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REVIEWS

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COVID-19 and the liver: A 2021 update

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Abstract

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China and has since resulted in a global pandemic in excess of 165 million reported infections and 3.4 million attributable deaths. COVID-19 is primarily a respiratory illness, which may be complicated by pneumonia and acute respiratory distress syndrome. SARS-CoV-2 is also responsible for numerous extrapulmonary manifestations involving the haematologic, cardiovascular, renal, gastrointestinal and hepatobiliary, endocrinologic, neurologic, ophthalmologic and dermatologic systems. This review will discuss the pathophysiology of COVID-19; focusing on the mechanisms and outcomes of liver injury associated with COVID-19; its impact on chronic liver disease (CLD); management of CLD during the COVID-19 pandemic and the long-term impact of COVID-19 on CLD.

KEYWORDS

COVID-19, liver disease, liver injury, liver transplantation, SARS-CoV-2

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China.[1] Its genomic sequence is 79.6% homologous with human SARS-CoV and is responsible for the now-known coronavirus disease 2019 or COVID-19.[2] Globally, to date, excess of 165 million people have been infected with 3.4 million attributable deaths, and the incidence continues to increase.[3]

COVID-19 is primarily a respiratory illness that may be complicated by pneumonia and acute respiratory distress syndrome (ARDS). However, the disease has also several extra-pulmonary manifestations involving the haematological, cardiovascular, renal, gastrointestinal and hepatobiliary, endocrine, neurological, ophthalmological and dermatological systems.[4] Here, we shortly review the pathophysiology of COVID-19, with a special focus on the

Abbreviations: ACE2, angiotensin-converting enzyme 2; ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CLD, chronic liver disease; CNI, calcineurin-inhibitor; CTP, Child–Turcotte–Pugh; ERCP, endoscopic retrograde cholangio-pancreatography; GGT, gamma-glutamyl transferase; GM-CSF, granulocyte macrophage colony-stimulating factor; HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; HR, hazard ratio; ICU, intensive care unit; IFN, interferon; IL, interleukin; IP-10, interferon-γ-inducible protein 10; LMWH, low molecular weight heparin; MAFLD, metabolic dysfunction associated fatty liver disease; MCP-1, monocyte chemoattractant protein-1; MELD, model for end-stage liver disease; MIP-1α, macrophage inflammatory protein-1 alpha; MMF, mycophenolate mofetil; NETosis, neutrophil extracellular trap; OR, odds ratio; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PSM, propensity score matched; RAAS, renin-angiotensin-aldosterone system; SOFA, Sequential Organ Failure Assessment scores; TIPS, transjugular intrahepatic portosystemic shunt; TNF-α, tumour necrosis factor-alpha; ULN, upper limit of normal.

mechanisms and outcomes of liver injury and its potential impact on CLD. Furthermore, we discuss chronic CLD management during the COVID-19 pandemic and the long-term impact of COVID-19 on CLD.

1 | PATHOPHYSIOLOGY OF COVID-19

SARS-CoV-2 is a single, positive-stranded RNA virus that replicates using a virally encoded RNA-dependent RNA polymerase. It binds to target cells via a hidden receptor-binding domain of the Spike protein to the angiotensin-converting enzyme 2 (ACE-2), which acts as a functional receptor.[5,6] Cell entry requires priming of the Spike protein by a cellular serine protease, TMPRSS2. Other proteases and co-expression are also required.[7] Cell entry of the virus is pre-activated by a target cell proprotein convertase called furin, reducing its dependence on target cell proteases for cell entry. Furin is found in the lungs, the liver and small intestine and enables efficient cell entry, while evading immune surveillance and promoting transmission.[8]

Following entry into the host cell, injury occurs as a result of potential direct virus-mediated cell damage with dysregulation of renin-angiotensin-aldosterone system (RAAS) as a consequence of downregulation of ACE-2 related to viral entry leading to decreased cleavage of angiotensin I and II. Endothelial cell damage and thrombo-inflammation leads to both micro- and macrovascular thromboses.[9] Virus-induced immune dysregulation and hyperinflammation through inhibition of type-I interferon (IFN) signalling, T-cell lympho-depletion, upregulated proinflammatory cytokines (especially interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), induces a hyperactive innate immune system with a resulting cytokine storm[4,10,11] (Figure 1).

SARS-CoV-2 variants have now emerged in the United Kingdom (501Y.V1 or B.1.1.7)[12] and South Africa (501Y.V2 or B.1.351)[13,14] and share the spike N501Y substitution located in the viral spike protein receptor-binding domain for cell entry. Another variant from Brazil (501Y.V3 or P.1) also contains mutations (N501Y, E484K and K417T) in the receptor-binding domain of the spike protein,[15] and, recently, in India, the B.1.617 variant containing the mutations, E484Q and L452R, has been identified. SARS-CoV-2 variants are more transmissible[12,16] and may be associated with a higher morbidity and mortality.[17,18]

2 | MECHANISMS OF LIVER INJURY IN COVID-19

The liver is a potential target for SARS-CoV-2 infection due to its expression of ACE2 and other coreceptors.[19] ACE2 expression is 20-fold higher in cholangiocytes than hepatocytes, a notable 59.6% to 2.6% differential expression.[20] This is analogous to type 2 alveolar cells. ACE2 is also expressed on hepatic sinusoidal endothelium and is highly expressed on resident Kupffer cells.[21,22] Direct evidence for specific SARS-CoV-2 hepatotropism is lacking.[23]

Key points

- 10%-58% of hospitalized patients with COVID-19 have deranged liver enzymes: predominantly elevated transaminases (1-2 × ULN <5×) with AST >ALT levels.
- COVID-19-associated liver injury is often multifactorial including direct virus-induced cytopathic injury, cytokine-driven immune-mediated damage, ischaemic/hypoxic injury and drug-induced liver injuries.
- Main risk factors for poor outcomes in individuals with CLD and COVID-19 are increasing age, advanced stage of liver disease and alcohol-related liver disease (ArLD).
- Liver transplant recipients are not at increased risk of death from COVID-19 compared to patients without liver transplants with similar co-morbidities.
- Vaccination against SARS-CoV-2 is recommended for individuals with CLD and liver transplant recipients.

Heralding liver dysfunction in severe COVID-19 is a greater activation of coagulative and fibrinolytic pathways, relatively depressed platelet counts, climbing neutrophil counts and neutrophil-to-lymphocyte ratios and elevated ferritin.[24] While these are relatively non-specific inflammatory markers, they reflect the paradigm of disease severity coinciding with failure of innate immune regulation.[25,26] This unbalanced immunity favours NETosis (neutrophil extracellular traps) and coagulation activation with an alteration of systemic iron metabolism consequent to macrophage activation.[27] This alteration of immune balance correlates with advancing age, and thus, older patients who have a greater reliance on this pathway are potentially at risk of more severe COVID-19 disease.[28] Collateral liver damage from virally induced cytotoxic T-cells and a dysregulated innate immune response is a potential explanation for the observation of deranged liver enzymes and COVID-19 disease severity.[25]

A recent study analyzing 43 post-mortem liver tissues in COVID-19 patients found a procoagulant endotheliopathy present in livers that is potentially mediating liver inflammation and injury. IL-6 trans-signalling in liver sinusoidal endothelial cells mediates endotheliopathy, cell surface expression of von Willebrand factor and platelet attachment likely causing liver injury.[29]

The reported frequency of elevated serum liver biochemistry in hospitalized patients with COVID-19 ranges from 10%-58% [pooled prevalence of 19%; 95% CI 9%-32%].[30] Primarily, elevated transaminases, usually one to three times the upper limit of normal (ULN) and seldom >5 times ULN, have been reported. AST levels are typically greater than the ALT, and the transaminases are elevated on admission typically increasing during hospitalisation. Early, in the course of COVID-19, normal to modestly elevated total bilirubin levels can be observed. Despite high cholangiocyte ACE2 expression, significant increases in serum alkaline phosphatase (ALP) are rarely reported, with modestly elevated gamma-glutamyl transferase (GGT) levels seen in up to 50% of cases.[31,32]

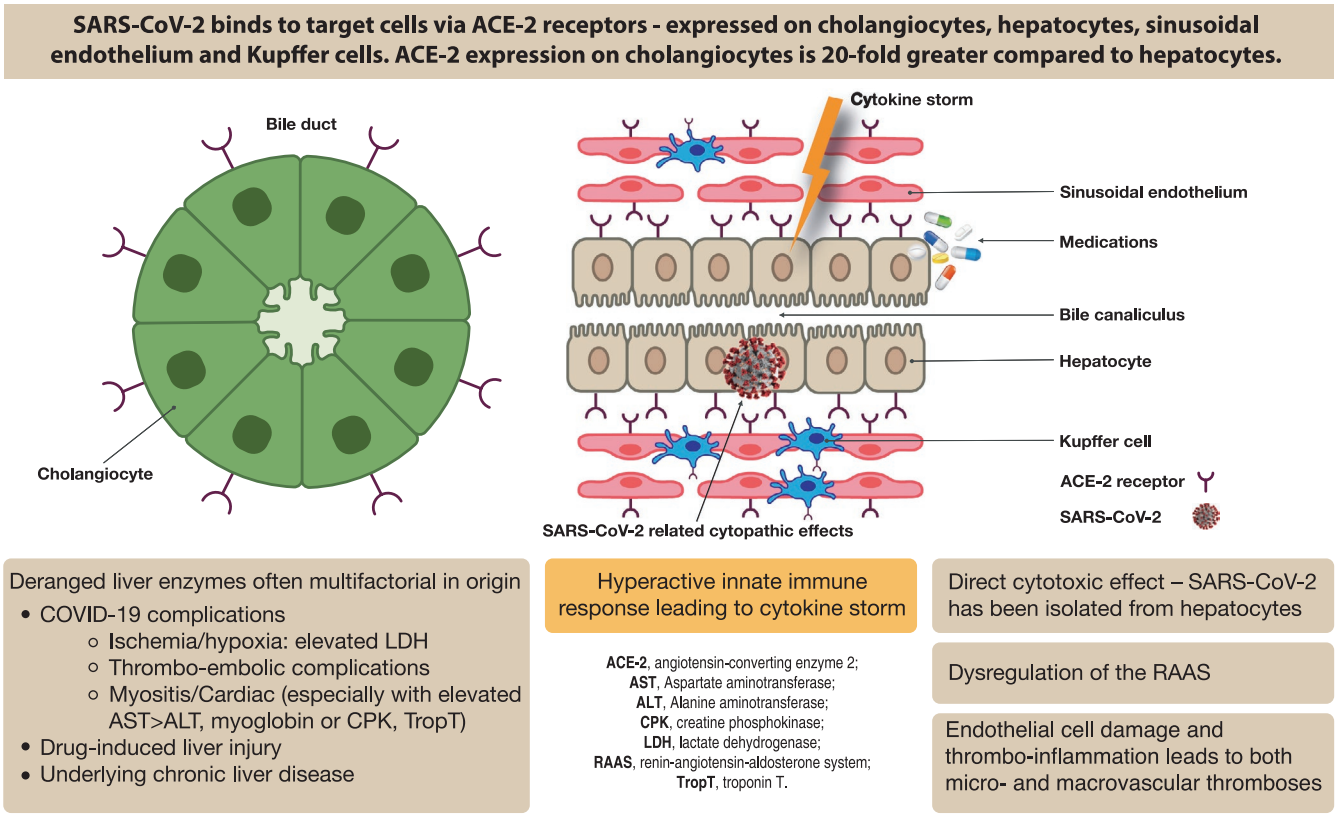

FIGURE 1 Mechanisms of liver injury in COVID-19

Liver injury with mild COVID is usually transient, but with severe disease, liver injury is more frequent. Here, AST levels are associated with mortality but not consistently with hospital length of stay.[11] Serum AST >40 IU/L has been reported in 52% of patients who died, but only in 16% of those recovering.[33] Lower platelet counts and albumin levels are seen in patients with more severe disease; 65% of deceased but only 14% of recovered patients had albumin levels of <32g/L.[33] Of importance, AST correlates with ALT levels and not creatinine kinase and thus reflects liver and not muscle injury.[34,35] To date, few cases of severe acute hepatitis from COVID-19 have been reported.[36–38] Overall, predictors of peak transaminases >5× ULN include age, male gender, body mass index (BMI), diabetes mellitus, medications and inflammatory markers.[37,39] However, transaminases >3 to 5× ULN and/or an elevated total bilirubin >3× ULN are infrequent in COVID-19, and other contributing causes should be considered as a deranged liver profile is likely multifactorial in origin.

3 | OUTCOMES OF SARS-COV-2 LIVER INJURY

Liver injury associated with SARS-CoV-2 infection is usually mild and self-limiting. Severe liver injuries correlate with a more severe clinical course reflected by higher rates of intensive care unit admission, mechanical ventilation, renal replacement therapy and mortality.[35,37,40]

A multicentre retrospective study from 10 hospitals in Wuhan, China of 5771 patients with COVID-19 pneumonia documented the median days from symptom onset to acute organ damage and revealed that acute liver injury occurs later in the course of COVID-19.[41] Acute liver injury (ALT >3× ULN) occurred at day 17 [IQR, 13-23] after symptom onset and followed the development of ARDS, acute cardiac injury and acute kidney injury. AST levels were associated with the highest all-cause mortality, risk increasing 4.8-fold with AST between 40 and 120 U/L and 14.9-fold with AST >120 U/L after adjusting for age, gender and co-morbidities.[41]

4 | LIVER HISTOPATHOLOGY IN COVID-19

Few liver histology-based COVID-19 case series have been published. Histopathological changes ranging from moderate microvesicular steatosis with mild, mixed lobular and portal inflammation to focal necrosis have been described.[42–44] Sinusoidal dilatation is noted, but no bile duct injury has been documented.[45] SARS-CoV-2 RNA has been isolated from liver tissue through RT-PCR, and the virus has been detected on electron microscopy.[44,46] In a USA post-mortem series, SARS-CoV-2 viral RNA was detectable by PCR in 55% of liver samples tested.[43] An Italian autopsy series of 48 post-mortem wedge liver biopsies revealed focal portal and lobular lymphocytic infiltrates and also diffuse intra-hepatic vascular abnormalities with partial or complete acute portal vein and sinusoidal

thrombosis.[47] It is uncertain as to whether this represents a direct effect of SARS CoV-2 infection or is consequent to overwhelming systemic complications of COVID-19. Proteomic assessment of post-mortem liver tissue from 19 patients who died from COVID-19 showed upgregulated profibrotic pathways, dysregulated fatty acid oxidation, oxidative phosphorylation and immune activation, but little evidence of active viral replication.[23,48] This proteomic dysregulation of liver proteins was associated with multiorgan dysfunction, hepatic steatosis and coagulative hepatocyte necrosis.[23,48]

A recent systemic review and meta-analysis of liver histopathological findings determined the following pooled prevalence estimates: hepatic steatosis 55.1% [95% CI: 46.2-63.8], congestion of hepatic sinuses 34.7% [95% CI: 7.9-68.4], vascular thrombosis 29.4% [95% CI: 0.4-87.2], fibrosis 20.5% [95% CI: 0.6-57.9], Kupffer cell hyperplasia 13.5% [95% CI: 0.6-54.3], portal inflammation 13.2% [95% CI: 0.1-48.8] and lobular inflammation 11.6% [95% CI: 0.3-35.7].[49]

5 | APPROACH TO ABNORMAL LIVER ENZYMES IN COVID-19 PATIENTS

Patients admitted to hospital with moderate-to-severe disease should have baseline liver tests including ALT, AST, GGT, ALP and bilirubin. Liver enzymes should be monitored as COVID-19 progresses. The aetiology of deranged liver enzymes is invariably multifactorial in the COVID-19 setting. Acute or chronic viral hepatitis and potential hepatotoxins such as statins, azithromycin, lopinavir/ritonavir, remdesivir, tocilizumab, enoxaparin and paracetamol need to be excluded. A direct cytopathic effect on hepatocytes of SARS-CoV-2 is possible as the virus has been isolated from the liver.[46] Furthermore, mitochondrial proteins may directly interact with the virus, which may explain the frequent AST predominance observed.[50] Lastly, the pro-inflammatory response enabling the cytokine storm (IL-2, IL-6, IL-7, GM-CSF, IP-10, MCP-1, MIP-1α, TNF-α) further exacerbated by intrahepatic cytotoxic T cells and Kupffer cell activation contributes to liver enzyme derangement. Myocarditis or skeletal muscle myositis can accentuate the AST levels and warrants consideration in those with disproportionately elevated AST levels.

6 | COVID-19 AND CHRONIC LIVER DISEASE

Chronic liver disease (CLD) and particularly cirrhosis is associated with alterations in both innate and adaptive immunity leading to increased susceptibility to infections and aberrant systemic responses during infections. This is referred to as cirrhosis-associated immune dysfunction (CAID) and includes macrophage activation, impaired neutrophil and lymphocyte function, Toll-like receptor dysfunction, impaired complement system and importantly increased gut permeability with alterations in the gut microbiome.[23,51,52]

Data on the prevalence of CLD in COVID-19 studies are limited, but it is estimated that 1%-11% have associated CLD. The stage of the CLD and associated co-morbidities influence outcomes with progressive increase in morbidity and mortality with increasing Child–Pugh (CP) class.[53–57] COVID-19 can precipitate hepatic decompensation, and this is associated with increased mortality: 63.2% vs 26.2% without decompensation.[54]

In a systemic review and meta-analysis of 73 studies of 24 299 patients, CLD prevalence was 3% amongst all COVID-19 patients. No increased risk of COVID-19 noted, but CLD was associated with more severe infection [pooled OR 1.48; 95% CI 1.17-1.87, $P = .001$] and overall increased mortality [pooled OR 1.78; 95% CI 1.09-2.93, $P = .02$].[58]

In USA, the Centres for Disease Control study of 122 653 COVID-19 patients, where only 5.8% of patients had clear data, 37.6% had at least one underlying condition or risk factor predicting for severe disease and poor outcomes. Of these, 41 patients (0.6%) had CLD, including 7 who required ICU admission.[59] Given the known high prevalence of fatty liver disease in the US population, the estimated CLD prevalence is likely underestimated. In another US cohort of 2780 COVID-19 patients, CLD was associated with significantly higher mortality [RR 2.8, 95% CI 1.9-4.0]. Cirrhotics carried the highest mortality risk [RR 4.6, 95% CI 2.6-8.3]. Fatty liver disease and non-alcoholic steatohepatitis (NASH) were the most common aetiologies in the liver disease group. Mortality risk was independent of risk factors such as BMI, hypertension and diabetes.[53]

A large United Kingdom review of electronic health record data of more than 17 million patients suggested that 114 796 patients with CLD had an elevated mortality from COVID-19 with a fully adjusted HR of 1.68 [95% CI 1.34-2.10].[60]

The collaborating International Registries of SECURE-Cirrhosis and COVID-Hep (29 countries) have confirmed increasing frequency of ICU admission, ventilation support, renal replacement therapy and mortality with increasing Child–Pugh class.[54] Overall mortality for CP-A is 19%, CP-B (35%) and CP-C (51%). The odds ratio (OR) for death was for CP-A [OR 1.90; 1.03-3.52], CP-B [OR 4.14; 2.4-7.65] and CP-C [OR 9.32; 4.80-18.08]. In CP-C, the mortality was 79% on admission to ICU and 90% once on mechanical ventilation. Acute hepatic decompensation occurred in 46% of patients with cirrhosis, of whom 21% had no respiratory symptoms. Half of those with hepatic decompensation had acute-on-chronic liver failure (ACLF).[54] COVID-19 can be a trigger for ACLF, and COVID-19 case fatality rates are associated with a rising ACLF SCORE.[54,55]

Reported overall mortality rates for cirrhotics hospitalized with COVID-19 range between 30% and 34% with respiratory complications being the main cause of death.[54,55,57]

6.1 | Viral hepatitis and COVID-19

To date, no evidence has demonstrated that individuals with chronic hepatitis B (HBV) or hepatitis C (HCV) infection, without advanced

fibrosis or cirrhosis, are at any greater risk for acquiring or having a worse outcome with COVID-19.[32,38,61–63] No independent association with death has been documented for HBV or HCV.[63–65] Although a population-based study using electronic health record data suggested that HCV-infected individuals with SARS-CoV-2 were more likely to be hospitalized, but were not at increased risk of death.[63]

Although guidance has recommended that direct acting antiviral (DAA) therapy for HCV could be delayed in patients with COVID-19, some data suggested a potentially beneficial effect of DAAs in COVID-19.[66–68] A meta-analysis of three trials point towards clinical recovery within 14 days of randomization being higher in the sofosbuvir/daclatasvir arms compared with control arms [RR 1.34; 95% CI 1.05-1.71, $P = .02$]. Sofosbuvir/daclatasvir improved time to clinical recovery [HR = 2.04; 95% CI 1.25-3.32, $P = .004$] with a significantly lower pooled risk of all-cause mortality [RR = 0.31; 95% CI 0.12-0.78, $P = .013$]. However, the sample size for analysis was 176 patients, one trial was not randomized, and the designs were not standardized, so data remains disappointing and no recommendation exists.[69] HBV reactivation remains a risk with COVID-19-specific therapies including tocilizumab and corticosteroids, and nucleos(t)ide analogues to prevent HBV flares are advisable. In summary, no contraindication exists to initiating anti-HBV or HCV DAA therapy during the pandemic and treatment initiation should be clinically guided.

6.2 | Fatty liver disease and COVID-19

Metabolic dysfunction-associated fatty liver disease (MAFLD), independent of BMI, is epidemiologically associated with an increased risk of severe COVID-19 requiring hospitalization.[70,71] Initial data suggest that MAFLD may mediate the impact of obesity on COVID-19.[72] The mechanism encompasses the promotion of inflammation by facilitation of liver injury, which is a frequent feature of severe COVID-19, increased release of cytokines and procoagulant mediators. Several studies now demonstrate that MAFLD is associated with an increased risk of developing severe COVID-19. Outcomes are worse, especially in those with advanced liver fibrosis.[73–76] A systematic review and meta-analysis confirmed an increased risk of severe COVID-19 and ICU admission, but no observable difference in mortality between patients with and without MAFLD.[77] A comprehensive evaluation of the literature detected a >2-fold higher risk of COVID-19 in individuals with MAFLD, independent of BMI.[74] MAFLD also increases viral shedding time, 17.5 ± 5.2 days vs 12.1 ± 4.4 days, $P < .0001$, compared to patients without MAFLD.[76] Furthermore, genetic data suggest that metabolic dysfunction rather than hepatic fat accumulation itself may facilitate COVID-19 progression.[71] The mechanism linking obesity and MAFLD with severe COVID-19 is probably not mediated by increased hepatic fat, but includes more severe insulin resistance, hypoxia and alterations of gut permeability and the gut-liver axis[78] (Figure 2). Although additional data are required to

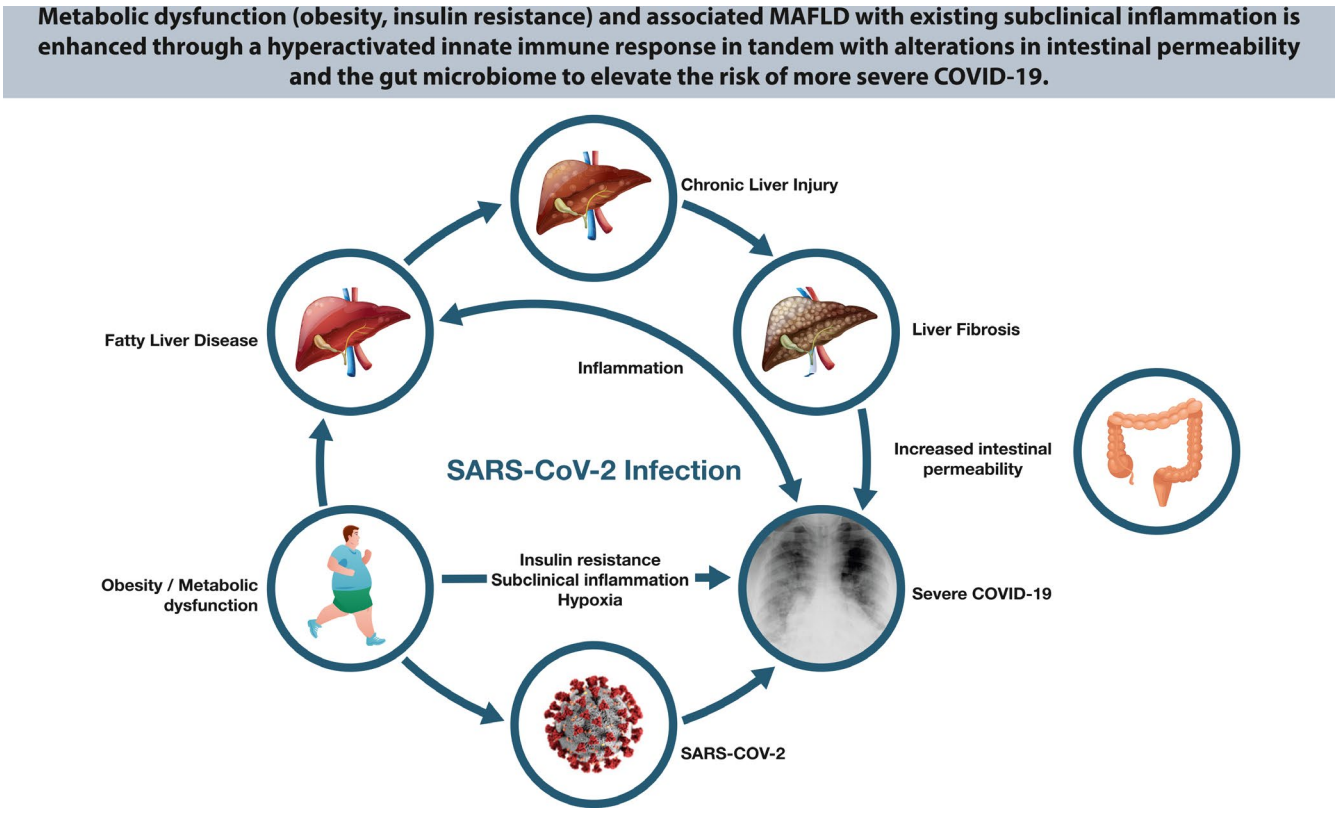

FIGURE 2 Mechanisms linking fatty liver disease and metabolic dysfunction with severe COVID-19

elucidate the relationship between hepatic fat and SARS-CoV-2, the presence of MAFLD can be considered a marker of increased susceptibility to develop severe COVID-19.

6.3 | Alcohol-related liver disease and alcohol-use disorders and COVID-19

The large international registry (SECURE-Cirrhosis, COVID-Hep) study of 745 patients with CLD and cirrhosis from 130 different institutions in 29 countries identified alcohol-related liver disease (ArLD) as a risk factor for COVID-19-related mortality [OR 1.79; 1.03-3.13].[54] A US multicentre retrospective cohort study confirmed ArLD as an independent risk factor for COVID-19-related death [HR 2.42; 95% CI 1.29-4.55].[65] The higher mortality in ArLD may relate to the presence of advanced disease and CAID. This immune dysregulation, especially alterations in the gut-liver axis, is exaggerated in ArLD with increased endotoxaemia and Kupffer cell activation leading to the transcription of proinflammatory cytokines (TNF-α) and superoxide production.[23,51,52] In addition, chronic alcohol exposure also interferes with the normal functioning of all aspects of the adaptive immune response, including both cell-mediated and humoral responses.[79]

Importantly, psychosocial stressors have led to increased alcohol abuse, and social distancing has limited participation in substance use disorder supports groups increasing the risk for alcohol relapse in patients.[80]

6.4 | Autoimmune liver disease and COVID-19

Immunosuppressed patients have higher SAR-CoV-2 viral titres, are more infectious and have prolonged viral shedding but seem not to be at increased risk of complications such as ARDS.[81,82] Registry data (SECURE-Cirrhosis, COVID-Hep and ERN RARE-LIVER) on 70 autoimmune hepatitis (AIH) patients have noted despite the use of immunosuppression in 86% of cases, no differences in the rates of major outcomes between AIH and non-AIH CLD patients including hospitalization (76% vs 85%; $P = .06$), ICU admission (29% vs 23%; $P = .240$) and death (23% vs 20%; $P = .643$). Propensity score-matched analysis of patients with AIH vs non-CLD (769 patients) demonstrated an increased risk of hospitalization with AIH [+18.4%; 5.6%-31.2%], but equivalent risk of all other outcomes including death [+3.2%; 9.1%-15.6%].[83] This suggests that, in stable patients, immunosuppression should not be reduced as a strategy to reduce the risk of COVID-19 infection. Steroid dosage may however warrant adjusting to manage severe COVID-19 or address adrenal insufficiency.[66]

Despite the increased ACE-2 expression on cholangiocytes, it is unclear whether patients with primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC), without underlying cirrhosis, are at increased risk of COVID-19 or if the virus exacerbates chronic cholestatic liver disease.[11] Ascending cholangitis must be excluded in PSC patients presenting with fever and deteriorating liver tests.

7 | ANTICOAGULATION IN THE SETTING OF CHRONIC LIVER DISEASE AND COVID-19

Advanced liver disease is associated with both coagulopathy and an increased risk of venous thromboembolism. SARS-CoV-2 infection in cirrhotics potentially increases the cumulative risk of prothrombotic complications, and anticoagulation is recommended to prevent thromboembolic complications.[9,84] Low molecular weight heparin (LMWH) in cirrhotics has shown a survival benefit in decompensated cirrhotics presenting with portal vein thrombosis.[85] A systematic review indicated no excess of bleeding events including variceal bleeds in anticoagulated cirrhotic patients with a portal vein thrombosis.[86] In a recent multicentre Italian study, where 80% of cirrhotics with COVID-19 received LMWH thromboprophylaxis, no evidence of any major haemorrhagic complications was noted.[55] There is no contraindication to LMWH in hospitalized cirrhotics.

8 | COVID-19 AND LIVER TRANSPLANTATION

It is not clear whether liver transplant recipients are at increased risk of SARS-CoV-2 infection. Data from United Kingdom and Spain suggest that SARS-CoV-2 infections are more frequently diagnosed in liver transplant recipients than in the general population, but this might reflect regular monitoring and a lower threshold for testing in these patients.[87,88]

The combined SECURE-Cirrhosis and COVID-Hep registries, ELITA/ELTR Multi-centre European Study and the US multicentre COLD consortium have all reported similar outcomes for liver transplantation and COVID-19.[89–91] The overall mortality is around 20%-25%, and outcomes are determined by age and co-morbid conditions such as type 2 diabetes mellitus, obesity, renal impairment and extrahepatic malignancies.[88,90,92] COVID-19 lung disease is the main cause of death. Of interest, liver transplant recipients with COVID-19 appear to have a high frequency of gastrointestinal symptoms, particularly diarrhoea.[92]

The immune response is an important driver for pulmonary injury attributable to COVID-19, and immunosuppression may thus be protective. Corticosteroids improve survival in critically ill patients with COVID-19 requiring oxygen support. Tacrolimus has been associated with better survival in liver transplant recipients with COVID-19 [HR, 0.55; 95% CI, 0.31-0.99],[90] whereas mycophenolate mofetil (MMF) was an independent predictor of severe COVID-19 [RR = 3.94; 95% CI 1.59-9.74; $P = .003$], especially doses higher >1 g/day ($P = .003$).[88]

COVID-19 in liver transplant recipients has similar mortality rates compared to the general population in contrast to the increased mortality in cirrhotics suggesting that CAID is more immunosuppressive than pharmaceutical immunosuppressive agents.[23]

9 | MANAGEMENT AND FOLLOW-UP OF PATIENTS WITH CLD, HCC AND LIVER TRANSPLANT RECIPIENTS

The scope of management is dependent on the phase of the pandemic in a given country or region and the demands on healthcare personnel and resource constraints.[66,67] The American Society for the Study of Liver Disease, EASL-ESCMID, World Gastroenterology Organization and APASL have published detailed guidance documents on the management of patients with CLD and liver transplant patients during the COVID-19 pandemic.[66–68,93]

New adult and paediatric patients with clinically significant liver disease should be prioritized viz. patients with jaundice, elevated ALT or AST >500 U/L, recent onset hepatic decompensation or newly diagnosed HCC. When limiting outpatient visits to those who must be seen in person, it is important to ensure an adequate supply of chronic medications and access to telephonic advice. All patients with CLD must receive influenza and pneumococcal vaccines.

9.1 | Hepatocellular carcinoma

Mortality in malignancy and COVID-19 is determined by age, gender and comorbidities and not the use of cytotoxic chemotherapy or other anticancer treatment. HCC surveillance must be continued in those at risk viz. cirrhosis, chronic hepatitis B, MAFLD and rising alpha-fetoprotein and done as close to the usual schedule as possible. An arbitrary 2-month delay in surveillance has been proposed as progression with poorer outcomes is associated with delaying interventions beyond two months.[66,94] The risks and benefits of delaying HCC surveillance must be discussed with the patient and the discussion documented. Images of new referrals of liver masses should be reviewed in a multi-disciplinary meeting prior to scheduling in-person visits. HCC systemic and ablative therapies or surgical resection should not be postponed.[66] In patients with COVID-19, the slow median doubling time of HCC supports a short delay in initiating HCC treatment.[95]

An international multicentre study, including 76 centres from Europe, South America, North America, Asia and Africa, revealed that 87% of centres had modified their clinical practice for liver cancer during the first wave with COVID-19: 80.9% modifying their screening programmes and 40.8% their diagnostic procedures; 50% cancelled curative and/or palliative treatments and 44.0% cancelled their liver transplantation programmes. The long-term impact of these modifications includes individuals presenting with advanced disease and no longer being candidates for curative procedures. About 65.2% centres modified their Clinical Trial treatments, and only 58.1% of centres were able to recruit new patients.[96]

Oncology nurses played an important role in the move from face–face visits to telephonic/video consultations. This active involvement of the Oncology nurse should be further developed together with optimal criteria for telephonic/video consultations.[96]

9.2 | Decompensated cirrhotics and management of the liver transplant waiting list

Transplant centres must assess their local situation and the impact of COVID-19 on patients awaiting transplantation on an ongoing basis. Transplant evaluation for patients with high MELD scores, risk of decompensation or HCC progression should be prioritized whilst considering constraints and utilization. Despite listing, potential recipients should be warned about expected reduction in organ recovery due to COVID-19-related limitations on institutional resources, risk of donor-derived disease transmission and concern around nosocomial SARS-CoV-2 infections.[66] There should be a low threshold for admitting transplant wait-listed patients with COVID-19. Any patient presenting with a new decompensation or ACLF must be tested for SARS-CoV-2 given up to 20% have no respiratory symptoms.[18]

Endoscopy is an aerosol-generating procedure and SARS-CoV-2 faecal-shedding persists for over a week after viral clearance from the lungs.[97,98] Swab tests are recommended before procedures if possible, and endoscopists should utilize full PPE, including N95 masks and double gloves. Endoscopic procedures for varices surveillance and treatment; ERCP and stent placement; percutaneous transhepatic cholangiography; TIPS; paracentesis and liver biopsies should be performed, as guided by the local active burden of COVID-19. Population vaccine coverage is as yet an unknown factor in mitigating risk. In patients with COVID-19, procedures should be limited to emergency endoscopic procedures only, for example, for management of variceal bleeds and biliary obstruction.

9.3 | Liver transplant recipients

Minimizing in-person visits for post-transplant patients by maximizing use of telemedicine reduces the risk of nosocomial infections. Liver graft function and immunosuppressant levels can be monitored remotely whilst ensuring an adequate supply of immunosuppressants. The immune response (IL-6; IL-8, TNF-α) may be main driver for pulmonary injury in COVID-19, and thus immunosuppression may be protective. However, the reported mortality rates of COVID-19 in liver and other solid organ transplant recipients are around 25%. Immunosuppression should not be pre-emptively reduced nor MMF stopped as this may precipitate acute rejection.[66] There should be a low threshold for COVID-19 screening in transplant recipients who present with non-specific symptoms. Indications to lower the overall level of immunosuppression especially antimetabolites (azathioprine and MMF) are as usual: drug-induced lymphopenia; superimposed bacterial or fungal infections. Acute kidney injury appears to be more common in transplant recipients with COVID-19, and it is important to monitor calcineurin-inhibitor levels and adjust dosages as necessary. Drug–drug interactions with calcineurin- and mTOR-inhibitors must be considered.[99] Acute cellular rejection as the cause of deranged liver enzymes requires biopsy confirmation.[66] Anti-IL6 has not been shown to increase the risk of acute cellular rejection.

10 | COVID-19 VACCINATION IN PATIENTS WITH LIVER DISEASES AND LIVER TRANSPLANT RECIPIENTS

Up to January 2021, 235 vaccine candidates for COVID-19 had been reported, and 63 of them are currently being studied in human clinical trials. Four vaccines completed Phase 3 trials, with published reports, while 19 more vaccines are in Phase 3 studies.[100–102] Availability of vaccines will be different among countries due to differences in approval dates, reimbursement rules and temperature storage suitability, thus providing a detailed report on all Covid-19 vaccines is beyond the scope of the current manuscript. Four Covid-19 vaccines have been EMA-approved: BNT162b2 mRNA (BioNTech and Pfizer), mRNA-1273 (Moderna and National Institute of Allergy and Infectious Diseases – NIAID), ChAdOx1 nCoV-19 (AstraZeneca and University of Oxford) and Ad26.COV2-S [recombinant] (Johnson & Johnson).

Safety and efficacy data for patients with liver disease are limited. In the BNT162b2 mRNA vaccination study, 217 (0.6%) of 37 706 participants had liver disease, and only three (<0.1%) had moderate-to-severe liver disease. A small number of patients with liver disease were included in the Moderna trial (196 [0.6%] of 30 351), while the ChAdOx1-nCoV-19 and Ad26.COV2-S [recombinant] vaccine trials explicitly omitted patients with pre-existing liver pathology. In addition, all trials listed systemic immunosuppression as an exclusion criterion, thus preventing extrapolation of the data to immunosuppressed liver transplant recipients or patients with autoimmune liver disease.

Given the small number of patients with pre-existing liver disease included in the Phase III RCTs, the efficacy of the available vaccines cannot be ascertained. Previous studies have shown that response to vaccines is not attenuated in patients with mild–moderate liver diseases of any aetiology; however, rates of seroconversion after hepatitis B virus vaccination and the durability of humoral immunity after pneumococcal and influenza vaccination are markedly reduced in patients with cirrhosis.[103–105] Similarly, reduced immune reponse to vaccination has been reported in patients who received liver transplantation.[106] Thus, it is likely that patients with cirrhosis or those who have received liver transplantation might have attenuated immune responses to COVID-19 vaccination.[107] The recent Global Hepatology Society Statement advises that patients with liver disease including those on immunosuppression and liver transplant recipients should be vaccinated against SARS-CoV-2 with any authorized COVID-19 vaccine as the benefits outweigh the potential risks.[108–110]

11 | CONCLUSION

SARS-CoV-2, which is responsible for COVID-19, has resulted in significant morbidity and mortality not only from pneumonia and complicating ARDS but also as a result of many extrapulmonary manifestations. Liver injury due to SARS-CoV-2 is most likely multifactorial involving direct viral cytopathic liver injury, immune-mediated injury, complications of COVID-19 including hypoxia/ischaemia and micro/macrovascular thromboses and drug-induced liver injury. The main risk factors for adverse outcomes in individuals with CLD and COVID-19 are increasing age, advanced stage of liver disease and ArLD. Although about a quarter of patients with CLD and COVID-19 have no respiratory symptoms, the majority of patients die as a result of respiratory complications. Cirrhotic patients with COVID-19 are at increased risk of decompensation, and cirrhotic patients presenting with decompensation must be screened for SARS-CoV-2. International registry data suggest that liver transplantation is not independently associated with mortality but increasing age and comorbidities are. Whilst limiting in-person visits to clinics and hospital are important in the height of the pandemic to limit nosocomial infections, it is essential to ensure an adequate supply of medications and access to telephonic/videoconsultation advice. The long-term effects of missed diagnoses, follow-ups and postponed HCC surveillance will need to be strategized and addressed. Hepatology services including liver transplantation need to be actively resumed to prevent further detrimental outcomes for patients with both acute and CLDs. The understanding around the pathophysiology of COVID-19 and recommendations around best management practices is rapidly expanding, and this requires constant re-evaluation of the appropriate approach to the optimal care of our patients during the ongoing COVID-19 pandemic.

CONFLICT OF INTEREST

The authors do not have any disclosure to report.

AUTHOR CONTRIBUTIONS

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