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Review article: COVID-19 and liver disease—what we know on 1st May 2020

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Summary

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen of coronavirus disease 2019 (COVID-19), became a global threat to human health. Liver impairment has been frequently reported as a common manifestation, although its clinical significance is still unclear, particularly in patients with underlying chronic liver disease (CLD).

Aims: To summarise the changes in liver function tests during SARS-CoV-2 infection and the impact of COVID-19 in patients with underlying CLD.

Methods: A literature review using online database PubMed was done using the search terms "SARS-CoV-2", "COVID-19", "liver", "cirrhosis" and "liver transplantation".

Results: COVID-19 is frequently associated with different degrees of abnormal liver function tests, most notably transaminases, which are usually transitory and of mild degree. Available evidence suggests that liver injury may result from direct pathogenic effect by the virus, systemic inflammation or toxicity from commonly used drugs in this subset of patients. SARS-CoV-2 infection in children is associated with minimal or no increase in liver enzymes, thus the presence of abnormal liver function tests should trigger evaluation for underlying liver diseases. Although it seems that patients with CLD are not at greater risk for acquiring the infection, those with cirrhosis, hepatocellular carcinoma, non-alcoholic fatty liver disease, autoimmune liver diseases or liver transplant may have a greater risk for severe COVID-19.

Conclusions: Abnormal liver function tests during the course of COVID-19 are common, though clinically significant liver injury is rare. Further research is needed focusing on the effect of existing liver-related comorbidities on treatment and outcome of COVID-19.

The Handling Editor for this article was Professor Grace Wong, and this uncommissioned review was accepted for publication after full peer-review.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the recently identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially reported in Wuhan, China, but that rapidly spread around the world and caused a serious threat to global public health.[1] Similar to SARS-CoV, SARS-CoV-2 mainly affects the respiratory system, with fever, cough and dyspnoea being the most frequently reported symptoms.[2] In severe cases, patients may develop pneumonia and associated complications, such as severe acute respiratory distress syndrome, septic shock and, eventually, death.[3] Liver impairment has also been reported as a common manifestation, although its clinical significance is still unclear. Moreover it is important to define if chronic liver disease (CLD) should be considered a risk factor for severe disease course. Thereby, we aimed to review the changes in liver function caused by SARS-CoV-2, in both adults and children, and the impact of COVID-19 in patients with CLD. In addition, we overview some of the therapies for COVID-19 under investigation and their risk of drug-induced hepatotoxicity.

2 | COVID-19 AND HEPATIC INJURY

Several studies have shown different degrees of elevated serum liver biochemistries in COVID-19 patients, mainly indicated by abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels accompanied by slightly elevated total bilirubin (TB) levels.[2,4-26] In fact, the incidence of elevated ALT and AST ranged from 2.5%-50.0% to 2.5%-61.1% respectively.[2,4-26] With regard to TB, studies have reported increased levels in 0%-35.3% of cases.[2,4-26] Relevant elevations of alkaline phosphatase (AKP) and gamma-glutamyl transferase (GGT) levels have not been reported in most studies (Table 1).[2,4-26] However, Ji et al examined 202 patients with confirmed COVID-19, 37.6% of which with non-alcoholic fatty liver disease (NAFLD), and showed that elevated GGT levels portend a more severe course of the disease.[26]

It remains unclear whether these laboratory test alterations are associated with a worse prognosis. In fact, the literature has shown different results. In a large cohort including 1099 patients from 552 hospitals, Guan and colleagues observed elevated levels of AST in 112 (18.2%) of patients with non-severe disease and 56 (39.4%) of patients with severe disease.[2] Moreover the proportion of abnormal ALT in severe cases (28.1%) was higher than in mild cases (19.8%). Similarly, Huang et al reported that the proportion of liver injury of intensive care unit (ICU) patients (61.5%) was higher than non-ICU patients (25.0%).[23]

Other studies, however, reported conflicting results. For example, Wu et al showed no significant differences in liver function tests when compared mild/moderate patients with severe patients.[8] Furthermore, Wang and colleagues analysed 339 elderly COVID-19 patients and reported that there were no evident differences in ALT levels between survival and death.[6] In addition, cases of severe acute liver injury have rarely been described.[27] Thereby, most recent studies argue that the COVID-19-related liver injuries are usually transitory and mild degree, with small clinical significance.[19] Hence, it is recommended close monitoring and no specific treatment is required.

It remains unclear whether liver injury is caused by the virus itself or reflects a severe inflammatory response with liver damage.[28] SARS-CoV-2 may directly infect liver cells as the receptor of the virus, angiotensin-converting enzyme 2 (ACE2), is expressed by liver and bile duct cells.[29] Data from two independent cohorts revealed ACE2 expression in 2.6% of hepatocytes and 59.7% of cholangiocytes, suggesting that SARS-CoV-2 might directly bind to ACE2-positive cholangiocytes to dysregulate liver function.[30] Moreover liver biopsies in patients with SARS-associated coronavirus infection showed a significant increase in mitotic cells and ballooned hepatocytes, suggesting that it may induce apoptosis of liver cells.[31] Additionally, although viral load was relatively low, virus was detected in liver tissue. Tan et al have also demonstrated that SARS-CoV-specific protein 7a induces apoptosis via a caspase-dependent pathway in cell lines of different organs, including the liver, further confirming the possibility that SARS-CoV directly affects liver tissue.[32] However, this hypothesis has been contested by some authors since the derangement of liver function is usually mild and there is no evidence that late-onset symptoms are associated with greater liver function damage.[33] Some systemic viral infections, such as Epstein-Barr virus, cytomegalovirus, herpes simplex virus, parvovirus and adenovirus, are associated with similar elevations of liver function biomarkers which reflect immune activation and inflammation caused by circulating cytokines.[34] Furthermore, few studies reported higher serum pro-inflammatory cytokines and chemokines levels in patients with abnormal liver function compared to those with normal liver function.[16,35] Hence, these data point to a relationship between liver damage and the inflammatory responses induced by SARS-CoV-2 infection. Lastly, some authors suggest that drug-induced liver injury is also a possible contributing factor to laboratory test abnormalities.[33,36] Liver injury may occur after the use of multiple drugs, such as antivirals, antibiotics, traditional Chinese medicine, antipyretics and analgesics.[7,10]

Although liver histology is poorly accessible in COVID-19, few studies have already reported pathological findings on autopsies performed on SARS-CoV-2 infected patients. Xu et al observed microvesicular steatosis and mild lobular and portal activity.[37] Zhang et al reported mild sinusoidal dilatation and minimal lymphocytic infiltration.[13] These changes are nonspecific and may be caused by either SARS-CoV-2 infection, hypoxemia or drug-induced liver injury. However, it is important to note that in none of these samples intranuclear or intracytoplasmic viral inclusions were identified.

3 | COVID-19 AND CLD

Patients with CLD, particularly those with autoimmune liver diseases or post-transplant patients under immunosuppressive therapy are at increased risk of infection because of their altered immune function.[38,39] Nevertheless, the interaction between underlying

CLD and COVID-19 has not been studied. Patients with cirrhosis are at increased risk of decompensation or development of acute-on-chronic liver failure when with bacterial, fungal or virus infection.[40] However, the incidence of complications in COVID-19 patients, including hepatic encephalopathy, upper gastrointestinal bleeding and liver failure has not been reported and needs to be assessed in large-cohort clinical studies. Given the paucity of data, contributing confirmed cases to the international registry (SECURE-Cirrhosis, https://covidcirrhosis.web.unc.edu) is encouraged. Finally, given the expression of the ACE2 receptor in cholangiocytes, SARS-CoV-2 infection could aggravate cholestasis in patients with primary biliary cholangitis or primary sclerosing cholangitis. Nevertheless, there are no data about exacerbations in these patients.[41]

Immunosuppressive drugs have impacts both innate and adaptive immune responses, thus increasing the risk for more severe or complicated infections caused by common viral agents (eg influenza).[42] In the coronavirus infection, the host response is an important contributor to the disease process. In fact, dysregulated and excessive innate immune responses to infection can result in tissue damage and cellular compromise. Surprisingly, when an infection of an immunocompromised host occurs, it may be protected by a weaker immune response against the infectious agent. This statement is corroborated by the experience made so far on coronaviruses outbreaks. An outbreak of SARS caused by SARS-CoV in 2002-2003, characterised by an atypical acute community-acquired pneumonia, caused a total of 8096 patients infected and 774 fatalities in over 30 countries.[43] Transplant patients were expected to have poor outcomes, however, at the end of the outbreak, no such case has been recorded. Middle East Respiratory Syndrome (MERS) is another lethal zoonosis caused by the coronavirus named MERS-CoV, most occurring in Saudi Arabia in 2018. Several risk factors were identified for poor outcomes including advanced age, male sex and presence of comorbidities. However, immunosuppressed status was not considered a risk factor.[44] In what concerns to COVID-19, the Hospital Papa Giovanni XXIII in Bergamo hosts one of the largest European centers for pediatric liver transplantation and is located in the "red zone" for the Italian outbreak. They reported that, among around two hundred transplant recipients, including ten current inpatients, none of them have developed clinical pulmonary disease, despite three tested positive for SARS-CoV-2.[45] Thus, immunosuppressed patients may not have an increased risk of severe complications by COVID-19 when compared to the general population. Nevertheless, the effects of immunosuppression on COVID-19 are not well established and it is urgent that clinics share their experience with immunocompromised patients.[46]

The incidence reported in the literature of CLD in patients with COVID-19 is 0.6%-37.6%.[2,4-26] However, the exact cause of pre-existing liver conditions has not been outlined in many of these case studies, which makes it difficult to analyse the impact of COVID-19 on the different aetiologies of CLD (Table 1).

Patients with liver cirrhosis may develop acute-on-chronic liver failure because of overwhelming inflammatory responses.[47] In fact, liver cirrhosis patients have a significantly higher risk of secondary bacterial infection and a more severe course of influenza, including the development of organ failures, secondary infections and death.[40] In a study of 111 decompensated cirrhotics in Wuhan, none of these patients had clinical symptoms suggestive of SARS-CoV-2 infection when a precautionary approach was implemented, namely protective measures for outpatients, hospital staff training, new processes for diagnosis and treatment and emergency plans.[48] In contrast, a comparative group of 101 decompensated cirrhotics at five other hospitals where preventing measures had not been implemented reported an incidence of 16.8% of COVID-19 cases. There are few data about SARS-CoV-2 infection in liver cirrhosis, however it is expected to be a risk factor for a severe COVID-19 course. Thus, protective measures aimed at preventing infection with SARS-CoV-2 and precautions for cirrhotic complications are of utmost importance.

Guan et al studied 1099 hospitalised patients and outpatients with laboratory-confirmed COVID-19, 2.1% of these had chronic hepatitis B (CHB), an infection much more prevalent in China than Europe.[2] Only one patient had severe disease, which suggests that CHB does not affect the outcome of COVID-19.

Patients with NAFLD or steatohepatitis (NASH) usually have diabetes, hypertension and obesity, all of them associated with a severe course of COVID-19.[49] Cai et al analysed 14 patients infected with SARS-CoV-2 and preexisting NAFLD, 6 of which had severe disease and worse outcomes.[7] Ji and colleagues showed that patients with NAFLD had a higher risk of progression to severe COVID-19 and longer viral shedding time.[26] Further research is needed to understand the impact of COVID-19 in NAFLD.

Several studies argue that patients with cancer might be at increased risk for severe COVID-19 and have a poorer prognosis because of their systemic immunosuppressive state and treatments, such as chemotherapy or surgery. Liang et al reported that patients with cancer have a higher risk of COVID-19 and poorer outcomes than individuals without malignant disease.[50] Zhang and colleagues studied clinical features of 28 severe COVID-19-infected cancer patients, two of them with hepatocellular carcinoma (HCC), from 3 hospitals in Wuhan, China.[51] They reported that about half of the patients had severe events and a mortality rate of 28.6%. Moreover anti-cancer therapy within the last 14 days significantly increased the risk of developing severe events. As HCC patients show deteriorating conditions and poor outcomes, it is recommended more intensive surveillance and early admission of these patients in case of COVID-19 co-infection. Furthermore, we believe that systemic treatments and evaluation for liver transplantation should be maintained according to guidelines.[52] However, some precautions should be taken, namely minimal exposure to medical staff using telemedicine, wherever possible, and screen patients for symptoms and fever before treatments. In patients with COVID-19, locoregional and immune-checkpoint inhibitor therapies should be temporarily withdrawn. The decision on whether to continue or reduced dose of kinase inhibitors should be taken on a case-by-case basis.

Reducing the dosage or stopping immunosuppressive therapy may cause a flare in a patient with autoimmune liver disease. However, there is little experience of SARS-CoV-2 infection in these patients since there are no reported cases in the literature of COVID-19 in

TABLE 1 Liver test abnormalities in patients with SARS-CoV-2 infection

Reference	Number of analysed patients	Pre-existing liver disease n (%)	Abnormal ALT n (%)	Abnormal AST n (%)	Abnormal AKP n (%)	Abnormal GGT n (%)	Abnormal BT n (%)	Abnormal liver tests are associated with worse prognosis	Notes
Guan et al[2]	1099	23 (2.1%) CHB	158/741 (21.3%)	168/757 (22.2%)	NA	NA	76/722 (10.5%)	Yes	The incidence of liver injury in severe cases was higher than mild cases
Jin et al[4]	651	25 (3.8%)	NA	NA	NA	NA	NA	NA	—
Zhang et al[5]	645	25 (3.9%)	NA	NA	NA	NA	NA	NA	—
Wang et al[6]	339	2 (0.6%)	96 (28.3%)	96 (28.3%)	NA	NA	NA	No	The ALT level showed no difference between survival and death ($P > 0.05$)
Cia et al[7]	298	28 (9.4%) CHB n = 5, AFLD n = 15, ALD n = 9	39 (13.1%)	25 (8.4%)	1 (0.3%)	51 (17.1%)	24 (8.1%)	Yes	The proportion of abnormal AST/ALT in severe patients was higher than in mild patients ($P < 0.001$)
Wu et al[8]	280	7 (2.5%)	7 (2.5%)	7 (2.5%)	NA	NA	NA	No	There was no difference in the liver function between mild/moderate patients and severe/critically ill patients ($P > 0.05$)
Zhou et al[9]	191	NA	59/189 (31.2%)	NA	NA	NA	NA	Yes	Elevated ALT levels were associated with death ($P < 0.05$)
Fan et al[10]	148	8 (5.4%) CHB or CHC	27 (18.2%)	32 (21.6%)	6 (4.1%)	26 (17.6%)	9 (6.1%)	NA	—
Wang et al[11]	138	4 (2.9%)	NA	NA	NA	NA	NA	Yes	The proportion of liver injury of ICU patients was higher than non-ICU patients ($P < 0.05$)
Wan et al[12]	135	2 (1.5%)	NA	30/135 (22.2%)	NA	NA	NA	No	There was no difference in the level of ALT and TB compared mild with severe patients ($P > 0.05$)
Zhang et al[13]	115	NA	11 (9.6%)	17 (14.8%)	0	15 (13.0%)	3 (2.6%)	No	There was no difference in liver function indexes after admission to ICU ($P > 0.05$)
Chen et al[14]	99	NA	28 (28.3%)	35 (35.4%)	NA	NA	18 (18.2%)	NA	—
Du et al[15]	85	5 (5.9%)	14 (16.5%)	28 (32.9%)	NA	NA	30 (35.3%)	NA	All patients were deceased cases

(Continues)

TABLE 1 (Continued)

Reference	Number of analysed patients	Pre-existing liver disease n (%)	Abnormal ALT n (%)	Abnormal AST n (%)	Abnormal AKP n (%)	Abnormal GGT n (%)	Abnormal BT n (%)	Abnormal liver tests are associated with worse prognosis	Notes
Li et al[16]	85	6 (7.1%) CHB n = 2, NAFLD n = 2, ALD n = 2	33 (38.8%)	33 (38.8%)	NA	NA	NA	Yes	Moderate and severe patients were more likely to have liver injury
Zhang et al[17]	82	2 (2.4%)	22/72 (30.6%)	44/72 (61.1%)	NA	NA	22/72 (30.6%)	NA	All patients were deceased cases
Shi et al[18]	81	7 (8.6%) Hepatitis or cirrhosis	NA	43 (53.1%)	NA	NA	NA	NA	—
Hansheng et al[19]	79	NA	25 (31.6%)	28 (35.4%)	NA	NA	4 (5.6%)	No	In noncritical patients, liver injury was common and most patients had slight elevated aminotransferases and good prognosis
Liu et al[20]	78	NA	NA	NA	NA	NA	NA	No	There were no differences in ALT/AST levels between progression group and improvement/stabilisation group ($P > 0.05$)
Xu et al[21]	62	7 (11.3%)	NA	10 (16.1%)	NA	NA	NA	NA	—
Yang et al[22]	52	NA	NA	NA	NA	NA	NA	No	No difference in the incidence of liver injury between survivors (30.0%) and nonsurvivals (28.1%)
Huang et al[23]	41	1 (2.4%)	NA	15 (36.6%)	NA	NA	NA	Yes	The proportion of liver injury of ICU patients was higher than non-ICU patients ($P < 0.05$)
Huang et al[24]	36	NA	4/30 (13.3%)	18/31 (58.1%)	NA	NA	4/31 (12.9%)	NA	All patients were deceased cases
Liu et al[25]	12	0	2/12 (16.7%)	2/12 (16.7%)	NA	NA	0	NA	—
Ji et al[26]	202	76 (37.6%) NAFLD	101 (50.0%)	34 (16.8%)	5 (2.5%)	46 (22.8%)	17 (8.4%)	Yes	Elevated GGT levels portend a more severe course of the disease ($P < 0.01$)

Abbreviations: AKP, alkaline phosphatase; ALD, alcoholic fatty liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CHC, chronic hepatitis C; GGT, gamma-glutamyl transferase; ICU, intensive care unit; NA, not available; NAFLD, non-alcoholic fatty liver disease; TB, total bilirubin.

autoimmune hepatitis. EASL-ESCMID currently advises against reducing immunosuppressive therapy in patients with autoimmune liver disease and recommends that reductions should only be considered in case of severe COVID-19 under special circumstances (eg drug-induced lymphopenia or bacterial/fungal superinfection).[49] The World Health Organization (WHO) suggests minimising high-dose prednisone but to maintenance small doses to avoid adrenal insufficiency.[53]

Post-transplant management is complex: insufficient immunosuppression results in graft loss due to rejection, whereas excessive immunosuppression may lead to severe infections.[54] Clinical data on COVID-19 infection in liver transplant recipients are still very limited. Qin et al described a case of a patient who underwent liver transplantation and experienced COVID-19 infection during the perioperative period.[55] Tacrolimus and glucocorticoids were maintained and gradually titrated to lower doses. The patient had no signs of multisystem organ failure during hospitalisation and SARS-CoV-2 RT-PCR was negative on discharge. Bin et al described a case of a 50-year-old male post-liver transplantation who was infected by SARS-CoV-2.[56] The patient recovered from severe COVID-19 pneumonia after a temporary withdrawal of immunosuppression and administration of a systemic low-dose corticosteroid. Huang and colleagues reported a case of COVID-19 in a patient who had transplantation three years previously for HCC with a poor outcome despite multiple aggressive therapeutic measures. The disease progressed rapidly from mild to critical illness because of multiple nosocomial infections and multiple organ failure.[57] Bhoori et al described the experience in an Italian transplant center in Lombardy.[58] Three of 111 long-term liver transplant survivors (transplanted more than 10 years ago) have died. Their immunosuppressive regimen had been gradually tapered off, however, all three patients rapidly developed severe respiratory distress syndrome and died in 3 weeks. The authors suggest that post-transplant metabolic complications might outweigh immunosuppression as a risk factor for development of severe COVID-19 disease. In this regard, EASL-ESCMID suggests a reduction of immunosuppressive therapy in post-transplant patients with severe COVID-19 only under special circumstances (eg medication-induced lymphopenia, bacterial/fungal superinfection).[49]

4 | COVID-19-RELATED LIVER DAMAGE IN CHILDREN

People of all ages are susceptible to SARS-CoV-2 infection. However, infected children appear to have a milder disease course and a better prognosis than adults.[59] In fact, children have a special immune response system with distinct clinical features in COVID-19.[60] Qiu et al analysed 36 paediatric patients (aged 0-16 years) with laboratory-confirmed COVID-19 in three hospitals in Zhejiang and they recorded only 2 children with elevated liver enzymes.[61] Wang et al studied 31 cases of SARS-CoV-2 infection in children from six provinces in northern China and reported 22.2% of patients with elevated transaminases levels, being the highest value registered of ALT and AST 68 U/L and 67 U/L respectively.[62] Moreover Zhu et al analysed the clinical features and outcomes of 10 neonates born to mothers with COVID-19 pneumonia and reported only two patients with abnormal liver function tests.[63] Since COVID-19 in children is associated with minimal or no increase in ALT and AST levels, American Association for the Study of Liver Diseases (AASLD) suggests evaluating all children with abnormal liver enzymes for underlying liver diseases and do not assume COVID-19.[64]

5 | NEW THERAPIES AND LIVER DISEASE

Currently, no therapies or vaccines have yet demonstrated to be effective in treating or preventing COVID-19. However, several drugs are now under investigation.[65] It is important to keep in mind that therapeutic agents may be hepatotoxic, especially in patients with underlying CLD. Moreover patients with certain immunosuppressive therapies should be closely monitored due to drug interactions. AASLD recommends that patients with COVID-19 and elevated liver tests should still be considered for investigational therapeutics.[64]

Lopinavir/ritonavir, an antiretroviral protease inhibitor, can cause transient and usually asymptomatic elevations in serum aminotransferase levels.[66] The risk of Lopinavir-associated hepatotoxicity in patients with very advanced liver disease is low, however Lopinavir plasma trough levels are increased and so it should be used with caution. In hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfected patients, highly active antiretroviral therapy with Lopinavir may result of an exacerbation of the underlying CHB or chronic hepatitis C (CHC).[67]

Hydroxychloroquine, an antimalarial agent, has not been associated with liver abnormalities and is an extremely rare cause of clinically apparent acute liver injury. Dose adjustments are not necessary in patients with hepatic impairment.[68] Nevertheless, Hydroxychloroquine should be used with caution since there continues to be no high-quality clinical data showing a clear benefit of these agents for COVID-19 and it has the potential to cause harm, including serious cardiac side effects.[69]

Tocilizumab, an interleukin-6 inhibitor, frequently causes mild serum elevations of aminotransferase and bilirubin levels, which are usually short lived and asymptomatic.[70] Tocilizumab has been used safety and without worsening of disease in patients with concurrent CHC.[71] Importantly, Tocilizumab may increase the risk of HBV reactivation; HBV screening is mandatory and when needed antiviral prophylaxis should follow international guidelines.[72-74]

Ivermectin, an anti-parasitic agent, has been associated with minor, self-limiting serum aminotransferase elevations and very rare instances of clinically apparent liver injury.[75] Dose adjustments are not necessary in patients with hepatic impairment.

Remdesivir is a novel nucleotide analog, currently under investigation, and with no experience in liver cirrhosis. Elevations of transaminase levels have been reported in up to 22.6% of patients.[76]

Similarly, there is no data available in patients with CLD about Favipiravir, an RNA polymerase inhibitor that may also cause liver cytolysis.[77]

6 | CONCLUSIONS

The COVID-19 epidemic has spread globally and raised many questions and public health challenges. SARS-CoV-2 infection is frequently associated with different degrees of abnormal liver function tests, most notably transaminases, which are usually transitory and of mild degree. Little data are available concerning the incidence of SARS-CoV-2 infection in immunosuppressed patients, however it seems that those with CLD are not at greater risk for acquiring the infection. In the other hand, patients with cirrhosis, NAFLD, HCC, autoimmune liver diseases or liver transplant may have a greater risk for severe COVID-19. It is suggested to keep close surveillance and identify potential ways to prioritise the care of these patients in times of limited healthcare resources, especially in the elderly and those with other comorbidities. Further research should focus on the effect of existing liver-related comorbidities on treatment and outcome of COVID-19.

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