COVID-19 and liver disease: mechanistic and clinical perspectives

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Abstract | Our understanding of the hepatic consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its resultant coronavirus disease 2019 (COVID-19) has evolved rapidly since the onset of the pandemic. In this Review, we discuss the hepatotropism of SARS-CoV-2, including the differential expression of viral receptors on liver cell types, and we describe the liver histology features present in patients with COVID-19. We also provide an overview of the pattern and relevance of abnormal liver biochemistry during COVID-19 and present the possible underlying direct and indirect mechanisms for liver injury. Furthermore, large international cohorts have been able to characterize the disease course of COVID-19 in patients with pre-existing chronic liver disease. Patients with cirrhosis have particularly high rates of hepatic decompensation and death following SARS-CoV-2 infection and we outline hypotheses to explain these findings, including the possible role of cirrhosis-associated immune dysfunction. This finding contrasts with outcome data in pharmacologically immunosuppressed patients after liver transplantation who seem to have comparatively better outcomes from COVID-19 than those with advanced liver disease. Finally, we discuss the approach to SARS-CoV-2 vaccination in patients with cirrhosis and after liver transplantation and predict how changes in social behaviours and clinical care pathways during the pandemic might lead to increased liver disease incidence and severity.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus first reported in humans in Wuhan, China, in December 2019. The virus has since spread rapidly worldwide causing coronavirus disease 2019 (COVID-19), which continues to have a devastating effect on global health[1]. The majority of patients with SARS-CoV-2 infection remain asymptomatic or have mild symptoms, including fever, cough, anosmia and headache. However, around 15% develop severe pulmonary disease typically over 10 days, leading to respiratory compromise, which might progress to multi-organ failure, coagulopathy and death[2–4]. Oxygen supplementation, invasive ventilation and other supportive measures now form part of the standard-of-care in hospitalized patients; however, mortality remains high among those with critical disease. Common risk factors consistently associated with severe COVID-19 are now well established and include advancing age, male sex and a burden of comorbidity, including hypertension, heart disease, diabetes and malignancy[5,6].

As the pandemic has evolved, most policy-makers, supported by a growing body of scientific evidence, have sought to protect their populations from infection. Those most at risk of severe COVID-19 have been advised to 'shield', effectively avoiding all social contact with others. A detailed understanding of the contribution of specific disease phenotypes to COVID-19 susceptibility and clinical outcomes has been crucial to enable the tailoring of public health advice to specific patient subpopulations.

In parallel, randomized clinical trials continue to evaluate therapeutic strategies against SARS-CoV-2, including direct antiviral and immune-modifying agents[7,8]. Understanding which patient groups require early or novel therapeutic interventions is a high clinical priority. In addition, SARS-CoV-2 vaccine development has progressed at an unprecedented rate, with the leading candidates all publishing extremely promising safety and efficacy data from phase III trials. There will now be an unprecedented global demand for vaccine deployment and, therefore, establishing which patients are most vulnerable to adverse COVID-19 outcomes is necessary to help inform who is prioritized in immunization programmes.

Since the onset of the pandemic there has been concern that pre-existing chronic liver disease (CLD) might predispose to poor outcomes following SARS-CoV-2 infection, particularly due to the overlapping risk factors for severe COVID-19 and CLD, for example, advancing

Key points

- Patients with cirrhosis have high rates of hepatic decompensation, acute-on-chronic liver failure and death from respiratory failure following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and should be prioritized for coronavirus disease 2019 (COVID-19) vaccination.
- The possible pathogenic mechanisms linking cirrhosis with severe COVID-19 lung disease include increased systemic inflammation, cirrhosis-associated immune dysfunction, coagulopathy and intestinal dysbiosis.
- Abnormal liver biochemistry values are common in patients with COVID-19; both the prognostic significance of these derangements and whether they are directly attributable to hepatic SARS-CoV-2 infection remain uncertain.
- Expression profiles of SARS-CoV-2 entry receptors vary across different in vitro and in vivo liver models; however, evidence of specific viral hepatotropism is limited.
- Liver transplant recipients do not appear to have an increased risk of mortality following SARS-CoV-2 infection compared with the matched general population.
- The pandemic has been associated with increased alcohol consumption, unhealthy eating habits, and interruptions to hepatology services, which might lead to an upward trend in liver disease incidence and severity.

age, obesity and diabetes. In addition, advanced liver disease is associated with immune dysregulation and coagulopathy, which could contribute to a more severe COVID-19 course[9,10]. The global burden of CLD is vast, with cirrhosis affecting more than 122 million people worldwide, of whom 10 million have decompensated disease[11]. Understanding the natural history of COVID-19 in patients with CLD, across different aetiologies and across the spectrum of liver disease severity, is therefore paramount.

This Review focuses on the pathogenesis and consequences of SARS-CoV-2 infection in patients with CLD based on evidence rapidly acquired through large international cohorts throughout 2020. We also explore the utility of liver biochemistry as a prognostic tool during COVID-19, summarize the evidence for direct viral infection of liver cells and explore the likely mechanisms underlying SARS-CoV-2-related liver injury. Finally, we discuss the profound effect of the pandemic on hepatology services and patient behaviours, which could lead to an increase in future liver disease incidence and severity.

Hepatotropism of SARS-CoV-2

The tissue reservoirs for SARS-CoV-2 replication remain to be fully elucidated, partly due to difficulties in accessing biopsy samples from actively infected individuals and the requirement for high level laboratory containment facilities. The virus spike protein binds ACE2 to gain cell entry and transmembrane serine protease 2 (TMPRSS2) and paired basic amino acid cleaving enzyme (FURIN) are also important for infection; therefore, the expression of these receptors provided early clues for putative hepatic permissive cells.

Single-cell RNA sequencing analyses in healthy livers have shown gene expression levels for ACE2 to be highest in cholangiocytes (comparable to alveolar type 2 cells), followed in turn by sinusoidal endothelial cells and hepatocytes[12,13]. TMPRSS2 and FURIN showed a broad gene expression profile across many liver cell types[12]. However, in a combined analysis of three single-cell RNA sequencing datasets from liver tissue from healthy individuals, very few hepatocytes co-expressed ACE2 and TMPRSS2 (REF.[14]). Experimental cellular and organoid models have therefore been important in trying to decipher the permissibility of liver cell types to SARS-CoV-2 infection. Hepatocellular carcinoma-derived cell lines Huh-7 and HepG2 are able to support the complete viral life cycle[15]; however, replication in primary hepatocytes has not yet been confirmed. This discrepancy between cellular models could be related to the presence of cancer-associated mutations in hepatoma cell lines, such as the tumour suppressor p53, which, under normal conditions, serves to downregulate intracellular SARS-CoV-2 replication[16]. Zhao et al. generated ACE2-expressing and TMPRSS2-expressing human liver ductal organoids that were able to recapitulate SARS-CoV-2 infection[17], suggesting that the bile duct epithelium could support pseudoparticle entry. It is worth noting that the seemingly high SARS-CoV-2 entry receptor expression and viral permissibility of cholangiocytes is at odds with the non-cholestatic pattern of liver biochemistry typically found in COVID-19; the precise reasons for this aspect are currently unknown. However, it is possible that SARS-CoV-2 can undergo low level replication in cholangiocytes in vivo without triggering cell death. This process would be consistent with other reservoirs of long-term viral replication, such as in the small intestine, which can help shape memory B cell responses to the virus over time[18]. Human pluripotent stem cell-derived liver organoids comprising mostly albumin-expressing hepatocytes have also been shown to express ACE2 and permitted SARS-CoV-2 pseudoparticle entry[19].

The influence of liver injury and underlying liver disease on the hepatotropism of SARS-CoV-2 remains unclear and no studies have yet specifically explored the histological changes found in patients with COVID-19 and pre-existing CLD. However, early studies in the era preceding COVID-19 found a greater than 30-fold increase in ACE2 expression in the liver of patients with hepatitis C virus-related cirrhosis compared with healthy individuals[20]. In addition, liver mRNA expression of ACE2 and TMPRSS2 was upregulated in non-infected patients with obesity and nonalcoholic steatohepatitis but not with steatosis alone[21]. Similarly, rodent models of liver injury via bile duct ligation have been associated with increased hepatic ACE2 expression and activity in parallel with markers of hypoxia[20,22]. Liver injury and inflammation could potentiate SARS-CoV-2 hepatotropism by modulating viral receptor expression, with ACE2 being identified as an interferon-inducible gene in human respiratory epithelia[23,24]. However, this finding must be interpreted with caution, as it might be the truncated isoform of ACE2, termed deltaACE2, rather than the viral receptor molecule itself that is being upregulated[25]. Whilst the tissue-specific factors controlling SARS-CoV-2 infection are poorly understood, there is an increasing recognition of the role of additional accessory receptors in viral entry. It has been shown that the high-density lipoprotein scavenger receptor B type 1 (SR-B1) helps facilitate ACE2-dependent coronavirus attachment in vitro[26], reminiscent of hepatitis C virus infection[27]. Furthermore, treatments targeting SR-B1 reduced the lipoprotein-mediated enhancement

of SARS-CoV-2 infection[26]. However, the histological assessment of liver tissue in this study confirmed only sparse hepatic ACE2 expression.

To obtain liver tissue and detect viral infection during the short window of active respiratory illness is technically and clinically challenging. However, extrapulmonary infection is recognized, particularly in the gastrointestinal tract, with stool SARS-CoV PCR remaining positive for up to a week after viral clearance from the lungs[28]. Furthermore, pervasive infection of enterocytes has been well documented[29,30], with viral protein and RNA found to persist in intestinal biopsies for many months after clinical infection has resolved[18]. In post-mortem wedge liver biopsy samples from 48 patients dying from severe COVID-19 lung disease, SARS-CoV-2 was detected via in situ hybridization in 68% of samples[31]. Histological assessment also revealed vascular abnormalities characterized by portal venous and sinusoidal microthromboses (100%), microvesicular and macrovesicular steatosis (50%), mild portal inflammation (66%), and portal fibrosis (60%). The latter finding could suggest a degree of underlying liver disease, most likely secondary to nonalcoholic fatty liver disease (NAFLD) given that metabolic risk factors, including hypertension and cardiovascular disease, were enriched in this cohort. Again, the absence of histological evidence of biliary injury is conspicuous given the degree of cholangiocyte viral entry receptor expression. Post-mortem electron microscopy of liver tissue in a case of fatal respiratory COVID-19 has also directly visualized possible coronavirus-like particles in hepatocyte cytoplasm in association with mitochondrial swelling and apoptosis[32]. This finding would be consistent with large protein interaction maps that have identified connectivity between NSP5, the main protein of SARS-CoV-2, and mitochondrial components[33]. Conversely, in-depth proteomic assessment of autopsy tissue from 19 patients with COVID-19 revealed little evidence of active viral replication in the liver[34]. However, hepatic protein signatures did indicate upregulated profibrotic pathways, dysregulated fatty acid oxidation and oxidative phosphorylation, and markers of immune activation. This shifting proteomic landscape was found to be associated with the presence of multi-organ dysfunction, hepatic steatosis and coagulative hepatocyte necrosis[34].

Whilst there is variation in viral entry receptor expression profiles across the different in vitro and in vivo liver models (FIG. 1), direct evidence of specific SARS-CoV-2 hepatotropism is lacking. Given the poor outcomes and high rates of hepatic decompensation in patients with cirrhosis and COVID-19, more work is needed to determine the pathogenic role of direct hepatic viral infection and the mechanisms leading to hepatic decompensation in patients with underlying liver disease.

Liver biochemistry in COVID-19

Patterns and frequency of liver biochemistry abnormalities in COVID-19. Although the precise influence of COVID-19 on the liver remains unclear, abnormalities in liver biochemistries are common in patients with COVID-19, occurring in approximately 15–65% of SARS-CoV-2-infected individuals[35–42]. The wide range in these reported frequencies could be attributable to different definitions of upper limit of normal, varying laboratory values considered as liver enzymes, and geographical variability in the prevalence and type of underlying CLD[43]. Liver biochemistry abnormalities in COVID-19 are generally characterized by mild (1–2 times the upper limit of normal) elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, reported in an estimated 29–39% and 38–63% of patients, respectively[36–38,44]. Hypoalbuminaemia, a non-specific marker of illness severity, has been reported to be associated with worse COVID-19 outcomes[45], but severe liver injury, elevation in serum bilirubin level and liver synthetic dysfunction are all rare in patients infected with SARS-CoV-2 (REFS[41,42,44]). Abnormalities in liver biochemistries are reported in similar frequencies regardless of the presence of pre-existing liver disease[46].

Underlying causes of elevated liver enzymes in COVID-19. There are a number of potential contributors to elevated liver enzyme levels in COVID-19. Liver biopsy results in patients with SARS-CoV-2 have been characterized by non-specific findings, including steatosis, mild lobular and/or portal inflammation, and vascular pathology[31,47,48]. In most cases, abnormal biochemistries are likely multifactorial with potential contributions from immune-mediated inflammatory response, drug-induced liver injury, hepatic congestion and extrahepatic release of transaminases[49] as well as possible direct infection of hepatocytes.

Among hospitalized patients with COVID-19, elevations of serum AST levels positively correlate with levels of ALT but not with markers of muscle breakdown (such as creatinine kinase) or systemic inflammation (such as C-reactive protein (CRP) and ferritin)[50]. These findings imply that elevated liver enzymes in COVID-19 result from direct hepatic injury, although COVID-19-associated rhabdomyolysis is rarely reported[51]. Lastly, AST is often found to exceed ALT during the course of COVID-19, which would be atypical for a classic hepatocellular pattern of liver injury outside of specific contexts such as alcohol-related liver disease, certain drug-induced liver injuries (for example, lamotrigine), ischaemic hepatitis and cirrhosis[50]. The mechanisms responsible for an AST-predominant aminotransferase elevation remain incompletely defined but could include COVID-19-related mitochondrial dysfunction[33], SARS-CoV-2-induced hepatic steatosis[31] and altered hepatic perfusion secondary to microthrombotic disease[31,52]. A systemic review and meta-analysis of biopsy and autopsy studies reported the prevalence of hepatic vascular thrombosis in COVID-19 to be 29%[53]. Systemic hypoxia in COVID-19 might also have a contributory role and, interestingly, AST elevations have previously been reported with other viral pneumonias, including influenza A H1N1 infection, where levels increased in parallel with diminishing peripheral oxygen saturations[54].

As with many other infections, SARS-CoV-2 is associated with systemic inflammation that could contribute

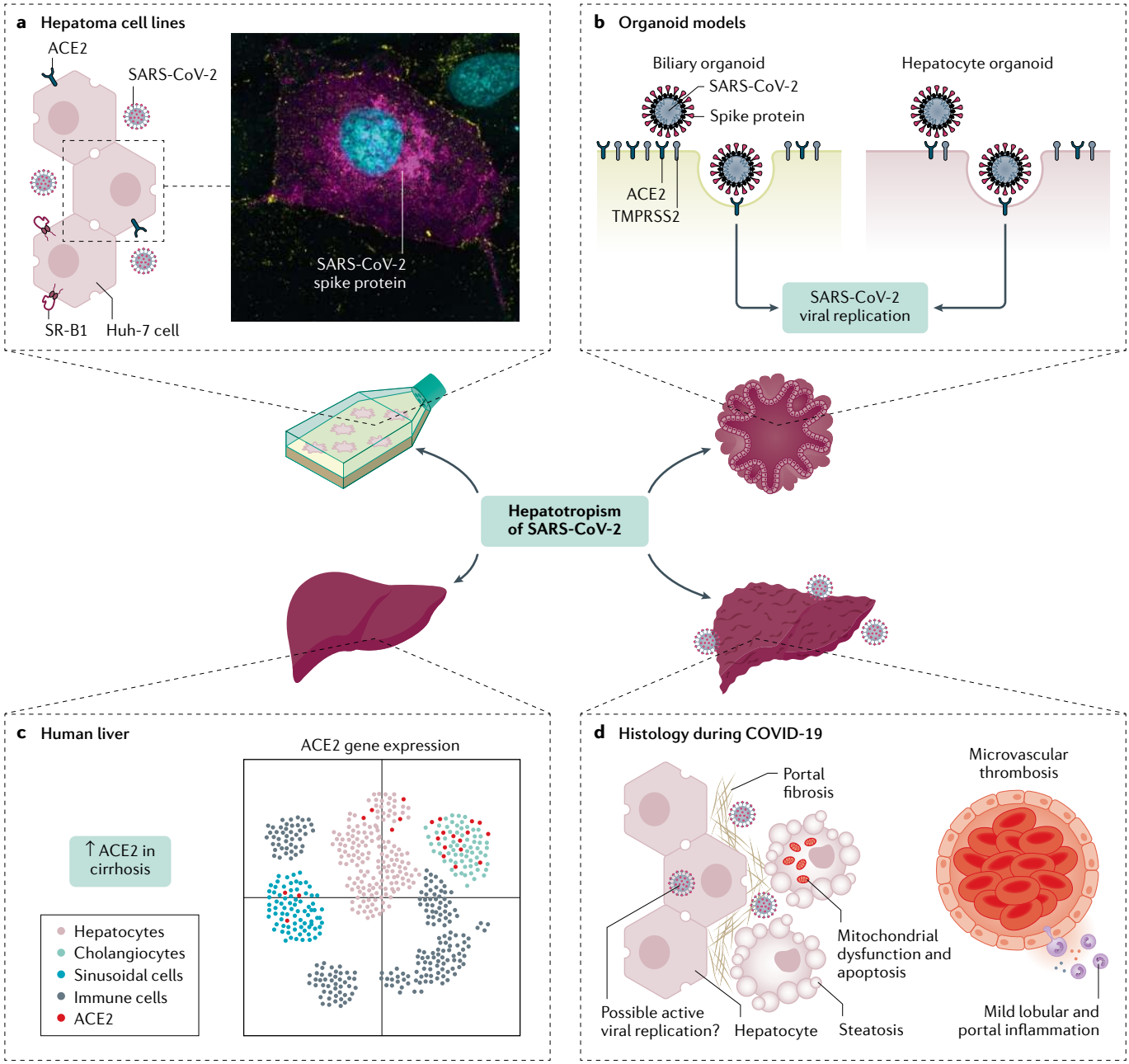

Fig. 1 | **Hepatotropism of SARS-CoV-2.** Understanding the hepatotropic effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has required a combination of experimental and clinical models. Hepatoma cell lines in vitro have been shown to support the entire life cycle of SARS-CoV-2 (part **a**, which shows a Huh-7 cell with widespread intracellular spike protein staining magenta). In vitro cell models have also demonstrated the role of accessory receptors such as high-density lipoprotein receptor scavenger receptor B type 1 (SR-B1) alongside ACE2 for cell entry. In addition, both biliary and hepatocyte organoid models have been shown to express necessary viral entry receptors and recapitulate SARS-CoV-2 infection (part **b**). Although there is some variability between gene expression studies regarding the distribution of ACE2 on liver cell types, cholangiocytes seem to have the greatest receptor concentration followed by hepatocytes (part **c**); there is also ACE2 upregulation in the parenchyma of cirrhotic livers. Lastly, histological examination of livers from patients with fatal respiratory coronavirus disease 2019 (COVID-19) have shown a range of microscopic changes such as widespread vascular abnormalities, steatosis and mitochondrial abnormalities (part **d**). The evidence for direct hepatocyte infection remains inconclusive. TMPRSS2, transmembrane serine protease 2. Part **a** microscopy image courtesy of S. Davies, University of Birmingham. Part **c** adapted with permission from REF.[12], Wiley.

to elevations in liver biochemistries via cytokine release[55]. Patients with substantial elevations in serum ALT levels often have high levels of CRP (which is synthesized by the liver), D-dimer, ferritin and IL-6 (REFS[44,45,56,57]). IL-6, which is produced by monocytes, macrophages and T cells in response to activation of the innate and adaptive immune system, is the key driver of CRP production and high IL-6 levels are associated with liver

injury in COVID-19 (REFS[44,56]). Notably, IL-6 increases during COVID-19 illness, declines as patients recover and correlates with severity of the disease course[58].

There are several other potential contributors to abnormal liver biochemistries in COVID-19, including ischaemic hepatitis, hepatic congestion related to cardiomyopathy, and transaminase release due to the breakdown of skeletal and cardiac muscle[49]. Venous and arterial thromboses are now a well-recognized feature of COVID-19 (REFS[59–62]), including in the liver[31,48], which could contribute to elevations in liver biochemistries. Lastly, drug-induced liver injury is likely to contribute to elevated liver enzymes and might have been more common early in the pandemic due to the use of experimental therapies[63]. However, no study has yet comprehensively mapped the pattern of liver function tests found within studies over the course of the pandemic. Specific COVID-19 treatments implicated in cases of drug-induced liver injury include lopinavir–ritonavir[64,65], tocilizumab[66,67] and remdesivir. The hepatotoxicity of remdesivir has been subject to debate. Although randomized trials in COVID-19 demonstrate equivalent liver enzyme elevations between treatment and control groups[68], screening of the WHO safety reports database still reveals a statistically significant odds ratio for liver injury with the use of remdisivir[69]. Fortunately, these considerations are likely to become less clinically relevant in light of the SOLIDARITY trial showing no benefit of remdesivir in hospitalized patients with COVID-19 (REF.[70]).

Prognostic significance of elevated liver enzymes in COVID-19. The prognostic significance of elevated liver enzymes in patients infected with SARS-CoV-2 is currently debated. Some reports have demonstrated that elevations of serum liver enzyme levels are associated with adverse outcomes, including shock, intensive care unit (ICU) admission and mechanical ventilation[43,65,71–74]. However, these studies could be prone to bias if patients with severe disease received more intensive laboratory monitoring, increasing the likelihood of detecting liver injury. Some have reported that there is no apparent association between liver enzyme level elevations and mortality[71,75], whereas others have found that elevated liver enzyme levels, and particularly AST and ALT level elevations greater than five times the upper limit of normal, are associated with an increased risk of death[42,44,76,77]. It has been proposed that the prognostic significance of elevated liver enzyme levels could be due to a more robust host response and aggressive therapies in those with severe illness[78].

SARS-CoV-2 infection and liver disease

Clinical course and outcomes following SARS-CoV-2 infection in pre-existing CLD. Patients with CLD and especially cirrhosis have multiple mechanisms of immune dysfunction that can lead to increased susceptibility to infection and an aberrant inflammatory response during infection — collectively known as cirrhosis-associated immune dysfunction (CAID). This immune dysfunction includes reduced components of the complement system, macrophage activation, impaired lymphocyte and neutrophil function, Toll-like receptor upregulation, and intestinal dysbiosis[9,79]. Although research attention has mostly focused on mechanisms leading to severe bacterial infection[80], CAID has also been shown to predispose to a variety of viral or fungal-related disease[81]. Whether patients with CLD and cirrhosis are more susceptible to SARS-CoV-2 infection has been the focus of much attention throughout 2020. Data from both large case series of thousands of consecutive patients with COVID-19 and population studies using health records do not suggest that patients with chronic liver disease are over-represented[5,37]. In fact, electronic health record data from the USA has demonstrated that patients with cirrhosis are actually at lower risk of testing positive for SARS-CoV-2 infection[82,83]. It remains improbable that cirrhosis is protective against SARS-CoV-2 acquisition and, therefore, this lower rate of positive testing is likely due to a combination of increased patient compliance with preventative measures (for example, social distancing, handwashing) and more frequent routine testing. Patients with cirrhosis who do acquire infections of all types have been shown to have worse clinical outcomes than patients without underlying liver disease[84,85] and SARS-CoV-2 infection seems to follow a similar pattern.

The aetiology of liver disease could influence clinical outcome in COVID-19. In the general population, advancing age, obesity and diabetes are risk factors for COVID-19 morbidity and mortality[5]; however, in these series, such patients were not explicitly diagnosed with NAFLD, in part because hepatic steatosis was not recorded or because alcohol use was not assessed. Indeed, there are wide inconsistencies throughout the literature regarding the influence of NAFLD on the COVID-19 course. This inconsistency could be related to difficulties in separating the effect of NAFLD from other metabolic comorbidities, due to the confounding effect of viral-induced steatosis or because of varying diagnostic criteria. The latter is of particular importance currently as the global hepatology community grapples with the proposed classification changes from NAFLD to metabolic dysfunction-associated liver disease[86]. One retrospective series of 202 consecutive patients with SARS-CoV-2 infection identified NAFLD as a risk factor for progressive COVID-19, abnormal liver enzyme levels and longer viral shedding time[87]. Another study in 327 patients showed an intersection between NAFLD and the risk of severe COVID-19 in patients under 60 years of age[88]. Similarly, MRI data from 287 patients tested for SARS-CoV-2 (79 positive, 208 negative) demonstrated that individuals with obesity and a concomitant liver fat fraction of ≥10% were at threefold increased risk of developing symptomatic laboratory-confirmed COVID-19 (available as a non-peer-reviewed Preprint only)[89]. However, in a series of 155 consecutive inpatients with COVID-19, the presence of steatosis (in 43%) was not independently associated with mortality[90]. These findings were confirmed in a larger international cohort of 745 patients with CLD and cirrhosis from 29 countries collected using the SECURE-Cirrhosis and COVID-Hep registries in which the odds ratio for death for patients with NAFLD

was 1.01 (95% CI 0.57–1.79)[91]. In this same study, alcohol-related liver disease was the only liver disease aetiology with a significant odds ratio for death (1.79, 95% CI 1.03–3.13)[91]. Registry data for 70 patients with autoimmune hepatitis and SARS-CoV-2 infection has also shown equivalent outcomes to patients with CLD of other aetiology and to propensity score-matched controls despite the use of baseline immunosuppression in 86% of cases[92]. In multiple series, the main cause of death in CLD patients was COVID-19-induced pulmonary disease followed by liver-related mortality[91,93].

Among patients with prevalent liver disease, once infected with SARS-CoV-2, there is a stepwise increase in morbidity and mortality with increasing severity of cirrhosis as measured by Child–Pugh (CP) class. Although the proportion of patients hospitalized in the SECURE-Cirrhosis and COVID-Hep registries was no different among patients with CLD and CP classes A, B and C, there was a stepwise increase in frequency of ICU admission, renal replacement therapy, invasive ventilation and death. There was also an increase in mortality for all patients as they required more intense medical support, with patients classed as CP-C having only a 10% survival once undergoing mechanical ventilation (FIG. 2). After adjusting for baseline characteristics, COVID-19-related mortality was significantly associated with the severity of pre-existing liver cirrhosis and the odds ratio for death increased across the stages of cirrhosis: CP-A 1.90 (95% CI 1.03–3.52), CP-B 4.14 (95% CI 2.24–7.65) and CP-C 9.32 (95% CI 4.8–18.08)[91]. Notably, registry data are vulnerable to reporting bias of more severe cases, which likely accounts for the inclusion of predominantly hospitalized patients in these studies. However, it is reassuring that the SECURE-Cirrhosis and COVID-Hep registries included a large proportion of patients without cirrhosis and with non-severe COVID-19 and that mortality was consistent with a range of other smaller cohorts (TABLE 1). A summary of studies reporting outcomes in patients with SARS-CoV-2 and pre-existing liver disease is presented in TABLE 1. Although the acute mortality associated with COVID-19 in patients with cirrhosis is high, in those who survive the initial insult, the rates of death and re-admission at 90-days are comparable to those with cirrhosis alone[94]. Therefore, beyond the acute infective period, SARS-CoV-2 infection does not seem to precipitate liver disease progression over and above the natural history of cirrhosis.

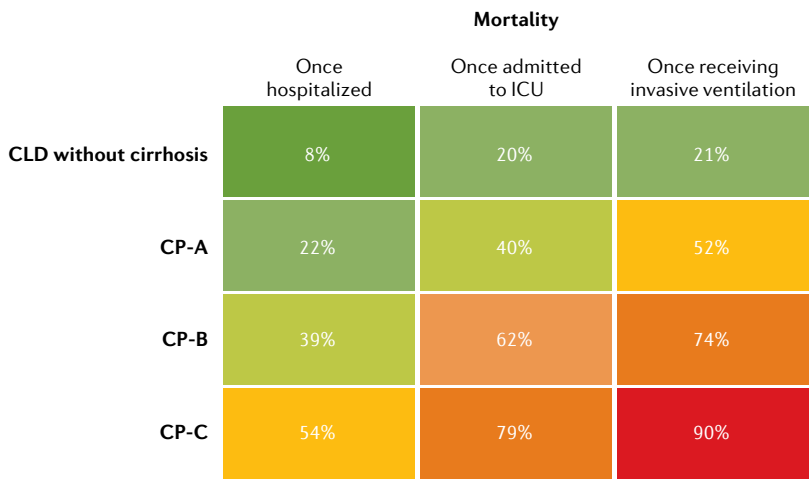

Fig. 2 | **Mortality following SARS-CoV-2 infection according to baseline liver disease stage and level of medical support.** Rates of mortality in patients with chronic liver disease (CLD) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection following hospitalization, admission to intensive care unit (ICU) and invasive ventilation separated by liver disease stage. CP, Child–Pugh. Adapted from REF.[91], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

COVID-19 can cause acute-on-chronic liver failure (ACLF). Although traditionally associated with bacterial infections, viral illness can also precipitate ACLF[85,95], which is marked by both liver-specific decompensation and increasing severity and frequency of extrahepatic organ system failure[96]. In the SECURE-Cirrhosis and COVID-Hep registries, hepatic decompensation events were more frequent with increasing severity of liver disease and mortality increased with worsening ACLF as measured by the CLIF-C score[91,93,97]. CAID likely underlies the intersection between severe COVID-19 pulmonary disease and ACLF. Cirrhosis is known to be associated with an increase in baseline endotoxemia and cytokine production that can lead to an exaggerated inflammatory response in the setting of infection (FIG. 3). This aspect might be particularly severe in patients with alcohol-induced liver disease[98], potentially explaining the increased mortality in this group[91]. It has also been shown that gut microbiota composition plays a role in regulating the magnitude of COVID-19 severity, possibly via modulating host immune responses[99]. Given that cirrhosis is characterized by changes to gut microbiota composition and function alongside intestinal permeability[100], it is possible that alterations in the gut–liver axis might contribute to the severe COVID-19 course observed in this patient group. However, further research into the mechanisms underlying CAID, ACLF and COVID-19 are required.

Lastly, the COVID-19 pandemic has unmasked the long-entrenched associations between race, socioeconomic status and adverse health outcomes. This issue includes patients with CLD for which socioeconomic disparities in American non-Hispanic Black and Hispanic communities have been associated with an increased risk of SARS-CoV-2 infection[101]. In addition, racial and socioeconomic disparities in internet access have been shown to translate into barriers for the use of telehealth, particularly video technology, in patients with CLD[102].

Specific management of patients with COVID-19 and underlying liver disease. The optimal approach to the management of patients with underlying liver disease who acquire SARS-CoV-2 infection is still evolving. However, the characterization of the COVID-19 course through multicentre and international cohorts has helped optimize the treatment strategies for this patient group, as summarized in various consensus guidelines[103–105].

Firstly, the recognition that patients with cirrhosis are particularly vulnerable to the severe complications of COVID-19 is paramount. This recognition should encourage a low threshold for SARS-CoV-2 testing and consideration of early admission for those with a positive diagnosis. Acute hepatic decompensation is

Table 1 | **Summary of COVID-19 outcome studies in patients with CLD and post-liver transplantation**

Study	Design	Country/region and number included	Major findings
Cirrhosis			
Marjot et al.[91] (Oct 2020)	Large international registry study	29 countries; SARS-CoV-2 infection plus cirrhosis (n = 386); SARS-CoV-2 plus CLD without cirrhosis (n = 359); SARS-CoV-2 plus non-CLD (n = 620)	Overall mortality: CP-A (19%), CP-B (35%), CP-C (51%), CLD without cirrhosis (8%); increased risk of death cirrhosis vs CLD without cirrhosis: CP-A (OR 1.9, 95% CI 1.03–3.5), CP-B (OR 4.1, 95% CI 2.4–7.77), CP-C (OR 9.32, 95% CI 4.80–18); increased risk of death compared with propensity score-matched patients without CLD: CP-B (+20%, 8.8–31.3%) and CP-C (+38%, 27.1–49.2%)
Iavarone et al.[93] (Jun 2020)	Multicentre retrospective cohort study	Italy; SARS-CoV-2 plus cirrhosis (n = 50); SARS-CoV-2 plus no cirrhosis (n = 399); cirrhosis plus bacterial infection (n = 47)	30-day mortality: SARS-CoV-2 plus cirrhosis vs SARS-CoV-2 plus no cirrhosis (34% vs 18%; P = 0.030); SARS-CoV-2 plus cirrhosis vs cirrhosis plus bacterial infection (34% vs 17%; P = 0.03)
Bajaj et al.[177] (Jun 2020)	Multicentre retrospective cohort study	North America and Canada; SARS-CoV-2 plus no cirrhosis (n = 108); SARS-CoV-2 plus cirrhosis (n = 37); cirrhosis alone (n = 127)	Overall mortality: cirrhosis plus SARS-CoV-2 higher mortality compared with patients with SARS-CoV-2 alone (30% vs 13%; P = 0.03) but not between patients with cirrhosis plus SARS-CoV-2 and patients with cirrhosis alone (30% vs 20%; P = 0.16)
Kim et al.[178] (Sep 2020)	Multicentre retrospective cohort study	North America; SARS-CoV-2 plus CLD without cirrhosis (n = 620); SARS-CoV-2 plus cirrhosis (n = 227)	Increased risk of death with decompensated cirrhosis (OR 2.91, 95% CI 1.70–5.00); no increased risk with compensated cirrhosis (OR 0.83, 95% CI 0.46–1.49)
Sarin et al.[179] (Jun 2020)	Multinational registry study	13 countries in Asia; SARS-CoV-2 plus CLD without cirrhosis (n = 185); SARS-CoV-2 plus cirrhosis (n = 43)	Overall mortality: SARS-CoV-2 plus CLD without cirrhosis vs SARS-CoV-2 plus cirrhosis (16% vs 3%; P = 0.002)
Clift et al.[128] (Sep 2020)	Population-based cohort study using electronic health record data	United Kingdom; 6 million adults: 11,865 with cirrhosis, 37 deaths from COVID-19 in patients with cirrhosis and 106 hospitalizations with COVID-19 in patients with cirrhosis	Hazard ratio for COVID-19-related mortality in patients with cirrhosis: women in derivation cohort, 1.8 (95% CI 1.15–2.99); men in derivation cohort, 1.29 (95% CI 0.83–2.02)
Ioannou et al.[83] (Nov 2020)	Population-based study using electronic health record data	North America; SARS-CoV-2 plus cirrhosis (n = 305); SARS-CoV-2 plus no cirrhosis (n = 9,826); cirrhosis alone (n = 3,301)	Patients with SARS-CoV-2 plus cirrhosis 3.5 times more likely to die than those with SARS-CoV-2 without cirrhosis
Liver transplant recipients			
Webb et al.[117] (Aug 2020)	Large international registry study	18 countries; SARS-CoV-2 plus LT recipient (n = 151); SARS-CoV-2 plus non-LT recipients from Oxford University Hospitals (n = 627)	Overall mortality (19%); LT did not significantly increase the risk of death (absolute risk difference 1.4%, 95% CI –7.7 to 10.4); risk factors for mortality within LT recipients: age, renal function and non-HCC cancer
Colmenero et al.[115] (Aug 2020)	Prospective multicentre cohort study	Spain; SARS-CoV-2 plus LT recipient (n = 111); SARS-CoV-2 plus general population during study period (n = 150,000); LT recipients without SARS-CoV-2 (n = 13,000)	Mortality in LT recipients (18%) lower than the matched general population; SMR 95.5 (95% CI 94.2–96.8); SIR 191.2 (95% CI 190.3–192.2) Baseline mycophenolate independent risk factor for severe COVID-19 (ICU, IPPV or death) (RR 3.94, 95% CI 1.59–9.74; P = 0.003).
Webb et al.[129] (Feb 2021)	Combined analysis of Webb et al[117] and Colmenero et al.[115]	18 countries including 108 cases from Spain; SARS-CoV-2 plus LT recipient (n = 258)	Age and Charlson Comorbidity Index independently associated with death; no association with type of immunosuppression regime
Rabiee et al.[127] (Sep 2020)	Multicentre retrospective cohort study	SARS-CoV-2 plus LT recipient (n = 112)	Overall mortality (22%); no independent risk factors for death identified
Ravanan et al.[116] (Aug 2020)	National cohort study: National Health Service Blood and Transplant registry data	England; SARS-CoV-2 plus LT recipient (n = 64); rates of infection and mortality compared with all SARS-CoV-2-positive general English population	Overall mortality (23%); reduced risk of SARS-CoV-2 infection (OR 0.53, 95% CI 0.40–0.70)
Kates et al.[180] (Aug 2020)	Multicentre prospective cohort study	USA; SARS-CoV-2 plus LT recipients (n = 73)	28-day mortality (21%); within whole solid organ transplant cohort (n = 482), LT not independently associated with death
Belli et al.[181] (Dec 2020)	European registry study	9 European countries; SARS-CoV-2 plus LT recipient (n = 243)	Overall mortality (20%); risk factors for mortality: age, diabetes, chronic kidney disease; Tacrolimus had positive independent effect of survival (0.55; 95% CI 0.31–0.99)
Alcohol-related liver disease			
Marjot et al.[91] (Oct 2020)	Large international registry study	29 countries; SARS-CoV-2 plus CLD (n = 745); SARS = CoV-2 plus ALD (n = 179)	ALD independent risk factor for death (OR 1.79, 95% CI 1.03–3.13)
Kim et al.[178] (Sep 2020)	Multicentre retrospective cohort study	North America; SARS-CoV-2 plus CLD (n = 867); SARS-CoV-2 plus ALD (n = 94)	ALD independent risk factor for death (HR 2.42, 95% CI 1.29–4.55)

Table 1 (cont.) | **Summary of COVID-19 outcome studies in patients with CLD and post-liver transplantation**

Study	Design	Country/region and number included	Major findings
Nonalcoholic fatty liver disease			
Marjot et al.[91] (Oct 2020)	Large international registry study	29 countries; SARS-CoV-2 plus CLD (n = 745); SARS-CoV-2 plus NAFLD (n = 322)	No independent association with death controlling for age, sex, ethnicity, liver disease stage, BMI, CVD, T2DM, hypertension, COPD, smoking status
Kim et al.[178] (Sep 2020)	Multicentre retrospective cohort study	North America; SARS-CoV-2 plus CLD (n = 867); SARS-CoV-2 plus NAFLD (n = 465)	No independent association with death controlling for age, sex, ethnicity, cirrhosis, T2DM, hypertension, CVD, COPD, smoking status
Viral hepatitis			
Marjot et al.[91] (Oct 2020)	Large international registry study	29 countries; SARS-CoV-2 plus CLD (n = 745); SARS-CoV-2 plus HBV (n = 96); SARS-CoV-2 plus HCV (n = 92)	No independent association with death
Kim et al.[178] (Sep 2020)	Multicentre retrospective cohort study	North America; SARS-CoV-2 plus CLD (n = 867); SARS-CoV-2 plus HBV (n = 62); SARS-CoV-2 plus HCV (n = 190)	No independent association with death
Butt et al.[182] (Feb 2021)	Population-based study using electronic health record data	USA; SARS-CoV-2 plus HCV (n = 975), SARS-CoV-2 no HCV (n = 975)	SARS-CoV-2 plus HCV more likely to be hospitalised but not at increased risk of death.
Hepatocellular carcinoma			
Marjot et al.[91] (Oct 2020)	Large international registry study	29 countries; SARS-CoV-2 plus CLD (n = 745); SARS-CoV-2 plus HCC (n = 48)	No independent association with death
Kim et al.[178] (Sep 2020)	Multicentre retrospective cohort study	North America;SARS-CoV-2 plus CLD (n = 867); SARS-CoV-2 plus HCC (n = 22); locoregional therapy (n = 8), immunotherapy (n = 2)	Independent risk factor for death (HR 3.96, 95% CI 1.74–8.98)
Autoimmune liver disease			
Marjot et al.[92] (Jan 2021)	Large international registry study	35 countries; SARS-CoV-2 plus AIH (n = 70); 86% immunosuppression; SARS-CoV-2 plus non-AIH CLD (n = 862); SARS-CoV-2 plus non-CLD (n = 769)	Immunosuppression not an independent risk factor for death in patients with AIH; equivalent rates of mortality for patients with AIH vs non-AIH CLD; higher rates of hospitalization but equivalent rates of mortality for patients with AIH compared to non-CLD

Summary of studies investigating the effect of SARS-CoV-2 infection on patients with chronic liver disease separated by disease aetiology or post liver transplantation. AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus diseases 2019; CP, Child–Pugh; CVD, cardiovascular disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; IPPV, invasive positive pressure ventilation; LT, liver transplant; NAFLD, nonalcoholic fatty liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SIR, standardized incidence ratio; SMR, standardized mortality ratio; T2DM, type 2 diabetes mellitus.

common, occurring in 47% of patients with cirrhosis and COVID-19, and typically manifests as worsening ascites and encephalopathy[91], which should be identified and managed along traditional lines[106]. Indeed, hepatic decompensation could be the first and only indication of SARS-CoV-2 infection in patients with cirrhosis, with 24% having no concurrent pulmonary symptoms[91]. Importantly, data have shown that patients with autoimmune hepatitis have similar rates of COVID-19-related mortality to the matched general population[92] and that the use of immunosuppression is not an independent risk factor for death. This finding should reassure clinicians and provides a clear rationale not to routinely reduce immunosuppression in these patients during the COVID-19 course.

The trajectory of patients with COVID-19 and decompensated cirrhosis at baseline is bleak, with up to 80% mortality in those requiring ICU support[91], although this number might decrease with time as the care of patients with COVID-19 continues to improve. Notably, the majority of deaths in patients with cirrhosis and COVID-19 are from respiratory failure, although the precise mechanisms underpinning this observation remain unclear. However, it is plausible that pulmonary venothromboembolic disease, a hallmark of critical COVID-19, has a contributory role given the additional hypercoagulable state associated with cirrhosis. Whilst routine thromboprophylaxis is universally recommended in hospitalized patients with COVID-19, unified risk stratification models and treatment algorithms have yet to emerge, with wide variation in clinical practice and between international guidelines[107,108]. However, given the coagulopathy associated with both cirrhosis and COVID-19, the coexistence of these conditions might yield a cumulative risk of thrombotic complications[103]. Although it remains to be determined whether enhanced venothromboembolic prophylaxis will be of benefit in this patient group, studies prior to the COVID-19 pandemic showed a benefit of anticoagulation in reducing portal pressures[109] without an excess bleeding risk[110]. In addition, a multicentre study in northern Italy reassuringly reported no major haemorrhagic complications with the use of thromboprophylaxis in 40 patients with cirrhosis admitted with COVID-19. Unfortunately, patients with advanced cirrhosis are excluded in many (but not all) published and active trials investigating optimal thromboprophylaxis following admission with SARS-CoV-2 infection[111,112].

The race to develop specific therapies for COVID-19 continues at pace. However, an international registry study involving 29 countries and 130 different institutions found that patients with cirrhosis were significantly

less likely to receive targeted antiviral therapy than those without (33% versus 52%; $P < 0.001$)[91]. This finding might reflect prescribing concerns and demonstrates the need for COVID-19 trials to carefully evaluate drug hepatotoxicity to prevent patients with cirrhosis, who are already at high risk of death, from being unnecessarily denied disease-modifying treatment.

Clinical course and outcomes of SARS-CoV-2 infection in liver transplant recipients. In population terms, SARS-CoV-2 infections in liver transplant (LT) recipients are relatively uncommon. However, there is keen interest in the effect of SARS-CoV-2 on this patient cohort, who have frequent exposure to health-care facilities and frequent concurrent comorbidities and among whom the majority have an absolute requirement for chronic immunosuppression[113,114].

Assessing the susceptibility of LT recipients to SARS-CoV-2 infection is challenging because of geographical and chronological variability in diagnostic methods, thresholds for testing and individual exposures. Nonetheless, country-wide data from Spain and the UK suggest that diagnoses of SARS-CoV-2 are more frequent among LT recipients than among the general population, although this finding might be partly attributable to more intensive monitoring and a lower threshold for viral testing in the liver transplantation setting[115,116]. Further data from primary care cohorts will increase our understanding of this area but will require careful correlation with contemporary epidemiology.

It is clear that not all LT recipients diagnosed with SARS-CoV-2 infection develop severe COVID-19. For example, in the Spanish series ($n = 111$), 6% were described as asymptomatic and, in a multinational series ($n = 151$), 14% had neither respiratory nor gastrointestinal symptoms[115,117]. In a German study that used serology to identify LT recipients with likely previous exposure to SARS-CoV-2, 5 of 8 individuals with a detectable IgG response reported no previous symptoms consistent with COVID-19 (REF.[118]).

In those who develop symptoms, the key respiratory features of COVID-19 appear similar in those with and without liver transplatation, with fever, cough and dyspnoea developing around 1 week following SARS-CoV-2 infection. In patients hospitalized with severe disease, marked elevations in ferritin, D-dimer and IL-6 levels alongside lymphopenia on laboratory assays, and diffuse parenchymal opacities without pleural effusion on chest radiology are well-recognized[119,120]. One difference among LT recipients seems to be a high frequency of gastrointestinal symptoms, with diarrhoea reported in 31% and 42% of two early cohorts, respectively[119,120]. In a

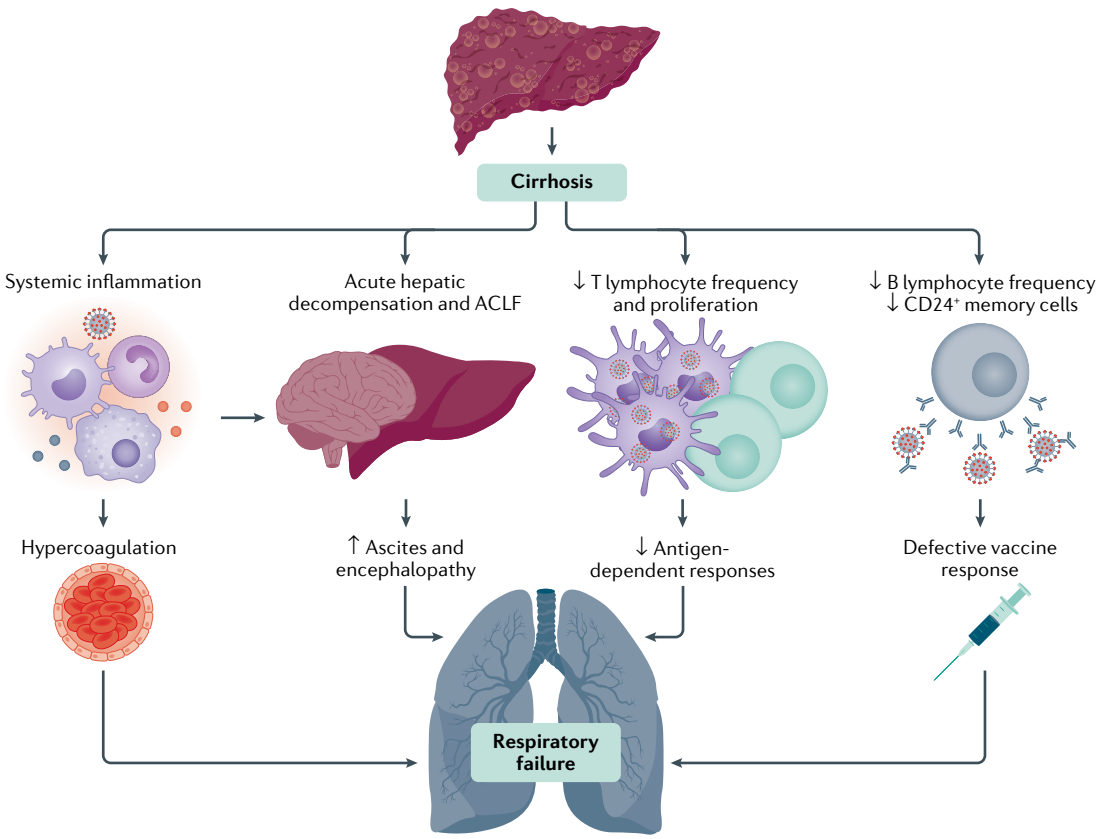

Fig. 3 | **Possible mechanisms for adverse COVID-19 outcomes in patients with cirrhosis.** Patients with cirrhosis have a high risk of mortality from respiratory failure following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This risk might occur through multiple converging pathways, including contributions from cirrhosis-associated immune dysfunction, acute hepatic decompensation and a systemic inflammatory response. Cirrhosis-associated immune dysfunction could also lead to defective immune responses following future SARS-CoV-2 vaccination. ACLF, acute-on-chronic liver failure; COVID-19, coronavirus disease 2019.

propensity-matched analysis, gastrointestinal symptoms were also more frequent among patients with LT than in those without[117].

Assessing the outcomes associated with liver transplantation among individuals infected with SARS-CoV-2 is complicated by the demography and pattern of comorbidity within the population. LT recipients are more likely to be male[121] and more likely to have renal impairment[122], type 2 diabetes mellitus[123] and obesity[124] than the general population. Furthermore, the age of LT recipients is increasing, with a median recipient age in both the USA and the UK of 56 years[125]. All of these factors are well established as being associated with an increased risk of adverse outcomes following SARS-CoV-2 infection and these risks seem to apply to LT recipients. Within cohort studies of LT recipients, age and burden of comorbidity (for example, Charlson Comorbidity Index) are strongly associated with death or severe disease course[115,117]. Although only a minority of LT recipients have clinically significant liver dysfunction, if present, this aspect could logically be considered a possible additional risk factor for severe COVID-19 as described elsewhere in this Review[126].

When considering the risk conveyed by liver transplantation itself in the context of SARS-CoV-2 infection, adjustment for concurrent comorbidity is required. Clinical data incorporating such adjustments suggest that LT recipients are not at increased risk of severe COVID-19 or death as compared to non-LT recipients[115,117]. Notably, such data derived from registry work are open to reporting biases, although case fatality rates are broadly consistent across cohort studies from the first wave of the pandemic at around 20%[115–117,119,127]. Importantly, the observation of there being no increased risk of severe COVID-19 seems to hold true when comparing the national LT and non-LT populations in Spain[115]. Furthermore, work combining a large cohort of primary care records and hospital episodes in the UK has confirmed an increased risk of death from COVID-19 in patients with CLD but shown no statistically significant difference in mortality in non-renal solid organ recipients[128]. When considering the relative importance of comorbidity, it is notable that in pooled data from the two large cohorts of SARS-CoV-2 infection in LT recipients, no patient with a Charlson Comorbidity Index of 0 died (points are attributed for age >50 years but not LT itself[129].

The current understanding that liver transplantation and the associated immunosuppression itself do not seem to confer an increased risk of poor outcome in SARS-CoV-2 infection is consistent with other observations. First, typical immunosuppression for LT recipients primarily limits the adaptive immune response rather than the innate response, with the latter seeming primary in determining COVID-19 outcome[130]. The only form of immunosuppression strongly linked with poor outcomes identified to date is of specific deficits in the type I interferon innate response[131,132]. Second, reactive corticosteroid immunosuppression with high-dose dexamethasone reduces mortality in severe COVID-19 (REF.[133]). Third, as noted by others, immunosuppression, including for liver transplantation, did not emerge as a risk factor for poor outcome in SARS-CoV-1 or Middle Eastern Respiratory Syndrome infections, whereas comorbidities analogous to those conferring risk in SARS-CoV-2 infection did[134]. Interestingly, the fact that LT recipients have similar outcomes to the matched general population is in stark contrast to the very high rates of mortality reported in those with advanced liver disease. This finding might suggest that, in the context of COVID-19, immunosuppression secondary to CAID has a more deleterious effect than pharmacological immunosuppression.

It therefore remains the case that major international guidelines currently recommend against the routine cessation or reduction of immunosuppressive therapy in LT recipients before any SARS-CoV-2 infection and that modification following SARS-CoV-2 be considered under special circumstances such as in superadded bacterial infection or worsening respiratory failure[103,104,135]. As already discussed, disturbances of liver biochemistry are frequent in COVID-19 but seem to be an indirect effect of SARS-CoV-2 infection analogous to that seen in the cytokine storm in other situations[55,57,130]. Although liver injury — as defined by elevated serum transaminase activities — occurs in LT recipients and is associated with mortality, it seems either no more frequent or less frequent than in comparison groups[117,127].

Whilst data about differences on SARS-CoV-2 infection in those with LT is accumulating, numerous issues remain (BOX 1). However, to date, it seems clear that the weight of comorbidity is more important in determining outcome than LT status per se and that being an immunosuppressed LT recipient confers less risk from SARS-CoV-2 than having advanced CLD, thereby supporting the continuation of liver transplantation programmes.

Challenges and considerations with SARS-CoV-2 vaccination in patients with CLD. SARS-CoV-2 vaccine development has progressed at an unprecedented rate. The Pfizer/BioNTech BNT162b2 mRNA, Moderna mRNA-1273, AstraZeneca/University of Oxford ChAdOx1-nCoV-19 chimpanzee adenovirus vector vaccine and the heterologous recombinant adenovirus-based Gam-COVID-Vac (Sputnik V) have each reported excellent safety profiles and marked efficacy in preventing symptomatic COVID-19 (62–95%)[136–139]. Despite the inclusion of over 100,000 participants in phase III trials, data in patients with liver disease are limited, representing less than 0.5% of those enrolled. Therefore, as vaccines accelerate into licensing and deployment, it is now vital to consider the specific implications for individual disease states, including CLD[140].

Cirrhosis is associated with both systemic inflammation and innate and adaptive immune dysfunction predisposing to infection-related morbidity and mortality[141–143]. Similarly, patients with cirrhosis have been shown to have impaired responses to existing licensed vaccinations such as those for pneumococcus and hepatitis B virus[144,145] (FIG. 3). Whilst it is biologically plausible that patients with cirrhosis might also respond poorly to SARS-CoV-2 vaccination, current data to support this notion are lacking. It is therefore difficult to speculate as

Box 1 | **Key unresolved issues for SARS-CoV-2 infection in LT recipients**

Susceptibility and disease course

- What is the role of health-care exposure? Health-care acquisition in liver transplant (LT) recipients has been reported[118]; it is unclear as to the optimum method of minimizing this exposure.
- Is recurrent infection more likely? With early reports of reinfection in non-transplant patients, it remains unknown as to whether LT recipients with impaired adaptive responses will be susceptible to reinfection[183].
- Is viral shedding prolonged in LT recipients? Case reports suggest prolonged viral shedding in some LT recipients, which might have public health implications[184].
- Is the post-infection immune response durable? Early reports suggest that the neutralizing IgG response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is of variable duration[185]. This aspect is unexplored in LT recipients. It is unclear whether a protective post-infection immune response will persist after transplantation.
- Is the apparent increased frequency of gastrointestinal symptoms of clinical importance? Gastrointestinal symptoms seem more frequent in LT recipients; the importance of this finding remains unclear.

Therapeutics and clinical management

- Caution with drug–drug interactions with novel therapies: drug interactions are frequent in transplant recipients, especially with calcineurin inhibitors, and must be considered with future novel therapies.
- Caution with putative future therapies that act to stimulate aspects of the immune response: putative coronavirus disease 2019 (COVID-19) therapies, such as interferon or checkpoint inhibition, might have severe adverse effects in LT recipients[186,187].
- The value of additional immunosuppression in severe COVID-19: it is unclear as to whether the benefit of dexamethasone that was demonstrated in those with severe COVID-19 applies to those already immunosuppressed[133]. Equally, the cytokine response to SARS-CoV-2 in LT recipients is undefined.

Immunization

- Response to SARS-CoV-2 vaccination: LT recipients typically have reduced rates of seroconversion and reduced antibody titres in response to vaccination[188].
- Duration of any response to SARS-CoV-2 vaccines: duration of immune response to vaccination might be reduced in LT recipients.

Immunosuppression

- Optimal long-term immunosuppressant regimen: whether interindividual variations in immunosuppression affect disease susceptibility is undefined; some have suggested a negative effect of mycophenolate but this issue has not been confirmed[115,180].
- The characteristics of infection in the immediate post-operative course are undefined: patients in the immediate post-operative period are typically more substantially immunosuppressed (including potentially with depleting antibodies) and might have a different response to SARS-CoV-2.

to which vaccine type might be most effective for patients with cirrhosis or whether modifications to the standard vaccine dosing or timing will be required. Similarly, the immunogenicity of SARS-CoV-2 vaccines in LT recipients and immunosuppressed patients with autoimmune liver disease remains to be determined, with these groups also known to have attenuated responses to vaccinations against other diseases[146].

Neither the adenoviral vector nor the mRNA vaccine platforms contain live or attenuated virus and it therefore seems unlikely that immunization represents a particular safety concern for liver disease cohorts. Whilst historically there have been anxieties that vaccination in solid organ transplant recipients might lead to the development of alloimmunity and graft rejection, no clinical evidence has ever emerged to support this concern[146]. In light of the high COVID-19-related mortality in patients with decompensated cirrhosis, it remains of utmost importance to prioritize vaccination in this subgroup. Although LT recipients have comparable rates of COVID-19-related mortality to the matched general population[117], they do have higher rates of admission to intensive care and could have been relatively more protected throughout the pandemic due to enhanced social distancing. Thus, this group remain a vulnerable population and should also be prioritized for vaccination, with the benefits far outweighing the potential risks. These principles regarding the prioritization of vaccine delivery are reflected in the American Association for the Study of Liver Diseases (AASLD) consensus statement on COVID-19 vaccination in patients with liver disease, published in January 2021 (REF.[147]).

As COVID-19 vaccines are disseminated globally, it will be crucial to monitor for post-vaccination infection in patients with CLD. This may be facilitated though existing international registry platforms such as COVID-Hep (supported by the European Association for the Study of the Liver) and SECURE-Liver (formerly known as SECURE-Cirrhosis) (supported by the American Association for the Study of Liver Diseases). This real-world data collection should occur in parallel with detailed mechanistic work assessing T cell and humoral immune responses after vaccination in liver subpopulations. Ideally, this should involve a coordinated response from the hepatology community to account for heterogeneity between vaccine candidates, laboratory immune assays and liver disease phenotype.

COVID-19 pandemic on hepatology care

During the early phase of the COVID-19 pandemic, the prevention, control and management of SARS-CoV-2-infected patients rightfully took centre stage and it was therefore reasonable to reduce and postpone services for other non-urgent medical conditions. Nonetheless, such policies will inevitably have collateral downstream effects on patients, including those with CLD. With time, because of the delayed diagnosis and treatment of various liver diseases, there will be escalating morbidity and mortality[148] (FIG. 4).

Cirrhosis. In patients with cirrhosis, it is important to treat the underlying liver disease, screen for hepatocellular carcinoma (HCC) and varices, and promptly detect and treat complications of cirrhosis [106,149]. All these strategies might be affected during the pandemic. For instance, the delayed initiation of antiviral therapy in patients with chronic viral hepatitis and the relapse of problem drinking could lead to disease progression and decompensating events[150]. Postponing routine therapeutic paracentesis for tense ascites might convert an elective procedure into one requiring emergency hospitalization. Acute variceal haemorrhage could also develop in patients without timely endoscopic surveillance.

Hepatocellular carcinoma. Currently, both the AASLD and the European Association for the Study of the Liver (EASL) support the resumption of HCC surveillance in high-risk patients (for example, advanced cirrhosis, chronic hepatitis B virus infection) during the COVID-19

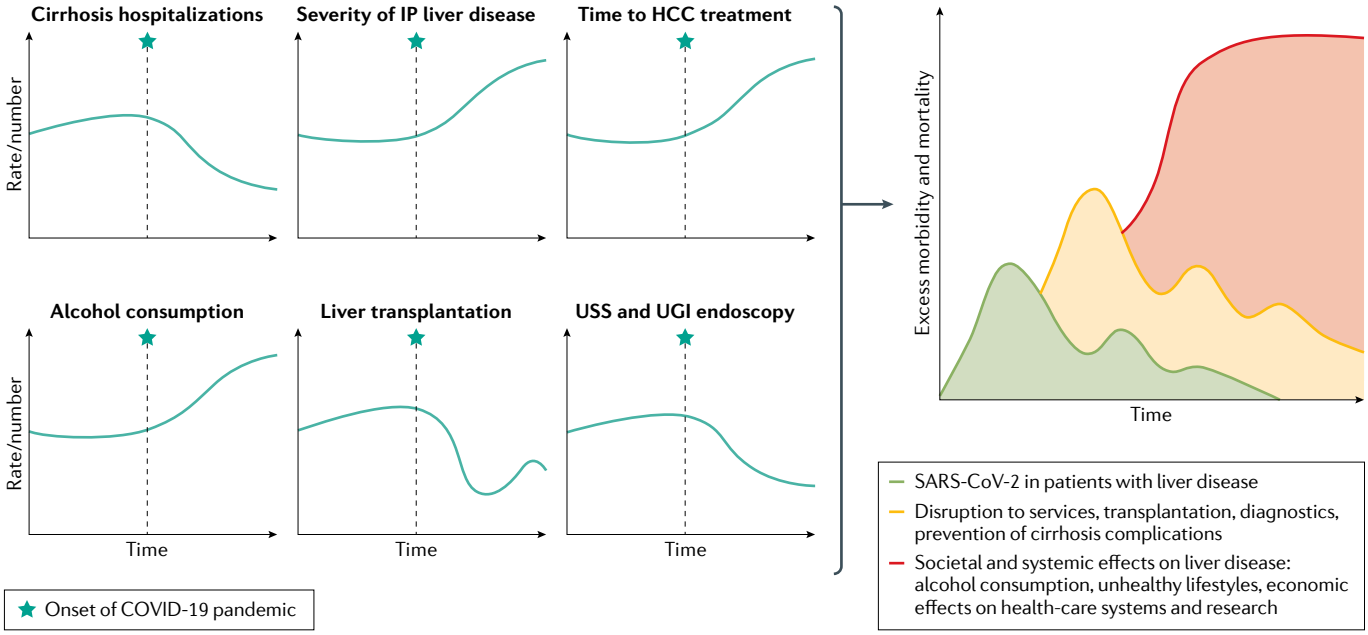

Fig. 4 | **Trends in liver disease risk factors and management and possible future effect on liver disease incidence and severity.** Trends over time in liver disease risk factors and hepatology care provision in relation to the onset of the coronavirus disease 2019 (COVID-19) pandemic and the cumulative short-term, medium-term and long-term effects this pandemic might have on liver health. HCC, hepatocellular carcinoma; IP, inpatient; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UGI, upper gastrointestinal; USS, ultrasound scan.

pandemic but recognize potential feasibility issues due to the strain on imaging and radiology resources[103,104]. The AASLD, therefore, recognises that an arbitrary delay of 2 months might be reasonable following the discussion of risks and benefits with the patient[104]. If HCC surveillance is deferred indefinitely, it is inevitable that the proportion of patients presenting with HCC not amenable to curative treatments will increase[151]. The proper management of HCC requires input from hepatologists, surgeons, intervention radiologists, oncologists and allied health workers, and therefore the maintenance of multidisciplinary care via telemedicine should be actively pursued. However, a multicentre study within the metropolitan area of Paris, France, during a period of high SARS-CoV-2 infection prevalence demonstrated a statistically significant reduction in the number of HCC diagnoses and double the rate of HCC treatment delay compared with the same period the previous year[152]. Nevertheless, the HCC treatment modality, including liver surgery, remained unchanged between the two time periods.

Liver transplantation. Liver transplantation programmes have been affected by the pandemic in a multitude of ways[153,154]. First, the recommendation against using organs from deceased donors with SARS-CoV-2 infection is consistent across all major guidelines[155]. Similarly, to avoid the risk of SARS-CoV-2 exposure and transmission, live donor transplantation has often been reduced or suspended[103,104]. During times of peak SARS-CoV-2 infection the strain on hospital resources, and particularly ICU availability, has meant that, for certain periods, liver transplantation has been reserved only for super-urgent and highly urgent cases[156]. Accordingly, data from both the American United Network for Organ Sharing–Organ Procurement Transplant Network and the UK National Health Service Blood and Transplant service show a clear inverse correlation between transplant activity and national rates of SARS-CoV-2 infection, with living donor liver transplantations most affected (FIG. 5). In order to maintain some transplant service provision, the pathways for organ procurement have had to remain flexible, with donors being sent to recipient centres or local organ retrieval and/or surgical teams from recipient centres travelling to donor hospitals.

Elimination of viral hepatitis. In 2017, the WHO published the first Global Hepatitis Report and set the aim to eliminate viral hepatitis as a major public health threat by 2030 (REF.[157]). Since then, healthcare providers, policymakers and patients have joined forces to scale-up screening, diagnosis, assessment and treatment of viral hepatitis. During the COVID-19 pandemic, although different countries have adopted measures, such as telemedicine and automatic drug refill, to ensure the continuation of current antiviral therapies, there has been a major impact on new case identification and treatment initiation. In a modelling study for 110 countries/territories, a 1-year delay in the progress of the hepatitis elimination programme is estimated to increase the number of HCC and liver-related deaths by 44,800 and 72,300, respectively[158]. However, despite these understandable concerns, there could be some positive ways to harness the widespread practical changes forced by the pandemic. For example, the decentralization of elimination efforts through postal blood-spot testing and medication delivery might have sustainable long-term benefits. Furthermore, political and health-care systems are now far more familiar with mass testing strategies,

contact tracing and vaccination delivery. There might now be an opportunity to harness this infrastructure to help combat chronic viral hepatitis at a population level[159]. This progress will also go hand-in-hand with other adaptations to health-care delivery such as telemedicine, remote monitoring and greater interaction with caregivers at home. These all represent promising opportunities to help deliver good hepatology care not only for viral hepatitis but across the spectrum of liver disease type and severity[160].

Liver research. COVID-19 has had a major effect on liver research, especially clinical trials, due to uncertainties surrounding infection control and difficulties adhering to the study protocols[161]. The follow-up, assessment and distribution of investigational products could all be hampered by quarantine measures and participant illness. For these reasons, many sponsors have stopped new case recruitment into clinical trials, which is likely to delay important drug development. It is therefore currently important to consider flexible solutions such as replacing less critical visits with phone or video calls, remote monitoring using local laboratories, and direct shipment of investigational products to the patients. There are also concerns about research funding due to economic downturn in the next few years[162]. The negative impact of the pandemic on existing non-COVID-19 basic and translational research must also not be underestimated. Institutions across the globe have endured major research set-backs, including laboratory closures, diversion of resources towards COVID-19 studies, and the loss of cell lines and animal models during national lockdowns[163]. Furthermore, the cancellation or postponement of national and international conferences has disrupted the valuable exchange of scientific information. In recovering from the COVID-19 pandemic it is therefore vital that policy and funding is structured in a way that helps rejuvenate basic science research activity.

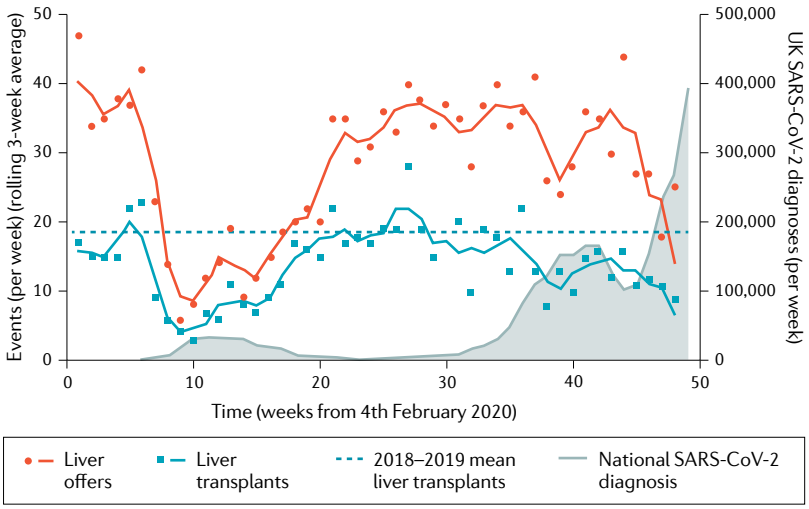

Fig. 5 | **UK Liver transplant activity before and during COVID-19 pandemic.** United Kingdom National Health Service Blood and Transplant service data on liver transplant activity before and during the coronavirus disease 2019 (COVID-19) pandemic. The data for FIG. 5 that support the plots within this paper are available from the NHS Blood and Transplant Organ Donation and Transplantation Reports and the Coronavirus (COVID-19) in the UK website. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

COVID-19 pandemic and patient behaviours

The COVID-19 pandemic has understandably modified human behaviour beyond recognition. However, some of these behaviours could negatively influence liver health, particularly with respect to alcohol use, diet and exercise, and patient interactions with medical services.

An increased alcohol consumption is now a well-recognized feature of the pandemic, particularly during periods of social isolation. In the weeks leading up the first national 'lockdown' in the UK, an additional £160 million were spent stockpiling alcohol compared with the same timeframe the previous year[164,165]. Furthermore, nationwide consumer data from the UK have shown a pervasive elevation in alcohol purchasing amongst all but the very poorest in society[166,167]. Data on alcohol sales have shown similar trends in the USA[168]. This change in behaviour has translated into harmful drinking habits, with national and international surveys consistently demonstrating an increase in regular alcohol use during the first wave of COVID-19 (REFS[169–171]) and an overall escalation in alcohol consumption reported in up to 48% of respondents[170]. In addition, 17% of abstinent individuals with a history of alcohol use disorder were found to relapse to drinking under lockdown conditions[172]. This finding contrasts with a decline in smoking, mostly due to a reduction in the number of lighter smokers[169]. Single-centre observations in the UK have also shown that referrals for alcoholic liver disease (ALD) and the proportion of critically unwell inpatients with ALD (but without COVID-19) more than doubled in June 2020 compared with June 2019 (REF.[173]). The upsurge in harmful drinking, alongside barriers to cessation services and the association between ALD and COVID-19 mortality (discussed earlier) is of major concern and suggests that alcohol advice should be central to the health messages delivered to patients and the general public during the pandemic.

The pandemic has also propagated unhealthy lifestyles predisposing to NAFLD. A study in northern Italy found that patients with obesity gained an average of 1.5 kg in weight during the national quarantine, in parallel with reduced exercise, excess calory intake, and increased self-reported anxiety and depression[174]. Similarly, a US survey of over 4,000 patients with diabetes found that one-third reported a less healthy diet and half reported performing less exercise during the pandemic[175]. Despite these observations, no study has yet directly evaluated the incidence of NAFLD in the COVID-19 era.

Lastly, the interaction of patients with secondary care services has changed. National US data from the Veterans Health Administration showed that that hospitalizations with cirrhosis decreased by a third following the onset of the pandemic compared with the previous year, with a significant increase in the severity of liver disease in those who were admitted[176]. This might reflect patient concerns about potential SARS-CoV-2 exposure leading to delayed presentations with more advanced complications of cirrhosis.

Conclusions

The hepatic consequences of SARS-CoV-2 infection are now recognized as an important component of COVID-19. This aspect is most clinically relevant in patients with pre-existing cirrhosis who are at remarkably high risk of severe COVID-19 and death. Whilst further work is required to understand the pathogenic mechanisms that drive this clinical deterioration, there are likely to be contributions from systemic inflammation, disordered coagulation and immune dysfunction. Although a range of in vitro and in vivo models have been used to help decipher the specific hepatotropism of SARS-CoV-2, the clinical impact of direct viral infection of liver cell types remains to be determined. The grave prognosis with COVID-19 in patients with cirrhosis contrasts with the LT population who have comparably better outcomes. It therefore seems that cirrhosis-associated immune dysfunction has a far more detrimental effect on the COVID-19 course than pharmacological immunosuppression. With efficacious SARS-CoV-2 vaccines now available, patients with cirrhosis should be seen as a priority for immunization and the hepatology community should prepare to carefully monitor the immune response in this subpopulation. Lastly, we must all be aware of the profound negative effect of the pandemic on liver services and unhealthy patient behaviours, which might culminate in an increase in the global burden of liver disease in the coming months and years.

Data availability

The UK Liver transplant and coronavirus data that support the plots within this paper are available from the NHS Blood and Transplant Organ Donation and Transplantation Reports website at https://www.odt.nhs.uk/statistics-and-reports/ and the Coronavirus (COVID-19) in the UK website at https://coronavirus.data.gov.uk/.

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Competing interests
A.S.B. has served as a consultant to Target RWE, Genfit and Intercept Pharmaceuticals. V.W.W. has served as a consultant or advisory board member for 3V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Center for Outcomes Research in Liver Diseases, Echosens, Gilead Sciences, Hanmi Pharmaceutical, Intercept, Merck, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, ProSciento, Sagimet Biosciences, Taerget RWE, and Terns and as a speaker for AbbVie, Bristol-Myers Squibb, Echosens and Gilead Sciences. The remaining authors declare no competing interests.

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