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COVID-19 and liver injury: An ongoing challenge

Papagiouvanni I *et al*. COVID-19 and liver injury

Ioanna Papagiouvanni, Serafeim-Chrysovalantis Kotoulas, Athanasia Pataka, Dionisios G Spyratos, Konstantinos Porpodis, Afroditi K Boutou, Georgios Papagiouvannis, Ioanna Grigoriou, Christos Vettas, Ioannis Goulis

Abstract

The new coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in December 2019, in Wuhan, China. The virus was rapidly spread worldwide, causing coronavirus disease 2019 (COVID-19) pandemic. Although COVID-19 is presented, usually, with typical respiratory symptoms (*i.e.*, dyspnea, cough) and fever, extrapulmonary manifestations are also encountered. Liver injury is a common feature in patients with COVID-19 and ranges from mild and temporary elevation of liver enzymes to severe liver injury and, even, acute liver failure. The pathogenesis of liver damage is not clearly defined; multiple mechanisms contribute to liver disorder, including direct cytopathic viral effect, cytokine storm and immune-mediated hepatitis, hypoxic injury, and drug-induced liver toxicity. Patients with underlying chronic liver disease (*i.e.*, cirrhosis, non-alcoholic fatty liver disease, alcohol-related liver disease, hepatocellular carcinoma, *etc*.) may have greater risk to develop both severe COVID-19 and further liver deterioration, and, as a consequence, certain issues should be considered during disease management. The aim of this review is to present the prevalence, clinical manifestation and pathophysiological mechanisms of liver injury in patients with SARS-CoV-2 infection. Moreover, we overview the association between chronic liver disease and SARS-CoV-2 infection and we briefly discuss the management of liver injury during COVID-19.

Key Words: COVID-19; Liver injury; Cytokine storm; Hypoxic hepatitis; Drug-induced liver injury; Chronic liver disease

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Core Tip: Liver injury is a common feature in coronavirus disease 2019 (COVID-19) patients and was associated with disease severity and prognosis. Multiple pathophysiological mechanisms are responsible for liver injury, including direct viral effect, cytokine storm, hypoxia and drug hepatotoxicity, however, further research is needed, in order, for them, to be clearly defined. Patients with underlying chronic liver disease may be more susceptible to severe acute respiratory syndrome coronavirus 2 infection; nevertheless, evidence is still limited. It is necessary to know the mechanisms of liver injury, the clinical manifestations and the effect of COVID-19 in underlying liver disease, in order to design appropriate management programs.

INTRODUCTION

In December 2019, severe acute respiratory syndrome coronavirus 2, (SARS-CoV-2), causing respiratory infection in humans, was detected in Wuhan, China[1]. The new coronavirus was spread worldwide, resulting in coronavirus disease 2019 (COVID-19) outbreak. On March 11th 2020, the World Health Organization declared COVID-19 as a global pandemic[2]. As of September 2022, over 603 million confirmed cases and over 6.4 million deaths have been reported worldwide[3].

Most COVID-19 patients present with typical respiratory symptoms (*i.e.*, cough, dyspnea) and fever. However, abnormal liver function is often developed in patients with COVID-19, and liver injury has been related with severe disease[4,5]. Liver damage ranges from mild asymptomatic elevation of liver enzymes to severe liver injury, while a few cases of acute liver failure have also been reported[6,7].

The aim of this review is to present the prevalence and clinical manifestations of liver injury in COVID-19, to overview the potential pathophysiological mechanisms leading to liver damage and to summarize the existing literature for patients with COVID-19 and underlying chronic liver disease. Furthermore, the management of liver complications during SARS-CoV-2 infection is also briefly discussed.

PREVALENCE AND RISK FACTORS

Numerous studies have focused on liver injury induced by COVID-19 infection. However, the definition of liver injury in COVID-19 patients has not been clearly established yet. Some researchers defined it, as any increase of liver enzymes above the upper limit of normal (ULN), while others, as an increase, at least 2 or 3 times above the ULN[8-12]. Moreover, the different statistical time points across the studies, could also affect the incidence of liver injury[8]. As a consequence, the prevalence of liver damage varies across studies. Wang *et al*[13] conducted a retrospective study and found that the 41% of 156 COVID-19 patients had abnormal liver function, while, Fan *et al*[10] demonstrated that 55 out of 148 patients (37.2%) had elevated liver enzymes on admission. In a recent retrospective study of 228 patients, without chronic liver disease, 29.4% had abnormal liver function on admission; the rate increased to 56.3% during hospitalization[14]. Cai *et al*[15] defining liver injury as alanine transaminase (ALT) or aspartate aminotransferase (AST) 3 times higher than ULN or alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin (TBIL) 2 times higher than ULN, observed that 41% of patients had abnormal liver tests and 5% had liver injury on admission. During hospitalization, patients with abnormal liver tests and patients with liver injury increased to 76.3% and 21.5%, respectively. Ding *et al*[16], also, demonstrated the same trend of liver function in a large retrospective cohort study of 2073 patients. On admission, 46.2% and 5.1% had abnormal liver tests and liver injury, respectively. Yet, during hospitalization, the incidence increased to 61.8% and 14.3%, respectively. Across several meta-analyses, the pooled prevalence of liver injury ranged between 19% and 27.4%[4,5,17]. Kulkarni *et al*[18], in their meta-analysis, found that the pooled incidence

of abnormal liver enzymes at initial presentation, only slightly increased during the course of disease (from 23.1% to 24.4%). Wu *et al*[19] observed a similar trend; the pooled incidence of elevated liver tests on admission and during hospitalization was 27.2% and 36%, respectively.

Liver injury has been associated with severe COVID-19 disease[4,5,19-21]. Chen *et al*[22] demonstrated that patients with deranged liver function had higher risk of systemic inflammatory response syndrome (53.5% *vs* 41.3%, $P = 0.007$) and higher mortality rate (28.9% *vs* 9.0%, $P < 0.001$). In another retrospective study, elevated AST (> 3-fold ULN) was associated with higher risk of mechanical ventilation and death[23]. Moreover, Wang *et al*[24] found that the levels of aminotransferases were significantly higher in ICU patients compared to non-ICU patients (ALT: 35 *vs* 23, normal range 9-50 U/L, $P = 0.007$ and AST: 52 *vs* 29, normal range 5-21 U/L, $P < 0.001$). Kumar *et al*[4], in their meta-analysis, confirmed that liver injury was higher in patients with severe COVID-19 disease, compared to non-severe COVID-19 disease (44.63% *vs* 20.02% respectively). Furthermore, Mao *et al*[5] conducted another meta-analysis and found that patients with severe COVID-19 infection exhibited a higher risk for abnormal liver function, including increased AST and ALT. Finally, in a recent meta-analysis of 15 studies, patients with deranged liver function and/or histopathological findings of liver disease, presented a significantly higher risk of poor COVID-19 outcomes[21]. Across several studies, other risk factors for liver injury were found to be male gender, higher BMI, older age, severe lung disease and underlying chronic liver disease[11,15,25].

CLINICAL MANIFESTATIONS

In most cases, liver injury is presented as elevated liver enzymes without specific symptoms and signs. The elevation of AST, ALT and/or TBIL is a very common manifestation in COVID-19 patients, while increased GGT and/or ALP is a less usual feature, observed in later stages of the disease[6,7]. The elevation of the aminotransferases is usually mild; their level is mostly < 5 times ULN[26]. Furthermore, liver injury in COVID-19 has been noted to be transient, while hepatic biochemical tests

return to normal within 2-3 wk[6]. Severe liver injury, with aminotransferases > 20 times ULN, has been observed in 0.1% of COVID-19 patients on admission and in 2% during hospitalization, while acute liver failure, induced by COVID-19, has been reported in extremely rare cases[27,28]. Febrile hepatitis, acute cholecystitis and hepatic artery thrombosis are, also, rare clinical presentations of COVID-19[29-31]. Moreover, in some cases reports, it is suggested that SARS-CoV-2 triggered a *de novo* development of immune-mediated liver disease, such as autoimmune hepatitis and primary bile cholangitis[32-35]. Interestingly, cholangiopathy, characterized by cholestasis and structural abnormalities of bile duct, has been reported in post-COVID-19 patients, who recovered from severe and critical disease[36,37].

MECHANISMS OF LIVER INJURY

The pathogenesis of live injury in COVID-19 disease is still unclear. According to the available literature, the underlying mechanisms of liver injury are multifactorial and mainly, include direct viral cytopathic damage, immune-mediated hepatitis, caused by cytokine storm, hypoxia and ischemic injury and drug-induced liver toxicity. The possible pathophysiologic mechanisms of liver injury are presented in Figure 1.

Direct cytopathic effect of SARS-CoV-2

Liver is a potential target of direct SARS-CoV-2 infection. Existing literature suggests that the new coronavirus could be detected in the liver and indicates typical histological lesions related to viral infection[38]. Indeed, a series of small sample size studies demonstrated that SARS-CoV-2 RNA and viral particles are detectable in the liver of patients with COVID-19[13,39-43]. Furthermore, in a recent cohort study of 45 autopsy cases, virus RNA was detected in 69% of cases[44].

SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) to invade into host cells, while cell entry is facilitated by transmembrane serine protease 2 (TMPRSS2) and paired basic amino acid cleaving enzyme (FURIN)[45,46]. Single-cell RNA sequencing analysis revealed that ACE2 is expressed among different cell types in liver; in parallel,

TMPRSS2 and FURIN are, also, expressed in liver cells[47-49]. The above evidence indicates that liver tissue could be susceptible to COVID-19 infection. Yet, the expression of ACE2 in bile duct cells is 20-fold higher than the expression level in hepatocytes[50]. Despite the high expression of ACE2 in cholangiocytes, which would be associated with cholestatic injury (*i.e.*, elevated levels of GGT and ALP), most studies found that hepatocellular damage is the most common pattern in COVID-19 patients (*i.e.*, elevated levels of ALT and AST)[17,51,52]. Therefore, alternative molecular pathways for liver infection cannot be excluded. The liver/Lymph node-specific intercellular adhesion molecule-3-grabbing integrin, a liver-specific capture receptor, and CD147, a receptor highly expressed in inflamed and/or pathogen-infected tissues, have been proposed as alternative receptors or enhancer factors, mediating in the SARS-CoV-2 cellular entry in the liver. Moreover, antibody-dependent enhancement may be responsible for liver infection[53]. Instead of neutralizing the virus completely, suboptimal non-neutralizing antibodies, attached to Fc receptor, promote viral entry into the liver cells[53]. In addition, existing evidence suggests that inflammatory signals [*i.e.*, interleukin-6 (IL-6), type 1 interferon] and hypoxia, related to SARS-CoV-2 infection, could result to hepatocyte regeneration, compensatory hyperplasia and upregulated expression of ACE2, leading to potentially increased hepatic susceptibility to SARS-Cov-2[45,53].

Despite that virus particles have been observed in hepatocytes and molecular pathways of virus invasion have been suggested, further evidence is needed to clearly establish the role of direct viral infection in liver injury.

Immune-mediated liver injury

COVID-19 infection can trigger uncontrolled immune response, called cytokine storm, which is characterized by exaggerated activation of immune cells and massive production of inflammatory mediators[54,55]. Indeed, pro-inflammatory cytokines [*i.e.*, IL-1β, IL-2, IL-6, IL-8, tumor necrosis factor-α, interferon-α (IFN-α), IFN-γ, granulocyte-macrophage colony-stimulating factor] were increased in severe COVID-19 disease[56].

Cytokine storm generates a process leading to tissue damage and even multiorgan failure[57]. Due to its anatomical location, liver is highly exposed to circulating cytokines, and thus, prone to inflammatory-mediated injury[58]. Furthermore, viral-induced $CD8^+$ T cells provoke the activation of Kupfer cells, resulting to T cell-mediated hepatitis[58].

Several studies have demonstrated a correlation between liver injury and increased levels of inflammatory mediators in COVID-19 patients. In a recent cohort study of 192 patients, increased IL-6 and IL-10 Levels and decreased number of $CD4^+$ T cells were identified as independent risk factors for severe liver injury[59]. Likewise, in another retrospective cohort study, inflammatory markers, such as IL-6, CRP and ferritin, were significantly higher in patients with liver injury[60]. Huang *et al*[61], conducting a retrospective study of 2623 patients, found a positive correlation between IL-6 and liver enzymes (*i.e.*, AST, ALT and GGT), indicating that COVID-19-induced cytokine storm leads to hepatotoxicity. In addition to that, Liao *et al*, suggested that, apart from IL-6, IL-2 and IL17A were also key inflammatory factors triggering liver damage.

Hypoxia-reperfusion injury

The liver is a highly aerobic organ, and, thus, it is remarkably susceptible to hypoxia[38]. Patients with COVID-19 can be complicated with respiratory failure, acute heart failure and systemic stress, causing low oxygen saturation level and/or decreased systemic arterial pressure. As a consequence, arterial perfusion and oxygenation of the liver can be reduced, leading to hepatic ischemia and hypoxia-reperfusion injury[38,62]. Furthermore, systemic inflammatory response, through microvascular dysfunction and microthrombosis, could worsen liver hypoxia[38]. Hepatic venous congestion, caused by heart failure, or high positive end-respiratory pressure, used in patients with respiratory failure, can, also, lead to hypoxic damage in the liver cells[58].

Hypoxic injury involves a biphasic process; ischemic cell damage and reperfusion-associated inflammatory response. Lipid accumulation, glycogen consumption, mitochondrial damage and increased reactive oxygen species and their peroxidation products lead to cell death, during ischemia[53]. Following ischemic injury, reperfusion

induces activation of immune response and release of pro-inflammatory cytokines, resulting in further cell damage[53].

In a retrospective cohort study, hepatocellular injury pattern in COVID-19 patients was associated with hypoxia[63]. Likewise, Fu *et al*[64], in a more recent multicenter retrospective study, confirmed that patients with hypoxia were more likely to have abnormal liver function.

Drug-induced liver injury

The liver plays a crucial role in drug metabolism. Several drug metabolites induce liver cell apoptosis/necrosis and can lead to liver damage. Drug-induced liver injury (DILI) is often detected by liver enzymes tests, using the following thresholds: (1) ALT > 5 times ULN; (2) ALP > 2 times ULN; and (3) ALT > 3 times ULN and TBL > 2 times ULN[65]. Based on ALT/ALP ratio, DILI pattern can be defined as hepatocellular, cholestatic or mixed. DILI can also be intrinsic, which is dose-dependent and predictable, or idiosyncratic, which is unpredictable, with variable latency period[65]. Concerning prognosis, DILI ranges from mild to severe or even fatal, with approximately 10% of patients requiring liver transplantation[65].

At present, many drugs have been used to treat COVID-19 patients, such as corticosteroids, antiviral agents, immunoregulatory factors and antibiotics, leading to potential hepatotoxicity. Systemic corticosteroids, especially dexamethasone, were widely prescribed to both outpatients and hospitalized patients with COVID-19. Despite that, the prolonged use of corticosteroids is related to side effects (*i.e.*, infections, hyperglycemia), DILI is uncommon[66]. Corticosteroids have been associated with liver steatosis, hepatomegaly, worsening non-alcoholic fatty liver disease (NAFLD) and exacerbating HBV re-activation, however, existing literature is limited[66,67]. With regards to COVID-19, Yip *et al*[68] found that the use of corticosteroids was an independent factor of liver injury. However, this association could be explained by the fact that patients with more severe disease received corticosteroids.

Remdesivir is an inhibitor of viral RNA-dependent RNA polymerases, used in COVID-19 disease. Among its side effects, remdesivir can cause hepatotoxicity, manifested as elevated AST and ALT[66]. In most studies, 10%-50% of patients developed mild-to-moderate increase of aminotransferases, while levels > 5 times ULN were reported in 9% of patients in clinical trials[69]. Subsequently, remdesivir is contraindicated in patients with ALT > 5 times ULN or severe liver dysfunction[70]. The elevation of aminotransferases is generally reversible without clinically apparent hepatic dysfunction[66].

Tocilizumab, a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody, is indicated in hospitalized COVID-19 patients with rapid respiratory deterioration[66]. Elevation of aminotransferases has been reported, but it is generally transient, dose-dependent, without significant liver complications[66,71]. Anakinra, an IL-1 inhibitor, has, also, been used in severe COVID-19, but hepatotoxicity is an extremely uncommon side effect. In addition to that, liver enzymes levels did not significantly differ between anakinra and placebo in clinical trials[66,72].

More recently, nirmatrelvir/ritonavir has been prescribed in COVID-19 patients, early in the course of infection, as a post-exposure protection. In clinical trials, elevation of aminotransferases was uncommon or mild in nirmatrelvir/ritonavir group and did not differ from placebo group. However, clinical data are still limited and further evidence is needed[73].

Table 1 presents the most studied drugs for COVID-19 and the existing evidence concerning their hepatotoxicity.

CHRONIC LIVER DISEASE AND COVID-19

Most studies have not provided sufficient data about the prevalence of underlying chronic liver disease (CLD) in COVID-19 patients. However, in a meta-analysis of 73 studies including 24299 COVID-19 patients, the pooled prevalence of CLD was estimated to be at 3%[74]. Patients with CLD may, already, have liver damage and SARS-Cov-2 infection is an additional "hit" to the liver, leading to further liver functional

impairment[75]. Although patients with stable CLD, without cirrhosis, are not more susceptible to severe COVID-19, those with cirrhosis, alcoholic liver disease (ALD), hepatocellular carcinoma (HCC) and NAFLD may be in a greater risk for severe disease with liver injury and poor outcome[6,75-77].

Cirrhosis

Patients with cirrhosis may be more susceptible to SARS-CoV-2 infection, due to their immunodeficient status, referred as cirrhosis-associated immune dysfunction[78]. In several studies, COVID-19 patients with cirrhosis presented worse prognosis, compared to patients without cirrhosis[79-84]. In a large multicenter study, including 745 COVID-19 patients with CLD (386 with and 359 without cirrhosis), cirrhotic patients exhibited higher mortality rate, compared to those without cirrhosis (32% *vs* 8%, $P < 0.001$) [81]. Mortality was correlated with the stage of liver cirrhosis; 19% in Child- Pugh class A, 35% in class B, and 51% in class C. A similar trend was also observed in the rates of ICU admission, mechanical ventilation and renal replacement therapy. In the same study, it was noted, that the main cause of death was respiratory failure (71%) followed by liver complications[81].

Moreover, COVID-19 patients with cirrhosis are in increased risk for acute decompensation and acute-on-chronic liver failure (ACLF)[77]. Sarin *et al*[85], conducting a multicenter cohort study, found that 20% of patients with compensated cirrhosis developed acute decompensation or ACLF during COVID-19 disease, while 57% of patients with decompensated cirrhosis had further liver complications. Acute decompensation is a common clinical feature in cirrhotic patients during SARS-CoV-2 infection, usually presented as new or worsening ascites or hepatic encephalopathy[81]. Interestingly, liver complications can also be developed and in the absence of typical symptoms of respiratory system[81,84].

Non-alcoholic fatty liver disease

Patients with NAFLD usually have other comorbidities, such as diabetes mellitus, obesity, hypertension and chronic cardiac disease, which are common risk factors for severe COVID-19[76]. Consequently, it is challenging to define an independent effect of NAFLD on COVID-19 and evidence from concomitant studies is controversial. More particularly, some studies did not prove an association between NAFLD and worse COVID-19 outcomes[86-88]. On the other hand, numerous observational studies demonstrated that NAFLD is related to more severe SARS-CoV-2 infection, while three meta-analyses confirmed this association[89-98]. Despite multiple confounding factors, NAFLD was considered as an independent risk factor for severe COVID-19. Hashemi *et al*[90] found that NAFLD was an independent risk factor for ICU admission and mechanical ventilation in COVID-19 patients. In a retrospective case-control study, NAFLD was associated with COVID-19 severity, irrespective of metabolic syndrome[89]. Furthermore, Sachdeva *et al*[96], in their pooled analysis, reported that NAFLD was a predictor of COVID-19 severity, even after adjusting for obesity.

Alcoholic liver disease

Although the existing evidence is limited, few studies demonstrated that ALD is related to increased COVID-19 mortality. In a multicenter cohort study of 867 COVID-19 patients, reported that ALD is an independent risk factor of higher mortality[99]. Likewise, Marjot *et al*[81] identified independent association between ALD and COVID-19 mortality. Mallet *et al*[100], also, found that ALD is a risk factor of day-30 mortality after COVID-19. The exact mechanism leading to the aforementioned correlation is not clear. However, ALD-related immune dysregulation and low nutritional status may have a negative impact on the course of SARS-CoV-2 infection[7,78].

Viral hepatitis

The influence of viral hepatitis on COVID-19 severity and COVID-19-related liver injury has not been clearly established. COVID-19 patients with chronic hepatitis B (CHB) may have prolonged virus shedding and infection[48]. Furthermore, during

SARS-CoV infection, replication of hepatitis B virus (HBV) was found to be enhanced, inducing more severe liver injury; similar enhancement could be noted during SARS-CoV-2 infection[101]. Wang *et al*[102], in a retrospective cohort study of 437 patients, found that those with co-infection SARS-CoV-2/HBV had higher risk of severe disease and mortality. Likewise, Zou *et al*[103] reported that COVID-19 patients with CHB and liver injury were more prone to poor outcomes. Nevertheless, other studies did not demonstrate the above associations. Chen *et al*[104] found no difference in terms of liver function and disease severity between COVID-19 patients with HBV and those without co-infection. Guan *et al*[105] also suggested that CHB does not affect COVID-19 outcome, as only one of 23 patients with CHB developed severe disease. In addition, Yip *et al*[106] demonstrated that current and past HBV infection were not related to higher risk of liver injury or mortality.

Due to extended use of immunosuppressive drugs for COVID-19 treatment (*i.e.*, tocilizumab), potential re-activation of HBV should be taken into consideration. Although the immunosuppressive therapies are short-term and results of clinical trials are contradictory, there are some clinical case reports of HBV re-activation in COVID-19 patients after administration of these immunosuppressive agents[107].

Of note, COVID-19 pandemic has disrupted the progress in the global hepatitis C virus (HCV) elimination program, resulting in delays in diagnosis and HCV therapy, which could extend the direct COVID-19-related morbidity and mortality in these patients[108].

Autoimmune liver disease

Although immunosuppressive therapy, used in patients with autoimmune liver diseases, could be associated with higher risk of severe disease, there is no evidence that patients with autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) are more prone to SARS-CoV-2 infection[6,76]. In a phone-based survey, there was no difference in percentage of COVID-19 diagnosis in patients with autoimmune liver diseases and the general population. Most of patients reported a

favorable disease outcome in the same survey[109]. Data derived from three multinational registries (SECURE-Cirrhosis, COVID-Hep and ERN RARE-LIVER) revealed that patients with AIH had increased risk of hospitalization compared to patients with other CLD, but there was no difference in adverse outcome, including ICU admission and death, despite the immunosuppressive treatment[110]. However, a recent retrospective study of 254 patients with COVID-19 and AIH demonstrated that baseline treatment with corticosteroids or azathioprine was associated with COVID-19 severity[111]. Evidence for patients with PBC and PSC is limited and no defined association with COVID-19 severity has been established yet[7].

Hepatocellular carcinoma

COVID-19 patients with may have a high risk for poor outcomes. Due to chemotherapy/immunotherapy, HCC patients are immunosuppressed, and, subsequently, vulnerable to severe SARS-CoV-2 infection[101]. Furthermore, most HCC patients have an underlying CLD (*i.e.*, cirrhosis, ALD *etc.*), and as a result, they are already identified as a high-risk group[101]. However, the corresponding literature is limited. A small retrospective study of 28 cancer patients with COVID-19, including 2 HCC patients) found that these patients had worse prognosis compared to general population[112].

VACCINATION AGAINST SARS-COV-2 IN CHRONIC LIVER DISEASE

Different types of SARS-CoV-2 vaccines have been developed, such as mRNA vaccines, adenoviral-vectored vaccines and inactivated vaccines. In general, patients with CLD may exhibit lower immune response to vaccination; according to previous studies, rate of seroconversion after HBV vaccine and cell-mediated immunity were reduced in cirrhotic patients[113,114]. Regarding efficacy, although trials of both mRNA vaccines included few patients with underlying CLD, they reported significant efficacy in the subgroup with coexisting comorbidities[115,116]. Of note, in a large retrospective cohort study of cirrhotic patients, a single mRNA vaccine dose appeared to reduce not only

rates of SARS-CoV-2 infection, but also, rates of hospitalization and mortality[117]. With regard to safety, none of vaccine contain living virus, and subsequently, they can be used even in immunosuppressed patients[118]. Moreover, no significant liver-associated side effects have been reported in the vaccinated population[119]. Given that benefits outweigh the potential risks, European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) recommend that patients with CLD should be vaccinated against SARS-CoV-2[120,121].

MANAGEMENT OF LIVER INJURY IN COVID-19

Liver injury in COVID-19 is usually mild and resolves spontaneously without any special treatment[76]. If present, hypoxia and circulatory failure should be regulated with standard symptomatic support (*i.e.*, oxygen therapy, intravenous fluids) in order to prevent further liver damage[45,122]. If liver injury persists, underlying chronic liver disease should be suspected[123]. With regard to DILI, there are no specific management guidelines. Discontinuation or dose's reduction of suspected medication is the most effective treatment in case of DILI, as the only available antidote is N-acetylcysteine for acetaminophen overdose[66]. In the case of severe COVID-19, benefits and risks have to be weighed in order to decide discontinuation of systematic treatment. This dilemma hardly arises for pharmaceutical agents which need short administration, such as remdesivir and tocilizumab[66]. Standard guidelines and supportive therapy should be followed for management of acute liver failure[66].

Regarding chronic liver diseases, comprehensive recommendations related to COVID-19 management have been published by EASL-ESCMID and AASLD[123,124]. Cirrhotic patients with acute decompensation or ACLF have to be tested for COVID-19, even without any other symptom[124]. Patients with HBV or HCV and SARS-CoV-2 coinfection should continue antiviral therapy, while in COVID-19 patients with chronic, occult or resolved HBV, who receive immunosuppressive agents (*i.e.*, tocilizumab, corticosteroids), clinicians have to consider and prevent potential HBV re-activation[123,124]. In COVID-19 patients with AIH, discontinuation or reduction of

immunosuppressive agents is not recommended. Reduction is considered in special cases, such as severe COVID-19 and bacterial/fungal co-infection, or severe lymphopenia[123,124].

CONCLUSION

Liver abnormalities are common in COVID-19 patients, especially in patients with severe and critical disease. The pathogenesis of liver injury may be multifactorial involving direct cytopathic viral effect, inflammatory storm, hypoxic/hypoperfusion injury and drug hepatotoxicity. Liver injury is usually mild and transient; however, some cases of severe liver injury and acute liver failure have been reported. Although, patients with stable chronic liver disease are not more vulnerable to SARS-CoV-2 infection, patients with cirrhosis, ALD, NAFLD and HCC have higher risk for severe COVID-19 and liver damage. Specific management issues should be taken into consideration during COVID-19 treatment in patients with underlying CLD. Further investigation is needed in order to clarify the association between SARS-CoV-2 and liver dysfunction, in terms of prognosis, pathophysiology and treatment.

Figure Legends

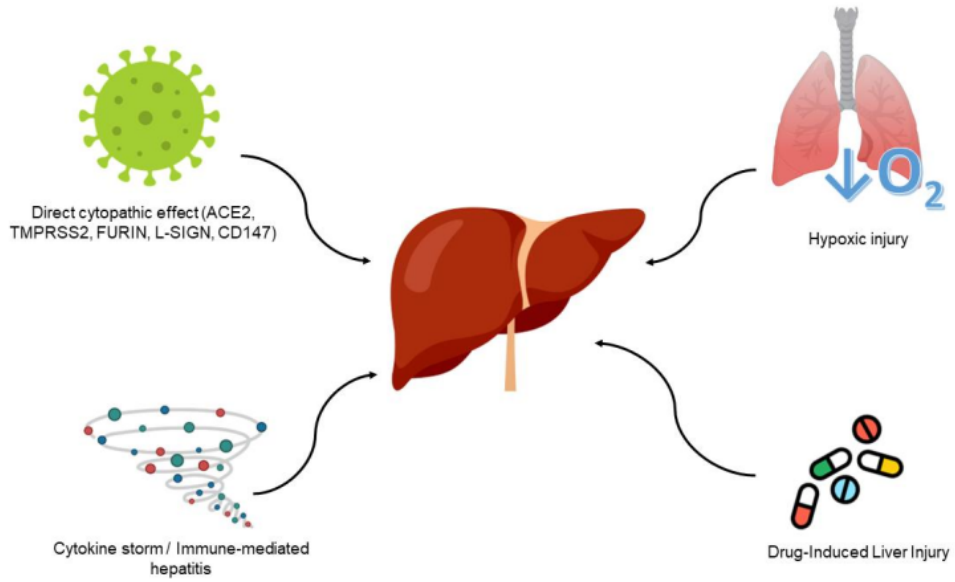

Figure 1 Mechanisms of liver injury in COVID-19. ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane serine protease 2; FURIN: Paired basic amino acid cleaving enzyme; SIGN: Specific intercellular adhesion molecule-3-grabbing non-integrin.

Table 1 Evidence of hepatotoxicity of most studied and used drugs in COVID-19

Drug	Mechanism of action	Characteristics of LI	Risk of DILI	DILI pattern
Corticosteroids[125]	Anti-inflammatory	Hepatomegaly, steatosis; triggering/worsening NAFLD; reactivation HBV (prolonged administration)	Low	Hepatocellular or mixed
Remdesivir[69]	Antiviral; active inhibitor of viral RNA-dependent RNA polymerases	Mild-to-moderate ALT and AST elevations; Elevation > 5 times ULN in 9% (resolved with discontinuation)	Moderate	Hepatocellular
Tocilizumab[71]	Anti-IL-6 receptor monoclonal antibody	Elevation of ALT and AST; no reports of severe LI or HBV reactivation (in COVID-19 trials)	Moderate	Hepatocellular
Anakinra[72]	IL-1 inhibitor	ALT elevation in < 1%; No association with HBV reactivation	Low	Hepatocellular
Nirmatrelvir/ ritonavir[73]	Antiviral; Inhibitor of the main protease of SARS-CoV-2/protease inhibitor and potent inhibitor of the enzyme	Mild ALT and AST elevation; no reports of clinical apparent LI; limited data	Low	Hepatocellular

	CYP 3A4			
Molnupiravir[126]	Antiviral; prodrug of the ribonucleoside analogue N-hydroxycytidine	Mild ALT and AST elevation; no reports of clinical apparent LI; limited data	Low	Hepatocellular
Low-molecular-weight heparins[127]	Anticoagulant	Mild ALT and AST elevation; LI with rapid onset and rapid recovery, without clinical symptoms	Low	Hepatocellular
NSAIDs[128]	Anti-inflammatory	Mild, transient and asymptomatic elevation of liver enzymes; more common in obese patients with comorbidities; reports of acute hepatitis (idiosyngratic, prolonged administration)	Moderate	Hepatocellular, cholestatic or mixed
Acetaminophen[129]	Analgesic and antipyretic	Dose-dependent; transient and asymptomatic elevation of ALT and AST; acute hepatitis and/or acute liver failure in overdose	High	Hepatocellular

DILI: Drug-induced liver injury; ALT: Alanine aminotransaminase; AST: Aspartate aminotransferase; HBV: Hepatitis B virus; IL-6: Interleukin-6; IL-1: Interleukin-1; LI: Liver injury; NAFLD: Non-alcoholic fatty liver disease; ULN: Upper limit of normal.

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