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Review Article

Potential histopathological and immunological effects of SARS-CoV-2 on the liver

Efeitos histopatológicos e imunológicos potenciais do SARS-CoV-2 no fígado

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Abstract

The coronavirus disease outbreak of 2019 (COVID-19) poses a serious threat to public health worldwide. Lung injury is the most common complication of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. However, other organs, including the liver, can also be affected. Currently, there is limited evidence that liver impairment is associated with severe SARS-CoV-2 infection. Clinicians will need to determine whether liver injury is caused by an underlying liver condition, COVID-19 therapy, the virus directly, or immune-mediated inflammation or represents a complicated disease course in the context of COVID-19. To address the scarcity of data on histopathological changes and immunological effects on the liver with COVID-19 positivity, we analyze and summarize recent findings. We searched PubMed, Medline, Google Scholar, Science Direct, Scopus, and Web of Science databases up to December 1, 2021, identifying published studies with the search terms "Histopathology in COVID-19," "COVID-19," "Pathological changes in liver in COVID-19," "Liver pathology in COVID-19," "immunological effects in liver in COVID-19," and "SARS-CoV-2." This concise review will aid clinicians and researchers in better understanding the tissue histopathology and immunological consequences of SARS-CoV-2 on the liver, enabling improved care planning and avoiding future dangers.

Keywords: SARS-CoV-2, COVID-19, liver injury, immunological effects, histopathology.

Resumo

O surto de doença por coronavírus de 2019 (COVID-19) representa uma séria ameaça à saúde pública em todo o mundo. A lesão pulmonar é a complicação mais comum da infecção por Coronavírus 2 da Síndrome Respiratória Aguda Grave (SARS-CoV-2). No entanto, outros órgãos, incluindo o fígado, também podem ser afetados. Atualmente, há evidências limitadas de que a insuficiência hepática está associada à infecção grave por SARS-CoV-2. Os médicos precisarão determinar se a lesão hepática é causada por condição hepática subjacente, terapia COVID-19, vírus diretamente, inflamação imunomediada ou se representa um curso complicado da doença no contexto da COVID-19. Para abordar a escassez de dados sobre alterações histopatológicas e efeitos imunológicos no fígado com positividade para COVID-19, analisamos e resumimos os achados recentes. Pesquisamos os bancos de dados PubMed, Medline, Google Scholar, Science Direct, Scopus e Web of Science até 1º de dezembro de 2021, identificando estudos publicados com os termos de pesquisa "Histopatologia em COVID-19", "COVID-19", "Alterações patológicas no fígado em COVID-19", "Patologia hepática em COVID-19", "Efeitos imunológicos no fígado em COVID-19" e "SARS-CoV-2". Esta revisão concisa ajudará médicos e pesquisadores a entender melhor a histopatologia do tecido e as consequências imunológicas do SARS-CoV-2 no fígado, permitindo um melhor planejamento de cuidados e evitando perigos futuros.

Palavras-chave: SARS-CoV-2, COVID-19, lesão hepática, efeitos imunológicos, histopatologia.

1. Introduction

The coronavirus disease 2019 (COVID-19) outbreak, caused by the novel severe acute respiratory syndrome (SARS) coronavirus (CoV) 2 (SARS-CoV-2), triggered a global health and economic disaster in just a few months. More than 40 million confirmed cases have been reported worldwide since October 2020, with more than one million deaths and 189 nations affected (Nardo et al., 2021). The major target organ of COVID-19 is the lungs, which are the most common cause of mortality and morbidity (Wang et al., 2020c). However, the effects on the nervous system, kidneys, hepatobiliary system, heart, and gastrointestinal tract are becoming more widely recognized (Zhu et al., 2020). The liver appears to be the next organ impacted after the lung (Bangash et al., 2020; Li and Fan, 2020; Rismanbaf and Zarei, 2020).

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The liver is one of the body's major organs of vertebrates and is situated between the portal and systemic circulation. It is continually exposed to antigens, viruses, and bacterial products that have the potential to cause inflammation. Exposure to pollutants, excessive alcohol intake, bile duct obstruction, and viral infections are examples of conditions that can harm the liver (Guicciardi and Gores, 2005). Any liver damage in COVID-19 patients with or without preexisting liver disease is referred to as COVID-19-associated liver injury (Sun et al., 2020). The percentage of patients with COVID-19 who developed liver injury is 14-53% (Xu et al., 2020b).

In addition, liver injury may be a risk factor for COVID-19 progression and worsening. Therefore, it is important to monitor for the possibility of liver injury during the diagnosis and treatment of COVID-19. Despite the dearth of data on COVID-19-related liver problems in patients, liver injury is associated with prolonged hospitalization (Zhang et al., 2020a). Wong et al. (2020) used a systemic meta-analysis to assess the prevalence and severity of liver disease in severe and non-severe SARS-CoV-2 infected patients. They reported that liver injury is more commonly associated with severe COVID-19 than non-severe COVID-19 (Wong et al., 2020).

The mechanisms of liver injury are caused mainly by direct viral infection and medication cytotoxicity, or entirely related to immune-mediated inflammation, such as cytokine storm, as determined by histology and blood testing. Hypoxic hepatitis, hepatic congestion caused by positive end-expiratory pressure (PEEP), and gut barrier dysfunction are also possible explanations (Kukla et al., 2020).

One of the COVID-19's hepatic symptoms is dysregulation of circulating liver-associated enzymes, which is found to be weakly to moderately affected in a significant majority of COVID-19 patients (Cai et al., 2020; Metawea et al., 2021; Nasa and Alexander, 2021; Yousif, 2021). However, little is known about the histopathological features of the liver during infection.

This review summarizes recent findings relating to the histopathological and immunological implications of SARS-CoV-2 infection and COVID-19 positivity on the liver to provide clinical hepatologists with the most up-to-date information to manage the pandemic in their daily practice.

2. SARS-CoV-2 Host Receptors in Liver Tissue

SARS-CoV-2 is detected not only in the lungs but also in the gastrointestinal tract, colon, kidneys, heart, liver, biliary system, and, unexpectedly, the brain (Xu et al., 2020a). It attaches to target cells via a hidden receptor-binding domain of the spike (S) protein to the functional receptor angiotensin-converting enzyme 2 (ACE2). Both SARS-CoV-1 and SARS-CoV-2 have been found to use ACE2 as their primary entry receptor (Hoffmann et al., 2020a). Notably, the S protein's interaction with ACE2 determines SARS-CoV-2 infection, and fusion and cell infection require transmembrane protease serine 2 (TMPRSS2) (Hoffmann et al., 2020b). However, other receptors and proteases have also been implicated (Cantuti-Castelvetri et al., 2020; Matsuyama et al., 2020; Wang et al., 2020a). The virus's affinity for ACE2, which is expressed by many human cells, may explain the wide range of COVID-19 symptoms observed (Gavriatopoulou et al., 2020). The virus's entry into the target cell is preactivated by the furin-paired basic amino acid cleaving enzyme (FURIN) proprotein convertase, which reduces the virus's reliance on target cell proteases (Figure 1) (Zhong et al., 2020).

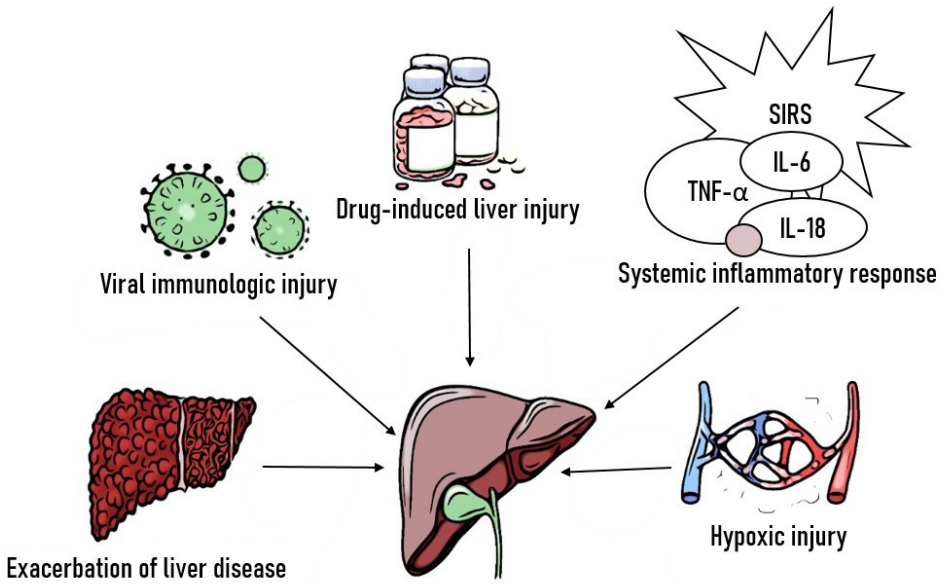

Figure 1. SARS-CoV-2 structure and life cycle adapted from Zhong et al. (2020).

SARS-CoV-2 binds with three receptors in liver tissue whose expression varies by cell type. Both cholangiocytes and hepatocytes express *ACE2*, and hepatocytes, cholangiocytes, erythroid cells, and sinusoidal endothelial cells express *TMPRSS2*. In addition, *FURIN* is expressed in all cell types, from hepatocytes to all populations of liver resident cells (Pirola and Sookoian, 2020). Single-cell RNA-sequencing (scRNA-seq) studies have found substantial enrichment of *ACE2* expression in cholangiocytes, and *ACE2* expression in cholangiocytes is comparable to that of alveolar type 2 (AT2) cells (Chai et al., 2020; Zou et al., 2020). SARS-CoV-2 infected human liver ductal organoids had increased viral mRNA expression 24 hours after infection (Zhao et al., 2020). Furthermore, Leng et al. found the S protein of SARS-CoV-2 and its functional receptor ACE2 concentrated around the portal vein (Leng et al., 2020).

According to Han et al. (2021), SARS-CoV-2 RNA was present in the bile of a severe COVID-19 patient. The viral load in the bile was substantially higher than in the sputum. Consequently, bile juice is one potential source of SARS-CoV-2 virus load found in stool samples (Han et al., 2021). In addition, SARS-CoV-2 infection was found to alter the epithelial barrier and bile acid transporter activities of cholangiocytes (Zhao et al., 2020). These data suggested that viral infiltration of ACE2-positive cholangiocytes may contribute to liver injury in COVID-19 patients.

3. Liver Injury in SARS-CoV-2

COVID-19-related liver injury refers to any damage to the liver that occurs throughout the course and treatment of COVID-19 patients, regardless of whether they have a preexisting liver illness (Bertolini et al., 2020; Garrido et al., 2020; Kulkarni et al., 2020; Wu et al., 2020b; Xu et al., 2020b; Yadav et al., 2021). In severe COVID-19 infections, hepatic and gastrointestinal symptoms are more common (Xu et al., 2020b; Zhang et al., 2020a). In a recent study, Jin et al. found that individuals with preexisting liver disorders were more likely to develop an intestinal phenotype after infection with SARS-CoV-2 (Jin et al., 2020).

Interleukin 6 (IL-6) is associated with severe COVID-19 and liver injury (Aziz et al., 2020; Zhu et al., 2021). A procoagulant endotheliopathy was identified in 43 postmortem liver tissues from COVID-19 patients, potentially mediating liver inflammation and injury (McConnell et al., 2021).

Elevated liver biochemical markers, particularly aspartate (AST) and alanine (ALT) transaminase, and mildly elevated bilirubin, are observed in 14-53% of hospitalized COVID-19 patients (Cai et al., 2020). Increases in liver enzymes are more common in men and are usually documented in more severe COVID-19. The most common abnormality in COVID-19 patients is an elevation in AST. Albumin deficiency is associated with severe infection and poor prognosis (Feng et al., 2020). However, no acute or subacute liver failure cases have been reported in COVID-19 patients. A large cohort study of 5,771 Chinese COVID-19 patients cases found that 81 (1.4%) had chronic liver disease. Impaired liver function has been associated with death in COVID-19 patients (Lei et al., 2020). Elevated AST was more common (39.4%) and significantly greater than ALT (28.1%) in severely hospitalized patients. Furthermore, elevated AST has been associated with high mortality risk (Rica et al., 2020). Most of the proposed mechanisms for hepatic damage caused by SARS-CoV-2 infection are shown in Figure 2.

4. Direct Cytotoxicity from Active Viral Replication of SARS-CoV-2 in the Liver

It remains unclear whether the hepatic injury in COVID-19 is caused by direct viral effects or reflects a more severe inflammatory response causing hepatic damage (Ali, 2020; Ji et al., 2020). SARS-CoV-1 and SARS-CoV-2 both exploit the ACE2 receptor (Wu et al., 2020a), which is frequently expressed in liver cells, bile duct cells, and liver endothelial cells (Chai et al., 2020; Hamming et al., 2004).

According to Chai et al., ACE2 levels were higher in bile duct cells than in liver cells and were comparable to AT2 cells (Chai et al., 2020). Because bile duct cells play such a crucial role in immunological defense and liver renewal, they may be a major source of COVID-19-related hepatic injury (Ali and Hossain, 2020). Zhao et al. (2020) discovered that viral infection impairs the cholangiocytes barrier and bile acid transporting activities by deregulating genes involved in tight junction formation and bile acid transport, potentially reflecting the direct cytopathogenic action of the virus on ACE2 and TMPRSS2-expressing target cells. Consequently, it is critical to recognize that liver damage seen in COVID-19 patients may partially reflect direct cholangiocytes injury induced by SARS-CoV-2 infection, resulting in bile acid accumulation (Zhao et al., 2020).

5. Hypoxic Changes

Hypoxic hepatitis can be caused by several factors. However, over 90% of all cases are caused by cardiovascular failure, sepsis, or respiratory failure (Horvatits et al., 2013). In addition, liver congestion caused by increased central venous pressure was found to exacerbate liver injury in patients with right-sided heart failure. Hypoxia causes hepatic cell death, histopathologically described as centrilobular necrosis, in long-term hemodynamic or respiratory failure (Nardo et al., 2021).

Another cause of liver damage is pneumonia-related hypoxia damage in the liver due to the hyperinflammatory response and multiple organ failure (Feng et al., 2020). Hepatic ischemia and hypoxia-reperfusion dysfunction will continue to cause hepatocyte cell death, leading to lipid deposition, the generation of reactive oxygen species, enhanced oxidative burden, and the release of more proinflammatory molecules (Zhang et al., 2018).

6. Drug-induced Liver Injury

Antiviral drugs, steroids, and antibiotics are used to treat SARS-CoV-2 patients. These drugs can cause hepatotoxicity since the liver is involved in their processing. The most common initial symptoms of COVID-19 are fever, cough,

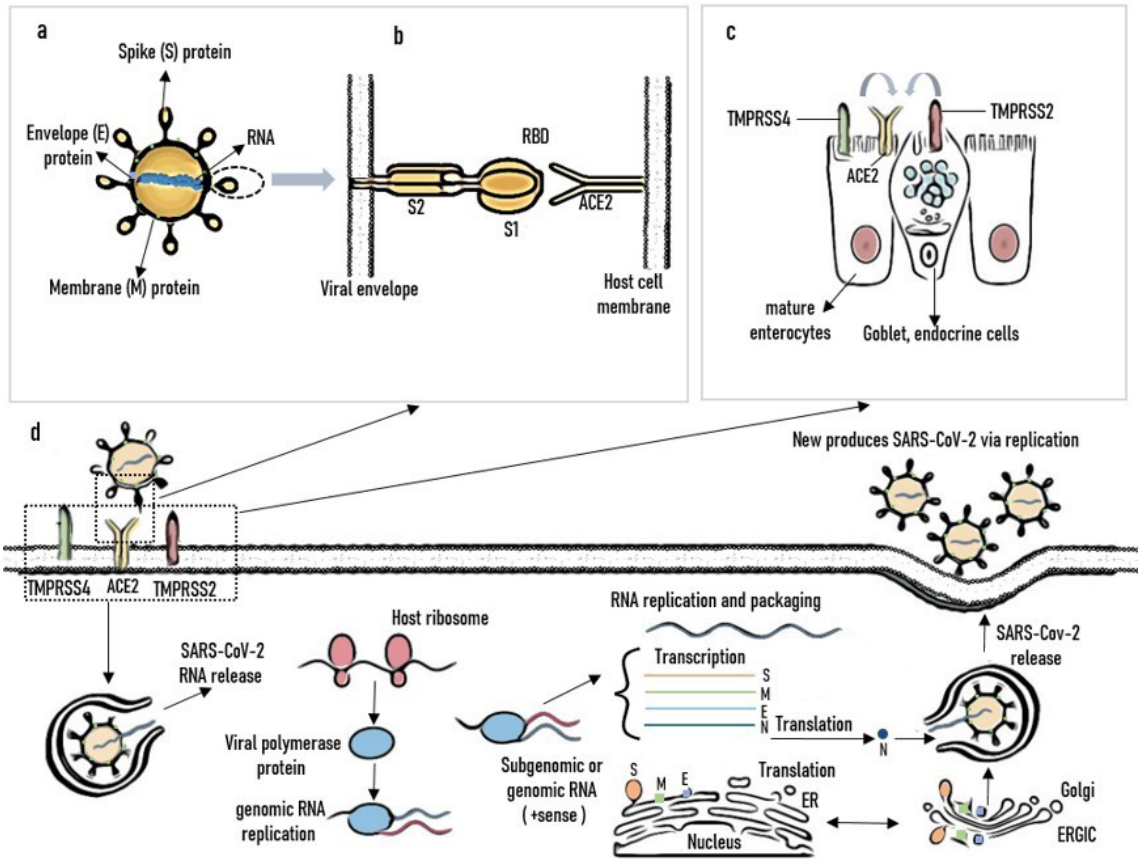

Figure 2. Potential mechanisms of hepatic injury with SARS-CoV-2 infection adapted from Yang et al. (2020).

dyspnea, and tiredness. Consequently, patients occasionally use antipyretic drugs that mostly contain acetaminophen, which is known to cause direct hepatocyte injury (Deng and Peng, 2020).

Antiviral, antibiotic, antimalaria, immunomodulation, and antipyretic therapy for severe COVID-19 patients have been approved (Zhang et al., 2020b). These therapies may cause abnormal liver function. Furthermore, ribavirin-induced hemolysis may cause tissue hypoxia, increasing serum liver enzymes. Antiviral drugs such as arbidol, oseltamivir, lopinavir, and ritonavir are used to treat serious COVID-19 patients and have been associated with their hepatic damage (Cai et al., 2020; Fan et al., 2020). According to Cai et al., ritonavir and lopinavir play a significant role in liver test abnormalities in SARS-CoV-2 patients (Cai et al., 2020). Using lopinavir with ritonavir resulted in a fourfold increase in liver injury. Moreover, the coronavirus antiviral nucleoside analog remdesivir was used in the United States to treat COVID-19 patients after showing antiviral activity *in vitro* against SARS-CoV-2 (Hoehl et al., 2020; Wang et al., 2020b).

The antiviral drugs chloroquine (CQ) and hydroxychloroquine (HCQ) work by blocking viral endosomal entry (Sanders et al., 2020). Because of their anti-SARS-CoV-2 activity and safety in treating malaria and autoimmune disease, CQ and HCQ were identified as promising anti-SARS-CoV-2 drugs (Hickley et al., 2011). CQ and HCQ have recently been associated with cardiotoxicity and high mortality in SARS-CoV-2 infected patients. Consequently, current treatment guidelines recommend using HCQ and CQ with caution in treating severe COVID-19 patients (Dawood et al., 2022).

The first example of drug-induced liver impairment associated with tocilizumab treatment in a COVID19 patient was recently published. Tocilizumab has low hepatic metabolism and interferes with the IL-6 pathway, which is important for liver regeneration and the most likely cause of its hepatotoxicity (Muhović et al., 2020).

Xu et al. used postmortem biopsies to investigate the pathological characteristics of a patient who died from a severe SARS-CoV-2 infection. Significant microvesicular steatosis, and minimal lobular and portal activity, were found in their liver biopsy specimens showing that injury was caused by SARS-CoV-2 infection or the drugs administered (Xu et al., 2020c).

7. Preexisting Liver Diseases

COVID-19 comorbidities, such as chronic diabetes, hypertension, obesity, and cardiovascular disease, have

been associated with 19 outcomes. According to the World Health Organization, chronic diseases account for about 46% of diseases and 59% of deaths worldwide (Fierro, 2020).

Chronic liver disease (CLD) and cirrhosis are common conditions associated with immune dysregulation, causing concern that SARS-CoV-2 infection will increase the risk of COVID-19 complications in these patients (Moon et al., 2020). The incidence of CLD in COVID-19 patients is unknown. However, it has been estimated that 1-11% of patients have CLD (Spearman et al., 2021). The most common CLDs are metabolic-associated fatty liver disease (MAFLD) and non-alcoholic fatty liver disease (NAFLD), which together affect around a quarter of the world's adult population (Eslam et al., 2020).

Proinflammatory and profibrotic cues, such as angiotensin II produced by the catalytic activity of the angiotensin-converting enzyme (ACE) via the profibrotic branch of the renin-angiotensin system, activate hepatic stellate cells, which are the predominant source of fibrosis in chronic liver disease. ACE2 inhibits ACE activity, lowering the angiotensin II/angiotensin ratio by creating anti-inflammatory and anti-fibrotic angiotensin (Mederacke et al., 2013; Shim et al., 2018). However, *ACE2* expression has not been found in quiescent or fibrogenic/activated hepatic stellate cells. These data show that SARS-CoV-2 may have difficulty infiltrating these cells (Akil et al., 2019).

Moon et al. published the results of a large, multicenter, multinational cohort of CLD and cirrhosis patients that looked at the first 152 cases of laboratory-confirmed COVID-19 in patients with CLD clinicians reported between March 25 and April 20, 2020, including 103 with cirrhosis and 49 with non-cirrhotic CLD from 21 countries on four continents. They reported that COVID-19-related morbidity and mortality are strongly associated with the severity of baseline liver impairment. Moreover, many SARS-CoV-2-infected cirrhosis patients had hepatic decompensation even in the absence of respiratory symptoms (Moon et al., 2020).

CLD was not significantly associated with COVID-19 severity based on a meta-analysis of nine single-center studies, the majority of which included more than 100 patients (Wang et al., 2020d). However, it did show that patients with severe COVID-19 had a higher risk of acute liver failure. Nevertheless, there was no difference in the incidence of liver injury between intensive care unit (ICU) and non-ICU patients in single-center cross-sectional Chinese studies (Xie et al., 2020).

The international SECURE-Cirrhosis and COVID-Hep registries spanning 29 countries have found increased ICU admissions, ventilator support, kidney transplant therapy, and mortality with increasing Child-Pugh class (Marjot et al., 2021).

8. SARS-CoV-2 and Immune-mediated Liver Damage

Some COVID-19 patients have been reported to initially have mild symptoms but rapidly progress to later-stage disease with multiple organ failures, presumably associated with the development of an inflammatory storm (systemic inflammatory response syndrome) brought on by viral infection. Hepatomegaly, increased serum transaminase levels, jaundice, and hepatic encephalopathy are all potential outcomes of the inflammatory response (Yang et al., 2020).

One element of COVID-19 liver injury is dysregulation of the innate immune response, with inflammatory markers and cytokines highly activated in COVID-19 patients, potentially leading to the development of pulmonary and extrapulmonary damage (Alqahtani and Schattenberg, 2020).

9. Immune Cell Response

Kupffer cells are found in the hepatic sinusoids of the reticuloendothelial system, where they act as the first line of defense against microbes and control immunological homeostasis in the liver with the aid of other immune cells such as neutrophils (Krenkel and Tacke, 2017). Kupffer cells in the liver contain the most resident macrophages of any single organ and play an important role in the innate immune response (Blériot and Ginhoux, 2019). Several histological results in COVID-19 patients showed Kupffer cell activation and hyperplasia (Díaz et al., 2020; Fassan et al., 2021). Based on the presence of the ACE2 receptor on the surface of Kupffer cells, SARS-CoV-2 may infect hepatic macrophages, triggering the host's primary defense response (Song et al., 2020).

Mast cells (MC) are specialized innate immune cells in the sub-endothelium that contribute to cytokine networking by producing interleukin 4 (IL-4) and IL-6. COVID-19 patients may benefit from MCs as a source of cytokines and chemokines. Activated MCs have been found in the lungs of deceased COVID19 patients, and MC-derived proteases are found at high levels in the sera and lung tissues of COVID-19 patients (Theoharides, 2021).

Macrophages are highly adaptable and play an important role in liver disease progression. Proinflammatory macrophages have a role in MAFLD progression and help determine its severity. The polarization process divides hepatic macrophages into sub-phenotypes. Macrophages divide into two groups in response to various inflammatory signals: M1 and M2. M1 macrophages are activated and promoted by Toll-like receptor (TLR) ligands and T helper type 1 (Th1) immune components that mediate the host's response against pathogens such as bacteria, viruses, and protozoa. Consequently, M1 macrophages induce inflammatory processes by producing high levels of reactive oxygen and nitrogen species and releasing large amounts of proinflammatory cytokines. Unlike M1 macrophages, M2 macrophages have an anti-inflammatory function and promote tissue repair and remodeling but also have phagocytic activity and different chemokine profiles (Miele et al., 2021).

10. Systemic Cytokine Storm and Liver Injury

The cytokine storm is a viral infection-induced hyperinflammatory response in which lymphocytes

and macrophages are constantly active and release large amounts of inflammatory cytokines. Pulmonary and non-pulmonary organ failure (kidneys, liver, and cardiac muscle) increases due to the inflammatory cytokine storm (Mangalmurti and Hunter, 2020).

COVID-19 infection can trigger an inflammatory cytokine storm involving innate and cellular adaptive immunity (Prompetchara et al., 2020). Levels of several cytokines increase, including interleukins (IL) and tumor necrosis factors (TNF), granulocyte-colony stimulating factor, and interferon γ (IFN γ) (Pedersen and Ho, 2020). Moreover, harm likely also occurs due to direct virus-mediated cell damage, with dysregulation of the renin-angiotensin-aldosterone system due to viral entry-related downregulation of *ACE2* reducing angiotensin I and II cleavage. Micro- and macro-vascular thromboses are caused by endothelial cell injury and thrombo-inflammation (Bikdeli et al., 2020).

Several studies have associated the inflammatory storm with liver damage and severe pneumonia in COVID-19 patients (Liu et al., 2020). Systemic viral infections, such as cytomegalovirus, Epstein-Barr virus, and herpes simplex virus, have been associated with liver dysfunction due to immune system overactivation and inflammation triggered by circulating cytokines (Adams and Hubscher, 2006). Severe hypercytokinemia can trigger a chain reaction that leads to tissue destruction and multiorgan failure, particularly in the liver (Mehta et al., 2020). Hepatic inflammation involves innate immune cell activation and cytokine release and is a primary cause of liver injury (McDonald and Kubes, 2016). Moreover, several studies found that patients with liver dysfunction had higher levels of proinflammatory cytokines and chemokines than those with normal liver function (Duan et al., 2003). Inflammatory indicators such as C-reactive protein, cytokines (e.g., IL-6), neutrophils, and lymphocytes were significantly activated in severe COVID-19 patients (Zhang et al., 2020a). These findings link liver damage and inflammatory responses triggered by severe COVID-19 infection (Figure 3) (Spearman et al., 2021).

11. Histopathologic Abnormalities of the Liver in SARS-CoV-2 Patients

SARS-CoV-1 and Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV) are the most common histopathology findings. An earlier study on SARS-associated viral hepatitis found considerably more mitotic cells, eosinophilic bodies, and balloon-like cells in the liver, indicating liver cell death and the onset of hepatic damage (Chau et al., 2004). The most notable histopathological abnormalities in the liver of SARS-CoV-2 infected patients are listed in Table 1.

A meta-analysis by Díaz et al. (2020) evaluated hepatic steatosis, hepatic sinus congestion, necrosis, arterial thrombosis, and other vascular changes such as fibrosis, Kupffer cell proliferation or hyperplasia, and portal and lobular inflammation (Figure 4) (Díaz et al., 2020).

A light microscopic study found hepatic cell degeneration and localized necrosis and the presence of some biliary plugs in the small bile duct. In addition to SARS-CoV-2 infection, hepatotoxic drugs, preexisting chronic liver disease, and COVID-19-related hyperinflammatory conditions can affect the liver, particularly when the patient is hypoxic (Yao et al., 2020).

Macrovesicular steatosis and glycogen buildup in liver cells, and unique lymphocyte infiltration in the portal system, are signs of cirrhosis and regeneration in a liver

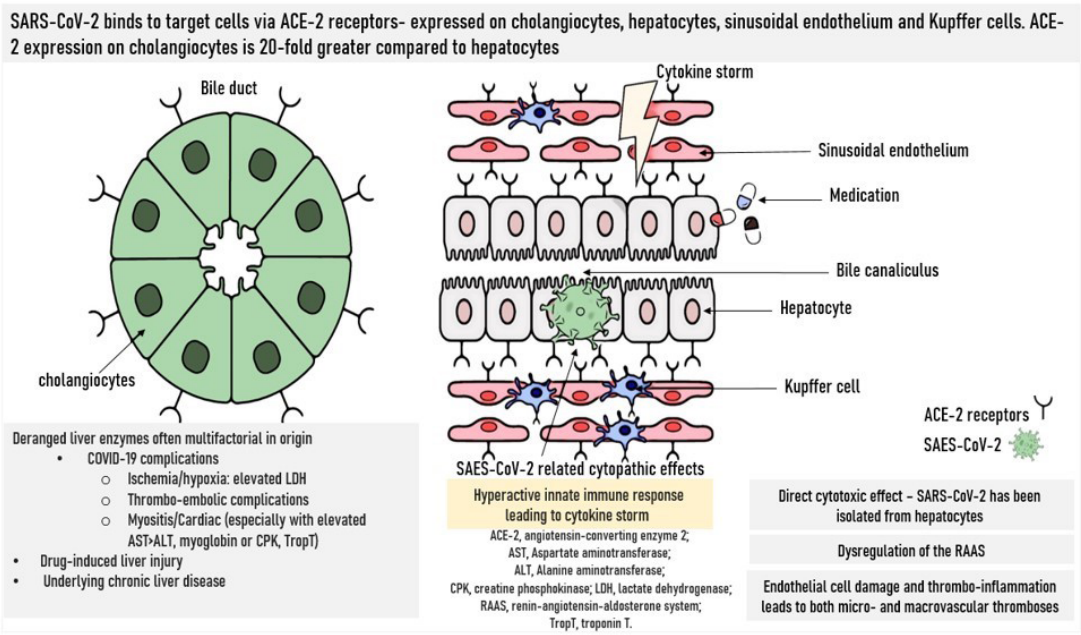

Figure 3. Immune-mediated liver injury adapted from Spearman et al. (2021).

Table 1. A list of the histological liver abnormalities found in SARS-CoV-2 patients.

Reference	Country	Sample size	Histopathological abnormalities
Wang et al. (2020e)	Beijing and Anhui province, China	156 (2 liver tissues only)	Apoptosis in the liver and some binuclear hepatocytes. Small numbers of CD4+ and CD8+ cells. S protein forms in the cytoplasm of hepatocytes with evident mitochondrial expansion, endoplasmic reticulum dilatation, and glycogen granule decrease typical of coronavirus infection. Increased CD68+ cells were primarily found in the hepatic sinusoids, indicating Kupffer cell activation.
Ji et al. (2020)	China	202	Damage to the liver was hepatocellular rather than cholestatic. Microvesicular steatosis and T cell overactivation were found in one patient.
Xu et al. (2020c)	Beijing, China	1	Minimal lobular and portal activity, moderate microvesicular steatosis.
Lagana et al. (2020a)	Columbia	40	Varying degrees of steatosis, congestion, and ischemia, but no other significant gross pathology. Granulomatous inflammation. The portal and lobular granulomas resembled a "fibrin ring" shape.
Sonzogni et al. (2020)	Bergamo, Italy	48	Inflammatory infiltrates and lobular lymphocytes were dispersed throughout the portal area, with varying degrees of portal vein endotheliitis and only mild to moderate portal fibrosis; the biliary intrahepatic tree showed no major histological changes.
Tian et al. (2020)	Wuhan, China	4	Mild lobular infiltration by small lymphocytes and centrilobular sinusoidal dilation. Patchy necrosis was also observed.
Zhang et al. (2020b)	Wuhan, China	115	Mild sinusoidal dilatation and minor lymphocytic infiltration were observed in the liver tissue.
Duarte-Neto et al. (2020)	Sao Paulo, Brazil	first 10 fatal cases	Liver macrovesicular steatosis, central coagulative necrosis, and sinusoidal congestion with fibrin thrombi.
Elsoukkary et al. (2021)	New York, NY, USA	32	Steatosis was the most common finding, explained by the presence of obesity, diabetes, or hyperlipidemia. Nonspecific portal-based moderate lymphocytic inflammation was detected. Signs of chronic liver disease, including bridging fibrosis and cirrhosis with an unknown cause.
Falasca et al. (2020)	Rome, Italy	22	Sinusoidal congestion and red blood cell extravasation into the Disse space, small vein congestion, and hepatocyte death with inflammatory cell infiltration. Macrovacuolar and microvacuolar steatosis.
Fassan et al. (2021)	Padua, Italy	3	Except for one cirrhotic sample, all showed well-preserved lobular architecture. A zone 3 sinusoidal ectasia with significant red cell congestion and parenchymal degeneration in the centrilobular. Pericellular and sinusoidal fibrosis are two types of fibrosis. It was found that there were sinusoidal diffuse platelet-fibrin microthrombi and portal vein thrombosis. Ischemic liver necrosis of the centroacinar type. Kupffer cells were activated.
McConnell et al. (2021)	New Haven, CT, USA	68	Dilated sinusoids with liver congestion, neutrophil infiltration, steatosis, and sinusoidal erythrocyte aggregation in zone 2.
Schmit et al. (2021)	Saint-Luc, Brussels, Belgium	78	In 12 cases, lobular and portal inflammation were observed (86%). In the portal region, two patients showed a mixed infiltration with neutrophils, and one patient had a primarily eosinophilic infiltrate. Except for one patient already diagnosed with NASH, fibrosis was often nonexistent or distinct. Five cases (36%) had a distinct iron excess, and two had ceroid macrophages. Cholestasis was detected in five cases, while distinct canalicular growth was observed in another five (36%). Endotheliitis and vascular thrombi were not observed.
Li et al. (2021)	Zhejiang, China	3	Lymphoid follicles collected and expanded due to lymphocytic infiltration in the portal tract. Immunolabeling with CD34 and Warthin-Starry staining was used to detect cirrhosis.
Beigmohammadi et al. (2021)	Tehran, Iran	7	Mild to moderate micro- and macro-vesicular steatosis was observed. Hepatocytes in four of the patients showed mild ballooning degeneration. Two patients had both focal and distributed bile clogs. There was focal confluent necrosis and focal hepatocyte dropout. Masson's trichrome special staining was typical. Reticulin staining showed focal regeneration sites. There was no evidence of the viral cytopathic impact in the liver tissue slices.

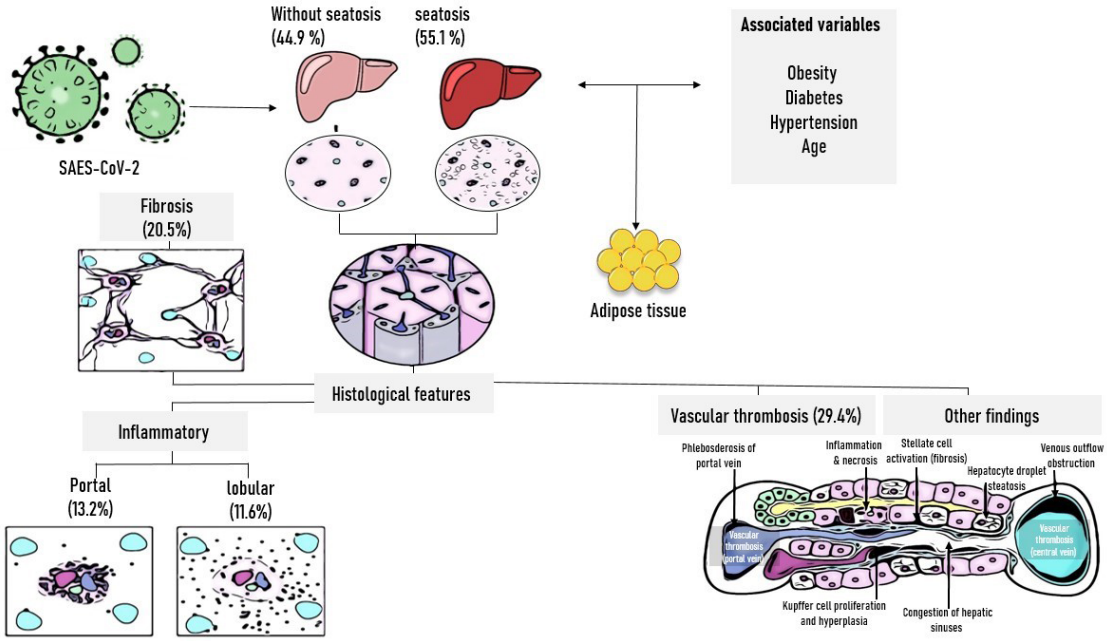

Figure 4. The major liver histological features adapted from Díaz et al. (2020).

injured by SARS-CoV-2 infection. Sinusoidal dilatation, mild lymphocytic infiltration, and patchy liver necrosis have also been observed in the portal triad and centrilobular areas (Li and Xiao, 2020).

Postmortem liver histology data on patients who died after catching SARS-CoV-2 was studied by Bradley et al., showing acute congestion, centrilobular necrosis, and mild periportal lymphocytic inflammation. Based on these findings, the authors hypothesized that lymphocyte infection and immunological dysregulation cause liver injury (Bradley et al., 2020).

A prospective study by Lax et al. found steatosis in all the patients, affecting 5-60% of the hepatocytes that were mostly macrovesicular. However, one case was microvesicular and mostly situated pericentrally but also periportally. All the patients had Kupffer cell growth, and eight had chronic hepatic congestion. Other liver changes included hepatic steatosis, portal fibrosis, lobular cholestasis, acute liver cell necrosis, and central vein thrombosis (Lax et al., 2020).

Prilutskiy et al. examined the reticuloendothelial organs of four COVID-19 patients and compared their clinical and laboratory characteristics, discovering hemophagocytic lymphohistiocytosis (HLH) and detecting hemophagocytosis. There was modest centrilobular congestion with minor steatosis in a subset of cases but no severe portal or lobular inflammation. CD163 labeling showed only minor Kupffer cell hyperplasia but no hemophagocytosis (Prilutskiy et al., 2020).

McConnell et al. examined postmortem liver histology to determine if there was endotheliopathy and associated liver injury. They found that the livers of COVID-19 patients had dilated sinusoids, steatosis, and sinusoidal erythrocyte aggregation. Moreover, they found a link between COVID-19 liver injury and endotheliopathy, identifying a putative thrombo-inflammatory mechanism in liver sinusoidal endothelial cells that is likely mediated by IL-6 trans-signaling (McConnell et al., 2021).

A comprehensive systemic review and meta-analysis of liver histopathology findings for 18 studies from seven countries found the following pooled prevalence estimates: Hepatic steatosis, hepatic sinus congestion, vascular thrombosis, fibrosis, and Kupffer cell hyperplasia (Gordon et al., 2020).

12. Direct Cytopathic Effects of SARS-CoV-2 Infection

Because it receives both portal and systemic circulation, the liver plays an important role in host defense against microorganisms and is associated with most systemic infections. While many viruses have a direct cytotoxic effect on hepatocytes and cholangiocytes, their etiology appears complex. SARS-CoV may cause direct cytopathic liver injury rather than causing cellular stress through reduced oxygen supply or cytokines, as seen in sepsis (Yang et al., 2005).

Wang et al. observed typical coronavirus particles with spiky characteristics in the cytoplasm of hepatocytes. Most viral particles possessed a full envelope with corona-like spikes, indicating that SARS-CoV-2 can both enter and replicate in hepatocytes. Based on ultrasound data, they determined that SARS-CoV-2 directly contributed to cytopathy and that apoptosis was also indicative of direct viral effects but ruled out ischemic liver disease

and drug-induced liver damage as causes of liver damage (Wang et al., 2020e).

The clinical findings of two COVID-19 hepatitis patients were detailed in a study published by Fiel et al. Histological examination found these patients had a mixed inflammatory infiltrate with extensive bile duct damage, endotheliitis, and many apoptotic bodies. The presence of SARS-CoV-2 in the liver was identified using in situ hybridization and electron microscopy, indicating the likelihood of direct cell damage. They concluded that extensive apoptosis and significant cholangiocytes injury based on histopathologic abnormalities suggest a direct cytopathic insult (Fiel et al., 2021).

In addition, Lagana et al. evaluated the clinical and histological data of patients who died from COVID-19-related causes. They found that livers had fibrosis and abscesses on a gross level, while the other livers showed varying degrees of steatosis, congestion, and ischemia but no other notable gross pathology. The fat droplets were mostly macrovesicular, and there was no evidence of real microvesicular steatosis. Active steatohepatitis with ballooning and Mallory-Denk bodies were found. Based on this clinical and histologic evidence, they concluded their findings are consistent with virally-induced liver damage. Furthermore, neither steatosis nor hepatitis is associated with established NAFLD risk factors or drug administration (Lagana et al., 2020a).

13. Patients with Preexisting Liver Diseases

Tian et al. performed postmortem needle core biopsies of the lung, liver, and heart of four patients who died of COVID-19 pneumonia. Each patient had at least one underlying condition, such as immunocompromised status (chronic lymphocytic leukemia and renal transplantation) or other ailments (cirrhosis, hypertension, and diabetes). The predominant histological results were in the lungs. Small lymphocytes infiltrated the lobules of the liver, causing centrilobular sinusoidal dilatation. Necrosis in patches was also visible. Only modest fibrosis and mild myocardial enlargement were visible in the heart, alterations that are most likely associated with the underlying diseases. They concluded that liver and heart alterations found in the postmortems could be attributed to preexisting disease or perimortem damage (Tian et al., 2020).

According to Ji et al., NAFLD is the primary cause of persistent liver injury. Patients with NAFLD were also more likely to acquire severe COVID-19 and had a longer viral shedding time. COVID-19 liver damage is likely immune-mediated rather than the outcome of direct cytopathic damage, as in other viral respiratory infections, based on postmortem liver biopsy (Ji et al., 2020).

Chu et al. observed hepatocellular necrosis, cholestasis, steatosis, lobular inflammation, portal inflammation, and fibrosis. They also discovered hepatocyte edema and sinusoidal dilatation. Hepatocytes showed significant edematous mitochondria and cristae disruption. Endoplasmic reticulum expansions were also observed. These findings suggest that liver harm may be associated with other underlying problems rather than coronavirus-induced damage (Chu et al., 2021).

14. Drug-induced Liver Injury During SARS-CoV-2 Treatment

Postmortem biopsies of a COVID-19 patient showed minor lobular and portal activity and moderate microvascular steatosis. Between January 18 and February 22, 2020, 115 confirmed COVID-19 patients at a single center were retrospectively studied in Wuhan, China. They found limited lymphocytic infiltration and modest sinusoidal dilatation in COVID-19 patients (Zhang et al., 2020b). These alterations were nonspecific and could be caused by SARS-CoV-2 infection, hypoxia, or drug-induced liver disease (Garrido et al., 2020; Xu et al., 2020c).

The livers of 57% were pale and yellowish, while the livers of the remaining 42% had a nutmeg appearance. Centrilobular necrosis was detected in most patients connected to minor to significant lobular or portal inflammation. In 57% of patients, steatosis was found, but fibrosis was not. The authors concluded that the majority of the histological abnormalities were caused by hypoxia due to severe hypoxemic pneumonia. However, drug toxicity may also be an issue in other situations. Other histological changes could be explained by prior hepatic states or underlying hepatic diseases (Schmit et al., 2021).

15. SARS-CoV-2 in Liver Transplant Recipients

The global spread of COVID-19 created additional obstacles to organ donation and transplantation. Due to a significant drop in the number of donors and the conversion of numerous care facilities to COVID-19 units, many hospitals had to cease or significantly restrict their transplantation operations. Respiratory viruses are more likely to infect transplant recipients due to preoperative organ decompensation and chronic illness. Cross-infection and the epidemiology of COVID-19 are key risk factors for liver transplant recipients, who may be exposed to more individuals while awaiting surgery (Zhong et al., 2020).

D'Amico et al. discovered two cases of symptomatic liver cysts that required fenestration. Both patients were admitted to the hospital after testing positive for SARS-CoV-2 and developed symptoms caused by an enlarged hepatic cyst post-infection, one with abdominal pain and the other with jaundice. The authors found no evidence of viral load in the hypothesized viral reservoir of cystic fluid after viral clearance during pharyngeal and nasal swabs. They concluded that this study could be relevant in evaluating the safety of COVID 19-infected donors with good hepatic function and a liver cyst undergoing liver transplantation (D'Amico et al., 2021).

According to Lagana et al., a 6-month-old newborn with biliary atresia who underwent a living donor liver transplant from her COVID-19-positive mother became infected and developed severe pneumonia and hepatitis due to the transplant. On the seventh postoperative day, a core biopsy showed inflammatory and plasma cell infiltration

of the portal tracts and mild interlobular cholangitis and portal perivenulitis (Lagana et al., 2020b).

Various COVID-19 vaccines have recently been approved for use in healthy individuals, with evidence of efficacy. Nevertheless, immunocompetent patients undergo a thorough immunization evaluation because of the dangers of immunological imbalance caused by their disease or immunosuppressive medication. Indeed, Boyarsky et al. discovered that solid organ transplant recipients had a sufficient humoral response after receiving the complete mRNA vaccine immunization schedule and that their poor response was associated with immunosuppression (Boyarsky et al., 2021).

16. Conclusion

COVID-19 is caused by the SARS-CoV-2 virus, which has a similar viral structure to SARS. SARS-CoV-2 infection is more harmful due to the specific features of its S protein. The virus was categorized as a pandemic, impacting more than 4 million people worldwide. The cytokine storm elicited by the virus and its virulence components contributes to disease severity with a mortality rate of 3-4%. Several published studies have highlighted the potential significance of the liver in COVID-19 disease. In 36% of COVID-19 patients, liver injury develops with mild to moderate elevations in hepatic enzymes. In this review, we summarized recent COVID-19 findings relating to its histopathological and immunological implications on the liver. This concise review will aid clinicians and researchers in better understanding the tissue histopathology and immunological consequences of SARS-CoV-2 infection on the liver, enabling improved care planning and avoiding future dangers. Elective treatments and routine examinations should be rescheduled based on the risk-benefit ratio. However, emergency medical care must be provided with infection-prevention measures in place.

17. Study Limitations

Important questions remain unanswered, and additional studies will be required to address them, such as: Which liver cells does SARSCoV2 infect? Which molecular pathways are disrupted by SARSCoV2 infection? What mechanisms lead liver impairment to cause respiratory failure and predispose patients to severe COVID-19 infection?

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