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REVIEW

SARS-CoV-2-mediated liver injury: pathophysiology and mechanisms of disease

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Abstract

Background SARS-CoV-2-induced severe inflammatory response can be associated with severe medical consequences leading to multi-organ failure, including the liver. The main mechanism behind this assault is the aggressive cytokine storm that induces cytotoxicity in various organs. Of interest, hepatic stellate cells (HSC) respond acutely to liver injury through several molecular mechanisms, hence furthering the perpetuation of the cytokine storm and its resultant tissue damage. In addition, hepatocytes undergo apoptosis or necrosis resulting in the release of pro-inflammatory and pro-fibrogenic mediators that lead to chronic liver inflammation.

Aims The aim of this review is to summarize available data on SARS-CoV-2-induced liver inflammation in addition to evaluate the potential effect of anti-inflammatory drugs in attenuating SARS-CoV-2-induced liver inflammation.

Methods Thorough PubMed search was done to gather and summarize published data on SARS-CoV-2-induced liver inflammation. Additionally, various anti-inflammatory potential treatments were also documented.

Results Published data documented SARS-CoV-2 infection of liver tissues and is prominent in most liver cells. Also, histological analysis showed various features of tissues damage, e.g., hepatocellular necrosis, mitosis, cellular infiltration, and fatty degeneration in addition to microvesicular steatosis and inflammation. Finally, the efficacy of the different drugs used to treat SARS-CoV-2-induced liver injury, in particular the anti-inflammatory remedies, are likely to have some beneficial effect to treat liver injury in COVID-19.

Conclusion SARS-CoV-2-induced liver inflammation is a serious condition, and drugs with potent anti-inflammatory effect can play a major role in preventing irreversible liver damage in COVID-19.

Keywords ACE 2 receptors · COVID-19 · Acute liver failure · Chronic liver failure · Ang2 · Inflammation · Hepatic stellate cells · Cytokine storm

Introduction

The liver carries numerous immunological, endocrine, and digestive functions. It occupies a major portion of the right upper abdominal cavity, beneath the diaphragm, with the left lobe located on top of the stomach, and the right lobe over the right kidney, and intestines. About 30% of the

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total blood is channeled through the liver every minute, thus carrying about 10^8 peripheral blood lymphocytes in around 24 h [1].

SARS-CoV-2 and liver cells

SARS-CoV-2 is known to bind to ACE2 receptors in various tissues including the lungs, kidneys, and liver [2, 3]. Specifically, the S protein S1 subunit binds to the ACE2 receptor leading to the cleavage of the S protein, and thus viral entry via cell membrane fusion [4, 5]. ACE2 receptor binding induces vasoconstrictive, pro-inflammatory, and oxidant effects. It also creates a hypercoagulable state by inducing the expression of plasminogen activator inhibitor 1 (PAI-1) in endothelial cells, thus leading to a suppression of fibrinolysis [6, 7].

Hepatocytes are the main constituents of the liver parenchyma, accounting for two thirds of the total cell population. These cells are involved in protein synthesis and storage, synthesis of cholesterol, bile salts and phospholipids as well as detoxification of exogenous and endogenous substances [1, 8].

The liver also contains resident antigen presenting cells that capture several antigens in the blood. They also detect cell-associated antigens that are released after hepatocytes death following liver injury [9] These include:

i. Kupffer cells which are the largest group of non-circulating local macrophages residing in the liver representing 20% of non-parenchymal cells in the liver [10]. They are located in the sinusoidal vascular space mainly in the periportal area. The functions of these cells are to phagocytose debris and microorganisms and to clear endotoxins from the passing blood. Kupffer cells pass through the Space of Disse, make direct contact with hepatocytes and phagocytose apoptotic hepatocytes [11].
ii. Liver sinusoidal endothelial cells (LSECS) make up 50% of non-parenchymal cells in the liver. They line up the sinusoids, forming a sieve-like, fenestrated endothelium[2]. They express molecules that induce antigen uptake such as the mannose receptors and the scavenger receptors [12, 13].
iii. Resident hepatic dendritic cells (DC) are located around the central veins and portal tracts of the liver. In healthy individuals, DCs are predominantly immature cells and function to capture and process antigens [14, 15]. Once activated, they migrate via the Space of Disse to the lymphatic vessels in the portal tracts and ultimately to extrahepatic lymph nodes [16, 17].

Hepatic stellate cells (HSCs) are resident mesenchymal cells and account for 15% of total resident cells in a normal human liver. They have features similar to that of fibroblasts and store vitamin (A) lipid droplets under physiological conditions. HSCs reside in a virtual subendothelial space between the basolateral surface of hepatocytes and the anti-luminal side of the Space of Disse which contains thin permeable connective tissue necessary for the exchange of biomolecules between portal blood flow from gastrointestinal tract and hepatocytes [18].

SARS-CoV-2 belongs to the Coronaviruses family. It shares 79.6% sequence identity with the previously identified SARS-CoV-1. It enters the host cell through binding to angiotensin-converting enzyme II (ACE2) receptors that are abundant in the lungs, heart, blood vessels, liver, and intestines. Once in the cytoplasm, SARS-CoV-2 releases its genomic RNA and starts replicating inside the host cell [19]. Previous RNA-seq data in the human protein atlas database demonstrated expression of ACE2 in the liver [20]. In a mouse model of acute liver injury, ACE2 expression in the liver was downregulated on the first day, but it was elevated up to twice the normal level on the third day due to the compensatory proliferation of hepatocytes and liver cells [21, 22]. Due to this upregulation, the liver is considered one of the most affected organs in COVID-19 infection. Upon viral entry, Kupffer cells and sinusoidal endothelial cells serve as the first gate against inflammatory stimuli in the portal circulation and produce inflammatory cytokines in the sinusoidal lumen [23].

Liver biochemistry

Abnormal liver biochemistry was reported in patients with SARS infection implying the association between liver injury and coronavirus infection [24, 25]. The most common blood tests used in clinical practice to assess liver function condition include serum aminotransferases, bilirubin, alkaline phosphatase, albumin, and prothrombin time—often referred to as "liver function tests" (LFTs) [26]. Clinical studies have reported a high prevalence of elevated LFTs in COVID-19 patients [27]. This increase in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) in COVID-19 patients suggests both hepatocellular and cholangiocellular damage [28]. A probable cause of hepatic injury may be the systemic effects of COVID-19, including hypoxia, sepsis, and multi-organ failure [29, 30]. The ensuing hypoxic damage and liver ischemia could potentially explain why total serum bilirubin, AST, and ALT levels are higher in severe COVID-19 patients, as opposed to less severe patients [31]. Following infection

with COVID-19, a severe inflammatory response takes place and is associated with a significant rise of a plethora of cytokines and chemokines including IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein-1 alpha (MIP1A), tumor necrosis factor (TNF), CXC-chemokine ligand-10 (CXCL-10), and C-reactive protein [21, 32]. HSCs respond to the latter inflammatory stimulus originating in the sinusoids by losing their lipid-rich granules. They also transdifferentiate into collagen-producing myofibroblasts (MFB) by expressing α-SMA (alpha smooth muscle actin) and deposit large amounts of extracellular matrix (ECM). Furthermore, they secrete pro-inflammatory cytokines such as interleukin IL-1β and IL-18, which further contribute to the cytokine storm. Among all the elevated inflammatory mediators, high blood IL-6 level significantly correlates with disease mortality suggesting that fatal COVID-19 infection is characterized by a cytokine release syndrome (CRS) induced by a cytokine storm [32, 33].

Liver inflammation and fibrosis

In relationship to HSC and inflammation, HSCs are known to play a role in the progression of liver fibrosis, regardless of the underlying causes [34]. Upon injury, hepatocytes undergo apoptosis or necrosis and release pro-inflammatory and pro-fibrogenic mediators that stimulate recruitment and activation of inflammatory cells in the liver resulting in chronic liver inflammation. The resident and infiltrating immune cells, in turn, secrete pro-inflammatory and pro-fibrogenic factors that activate quiescent HSCs [35]. Quiescent HSCs transdifferentiate into myofibroblast-like cells and become highly proliferative, migratory, and contractile cells producing excessive amounts of ECM components that accumulates in the liver parenchyma, disrupting liver architecture and forming the characteristic scar tissue [36]. Factors that were shown to regulate HSCs differentiation and liver fibrosis include fibroblasts growth factors (FGFs) with the tissue-specific subfamilies [37].

Liver injury in COVID-19 setting

Liver injury was noticed during MERS and SARS-CoV-1 infection with 60% of the latter having liver impairment. The presence of SARS-coronavirus was confirmed by RT-PCR in liver biopsies showing mild to moderate lobular inflammation and apoptosis [24]. In COVID-19, the GI tract is one of the most commonly affected systems after the lungs, with the liver being a prime target to SARS-CoV-2 infection [38]. The latter findings are evidenced by abnormal liver biochemical tests including aminotransferases, gamma-glutamyl transferase, and alkaline phosphatase [39] commonly found in patients admitted with COVID-19 [40].

COVID-19 and chronic liver disease

Patients with chronic liver disease may be more vulnerable to the severe clinical consequences of COVID-19, including oxygen desaturation and hypoxemia due to severe pneumonia and/or the perpetuation of the cytokine storm [41]. In one study, SARS-CoV-2 infection was shown to have produced acute liver injury in 43% of CLD patients without cirrhosis. Around 20% of compensated cirrhosis patients developed either acute or chronic liver failure (ACLF), or acute decompensation. Liver-related complications were found in nearly half of the decompensated cirrhotic patients, which exhibited greater severity and higher mortality [42]. Finally, patients with liver injury presented more severe COVID-19-related symptoms [43].

Drug-induced liver injury (DILI)

Medications used in the treatment of COVID-19, including antibiotics, antivirals, and steroids, are known to cause DILI [44]. A recent study reported a positive correlation between the use of these drugs and elevated liver enzymes [45].

a. Antiviral drugs

    i. Favipiravir: In one case study, Favipiravir was speculated to cause cholestatic liver injury in a COVID-19 patient with no previous history of hepatotoxicity [46]. Liver injury caused by Favipiravir, and possible risk factors are yet unknown. The administered Favipiravir dose was high in this context. Favipiravir may cause liver damage based on its chemical structure. Pyrazinamide, an antituberculosis drug, has a typical hepatotoxic side effect, although the exact mechanism is unclear [47]. Favipiravir is structurally very similar to pyrazinamide, and can be classified as a potentially hepatotoxic drug [46]. But still, the main interpretation of Favipiravir's hepatotoxicity is in the context of its predominant hepatic metabolism via aldehyde oxidase [48]. Recent in vivo and in vitro studies indicated that amidase-mediated pyrazinoic acid (PA) generation from PZA was the

cause of PZA hepatotoxicity. Additionally, xanthine oxidase (XO) can further metabolize PA to generate 5-hydroxy pyrazinamide (5-OH-PA), which was shown to be more hepatotoxic than PA [49].

ii. Remdesivir: A study reported an incidence of 23% of increased aminotransferase serum level in patients treated with Remdesivir and was considered the main cause for discontinuing the drug in some COVID-19 patients [50]. Those results were comparable to another study reporting that COVID-19 patients treated with IV administration of the drug had elevated ALT and AST serum levels as the most common liver adverse effect [51]. Other studies also reported an elevation in bilirubin and not just AST and ALT causing the drug discontinuation [52].

iii. Lopinavir/Ritonavir: Several studies have showed significant association between Lopinavir/Ritonavir administration in COVID-19 patients and adverse liver effects approximating that over 50% of patients with an established abnormal liver functions were administered a combination of Lopinavir/Ritonavir [53]. In addition, other studies reported significantly higher liver dysfunction in COVID-19 patients treated with Lopinavir/Ritonavir and mainly monitored through an increase in gamma-glutamyl transferase and total bilirubin [28].

b. Antipyretic medications and NSAIDs:

The risk of using acetaminophen and NSAIDs in COVID-19 is not yet confirmed by observational data and meta-analysis [54]. Accordingly, Rouphael et al. (2021) reported no increase in mortality or respiratory morbidity in COVID-19 patients treated with acetaminophen or NSAIDs. Oppositely, in a different case report of an orthotopic liver transplant patient with COVID-19, acute liver injury was attributed to acetaminophen toxicity [55].

c. Antibiotics:

Azithromycin, widely used in COVID-19 treatment, was shown in some studies to cause acute cholestatic hepatitis within 1 to 3 weeks after starting the treatment [56]. Another study reported that more than 20% of COVID-19-developed liver dysfunction attributed to Azithromycin use [57]. Liver disturbances included elevated ALT, hypoalbuminemia, and AST. Alternatively, other studies claimed that the incidence of liver disturbances in patients treated with azithromycin is low [58].

d. Hydroxychloroquine (HCQ):

While some studies reported no significant differences in liver function tests between patients treated with Hydroxychloroquine/Azithromycin and those without [59], other studies have reported severe hepatotoxicity related to Hydroxychloroquine evidenced by an increase in transaminases that was resolved after Hydroxychloroquine withdrawal [60]. The causes of HCQ-related hepatic injury are poorly understood, and toxicity may result from the drug' reactive metabolites, oxidative stress, or mechanisms linked to various inflammatory processes [61].

e. Antifibrotic drugs

Pirfenidone is an antifibrotic drug, which through an unknown mechanism, was associated with serum aminotransferase elevation and hepatotoxicity, despite reports of reduced instances of hepatic fibrosis [62]. It is shown that Pirfenidone-induced hepatotoxicity, resulting from the treatment of pulmonary fibrosis, is uncommon and often presents as a little increase in serum aminotransferases [63].

SARS-CoV-2 and patterns of liver injury

SARS-CoV-2 may directly or indirectly cause liver injury. In a poorly explored clinical scenario, SARS-CoV-2 viral load in the stool (detected in around 48% of patients after respiratory samples tested negative) is likely to be associated with portal venous viremia [64]. It was shown that all three human host receptors (ACE2, TMPRSS2, and FURIN) are expressed in liver tissues with variable expression levels across cell types [65, 66]. Accordingly, the highest expression level of ACE2 receptor was found in cholangiocytes followed by hepatocytes. TMPRSS2 is expressed in cholangiocytes, hepatocytes, periportal liver sinusoidal endothelial cells, erythroid cells, and to a lesser extent in non-inflammatory macrophages and alpha–beta T cells. Finally, FURIN is expressed in both hepatocytes and liver resident cells including plasma cells, natural killer cells, erythroid cells, periportal sinusoidal cells, portal sinusoidal cells, central venous sinusoidal cells, non-inflammatory macrophages, inflammatory macrophages, and cholangiocytes. The abundance of SARS-CoV-2 receptors within the liver supports the possibility that the virus may cause direct liver injury by viral cytopathic effect through lysis or necrosis/apoptosis induction. Also, SARS-CoV-2 can possibly cause immune-mediated liver damage due to the expression pattern in cell clusters associated with numerous active immune pathways such as inflammatory macrophages, natural killer cells, plasma cells, mature B cells, and cells of the

liver endothelial microenvironment [67]. A recent study by Chai et al., using single cell RNA-seq data of two independent cohorts, reported a predominance of ACE2 expression in cholangiocytes (59%) compared to hepatocytes (2.6%) [68], suggesting a predominant cholestatic pattern. However, based on mice model of liver injury, there was a transient upregulation of ACE2 expression caused by a compensatory differentiation of cholangiocyte epithelial cells into hepatocytes [22]. Although other studies have showed the existence of the viral RNA in liver cells [69], liver histology obtained from positive COVID-19 patients did not show any intracytoplasmic or intranuclear viral inclusion bodies to suggest direct liver damage [70]. Nevertheless, a recent study conducted by Chornenky et al. [71] found viral RNA in formalin-fixed, paraffin-embedded liver tissue from COVID-19 patients (4/9, 44%) [71]. Lobular and portal inflammation were described as the most frequent histopathological findings, apart from macrovesicular steatosis [72]. SARS-CoV-2 could cause direct cytopathic liver injury rather than inducing cellular stress from low oxygen supplies or cytokines as observed in sepsis [73]. The pathological findings of liver biopsy specimens from COVID-19 patients showed hepatocellular necrosis, mitosis, cellular infiltration, and fatty degeneration. In a recent autopsy analysis of liver tissues from a patient with COVID-19, moderate microvesicular steatosis and mild inflammation in the lobular and portal areas were observed. However, this pattern of histological injury is not specific for one etiology but can also be observed during sepsis or drug-induced liver injury (DILI) [74].

Immune-mediated liver injury

Immune-mediated liver injury may result from abnormal over-activated immune response and cytokine activation including interleukin 2, 6, 7, and − 10, tumor necrosis factor alpha, granulocyte colony-stimulating factor among others. The latter response is frequently reported in SARS-CoV-2 positive patients and is associated with multi-organ dysfunction/failure. Presence of hypoxia/ischemia from pneumonia and sepsis could also contribute to liver injury in critically ill patients [45]. Another aspect of liver injury in COVID-19 is the dysregulation of the innate immune response. Patients with COVID-19 exhibited marked activation of inflammatory markers, including abnormal high levels of C-reactive protein (CRP), lymphocytes, neutrophils, and cytokines, in particular interleukin-6 (IL-6) [41]. These inflammatory products may contribute to pulmonary and extrapulmonary injuries [30], and the control of deregulated cytokine production at an early stage could be beneficial to suppress the disease progression [75]. Hepatic inflammation involving the activation of innate immune cells and the release of cytokines is a well-established driver of liver injury from various causes [76]. Notably, lymphopenia observed in 63% to 70.3% of COVID-19 patients seemed to be linked to fatal outcomes [77]. Moreover, the absence of severe biliary tree or vascular damage, as well as mild/absent lymphocytic hepatitis, were other main histological findings in a recent study [78].

Histological findings and imaging features

Histopathologic studies on liver specimens revealed that SARS-CoV-2 can cause direct and indirect injury, and SARS-CoV-2 viral RNA could be found in hepatic tissues. Features of hepatocellular injury included ballooned cells, acidophilic bodies, moderate microvascular steatosis, and lobular inflammation [69, 73]. Macrovesicular steatosis was commonly reported, with fat distribution not typical of non-alcoholic fatty liver disease (NAFLD) [72]. The latter pattern is consistent with the findings from another study performed in affiliation with the Centers for Disease Control (CDC), which detected steatosis in 50% of liver autopsy [79]. The etiology may be multifactorial, including direct viral effects, hypoxia, malnutrition, and corticosteroid administration [72]. Moreover, a higher neutrophil-to-lymphocyte ratio (NLR) was associated with more severe systemic inflammation, and consequently predicted the risk of steatosis [80]. Lobular necroinflammation is also common, with foci consisting of one to several dead and dying hepatocytes, and few accompanying lymphocytes and histiocytes. COVID-19-induced systemic changes promoted marked derangement of the intrahepatic blood vessel network, portal fibrosis, and incomplete fibrous septa [81]. The excessive release of pro-inflammatory cytokines, triggered partially by SARS-CoV-2 binding to ACE2 receptor among other mechanisms, can lead to a cytokine storm characterized by increased levels of CRP, IL-6, lactate dehydrogenase (LDH), and ferritin as part of the systemic inflammatory response [75, 82]. IL-6 signaling affects liver sinusoidal endothelial cells (LSEC) by increasing neutrophil infiltration, pro-inflammatory gene expression such as ICAM1, P-selectin, and E-selectin, and coagulation genes such as Factor VIII and Von Willebrand disease (vWF) [83]. Furthermore, COVID-19-induced liver injury can present with a cholestatic pattern due to the presence of ACE2 receptors on biliary epithelial cells [84, 85]. The presence of high LDH levels observed in COVID-19 patients might be linked to the development or the progression of hepatocellular carcinoma (HCC). Consequently, HCC patients are more vulnerable to the negative impacts of the COVID-19 pandemic than patients with different types

of cancer knowing that hepatic injury caused by SARS-CoV-2 could exacerbate cirrhosis and hepatitis observed in the majority of HCC patients [86]. Consistently, HCC tumor sizes were bigger during the pandemic year (60 4.6 mm vs 48 2.6 mm, $p = 0.017$), and spontaneous tumor hemorrhage was more common. Slightly fewer new cases of intrahepatic cholangiocarcinoma (ICC) were reported, although symptoms were frequently present [87]. Patients with high risk of liver malignancies, particularly those with advanced tumor stages, may have high mortality rate. Thus, cancer patients are more likely to acquire SARS-CoV-2 infection and a worse prognosis than non-cancer patients [88]. The probability of death among cancer patients infected with COVID-19 is mostly influenced by age, sex, and comorbidities and is not likely to depend on the type of treatment the patient have received which include radiotherapy, targeted therapy, immunotherapy, or hormonal therapy [89]. An observational cohort study revealed that COVID-19-positive HCC patients could experience an all-cause death rate of up to 52.4%, which is about seven times greater than that of HCC-negative patients [90]. In a large research study done on SARS-CoV-2-infected liver cancer patients, a total of 52 patients died within 30 days of infection, and in 82.7% (42) of this group, the cause was attributed to SARS-CoV-2 infection demonstrating the devastating effects of COVID-19 on patients with hepatocarcinoma [91].

Patients with liver cirrhosis are at a higher risk of COVID-19-induced liver injury due to the upregulation of ACE2 expression in hepatocytes, thus enhancing liver dysfunction and failure [92–94]. Complications of COVID-19 such as acute respiratory distress syndrome can lead to hypoxemia, ischemia, and shock [95, 96]. Hypoxia can lead to cell necrosis and persistent reactive oxygen species generation promoting the release of pro-inflammatory factors, and thus further liver injury [97–99]. Radzina et al. [100], using multiparametric ultrasound (mpUS) to evaluate liver parenchyma in COVID-19 patients, found increased liver stiffness suggestive of liver injury. This increase was demonstrated by higher shear wave (SWE) values. This finding was also associated with an increase in other multiparametric ultrasound (US) indicators of hepatic injury, such as viscosity (inflammation) and steatosis [100]. Moreover, another study on COVID-19 patients revealed that homogeneous or heterogeneous hepatic hypodensity as the most common upper abdominal computed tomography (CT) finding, in addition to the presence of pericholecystic fat stranding [101]. In some severe cases, evidence of patients with acute liver infarction on CT was also reported [102].

Cytokine storm in COVID-19

A cytokine storm is an aggressive systemic hyperinflammatory reaction characterized by massive and augmented output of many pro-inflammatory cytokines, leading to critical illness and high mortality rate [103, 104]. It was observed in various viral infections, including influenza H5N1, H1N1 viruses, and two SARS-CoV and MERS-CoV coronaviruses [105–108]. Pertinently, the cytokine storm is closely implicated in the rising number of death among COVID-19 patients [109]. Following the infection by SARS-CoV-2, endocytosis of ACE2 occurs together with the virus in target cells, including epithelial and endothelial cells. This leads to an increase of serum angiotensin II (Ang II), which functions not only as a vasoconstrictor but also as a pro-inflammatory cytokine via activating the Ang II type 1 receptor (AT1R) [94, 110, 111]. As such, it was hypothesized that the renin–angiotensin system (RAAS) may be implicated in the development of acute respiratory distress syndrome (ARDS) observed in COVID-19 [33]. Both IL-6 and IL-10 are particularly elevated in COVID-19. IL-6 plays a pertinent role in the pathology of the disease through the chemotaxis of neutrophils and lymphocyte necrosis, thus leading to cytotoxic lymphocytes exhaustion [103]. Moreover, Ang II-AT1R signaling pathway generate an IL-6-mediated induction of a positive feedback loop involving NF-κB signaling, a mechanism known as the IL-6 amplifier, during lung inflammation followed by ARDS with multi-organ failure and coagulation [33, 110, 112].

Cytokine storm effects on hepatic stellate cells (HSCs)

The systemic spread of inflammation secondary the cytokine storm significantly affects the liver in COVID-19 patients. Various molecules are involved in the inflammatory cascade, which afflicts hepatic function. Accordingly, viral infection stimulates the complement cascade initiating the inflammatory response [113]. The complement cascade includes the well-known complement factor 5a (C5a) that it is the most potent inflammatory peptide in the complement cascade which increases the production of pro-inflammatory cytokines IL-6, IL-1, and TNF-α from macrophages under the effect of TLR-2, TLR-4, and TLR-9 [114, 115]. Also, the

terminal complement variable C5b-9 stimulates the release of IL-6 from vascular smooth muscle cells by stimulating the redox-sensitive transcription factor NF-κB, activator protein 1 (AP-1), and MCP-1 [116]. The overexpression of C3a also results in increased production of IL-1, IL-6, and TNF-α [117]. The complement cascade plays a pivotal role in the pathogenesis of SARS-CoV-2 infection. It promotes viral nucleocapsid protein-mediated auto-activation of mannan-binding lectin serine peptidase-2 (MASP-2) [118]. MASP-2 is considered the main serine–protease in the lectin pathway. It binds to the mannose-binding lectin pathway to induce the downstream complement cascade, which in turn accelerates inflammatory responses. In two patients with COVID-19 who received an anti-C5a antibody, a positive clinical response was documented as evidenced by enhanced lung oxygenation and alleviated systemic inflammation [119].

In severe cases of COVID-19, liver dysfunction was associated with extensive activation of coagulative and fibrinolytic pathways as well as alteration of platelets, neutrophils, and lymphocytes profiles. In parallel, patients with chronic liver disease (CLD) due to hepatotropic viruses, NAFLD, or non-alcoholic steatohepatitis (NASH) were more susceptible to COVID-19, and may present worse outcomes from acute respiratory distress syndrome (ARDS) compared with the other critically ill patients [120]. These patients are at greater risk of loss of hepatic regeneration, exacerbation of their liver disorders, and decompensation of CLD [121]. Other sources indicated a minor role for CLD in the disease progression, severity, and mortality [122, 123].

The hepatic injury in COVID-19 patients could result from a cytokine storm rather from direct cytopathic effects that induces stress on endoplasmic reticulum and mitochondrial dysfunction [124]. Hypoxia is also a common characteristic of extreme COVID-19 illness that promotes ROS production and the release of multiple pro-inflammatory factors that enhance liver damage [125].

HSCs play a fibrogenic role in response to inflammation. Fibrogenic signaling, chemokines pathway, adipokine pathways, neuroendocrine pathways, immune interactions, angiogenesis, and NADPH oxidase/oxidant stress have all been shown to induce hepatic fibrogenesis [126]. Chemokines are well known to be involved in the inflammatory responses within different organs [127]. HSCs express several chemokine receptors including CXCR3, CCR5, and CCR7, as well as secrete numerous chemokines, including CCL2, CCL3, CCL5, CXCL1, CXCL8, CXCL9, and CXCL10 [128]. These chemokines are known to promote fibrogenic cell migration to sites of injury, further increasing cell numbers and amplifying inflammation specifically through the CCR5 that binds the RANTES receptor, which stimulates the migration and proliferation of HSC [129].

Treatment of COVID-19-induced liver injury

Most COVID-19-related liver injuries are transient and reversible and do not require any special treatment [130]. Nonetheless, retrospective analysis by Hu et al. [38] highlighted the importance of suppressing inflammation, treating hypoxemia, and providing symptomatic support for patients with COVID-19-induced liver injury. Accordingly, the Chinese pharmaceutical association formulated the "Four-Anti and Two-Balance" plan which consisted of antiviral, anti-shock, anti-hypoxemia, and anti-secondary infection therapies on one arm, and homeostatic maintenance of fluid, electrolytes, acid–base, and microecological balance on the other [131]. In patients with acute liver injury, there is a need for the assessment of the etiology and the extent of liver damage. Initial evaluation requires baseline identification of liver function (i.e., preexisting liver damage, hepatotoxin exposure), respiratory, and circulatory statuses. Consequently, patients with hypoxic hepatitis should have amplified respiratory and circulatory support [130]. Treatment choice should be based on the cause of functional liver injury and requires the use of only 1–2 drug types to limit possible drug–drug interactions or any liver burden [132, 133]. In COVID-19 patients with severe liver problems, the cytokine storm and circulatory damage at the base of liver injury necessitate strengthening of respiratory and circulatory support, including the introduction of extracorporeal membrane oxygenation when oxygen saturation is low [132]. Hepatoprotective or anti-inflammatory drugs as well as drugs to decrease jaundice should also be considered in cases with severe liver injuries [131]. On the other hand, patients with potential acute liver injury should be closely monitored for early signs of acute liver failure. Supportive and symptomatic treatment should also be offered (e.g., correct hypoproteinemia, administer hepatoprotective and enzyme-lowering drugs such as Ursodeoxycholic acid, Stronger Neo-Minophagen C, and glycyrrhizin) [132, 134]. For instance, according to Carothers et al. [135], acetylcysteine may be useful in the treatment of acute liver failure (ALF) caused by Remdesivir [135]. The major cause of ALF, acetaminophen, has an antidote in the form of acetylcysteine, which may also be helpful for ALF brought on by medicines other than acetaminophen [136].

In conclusion, liver inflammation plays a cardinal role in the etiology of SARS-CoV-2-induced liver injury and requires close attention to prevent irreversible liver damage (Fig. 1). Anti-inflammatory and supportive therapy can play key roles in the recovery process but it has to be individualized. While the best anti-inflammatory approaches to treat/

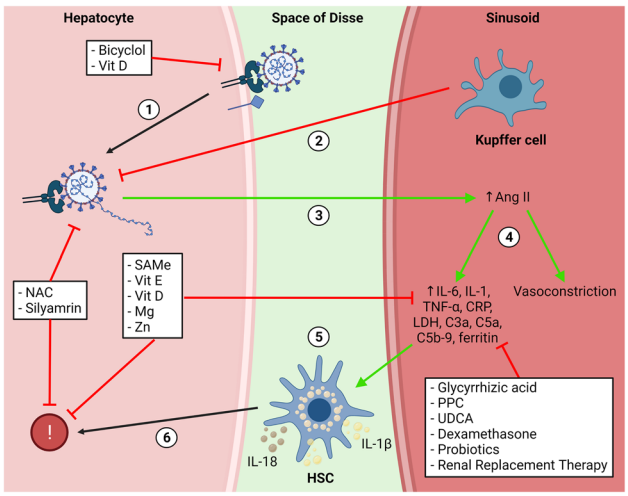

Fig. 1 Mechanism of COVID-19-induced liver injury. (1) SARS-CoV-2 virus enters the host cell through binding to angiotensin converting enzyme 2 (ACE2) and TMPRSS receptors that are abundant in the liver. Once in the cytoplasm, SARS-CoV-2 releases its genomic RNA and starts replicating inside the host cell. (2) Upon viral entry, Kupffer cells serve as the first gate against inflammatory stimuli in the portal circulation and produce inflammatory cytokines in the sinusoidal lumen. (3) The endocytosis of SARS-CoV-2 and ACE2 triggers an increase of serum angiotensin II, which acts as a vasoconstrictor and pro-inflammatory cytokine. (4) Increased inflammatory markers include increased levels of ACE2 which is characterized by high C-reactive protein, lactate dehydrogenase, IL-6, and ferritin levels, C5a and C3a which increase production of interleukin-6 (IL-6), IL-1, and tumor necrosis factor-α (TNF- α), and C5b-9 which stimulates release of IL-6. (5) Hepatic stellate cells in the Space of Disse respond to this inflammatory stimulus originating in the sinusoids and lose their lipid-rich granules. Furthermore, they secrete pro-inflammatory cytokines such as IL-1β and IL-18, which further contribute to the cytokine storm. (6) The cytokine storm induces liver damage and injury including portal fibrosis, ballooned cells, acidophilic bodies, microvascular steatosis, lobular inflammation, vascular derangement, etc. (Created with BioRender.com) expression (3) as well as induction of a set of pro-inflammatory factors (4). Mechanisms involved in reducing the inflammatory processes are shown in red arrows

reverse the course of liver are still debatable, fortunately many patients showed spontaneous recovery highlighting the enormous ability of self-recovery/healing process of the liver.

Methods

Data search was performed on the databases, PUBMED and BioRxvi, using the keyword: SARS-Cov-2, COVID-19, liver, hepatic, hepatic stellate cells. Papers selection was based on novelty, year of publication as well as content. Most paper covering COVID-19 were used as it is started to appear in 2019 till 2022 unless historical description of the virus family is needed and requires the documentation of manuscript publication at earlier years.

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Declarations

Conflict of interest The authors declare that they have no competing interest.

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