, Lim JCT, Lee JN, Tan B, Tay ZEA, Wan WY, Chen EX, Nerurkar SN, Loong S, Cheow PC, Chan CY, Koh YX, Tan TT, Kalimuddin S, Tai WMD, Ng JL, Low JG, Yeong J, Lim KH. Residual SARS-CoV-2 viral antigens detected in GI and hepatic tissues from five recovered patients with COVID-19. *Gut* 2022; **71**: 226-229 [PMID: 34083386 DOI: 10.1136/gutjnl-2021-324280]

30 **Delorey TM**, Ziegler CGK, Heimberg G, Normand R, Yang Y, Segerstolpe Å, Abbondanza D, Fleming SJ, Subramanian A, Montoro DT, Jagadeesh KA, Dey KK, Sen P, Slyper M, Pita-Juárez YH, Phillips D, Biermann J, Bloom-Ackermann Z, Barkas N, Ganna A, Gomez J, Melms JC, Katsyv I, Normandin E, Naderi P, Popov YV, Raju SS, Niezen S, Tsai LT, Siddle KJ, Sud M, Tran VM, Vellarikkal SK, Wang Y, Amir-Zilberstein L, Atri DS, Beechem J, Brook OR, Chen J, Divakar P, Dorceus P, Engreitz JM, Essene A, Fitzgerald DM, Fropf R, Gazal S, Gould J, Grzyb J, Harvey T, Hecht J, Hether T, Jané-Valbuena J, Leney-Greene M, Ma H, McCabe C, McLoughlin DE, Miller EM, Muus C, Niemi M, Padera R, Pan L, Pant D, Pe'er C, Pfiffner-Borges J, Pinto CJ, Plaisted J, Reeves J, Ross M, Rudy M, Rueckert EH, Siciliano M, Sturm A, Todres E, Waghray A, Warren S, Zhang S, Zollinger DR, Cosimi L, Gupta RM, Hacohen N, Hibshoosh H, Hide W, Price AL, Rajagopal J, Tata PR, Riedel S, Szabo G, Tickle TL, Ellinor PT, Hung D, Sabeti PC, Novak R, Rogers R, Ingber DE, Jiang ZG, Juric D, Babadi M, Farhi SL, Izar B, Stone JR, Vlachos IS, Solomon IH, Ashenberg O, Porter CBM, Li B, Shalek AK, Villani AC, Rozenblatt-Rosen O, Regev A. COVID-19 tissue atlases reveal SARS-CoV-2 pathology and cellular targets. *Nature* 2021; **595**: 107-113 [PMID: 33915569 DOI: 10.1038/s41586-021-03570-8]

31 **Kumar P**, Sharma M, Kulkarni A, Rao PN. Pathogenesis of Liver Injury in Coronavirus Disease 2019. *J Clin Exp Hepatol* 2020; **10**: 641-642 [PMID: 32837092 DOI: 10.1016/j.jceh.2020.05.006]

32 **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]

33 **Ji D**, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020; **73**: 451-453 [PMID: 32278005 DOI: 10.1016/j.jhep.2020.03.044]

34 **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 [PMID: 32352224 DOI: 10.1111/liv.14500]

35 **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, Witzenrath 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]

36 **Onabajo OO**, Banday AR, Stanifer ML, Yan W, Obajemu A, Santer DM, Florez-Vargas O, Piontkivska H, Vargas JM, Ring TJ, Kee C, Doldan P, Tyrrell DL, Mendoza JL, Boulant S, Prokunina-Olsson L. Interferons and viruses induce a novel truncated ACE2 isoform and not the full-length SARS-CoV-2 receptor. *Nat Genet* 2020; **52**: 1283-1293 [PMID: 33077916 DOI: 10.1038/s41588-020-00731-9]

37 **Banales JM**, Huebert RC, Karlsen T, Strazzabosco M, LaRusso NF, Gores GJ. Cholangiocyte pathobiology. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 269-281 [PMID: 30850822 DOI: 10.1038/s41575-019-0125-y]

38 **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, Liang J, 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]

39 **Sahu T**, Pande B, Pl M, Verma HK. Liver dysfunction during COVID-19 pandemic: Contributing role of associated factors in disease progression and severity. *World J Hepatol* 2022; **14**: 1099-1110 [PMID: 35978661 DOI: 10.4254/wjh.v14.i6.1099]

40 **Pedersen SF**, Ho YC. SARS-CoV-2: a storm is raging. *J Clin Invest* 2020; **130**: 2202-2205 [PMID: 32217834 DOI: 10.1172/JCI137647]

41 **Lu Q**, Liu J, Zhao S, Gomez Castro MF, Laurent-Rolle M, Dong J, Ran X, Damani-Yokota P, Tang H, Karakousi T, Son J, Kaczmarek ME, Zhang Z, Yeung ST, McCune BT, Chen RE, Tang F, Ren X, Chen X, Hsu JCC, Teplova M, Huang B, Deng H, Long Z, Mudianto T, Jin S, Lin P, Du J, Zang R, Su TT, Herrera A, Zhou M, Yan R, Cui J, Zhu J, Zhou Q, Wang T, Ma J, Koralov SB, Zhang Z, Aifantis I, Segal LN, Diamond MS, Khanna KM, Stapleford KA, Cresswell P, Liu Y, Ding S, Xie Q, Wang J. SARS-CoV-2 exacerbates proinflammatory responses in myeloid cells through C-type lectin receptors and Tweety family member 2. *Immunity* 2021; **54**: 1304-1319.e9 [PMID: 34048708 DOI: 10.1016/j.immuni.2021.05.006]

42 **Ren X**, Wen W, Fan X, Hou W, Su B, Cai P, Li J, Liu Y, Tang F, Zhang F, Yang Y, He J, Ma W, He J, Wang P, Cao Q, Chen F, Chen Y, Cheng X, Deng G, Deng X, Ding W, Feng Y, Gan R, Guo C, Guo W, He S, Jiang C, Liang J, Li YM, Lin J, Ling Y, Liu H, Liu J, Liu N, Liu SQ, Luo M, Ma Q, Song Q, Sun W, Wang G, Wang F, Wang Y, Wen X, Wu Q, Xu G, Xie X, Xiong X, Xing X, Xu H, Yin C, Yu D, Yu K, Yuan J, Zhang B, Zhang P, Zhang T, Zhao J, Zhao P, Zhou J, Zhou W, Zhong S, Zhong X, Zhang S, Zhu L, Zhu P, Zou B, Zou J, Zuo Z, Bai F, Huang X, Zhou P, Jiang Q, Huang Z, Bei JX, Wei L, Bian XW, Liu X, Cheng T, Li X, Zhao P, Wang FS, Wang H, Su B, Zhang Z, Qu K, Wang X, Chen J, Jin R, Zhang Z. COVID-19 immune features revealed by a large-scale single-cell transcriptome atlas. *Cell* 2021; **184**: 1895-1913.e19 [PMID: 33657410 DOI: 10.1016/j.cell.2021.01.053]

43 **Li T**, Yang Y, Li Y, Wang Z, Ma F, Luo R, Xu X, Zhou G, Wang J, Niu J, Lv G, Crispe IN, Tu Z. Platelets mediate inflammatory monocyte activation by SARS-CoV-2 spike protein. *J Clin Invest* 2022; **132** [PMID: 34964720 DOI: 10.1172/JCI150101]

44 **Yan B**, Freiwald T, Chauss D, Wang L, West E, Mirabelli C, Zhang CJ, Nichols EM, Malik N, Gregory R, Bantscheff M, Ghidelli-Disse S, Kolev M, Frum T, Spence JR, Sexton JZ, Alysandratos KD, Kotton DN, Pittaluga S, Bibby J, Niyonzima N, Olson MR, Kordasti S, Portilla D, Wobus CE, Laurence A, Lionakis MS, Kemper C, Afzali B, Kazemian M. SARS-CoV-2 drives JAK1/2-dependent local complement hyperactivation. *Sci Immunol* 2021; **6** [PMID: 33827897 DOI: 10.1126/sciimmunol.abg0833]

45 **Merad M**, Blish CA, Sallusto F, Iwasaki A. The immunology and immunopathology of COVID-19. *Science* 2022; **375**: 1122-1127 [PMID: 35271343 DOI: 10.1126/science.abm8108]

46 **Buso G**, Becchetti C, Berzigotti A. Acute splanchnic vein thrombosis in patients with COVID-19: A systematic review. *Dig Liver Dis* 2021; **53**: 937-949 [PMID: 34120860 DOI: 10.1016/j.dld.2021.05.021]

47 **Wang M**, Yan W, Qi W, Wu D, Zhu L, Li W, Wang X, Ma K, Ni M, Xu D, Wang H, Chen G, Yu H, Ding H, Xing M, Han M, Luo X, Chen T, Guo W, Xi D, Ning Q. Clinical characteristics and risk factors of liver injury in COVID-19: a retrospective cohort study from Wuhan, China. *Hepatol Int* 2020; **14**: 723-732 [PMID: 33026573 DOI: 10.1007/s12072-020-10075-5]

48 **Da BL**, Kushner T, El Halabi M, Paka P, Khalid M, Uberoi A, Lee BT, Perumalswami PV, Rutledge SM, Schiano TD, Friedman SL, Saberi B. Liver Injury in Patients Hospitalized with Coronavirus Disease 2019 Correlates with Hyperinflammatory Response and Elevated Interleukin-6. *Hepatol Commun* 2021; **5**: 177-188 [PMID: 33230491 DOI: 10.1002/hep4.1631]

49 **Effenberger M**, Grander C, Grabherr F, Griesmacher A, Ploner T, Hartig F, Bellmann-Weiler R, Joannidis M, Zoller H, Weiss G, Adolph TE, Tilg H. Systemic inflammation as fuel for acute liver injury in COVID-19. *Dig Liver Dis* 2021; **53**: 158-165 [PMID: 32873520 DOI: 10.1016/j.dld.2020.08.004]

50 **Shafran N**, Issachar A, Shochat T, Shafran IH, Bursztyn M, Shlomai A. Abnormal liver tests in patients with SARS-CoV-2 or influenza - prognostic similarities and temporal disparities. *JHEP Rep* 2021; **3**: 100258 [PMID: 33644724 DOI: 10.1016/j.jhepr.2021.100258]

51 **McConnell MJ**, Kondo R, Kawaguchi N, Iwakiri Y. Covid-19 and Liver Injury: Role of Inflammatory Endotheliopathy, Platelet Dysfunction, and Thrombosis. *Hepatol Commun* 2022; **6**: 255-269 [PMID: 34658172 DOI: 10.1002/hep4.1843]

52 **Marjot T**, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, Pose E, Brenner EJ, Cargill T, Catana MA, Dhanasekaran R, Eshraghian A, García-Juárez I, Gill US, Jones PD, Kennedy J, Marshall A, Matthews C, Mells G, Mercer C, Perumalswami PV, Avitabile E, Qi X, Su F, Ufere NN, Wong YJ, Zheng MH, Barnes E, Barritt AS 4th, Webb GJ. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol* 2021; **74**: 567-577 [PMID: 33035628 DOI: 10.1016/j.jhep.2020.09.024]

53 **Russo FP**, Burra P, Zanetto A. COVID-19 and liver disease: where are we now? *Nat Rev Gastroenterol Hepatol* 2022; **19**: 277-278 [PMID: 35301465 DOI: 10.1038/s41575-022-00607-9]

54 **Zou X**, Fang M, Li S, Wu L, Gao B, Gao H, Ran X, Bian Y, Li R, ShanshanYu, Ling J, Li D, Tian D, Huang J. Characteristics of Liver Function in Patients With SARS-CoV-2 and Chronic HBV Coinfection. *Clin Gastroenterol Hepatol* 2021; **19**: 597-603 [PMID: 32553907 DOI: 10.1016/j.cgh.2020.06.017]

55 **Lin Y**, Yuan J, Long Q, Hu J, Deng H, Zhao Z, Chen J, Lu M, Huang A. Patients with SARS-CoV-2 and HBV co-infection are at risk of greater liver injury. *Genes Dis* 2021; **8**: 484-492 [PMID: 33225036 DOI: 10.1016/j.gendis.2020.11.005]

56 **Anugwom CM**, Aby ES, Debes JD. Inverse Association Between Chronic Hepatitis B Infection and Coronavirus Disease 2019 (COVID-19): Immune Exhaustion or Coincidence? *Clin Infect Dis* 2021; **72**: 180-182 [PMID: 32502247 DOI: 10.1093/cid/ciaa592]

57 **Brooks DG**, Teyton L, Oldstone MB, McGavern DB. Intrinsic functional dysregulation of CD4 T cells occurs rapidly following persistent viral infection. *J Virol* 2005; **79**: 10514-10527 [PMID: 16051844 DOI: 10.1128/JVI.79.16.10514-10527.2005]

58 **Sapir T**, Averch Z, Lerman B, Bodzin A, Fishman Y, Maitra R. COVID-19 and the Immune Response: A Multi-Phasic Approach to the Treatment of COVID-19. *Int J Mol Sci* 2022; **23** [PMID: 35955740 DOI: 10.3390/ijms23158606]

59 **Papatheodoridis GV**, Lekakis V, Voulgaris T, Lampertico P, Berg T, Chan HLY, Kao JH, Terrault N, Lok AS, Reddy KR. Hepatitis B virus reactivation associated with new classes of immunosuppressants and immunomodulators: A systematic review, meta-analysis, and expert opinion. *J Hepatol* 2022; **77**: 1670-1689 [PMID: 35850281 DOI: 10.1016/j.jhep.2022.07.003]

60 **Chang Y**, Jeong SW, Jang JY. Hepatitis B Virus Reactivation Associated With Therapeutic Interventions. *Front Med (Lausanne)* 2021; **8**: 770124 [PMID: 35096867 DOI: 10.3389/fmed.2021.770124]

61 **Loomba R**, Liang TJ. Hepatitis B Reactivation Associated With Immune Suppressive and Biological Modifier Therapies: Current Concepts, Management Strategies, and Future Directions. *Gastroenterology* 2017; **152**: 1297-1309 [PMID: 28219691 DOI: 10.1053/j.gastro.2017.02.009]

62 **Gerussi A**, Rigamonti C, Elia C, Cazzagon N, Floreani A, Pozzi R, Pozzoni P, Claar E, Pasulo L, Fagiuoli S, Cristoferi L, Carbone M, Invernizzi P. Coronavirus Disease 2019 in Autoimmune Hepatitis: A Lesson From Immunosuppressed Patients. *Hepatol Commun* 2020; **4**: 1257-1262 [PMID: 32838102 DOI: 10.1002/hep4.1557]

63 **Sun J**, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. *Liver Int* 2020; **40**: 1278-1281 [PMID: 32251539 DOI: 10.1111/liv.14470]

64 **Pan Q**, Tilanus HW, Metselaar HJ, Janssen HL, van der Laan LJ. Virus-drug interactions--molecular insight into immunosuppression and HCV. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 355-362 [PMID: 22508161 DOI: 10.1038/nrgastro.2012.67]

65 **Torres HA**, Hosry J, Mahale P, Economides MP, Jiang Y, Lok AS. Hepatitis C virus reactivation in patients receiving cancer treatment: A prospective observational study. *Hepatology* 2018; **67**: 36-47 [PMID: 28653760 DOI: 10.1002/hep.29344]

66 **Lee HL**, Bae SH, Jang B, Hwang S, Yang H, Nam HC, Sung PS, Lee SW, Jang JW, Choi JY, Han NI, Song BJ, Lee JW, Yoon SK. Reactivation of Hepatitis C Virus and Its Clinical Outcomes in Patients Treated with Systemic Chemotherapy or Immunosuppressive Therapy. *Gut Liver* 2017; **11**: 870-877 [PMID: 28750484 DOI: 10.5009/gnl16434]

67 **Ciesek S**, Steinmann E, Iken M, Ott M, Helfritz FA, Wappler I, Manns MP, Wedemeyer H, Pietschmann T. Glucocorticosteroids increase cell entry by hepatitis C virus. *Gastroenterology* 2010; **138**: 1875-1884 [PMID: 20152835 DOI: 10.1053/j.gastro.2010.02.004]

68 **Dumortier J**, Boillot O, Scoazec JY. Natural history, treatment and prevention of hepatitis C recurrence after liver transplantation: past, present and future. *World J Gastroenterol* 2014; **20**: 11069-11079 [PMID: 25170196 DOI: 10.3748/wjg.v20.i32.11069]

69 **Rosen HR**, Hinrichs DJ, Gretch DR, Koziel MJ, Chou S, Houghton M, Rabkin J, Corless CL, Bouwer HG. Association of multispecific CD4(+) response to hepatitis C and severity of recurrence after liver transplantation. *Gastroenterology* 1999; **117**: 926-932 [PMID: 10500076 DOI: 10.1016/s0016-5085(99)70352-5]

70 **Magrin S**, Craxi A, Fabiano C, Simonetti RG, Fiorentino G, Marino L, Diquattro O, Di Marco V, Loiacono O, Volpes R. Hepatitis C viremia in chronic liver disease: relationship to interferon-alpha or corticosteroid treatment. *Hepatology* 1994; **19**: 273-279 [PMID: 8294085]

71 **Shokri S**, Mahmoudvand S. The possibility of hepatitis C reactivation in COVID-19 patients treated with corticosteroids. *Ann Hepatol* 2022; **27**: 100704 [PMID: 35398269 DOI: 10.1016/j.aohep.2022.100704]

72 **Asrani SK**, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol* 2019; **70**: 151-171 [PMID: 30266282 DOI: 10.1016/j.jhep.2018.09.014]

73 **Qi X**, Liu Y, Wang J, Fallowfield JA, Wang J, Li X, Shi J, Pan H, Zou S, Zhang H, Chen Z, Li F, Luo Y, Mei M, Liu H, Wang Z, Li J, Yang H, Xiang H, Li X, Liu T, Zheng MH, Liu C, Huang Y, Xu D, Li X, Kang N, He Q, Gu Y, Zhang G, Shao C, Liu D, Zhang L, Li X, Kawada N, Jiang Z, Wang F, Xiong B, Takehara T, Rockey DC; COVID-Cirrhosis-CHESS Group. Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study. *Gut* 2021; **70**: 433-436 [PMID: 32434831 DOI: 10.1136/gutjnl-2020-321666]

74 **Iavarone M**, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, Perricone G, Massironi S, Spinetti A, Buscarini E, Viganò M, Carriero C, Fagiuoli S, Aghemo A, Belli LS, Lucà M, Pedaci M, Rimondi A, Rumi MG, Invernizzi P, Bonfanti P, Lampertico P. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol* 2020; **73**: 1063-1071 [PMID: 32526252 DOI: 10.1016/j.jhep.2020.06.001]

75 **Shah BA**, Ahmed W, Dhobi GN, Shah NN, Khursheed SQ, Haq I. Validity of pneumonia severity index and CURB-65 severity scoring systems in community acquired pneumonia in an Indian setting. *Indian J Chest Dis Allied Sci* 2010; **52**: 9-17 [PMID: 20364609]

76 **Moon AM**, Webb GJ, Aloman C, Armstrong MJ, Cargill T, Dhanasekaran R, Genescà J, Gill US, James TW, Jones PD, Marshall A, Mells G, Perumalswami PV, Qi X, Su F, Ufere NN, Barnes E, Barritt AS, Marjot T. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry. *J Hepatol* 2020; **73**: 705-708 [PMID: 32446714 DOI: 10.1016/j.jhep.2020.05.013]

77 **Kushner T**, Cafardi J. Chronic Liver Disease and COVID-19: Alcohol Use Disorder/Alcohol-Associated Liver Disease, Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis, Autoimmune Liver Disease, and Compensated Cirrhosis. *Clin Liver Dis (Hoboken)* 2020; **15**: 195-199 [PMID: 32537135 DOI: 10.1002/cld.974]

78 **Kim D**, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, Perumalswami P, Roytman M, Li M, Vogel AS, Catana AM, Wegermann K, Carr RM, Aloman C, Chen VL, Rabiee A, Sadowski B, Nguyen V, Dunn W, Chavin KD, Zhou K, Lizaola-Mayo B, Moghe A, Debes J, Lee TH, Branch AD, Viveiros K, Chan W, Chascsa DM, Kwo P, Dhanasekaran R. Predictors of Outcomes of COVID-19 in Patients With Chronic Liver Disease: US Multi-center Study. *Clin Gastroenterol Hepatol* 2021; **19**: 1469-1479.e19 [PMID: 32950749 DOI: 10.1016/j.cgh.2020.09.027]

79 **Sarin SK**, Choudhury A, Lau GK, Zheng MH, Ji D, Abd-Elsalam S, Hwang J, Qi X, Cua IH, Suh JI, Park JG, Putcharoen O, Kaewdech A, Piratvisuth T, Treeprasertsuk S, Park S, Wejnaruemarn S, Payawal DA, Baatarkhuu O, Ahn SH, Yeo CD, Alonzo UR, Chinbayar T, Loho IM, Yokosuka O, Jafri W, Tan S, Soo LI, Tanwandee T, Gani R, Anand L, Esmail ES, Khalaf M, Alam S, Lin CY, Chuang WL, Soin AS, Garg HK, Kalista K, Batsukh B, Purnomo HD, Dara VP, Rathi P, Al Mahtab M, Shukla A, Sharma MK, Omata M; 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**: 690-700 [PMID: 32623632 DOI: 10.1007/s12072-020-10072-8]

80 **Jose RJ**, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020; **8**: e46-e47 [PMID: 32353251 DOI: 10.1016/S2213-2600(20)30216-2]

81 **Cai Q**, Chen F, Wang T, Luo F, Liu X, Wu Q, He Q, Wang Z, Liu Y, Liu L, Chen J, Xu L. Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China. *Diabetes Care* 2020; **43**: 1392-1398 [PMID: 32409502 DOI: 10.2337/dc20-0576]

82 **Mahamid M**, Nseir W, Khoury T, Mahamid B, Nubania A, Sub-Laban K, Schifter J, Mari A, Sbeit W, Goldin E. Nonalcoholic fatty liver disease is associated with COVID-19 severity independently of metabolic syndrome: a retrospective case-control study. *Eur J Gastroenterol Hepatol* 2021; **33**: 1578-1581 [PMID: 32868652 DOI: 10.1097/MEG.0000000000001902]

83 **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]

84 **Singh A**, Hussain S, Antony B. Non-alcoholic fatty liver disease and clinical outcomes in patients with COVID-19: A comprehensive systematic review and meta-analysis. *Diabetes Metab Syndr* 2021; **15**: 813-822 [PMID: 33862417 DOI: 10.1016/j.dsx.2021.03.019]

85 **Hegyi PJ**, Váncsa S, Ocskay K, Dembrovszky F, Kiss S, Farkas N, Erőss B, Szakács Z, Hegyi P, Pár G. Metabolic Associated Fatty Liver Disease Is Associated With an Increased Risk of Severe COVID-19: A Systematic Review With Meta-Analysis. *Front Med (Lausanne)* 2021; **8**: 626425 [PMID: 33777974 DOI: 10.3389/fmed.2021.626425]

86 **Mushtaq K**, Khan MU, Iqbal F, Alsoub DH, Chaudhry HS, Ata F, Iqbal P, Elfert K, Balaraju G, Almaslamani M, Al-Ejji K, AlKaabi S, Kamel YM. NAFLD is a predictor of liver injury in COVID-19 hospitalized patients but not of mortality, disease severity on the presentation or progression - The debate continues. *J Hepatol* 2021; **74**: 482-484 [PMID: 33223215 DOI: 10.1016/j.jhep.2020.09.006]

87 **Valenti L**, Jamialahmadi O, Romeo S. Lack of genetic evidence that fatty liver disease predisposes to COVID-19. *J Hepatol* 2020; **73**: 709-711 [PMID: 32445883 DOI: 10.1016/j.jhep.2020.05.015]

88 **Innes H**, Buch S, Barnes E, Hampe J, Marjot T, Stickel F. The rs738409 G Allele in PNPLA3 Is Associated With a Reduced Risk of COVID-19 Mortality and Hospitalization. *Gastroenterology* 2021; **160**: 2599-2601.e2 [PMID: 33652012 DOI: 10.1053/j.gastro.2021.02.059]

89 **Liu D**, Zhang Q, Bai P, Zhao J. Assessing causal relationships between COVID-19 and non-alcoholic fatty liver disease. *J Hepatol* 2022; **76**: 740-742 [PMID: 34813919 DOI: 10.1016/j.jhep.2021.11.014]

90 **Boettler T**, Marjot T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Jalan R, Moreau R, Cornberg M, Berg T. Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic. *JHEP Rep* 2020; **2**: 100169 [PMID: 32835190 DOI: 10.1016/j.jhepr.2020.100169]

91 **Sharma R**, Pinato DJ. Management of Hepatocellular Cancer in the time of SARS-CoV-2. *Liver Int* 2020; **40**: 1823-1825 [PMID: 32416633 DOI: 10.1111/liv.14517]

92 **Dai M**, Liu D, Liu M, Zhou F, Li G, Chen Z, Zhang Z, You H, Wu M, Zheng Q, Xiong Y, Xiong H, Wang C, Chen C, Xiong F, Zhang Y, Peng Y, Ge S, Zhen B, Yu T, Wang L, Wang H, Liu Y, Chen Y, Mei J, Gao X, Li Z, Gan L, He C, Li Z, Shi Y, Qi Y, Yang J, Tenen DG, Chai L, Mucci LA, Santillana M, Cai H. Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. *Cancer Discov* 2020; **10**: 783-791 [PMID: 32345594 DOI: 10.1158/2159-8290.CD-20-0422]

93 **Guarino M**, Cossiga V, Capasso M, Mazzarelli C, Pelizzaro F, Sacco R, Russo FP, Vitale A, Trevisani F, Cabibbo G; The Associazione Italiana Per Lo Studio Del Fegato AISF HCC Special Interest Group. Impact of SARS-CoV-2 Pandemic on the Management of Patients with Hepatocellular Carcinoma. *J Clin Med* 2022; **11** [PMID: 35956091 DOI: 10.3390/jcm11154475]

94 **Qin J**, Wang H, Qin X, Zhang P, Zhu L, Cai J, Yuan Y, Li H. Perioperative Presentation of COVID-19 Disease in a Liver Transplant Recipient. *Hepatology* 2020; **72**: 1491-1493 [PMID: 32220017 DOI: 10.1002/hep.31257]

95 **Bhoori S**, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol* 2020; **5**: 532-533 [PMID: 32278366 DOI: 10.1016/S2468-1253(20)30116-3]

96 **D'Antiga L**. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. *Liver Transpl* 2020; **26**: 832-834 [PMID: 32196933 DOI: 10.1002/lt.25756]

97 **Belli LS**, Duvoux C, Karam V, Adam R, Cuervas-Mons V, Pasulo L, Loinaz C, Invernizzi F, Patrono D, Bhoori S, Ciccarelli O, Morelli MC, Castells L, Lopez-Lopez V, Conti S, Fondevila C, Polak W. COVID-19 in liver transplant recipients: preliminary data from the ELITA/ELTR registry. *Lancet Gastroenterol Hepatol* 2020; **5**: 724-725 [PMID: 32505228 DOI: 10.1016/S2468-1253(20)30183-7]

98 **Lee BT**, Perumalswami PV, Im GY, Florman S, Schiano TD; COBE Study Group. COVID-19 in Liver Transplant Recipients: An Initial Experience From the US Epicenter. *Gastroenterology* 2020; **159**: 1176-1178.e2 [PMID: 32442561 DOI: 10.1053/j.gastro.2020.05.050]

99 **Becchetti C**, Zambelli MF, Pasulo L, Donato MF, Invernizzi F, Detry O, Dahlqvist G, Ciccarelli O, Morelli MC, Fraga M, Svegliati-Baroni G, van Vlierberghe H, Coenraad MJ, Romero MC, de Gottardi A, Toniutto P, Del Prete L, Abbati C, Samuel D, Pirenne J, Nevens F, Dufour JF; COVID-LT group. COVID-19 in an international European liver transplant recipient cohort. *Gut* 2020; **69**: 1832-1840 [PMID: 32571972 DOI: 10.1136/gutjnl-2020-321923]

100 **Boyarsky BJ**, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, Garonzik-Wang JM. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. *JAMA* 2021; **325**: 2204-2206 [PMID: 33950155 DOI: 10.1001/jama.2021.7489]

**Footnotes**

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** September 5, 2022

**First decision:** November 5, 2022

**Article in press:**

**Specialty type:** Infectious diseases

**Country/Territory of origin:** Argentina

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

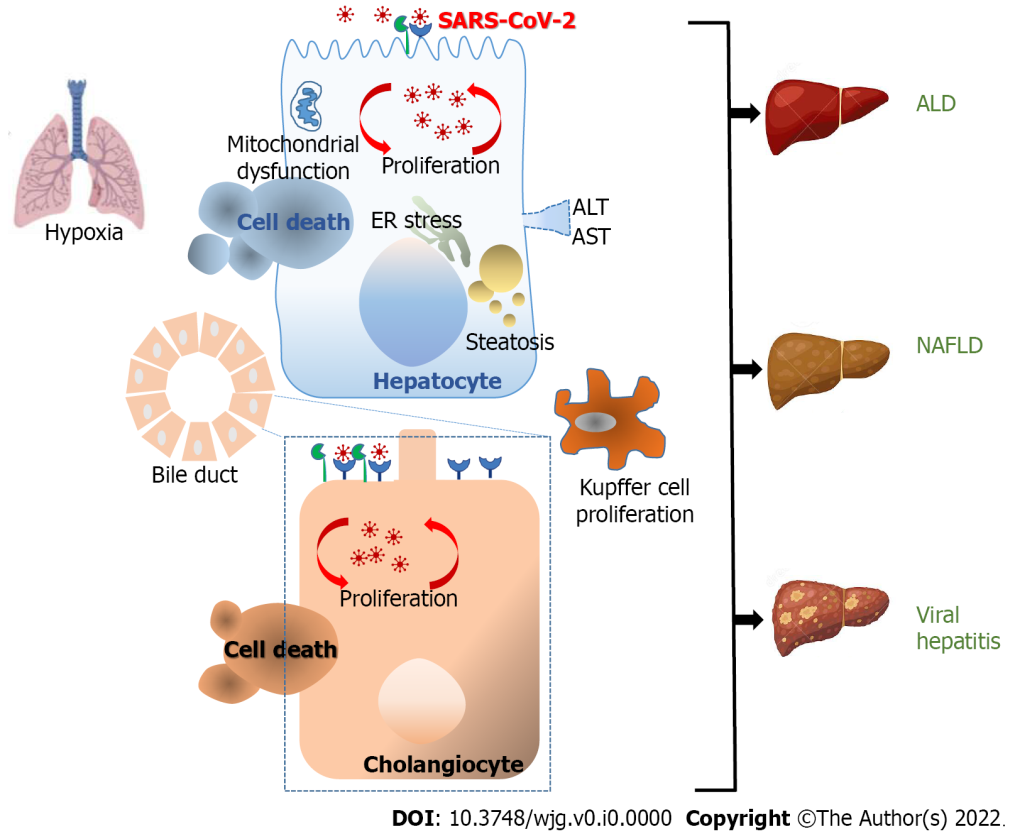
Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Shekouhi R, Iran; Wang CY, Taiwan **S-Editor:** Chen YL **L-Editor:** Filipodia **P-Editor:** Chen YL

**Figure Legends**



**Figure 1 Mechanisms of pathological injury upon severe acute respiratory syndrome coronavirus 2** **infection.** The major cause of mortality in coronavirus disease 2019 (COVID-19) is largely caused by lung damage with the increase of acute respiratory distress syndrome (ARDS). Liver damage or liver dysfunction has been linked with the general severity of COVID-19 infection and serves as a prognostic factor for ARDS progress. The scale of liver injury may range from direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral antigens, inflammatory progressions, hypoxemia, the antiviral treatments that induced hepatic damage and the existence of previous liver diseases. Angiotensin-converting enzyme 2 was mostly expressed in cholangiocytes and to a lesser extent in hepatocytes. These findings are in line with the viral presence reported in cholangiocytes and hepatocytes and the direct cytopathic effects observed. SARS-CoV-2 infection of hepatocytes and the indirect effects of “cytokine storm” induce a significant increase in alanine aminotransferase and aspartate aminotransferase indicating abnormal liver function. This leads to endoplasmic reticulum stress, steatosis, and finally to hepatocyte cell death. Consequently, Kupffer cell activation appears to be commonly funded in livers. The synergism between SARS-CoV-2 and chronic viral hepatitis B and C has also been suggested. Additionally, the superimposed cytokine storm caused by SARS-CoV-2 in patients with alcohol-associated liver disease, and non-alcoholic fatty liver disease (NALDF) displayed a higher risk of severe COVID-19. ALD: Alcohol-associated liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.