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Impact of COVID-19 on the liver and on the care of patients with chronic liver disease, hepatobiliary cancer, and liver transplantation: An updated EASL position paper

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Summary
The COVID-19 pandemic has presented a serious challenge to the hepatology community, particularly healthcare professionals and patients. While the rapid development of safe and effective vaccines and treatments has improved the clinical landscape, the emergence of the omicron variant has presented new challenges. Thus, it is timely that the European Association for the Study of the Liver provides a summary of the latest data on the impact of COVID-19 on the liver and issues guidance on the care of patients with chronic liver disease, hepatobiliary cancer, and previous liver transplantation, as the world continues to deal with the consequences of the COVID-19 pandemic.

Preface
Since the onset of the COVID-19 pandemic in early 2020, the European Association for the Study of the Liver (EASL) has published several position papers designed to provide guidance on the care of adult patients with liver diseases.1–3 As the landscape of COVID-19 continues to change, particularly with the emergence of new strains of SARS-CoV-2 and the development of novel treatment and vaccination strategies, there is an urgent need to provide updated information for clinicians and researchers. By the end of 2021, the B.1.1.529 (omicron) SARS-CoV-2 variant displaced the B.1.617.2 (delta) variant as the predominant circulating strain in many countries.4–6 Compared to earlier variants, omicron is more transmissible4 and resistant to neutralisation by antibodies induced by current vaccine platforms or following SARS-CoV-2 infection.6 Although infection with omicron appears to be associated with a less severe disease course,9–11 which may be explained by a lower replication competence in the lung parenchyma,12,13 it is still associated with a significant burden of morbidity and mortality worldwide.14 Whilst our understanding of omicron continues to evolve rapidly, a majority of the EASL position statements in this document are based on data derived from the pre-omicron era. Therefore, at present, it is not clear whether all recommendations may also apply to omicron or indeed to any future variants or sub-variants which may arise. Finally, prior infection with omicron may not provide adequate protection against earlier variants (such as delta) or new variants unless COVID-19 vaccination has been optimised.14 Despite these caveats, this position paper seeks to review all the available data, comprehensively summarise the liver-specific effects of SARS-CoV-2 infection, and highlight important care considerations for patients with COVID-19 and chronic liver disease (CLD), hepatobiliary cancer, and previous liver transplantation.

Liver-related complications of SARS-CoV-2 infection
Acute liver injury during COVID-19
Acute liver injury indicated by abnormal liver biochemistry parameters is common (occurring in 10–65% of individuals) during the course of COVID-19.15 These abnormalities are usually characterised by mild elevations in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), whereas severe liver injury with raised bilirubin and hepatic synthetic dysfunction is rare. The cause of liver injury during COVID-19 is likely multifactorial with contributions from systemic inflammation, cytokine signalling, ischaemia, and drug toxicity. Alongside this ‘bystander’ hepatitis, SARS-CoV-2 may cause direct liver injury via infection of hepatocytes. Multimodal investigations of autopsy liver tissue from patients with severe COVID-19 have convincingly demonstrated intrahepatic SARS-CoV-2 RNA alongside consistent molecular signatures associated with viral infections, suggesting that SARS-CoV-2 may trigger immunopathology directly in the liver.16 The presence and severity of acute liver injury in patients with COVID-19 does seem to correlate with overall

Keywords: SARS-CoV-2; COVID-19; cirrhosis; liver transplantation; chronic liver disease; hepatobiliary cancer; vaccination.

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disease severity and outcome although there is some inconsistency across studies. The longer-term trajectory of abnormal liver biochemistry following recovery from COVID-19 remains incompletely defined. In a large cohort of patients with COVID-19 who were hospitalised and then subsequently discharged, 43% had liver biochemistry abnormalities at the point of admission and 32% still showed abnormalities at the point of discharge suggesting that resolution of liver injury may lag behind recovery from respiratory symptoms. The time taken for complete normalisation of liver biochemistry has not been systematically investigated but persisting abnormalities following complete recovery from COVID-19 may indicate undiagnosed pre-existing CLD.

### EASL position

- **Liver parameters** (including AST, ALT, gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP) and bilirubin should be regularly assessed during hospitalisation with COVID-19.
- Ongoing monitoring may be required after hospital discharge in patients with persistent elevations in liver biochemistry parameters.

### Secondary sclerosing cholangitis after COVID-19

As discussed above, liver biochemistry abnormalities, particularly elevations in ALT and AST levels are common during the course of COVID-19 and are most likely multifactorial. In contrast, cholangitis, characterised by elevated bilirubin and ALP is not typically identified during acute COVID-19. Interestingly, this is despite cholangiocytes exhibiting high SARS-CoV-2 entry receptor expression and viral permissibility in vitro. However, over the course of the pandemic several case series have reported delayed-onset and progressive cholangitis as a unique clinical entity in patients following severe, and often critical, COVID-19. Furthermore, this may be a more frequent complication in patients with pre-existing CLD.

In a European cohort of 34 patients with COVID-19 who required admission to the intensive care unit (ICU), 9 (27%) developed severe cholestasis (total bilirubin ≥2x upper limit of normal [ULN]) of whom 4 (44%) subsequently developed features of secondary sclerosing cholangitis (SSC) defined by bile duct irregularities and strictures on magnetic resonance cholangiopancreatography (MRCP). Of these 4 patients with SSC, 2 died from respiratory failure, 1 developed decompensated cirrhosis and was listed for transplantation, and 1 had persistently elevated ALP 9 months after discharge from ICU. Notably, in a historic cohort of 34 patients admitted to ICU with influenza A, only 6% developed severe cholestasis and none exhibited features of SSC. Similarly, in a single-centre North American study, 12 patients admitted to the ICU with severe COVID-19 subsequently developed delayed-onset cholestasis (ALP >3x ULN) with associated MRCP abnormalities. This clinical picture was present in <0.6% of all patients hospitalised with COVID-19. Five of these patients were ultimately referred for consideration of liver transplantation after experiencing persistent jaundice, hepatic insufficiency, and/or recurrent bacterial cholangitis. Across both cohorts, organ support requirements during COVID-19 were strongly associated with the development of cholestasis. Indeed, patients who developed SSC had protracted ICU stays (36-138 days) with long periods of prone ventilation, and high respiratory support and vasopressor requirements, with a substantial proportion receiving extracorporeal membrane oxygenation (ECMO). The mean interval between COVID-19 diagnosis and the onset of cholangiopathy was 93 and 118 days in European and American cohorts, respectively. In patients where a liver biopsy was performed, histological features included large duct obstruction (but without definite bile duct loss), portal tract oedema, lobular biliary infarcts, and hepatocellular cholestasis. These cholestatic complications also appear more frequent and pronounced in patients with pre-existing CLD. In a retrospective study from Austria, approximately 20% of patients with CLD developed progressive cholestasis following SARS-CoV-2 infection, with 10/65 (15%) meeting criteria for SSC. Seventy percent of these patients with SSC had non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), 90% were treated with ursodeoxycholic acid, all patients had severe COVID-19 requiring ICU admission and 50% died.

Notably in both European series, >90% of patients who developed severe cholestasis or SSC were exposed to ketamine as an anaesthetic agent in the ICU. This contrasts with no ketamine use in an influenza cohort who developed SSC relatively rarely. Whilst recreational ketamine misuse has been associated with cholangiopathy, acute biliary injury in the context of critical illness is less well recognised. However, since the onset of the pandemic several case reports and series have postulated a mechanistic link between ketamine use and cholangiopathy following COVID-19.

Critical illness-SSC has long been recognised as a distinct pathological entity typically developing after burns, polytrauma, complex surgery, hypovolemic shock or other life-threatening diseases including influenza-associated acute respiratory distress syndrome. However, it is a rare condition, with only 200 cases reported in the...
Autoimmune and autoimmune-like hepatitis after COVID-19

The relationship between autoimmunity and COVID-19 is complex.31 Some of the clinical manifestations of COVID-19, including hyperinflammation and macrophage activation, can resemble the immunopathology of various autoimmune diseases such as juvenile idiopathic arthritis and systemic lupus erythematosus.32 De novo autoimmunity following SARS-CoV-2 infection is also well recognised, manifesting in a range of clinical phenomena including systemic lupus erythematosus, immune thrombocytopenic purpura, Guillain-Barré syndrome, and autoimmune/autoimmune-like hepatitis (AIH).33 Mechanistically, this could be related to viral-induced molecular mimicry31 resulting in the development of new-onset autoantibodies targeting traditional autoantigens or cytokines.34 To date, at least 6 cases of AIH following COVID-19 have been reported including a case of overlap with primary biliary cholangitis35–39 (Table 1). In each case, a diagnosis of AIH was made based on characteristic laboratory parameters including elevated transaminases, IgG, and the presence of associated autoantibodies. Liver biopsy was performed in 3 patients, all of whom demonstrated typical histological features of AIH, including lymphoplasmacytic inflammation and interface hepatitis. Most cases occurred within 1 month of mild COVID-19 and responded well to immunosuppressive therapy. Beyond these isolated reports, the broader population-level epidemiology of autoimmune liver disease during the pandemic remains to be determined, including both the incidence of de novo AIH and flares in those with pre-existing AIH. Prospective series have demonstrated a high prevalence of tissue-specific autoantibodies during or soon after recovery from COVID-19, including smooth muscle antibody and antinuclear antibody positivity in up to 30% and 44%, respectively.34,40,41 However, the longer-term clinical significance of these autoantibodies remains unclear. Given that new-onset clinically overt AIH appears rare and may occur even following mild COVID-19, we cannot currently recommend routine monitoring for this condition in all patients following SARS-CoV-2 infection.

EASL position

- Patients admitted to ICU with critical COVID-19 who develop severe cholestasis should undergo MRCP during the disease course (where possible) and monitoring of liver biochemistry for at least 3 months following ICU discharge to check for SSC.
- Where possible, ketamine may be avoided as a sedating agent in patients with CLD and critical COVID-19 who require ICU admission.

Risk stratification and disease course of SARS-CoV-2 infection in patients with CLD, hepatobiliary cancer, and liver transplant recipients

CLD and cirrhosis

During the first wave of the pandemic, patients with CLD and cirrhosis were not found to be over-represented in large COVID-19 case series and population studies, suggesting that these conditions were unlikely to increase susceptibility to infection.42,43 One large North American study even found that patients with cirrhosis had lower risk of SARS-CoV-2 positivity than the general population.44 This most likely reflects heightened vigilance and greater patient adherence to public health advice although interpretations are limited by retrospective design and lack of adjustment for certain relevant cofactors including socioeconomic status and occupational exposure. However, once patients with cirrhosis acquire SARS-CoV-2 infection it has become clear that they are at increased risk of adverse COVID-19 outcomes including death.

Overall mortality in patients with cirrhosis following SARS-CoV-2 infection was found to be 32% in a large registry cohort of 729 predominantly hospitalised patients with CLD across 29 countries, with case fatality rates incrementally increasing with each Child-Pugh (CP) class (CLD without cirrhosis; 8%, CP-A; 19%, CP-B; 35%, CP-C; 51%).45 Similar stepwise trends were observed in the rates of ICU admission, renal replacement therapy, and invasive mechanical ventilation. Furthermore, the risk of mortality in those with decompensated cirrhosis was significantly elevated compared to that in patients without CLD, after matching for age and comorbidity. Decompensated cirrhosis was also shown to be an independent risk factor for death based on outcome data from patients with
CLD across 21 North American institutions.46 High rates of COVID-19 mortality in cirrhosis, ranging between 20-30%, have also been replicated in an exclusively Asian registry47 and in several multicentre cohort studies across different geographical regions.46,48,49 This risk of death following SARS-CoV-2 infection appears to be higher compared to other infective insults including spontaneous bacterial peritonitis.48 An analysis of >220,000 patients with CLD in North America further emphasized the negative impact of advanced liver disease at a population level, with cirrhosis being associated with a 2.38-fold adjusted hazard of mortality 30 days after SARS-CoV-2 infection.50 Similarly, a retrospective French cohort of >259,000 inpatients with COVID-19 including >15,000 with pre-existing CLD, demonstrated that patients with decompensated cirrhosis were at an increased adjusted risk for mortality.51 This is further corroborated by data derived from the electronic health records of >6 million UK adults which indicated an elevated adjusted hazard ratio for both hospitalisation and death related to COVID-19 in patients coded as having cirrhosis.52 These findings contrast with those from a nationwide Swedish CLD cohort which did not demonstrate associations between cirrhosis and COVID-19-related mortality.53 However, this study was limited to patients with biopsy-proven CLD prior to 2017, and therefore more advanced liver disease may have been under-represented because these patients did not undergo biopsy or died before the onset of the pandemic. Lastly, meta-analysis of 63 outcome studies up until February 2021 revealed a pooled odds ratio for mortality of 2.48 (95% CI 2.02-3.04) in patients with cirrhosis and COVID-19.54 Of note, cirrhosis has also been found to be an independent risk factor of mortality and hospitalisation in patients with COVID-19 after vaccination.55 It is important to recognise that our understanding of the disease course of COVID-19 in patients with cirrhosis is nearly exclusively derived from data collected in the era preceding COVID-19 vaccination and the emergence of viral variants of concern (e.g. omicron). However, in a retrospective analysis of US veterans with cirrhosis, receipt of even a single mRNA vaccine dose not only reduced rates of SARS-CoV-2 infection but markedly improved rates of hospitalisation and death in those developing breakthrough COVID-19.56 The impact of the highly prevalent omicron variant including all subvariants in patients with CLD, as well as the modifying effect of COVID-19 vaccination, needs to be further investigated.

There are several clinical hallmarks of COVID-19 in patients with cirrhosis. Firstly, new or worsening acute hepatic decompensation, predominantly with ascites and/or hepatic encephalopathy, is a common presenting feature in up to 46% of patients.45 In 20–58% of cases, this decompensation occurs in the absence of typical respiratory symptoms of COVID-19.45,46 Presentation with gastrointestinal symptoms is more frequent in patients with cirrhosis than matched controls45 and is associated with a worse disease trajectory.46 This is already a well-recognised phenomena within the general population47 and is thought to be secondary to greater gut permeability and systemic inflammation. Historic studies have shown a >30-fold increase in angiotensin-converting enzyme 2 (ACE2) receptor expression in cirrhotic vs. healthy livers, suggesting that patients with cirrhosis may be uniquely susceptible to SARS-CoV-2-mediated hepatic dysfunction.48 In addition, Wanner et al. have shown clear evidence of specific SARS-CoV-2 hepatotropism, further indicating that the virus could trigger decompensation in patients with pre-existing CLD.16 Acute-on-chronic liver failure (ACLF) following SARS-CoV-2 infection is also well recognised, being reported in up to 12%–50%45,47,49 of decompensating patients. In this context, several scoring models have been applied, with the CLIF-C (Chronic Liver Failure-Consortium) ACLF and organ failure scores appearing to outperform model for end-stage liver disease, NACSELD (North American Consortium for the Study of End-stage Liver Disease), and CP scores.45,59 Despite SARS-CoV-2 triggering acute hepatic decompensation and ACLF, the predominant cause of death remains respiratory failure (71%) followed by liver-related complications (19%).45 The mechanistic links between hepatic dysfunction and subsequent lung injury are likely to be numerous and overlapping including cirrhosis-associated immune dysfunction, gut dysbiosis, altered pulmonary dynamics secondary to ascites and hepatic encephalopathy, and coagulopathy.55 In a large nationwide cohort study in France, Mallet et al. described an associated between pulmonary embolism and COVID-19 mortality, and reported a modest but significant increase in rates of pulmonary emboli in patients with vs. without CLD.51 In addition, this study introduced the concept of limited ‘therapeutic effort’ for patients with cirrhosis and alcohol-related liver disease (ALD), both of whom had a lower chance of mechanical ventilation and a higher risk of death. This suggests that there were barriers to patients with cirrhosis receiving invasive ventilation. Indeed, this may reflect a perception that patients with cirrhosis represent an underserved population analogous to racial and socioeconomic minorities who also exhibit a higher risk of severe COVID-19.52,60 Balancing the costs and benefits of ICU admission in severely unwell patients with cirrhosis has remained a consistent clinical challenge for decades,52 which may have become acutely unmasked during the COVID-19 pandemic.
The immunomodulating effects of alcohol are well recognised, with increased alcohol consumption known to predispose to a range of septic insults including community acquired bacterial and viral pneumonias. A history of harmful alcohol use also appears to increase susceptibility to acute respiratory distress syndrome, a hallmark of severe COVID-19, in critically ill patients with sepsis. Both registry data and multicentre studies have identified ALD as being independently associated with COVID-19 mortality after controlling for important cofactors including baseline liver disease severity. However, alcohol consumption in patients with CLD, categorised as either social drinking or current daily drinking, was not associated with all-cause mortality compared to abstinence in a multivariable model. The precise nature of this negative association exceeded that observed with any other individual comorbidity or category of Charlson comorbidity index, suggesting that mortality in hospitalised patients with ALD and COVID-19 may be partly explained by discrepancies in the allocation of healthcare resources. These findings are especially alarming given that the incidence of harmful drinking, ALD, and alcohol-related hospital admissions have dramatically increased since the onset of the pandemic (see below) and collectively highlights the urgent need for concerted institutional and public health efforts to tackle the rise in alcohol-related harm.

**EASL position**
- Patients with CLD do not appear to have a higher risk of SARS-CoV-2 infection but are at increased risk of mortality following SARS-CoV-2 infection compared to patients with CLD of other aetiology.

### Alcohol-related liver disease

The immunomodulating effects of alcohol are well recognised, with increased alcohol consumption known to predispose to a range of septic insults including community acquired bacterial and viral pneumonias. A history of harmful alcohol use also appears to increase susceptibility to acute respiratory distress syndrome, a hallmark of severe COVID-19, in critically ill patients with sepsis. Both registry data and multicentre studies have identified ALD as being independently associated with COVID-19 mortality after controlling for important cofactors including baseline liver disease severity. However, alcohol consumption in patients with CLD, categorised as either social drinking or current daily drinking, was not associated with all-cause mortality compared to abstinence in a multivariable model. The precise mechanisms through which ALD negatively impacts on prognosis in COVID-19 remain to be established although this may plausibly be underpinned by poor nutritional status and functional immunosuppression. In addition, patients with ALD and severe COVID-19 were significantly less likely to receive mechanical ventilation in a large French cohort. The strength of this negative association exceeded that observed with any other individual comorbidity or category of Charlson comorbidity index, suggesting that mortality in hospitalised patients with ALD and COVID-19 may be partly explained by discrepancies in the allocation of healthcare resources. These findings are especially alarming given that the incidence of harmful drinking, ALD, and alcohol-related hospital admissions have dramatically increased since the onset of the pandemic (see below) and collectively highlights the urgent need for concerted institutional and public health efforts to tackle the rise in alcohol-related harm.

### NAFLD

The impact of NAFLD on COVID-19 outcomes has been closely scrutinised due to its association with well-established risk factors for severe COVID-19 including obesity, type 2 diabetes, cardiovascular disease, and hypertension. However, it has been challenging to accurately decipher an independent effect of NAFLD on COVID-19 disease course due to confounding factors and heterogeneity in diagnostic criteria and populations investigated. Several observational cohorts have demonstrated a significant increase in the risk of severe COVID-19 in patients with NAFLD, which is corroborated by interval meta-analyses of epidemiological studies. Mechanistically, this observation may be supported by gene expression datasets showing increased expression of key viral entry receptors (ACE2, FURIN, TMPRSS2) in patients with NAFLD and NASH. In addition, ACE2 is upregulated in the liver, and in subcutaneous and visceral adipose tissue, in obese patients with NAFLD compared to obese controls without NAFLD. This increased receptor expression strongly correlated with degree of insulin resistance. Collectively this indicates that NAFLD in the context of the wider metabolic syndrome likely contributes to more severe and multisystem involvement of COVID-19. However, in contrast, some groups have failed to draw a link between NAFLD with severe COVID-19 or death after controlling for relevant comorbidities. In addition, there appears to be a lack of association between gene variants associated with NAFLD (PNPLA3, TM6SF2, MBOAT7, GCKR) and severe COVID-19. Indeed, a study from the UK biobank even reported a possible protective immunomodulatory effect of the PNPLA3 rs738409 G allele.
although this was not replicated following targeted PNPLA3 genotyping in 383 consecutive Sicilian patients with COVID-19.\(^7\) Separate independent analyses using 2-step Mendelian randomisation techniques have also failed to identify a causal relationship between NAFLD and COVID-19 susceptibility and severity.\(^7\)\(^9\) This approach attempts to overcome confounding by using genetic variants as instrument variables to draw causal inferences between risk factors and health outcomes.\(^7\) In summary, from a purely epidemiological perspective it appears that patients with NAFLD are at increased risk of severe COVID-19. However, the extent to which this is driven by hepatic steatosis, or the presence of overlapping risk factors and comorbidities remains incompletely resolved.

EASL position

- Patients with NAFLD are at increased overall risk of developing severe COVID-19 which may be attributed to the presence of other high-risk comorbidities.

Autoimmune liver disease

Understanding the clinical impact of pre-existing immunosuppression on COVID-19 risk and severity remains complex. Various concerns have been raised in specific disease groups, e.g. regarding the use of maintenance corticosteroids and thiopurines in patients with rheumatoid arthritis and inflammatory bowel disease, respectively.\(^8\)\(^1\)\(^2\) Conversely, the disease course in those on immunosuppression following solid organ transplantation appears comparable to non-immunosuppressed individuals.\(^8\)\(^3\)\(^4\) A large-scale European survey of 1,752 individuals with AIH performed between June and October 2020 indicated low rates of self-reported COVID-19, providing reassuring real-world data that these patients are unlikely to be at significantly increased risk of severe disease.\(^8\)\(^5\) Subsequently, in an international cohort of 70 patients with AIH and COVID-19, of whom 86% were immunosuppressed, no differences were found in the rates of adverse outcomes including hospitalisation, ICU admission, and death compared to those with other causes of CLD.\(^8\)\(^6\) When compared to propensity score-matched patients without CLD, patients with AIH had no increased risk of ICU admission or death but did appear to have higher rates of hospitalisation which may have reflected heightened clinical concern. Age and baseline liver disease severity constituted independent risk factors for death in this analysis, but not the use of immunosuppressive medications. Similar findings were concurrently reported in a multicentre cohort of 110 patients with AIH who also had comparable outcomes to other liver disease types.\(^8\)\(^7\) However, a larger retrospective study from the same group including 254 patients with AIH and COVID-19 did indicate that baseline treatment with systemic glucocorticoids (median dose 5 mg/day) or azathioprine (median dose 75 mg/day) was associated with more severe COVID-19\(^8\)\(^8\) after adjusting for age, sex, comorbidities, and presence of cirrhosis. Data for patients with primary biliary cholangitis and primary sclerosing cholangitis are limited. One nationwide study in Spain did observe a higher cumulative incidence of hospitalisation and mortality in patients with primary biliary cholangitis compared with the general population although interpretations are limited by the lack of adjustment for comorbidities.\(^8\)\(^9\)

Chronic viral hepatitis

Several studies have investigated the clinical impact of co-existing chronic HBV or HCV infection with SARS-CoV-2. A large territory-wide retrospective cohort study in Hong Kong\(^1\)\(^0\) showed that COVID-19 outcomes were no different between 359 patients with previous exposure to HBV, 353 patients with HBV infection, and a comparator group of 4,927 individuals without HBV. In addition, the rates and pattern of acute liver biochemical abnormalities during COVID-19 were the same across groups. Notably, 73 treatment-naïve patients with chronic HBV were started on HBV-targeted nucleoside analogues (NAs) during the course of COVID-19, either as a prophylactic measure against HBV reactivation due to the introduction of steroids (n = 48) or following marked elevations in ALT and HBV DNA levels (n = 16). Whilst patients who received NA treatment had a higher peak ALT than those who did not receive NAs, the ALT level at discharge was comparable between treated and untreated groups. A retrospective review of health insurance records in Korea also demonstrated that patients with chronic HBV did not have a significantly greater risk of severe COVID-19.\(^1\)\(^1\) Furthermore, in those with COVID-19 the proportion of patients with chronic HBV was lower than the general population after adjusting for comorbidities and socioeconomic factors.
status, indicating that patients with HBV may be less susceptible to SARS-CoV-2 infection.\textsuperscript{95} It has been suggested that this protective effect is mediated by the use of antiviral treatments, including tenofovir and entecavir, which have been shown to be associated with a reduced rate of SARS-CoV-2 positivity.\textsuperscript{91,92} Similar protective effects have also been reported in HIV-positive patients receiving tenofovir as part of antiretroviral combinations.\textsuperscript{93} NAs may have immunomodulatory effects and possibly specific antiviral properties against SARS-CoV-2, as postulated in pilot studies and preclinical models.\textsuperscript{94–96} However, the use of these agents in patients with chronic HBV has not been consistently shown to attenuate the disease course of subsequent COVID-19.\textsuperscript{97}

Analysis from a large American Veterans dataset demonstrated that a greater proportion of HCV-positive patients (n = 975) with COVID-19 were hospitalised compared to propensity score-matched HCV-negative individuals, particularly among those with elevated non-invasive markers of advanced fibrosis. However, rates of ICU admission and mortality did not differ between those with and without HCV infection.\textsuperscript{97} Two subsequent single-centre studies have indicated adverse outcomes in patients with co-existing HCV and SARS-CoV-2, including increased ICU admissions and mortality, particularly in those with elevated HCV RNA levels.\textsuperscript{98,99} However, interpretations are limited by small sample sizes and the lack of adjustment for the presence of cirrhosis. The repurposing of direct-acting antivirals (DAAs) for the treatment of COVID-19 has been investigated but results remain contentious (discussed below).\textsuperscript{100–102}

**EASL position**

- Patients with chronic viral hepatitis (HBV or HCV) without cirrhosis do not appear to have an increased risk of SARS-CoV-2 infection or COVID-19-related mortality.

**Liver transplant recipients**

Early in the pandemic, country-wide data from Spain and the UK suggested that diagnoses of SARS-CoV-2 infection were more frequent in LT recipients than in the general population.\textsuperscript{104,105} Given that LT recipients have been shown to have diminished responses to COVID-19 vaccination these patients should continue to be considered as being particularly susceptible to SARS-CoV-2 acquisition (discussed below). However, LT recipients who develop COVID-19 do not appear to have an increased risk of mortality compared to patients without LT after matching for relevant cofactors.\textsuperscript{106} In line with the general population, the major risk factors for developing severe COVID-19 in LT recipients are advancing age and burden of comorbidity.\textsuperscript{107,108} Concerns that immunosuppressive medications in LT recipients may increase susceptibility to SARS-CoV-2 infection must be balanced with their potential to positively influence the course of COVID-19 by suppressing inflammation in the later stages of the disease. Whilst antimetabolic drugs seem to have a negative effect,\textsuperscript{104} calcineurin inhibitors (e.g. tacrolimus, cyclosporin) and mTOR inhibitors may have a favourable impact on disease course.\textsuperscript{109–112} Therefore, adjustments to the dose and type of immunosuppression during SARS-CoV-2 infection should be individually tailored based on COVID-19 severity, the specific regimen used, time post-transplant, and the risk of allograft rejection. Clinical features of COVID-19 among solid organ transplant (SOT) recipients are variable. However, gastrointestinal symptoms including diarrhoea appear more frequent, particularly in patients receiving mycophenolate mofetil (MMF).\textsuperscript{113,107,113}
Position Paper

EASL position

- At present, there is no convincing evidence that liver transplantation by itself is an independent risk factor for COVID-19-related mortality. However, liver transplant recipients should be considered at high-risk of SARS-CoV-2 infection because of their comorbidities, non- or hypo-responsiveness to COVID-19 vaccination and immunosuppression.
- In liver transplant recipients with COVID-19, a dose reduction or temporary discontinuation of anti-metabolites (e.g. azathioprine or MMF) may be considered.

Effects of the COVID-19 pandemic on incidence and management of CLDs

Impact on harmful alcohol use and ALD

COVID-19 has had a vast collateral impact on the incidence and severity of alcohol use disorder and ALD. Early on in the pandemic, an upsurge in harmful drinking was widely documented with large-scale survey data showing pervasive increases in both the frequency and severity of alcohol consumption across men, women, and the breadth of racial and socioeconomic backgrounds. This was corroborated by retail and e-commerce statistics reflecting huge surges in alcohol purchasing by up to 400%. In addition, 17% of abstinent individuals with a history of alcohol use disorder were found to relapse to drinking under lockdown conditions. These behaviours are likely to have been triggered by heightened anxiety, social isolation, deteriorating mental health, and disruption to alcohol support services. Furthermore, these early drinking trends appear to have persisted, with UK public health data compiled from 18 national surveys demonstrating a widespread increase in harmful alcohol consumption throughout 2020 and 2021. Indeed, the proportion of respondents with high-risk drinking was consistently elevated, increasing by up to 58% compared to peak values recorded in 2019. In parallel, the epidemiology of ALD appears to have shifted. In a large study of electronic health records in Canada, the average number of monthly admissions due to alcoholic hepatitis was found to have doubled during the pandemic compared to the previous 2 years (22.1/10,000 admissions vs. 11.6/10,000 admissions; p <0.001). Similarly, UK data have indicated unprecedented increases in the number of alcohol-related hospital admissions and alcohol-related deaths throughout 2020/21. Alarmingly, 80% of these alcohol-related deaths are accounted for by liver disease, representing an increase in 20% from pre-pandemic levels. Alcohol consumption during the pandemic has also heavily influenced liver transplantation programmes, with ALD now accounting for 40% of transplant listings in North America, more than NASH and HCV combined. Furthermore, the severity of liver disease at the time of transplantation was found to be significantly worse during the COVID-19-era, driven predominantly by higher model for end-stage liver disease-Na scores in patients with ALD. Lastly, simulation modelling in the United States has estimated that a single year of increased alcohol consumption during the pandemic may result in 8,000 additional deaths from ALD, 18,700 cases of decompensated cirrhosis, 1,000 cases of HCC, and 8.9 million disability-adjusted life years between 2020 and 2040. Collectively, these data paint a bleak picture and highlight the immense current and future burden of morbidity and mortality precipitated by COVID-19-associated alcohol consumption. This should provide additional impetus to urgently re-establish alcohol support services and to implement evidence-based population-level interventions such as minimum unit pricing and taxation of alcohol, which is also a key consideration in the EASL Lancet Liver Commission.

EASL position

- There has been an unprecedented rise in the incidence and severity of ALD during the COVID-19 pandemic which requires urgent implementation of local and population-level interventions alongside clear public health messaging about the risks of harmful drinking.

Impact on NAFLD

The COVID-19 pandemic has led to the adoption of unhealthy lifestyles and has impeded strategies to manage obesity and metabolic dysfunction which may influence the development and progression of NAFLD. Several survey studies have documented increased consumption of unhealthy foods, excess calorie intake, and reduced physical activity during periods of enhanced social distancing. This appears to have translated into an increased prevalence of obesity during the pandemic, particularly in paediatric and adolescent populations. According to figures from the Centers for Disease Control and Prevention, among a cohort of 432,302 individuals aged 2–19 years, the rate of increase in BMI approximately doubled during the pandemic compared to the period preceding it. The greatest increase was observed in children aged 6–11 years and in those who were overweight at baseline. These data coincided with similar findings from electronic health records for 46,151 children in Massachusetts, USA, which identified a particularly high obesity risk in boys (aged 6–11 years),...
and Black and Hispanic subgroups. Paradoxically, a study of primary care practices in the UK observed a 70% decrease in the rate of type 2 diabetes diagnoses in the initial months following the onset of the pandemic, reflecting reduced testing and limited population engagement with health services. This subsequently normalised throughout 2020 and there are concerns that a rebound in the incidence of type 2 diabetes mellitus and its complications may be imminent. Although no study has yet directly evaluated the epidemiology of NAFLD in the COVID-19 era, it is highly likely that the pandemic will have a detrimental effect on liver health via the negative impact on obesity, diabetes care, and patient lifestyle choices.

Impact on viral hepatitis elimination strategies
In 2016, the World Health Organization released a strategy aiming for elimination of viral hepatitis by 2030. Several countries introduced policies and strategies to meet this ambitious goal; however, many of these programmes were significantly affected by the pandemic and newly diagnosed cases of HBV and HCV declined in many countries, profoundly impacting meticulously planned elimination strategies and policies. A modelling study has predicted that a delay of just 1 year in hepatitis C diagnosis and treatment due to the pandemic could result in 44,800 additional liver cancer cases and 72,300 deaths worldwide by 2030. Nevertheless, SARS-CoV-2 testing requirements and the roll-out of mass vaccination campaigns offer a unique opportunity to approach large parts of the population and offer screening for viral hepatitis. Although several groups have successfully seized this opportunity, efforts to meet the World Health Organization (WHO)’s goal of viral elimination should continue without further delay.

Changes in the standard of care and adherence to surveillance programmes
In the early phases of the pandemic, when little was known about the transmissibility of SARS-CoV-2 and personal protective equipment was in short supply in many places, hospitals and other health care providers represented SARS-CoV-2 hotspots, prompting many medical associations, including EASL, to advocate for rapidly escalating telemedicine and postponing surveillance visits (e.g. ultrasound for HCC surveillance, endoscopy for surveillance of oesophageal varices) for selected patient cohorts in order to reduce the likelihood of nosocomial infections and to respond to the reallocation of healthcare resources. Even this transient interruption of surveillance programmes and standard care was anticipated to impact patients for years to come. Indeed, the number of liver transplantations declined in 2020 compared to 2019 primarily in those countries that were most strongly affected by the first wave of the pandemic in early 2020. Similarly, numbers of first HCC diagnosis declined from 2019 to 2020 and the percentage of patients in whom treatment initiation had to be delayed increased in that period. More than 80% of European centres had to change their clinical practices because diagnostic procedures, screening programmes, curative and/or palliative treatments, and liver transplant programmes were affected by lockdown measures.

EASL position
The pandemic has led to increased adoption of unhealthy lifestyles and a rise in the prevalence of obesity which is likely to drive the development and progression of NAFLD.

Impact on viral hepatitis elimination strategies
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EASL position
The WHO goal of viral hepatitis elimination by 2030 should be pursued without further delay.
Diagnosis of viral hepatitis and linkage to care through SARS-CoV-2 testing and vaccination programmes are strongly encouraged.

EASL position
The pandemic profoundly altered the standard of care within hospitals and the outpatient setting. All efforts should be made to return to these standards and resume and improve surveillance programmes in order to reduce the backlog of deferred care for the future.

Treatment of COVID-19 in patients with CLD, transplant recipients and patients with hepatobiliary carcinoma
General concepts of COVID-19 treatment
The pathogenesis of COVID-19 is mainly determined by 2 main processes. Early in the clinical course, the disease is mainly triggered by SARS-CoV-2 replication. Later, the disease appears to be driven by a dysregulated immune/inflammatory response resulting in tissue injury. Based on this understanding, direct antiviral therapies should have the greatest effect when employed as early as possible in the disease course, whereas immune/inflammation-modulating therapies are likely to be more beneficial when SARS-CoV-2 infection has
already reached a stage characterised by tissue damage and hypoxia (Fig. 1). In this section, we will review current COVID-19 treatment strategies (Table 2 and Table 3 show the currently recommended therapies) with a focus on considerations for patients with CLD, hepatobiliary cancer, and LT recipients.

**Antiviral therapies**

Direct antiviral approaches aim to inhibit viral replication by interacting with key proteins or other structures necessary for viral replication, whereas viral neutralising monoclonal antibodies (mAbs) can inhibit viral replication by interacting with the SARS-CoV-2 spike protein to prevent cell entry. Due to the dynamics of acute respiratory tract infections, in which viral replication is known to be greatest during the first few days after infection, the therapeutic window for antiviral approaches is narrow compared to immunomodulatory therapies which can be employed later in the disease course (Fig. 1).

**Remdesivir**

Remdesivir, an adenosine analogue, inhibits the RNA-dependent RNA polymerase of coronaviruses and has demonstrated potent activity against SARS-CoV-2 in vitro and in animal models. In the ACTT-1 study, which included 1,062 hospitalised patients with COVID-19 and evidence of lower Table 1. Case reports of de novo AIH following COVID-19.

| Case, COVID-19 severity | Laboratory parameters | Liver histology | Time to AIH diagnosis | Treatment |
|------------------------|-----------------------|-----------------|-----------------------|-----------|
| 49 years, male, hospitalised | ALT 264 IU/L Bili 1.6 mg/dl IgG 2,260 mg/dl ANA 1,800 | Not performed | 20 days | Prednisolone + azathioprine (relapsed after discontinuation) |
| 72 years, female, hospitalised | ALT 660 IU/L Bili 11.2 mg/dl IgG 4,250 mg/dl SMA+ 1/640 | Not performed | 2 days | Prednisolone + tacrolimus |
| 54 years, male, mild | ALT 1,238 IU/L Bili 25 mg/dl IgG 3,151 mg/dl ANA+ 1:2,560 SMA+ 1:45 | Portal & lobular inflammation, plasma cell infiltrate, interface hepatitis | 1 month | Prednisolone |
| 60 years, female, mild | ALT 1,433 IU/L Bili 11.7 mg/dl IgG 2,775 mg/dl SMA+ 1:80 | Lobular lymphoplasmacytic infiltration, interface hepatitis | 0 days | 'Induction therapy' + azathioprine |
| 57 years, male | ALT 106 IU/L Bili 2.1 mg/dl IgG 4,049 mg/dl SMA+ ANA+ | Not performed | 1 month | No immunosuppression |
| 40 years, female, mild | ALT 1,300 IU/L Bili 22 mg/dl IgG 2,190 mg/dl ANA+ | Portal and lobular inflammation, plasma cell infiltrate | 1 month | Prednisolone |

AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibody; ANA, antinuclear antibody; Bili, bilirubin; dsDNA, double-stranded DNA; SMA, smooth muscle antibody.
Antiviral therapies must be administered in the timing of remdesivir treatment initiation. Variability in remdesivir treatment initiation led to varying treatment results, which are most likely explained by variability in the timing of remdesivir treatment initiation. This is corroborated by the DisCoVeRy trial, which showed no clinical benefit of remdesivir vs. standard of care. Nevertheless, other real-world data have indicated remdesivir to be associated with improved survival among patients with COVID-19. These conflicting results are most likely explained by variability in the timing of remdesivir treatment initiation. Antiviral therapies must be administered in the early phase of infection when patients are asymptomatic or have mild symptoms (Fig. 1). Large-scale electronic health record data have suggested that remdesivir is unlikely to be of benefit in more severely ill patients with well-established disease. This is corroborated by the DisCoVeRy study which showed no clinical benefit of remdesivir in hospitalised patients who required oxygen support and had been symptomatic for >7 days. Conversely, the PINETREE study showed that early introduction of 3-days treatment with remdesivir in high-risk non-hospitalised patients with symptoms <7 days appeared safe and resulted in an 87% lower risk of hospitalisation or death compared to placebo. However, use of remdesivir as a preemptive treatment in an outpatient setting is limited by the need for intravenous administration. Despite preclinical investigations demonstrating reversible ALT elevations with remdesivir, its use in controlled trials has not been associated with significant ALT elevations compared with placebo (4% vs. 5.9%) although most trials have excluded patients with baseline ALT >5 ULN. There are no specific drug interaction concerns with the use of remdesivir.

### Table 2. Treatment of patients with SARS-CoV-2 infection.

| Therapy               | Non-hospitalised WHO 1-3 | Hospitalised w/o oxygen demand WHO 4 | Low-flow oxygen demand WHO 5 | High-flow oxygen or NIV/CPAP WHO 6 | Invasive ventilation, ECMO WHO 7-9 |
|-----------------------|--------------------------|--------------------------------------|-------------------------------|-----------------------------------|----------------------------------|
| **Antivirals***       | Indicated (strong recommendation)** | Indicated (weak recommendation)** | Inconclusive (data lacking)** | Inconclusive (data lacking)** | Not indicated                     |
| mAbs**                | Indicated (weak recommendation)** | Indicated (strong recommendation)** | Inconclusive (data lacking)** | Not indicated | Not indicated                     |
| Dexamethasone         | Not indicated            | Not indicated                         | Indicated (strong recommendation)** | Indicated (strong recommendation)** | Not indicated                     |
| JAKI***               | Not indicated            | Not indicated                         | Indicated (strong recommendation)** | Indicated (weak recommendation)** | Not indicated                     |
| Anti-IL6***           | Not indicated            | Not indicated                         | Not indicated                  | Indicated (strong recommendation)** | Not indicated                     |

CPAP: continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; IL-6, interleukin-6; JAKIs, Janus kinase inhibitors; mAbs, monoclonal antibodies; NIV, non-invasive ventilation; WHO, World Health Organization.

*Indicated in high-risk patients (lack of immune protection, especially immunosuppression) within 5 days of symptom onset, this includes inpatients with recently diagnosed nosocomial SARS-CoV-2 infection; whether later administration is appropriate in highly immunosuppressed patients must be decided on a case-by-case basis.

**Indicated in high-risk patients when symptom onset was ≤7 days ago or when SARS-CoV-2 detection was ≤7 days ago and when there are no or only mild symptoms. This includes inpatients with recently diagnosed nosocomial SARS-CoV-2 infection. The use of mAbs requires a negative antibody test, which, however, can be omitted in highly immunosuppressed patients.

***In combination with dexamethasone.

**EASL position**

- Remdesivir should not be used in symptomatic patients requiring invasive ventilation.
- For hospitalised patients with COVID-19 pneumonia who require oxygen therapy or non-invasive ventilation, no recommendation can be made at present for or against therapy with remdesivir. Treatment may be considered in this setting based on experience and the availability of alternative options.
- Remdesivir can be given pre-emptively within 7 days of symptom onset to patients with SARS-CoV-2 infection who are at increased risk of a severe COVID-19 course.
- Patients with CLD, transplant recipients and patients with hepatobiliary cancer can be treated with remdesivir in the condition listed above.

**Nirmatrelvir/ritonavir**

Nirmatrelvir is an oral inhibitor of viral 3CL protease which can be boosted with both ritonavir (r), a potent inhibitor of cytochrome P450 (CYP) and P-glycoprotein that enables peroral use with good bioavailability. In a phase II/III study including 2,246 patients, nirmatrelvir/r given as early as possible and within 5 days of symptom onset, significantly reduced hospitalisation and/or death rates compared with placebo in non-hospitalised...
patients with mild/moderate COVID-19 (without supplemental oxygen requirements) and at least 1 risk factor for a severe disease course (7.0% vs. 0.8%). This equates to a relative risk reduction of 88.9% if given within 3 days of symptom onset, and 87.8% if given within 5 days.\(^{158}\) The most common adverse events reported during treatment with nirmatrelvir/r vs. placebo were dyseusia (5.6% vs. 0.3%) and diarrhoea (3.1% vs. 1.6%).\(^{158}\) Numerous clinically relevant drug-drug interactions (DDIs) must be considered with the use of nirmatrelvir/r due to the inhibition of CYP450 enzymes by ritonavir.\(^{158}\) Websites to check the DDIs are available (https://www.covid19-druginteractions.org/checker, https://www.fda.gov/media/155050/download). This is particularly important for SOT recipients as ritonavir will lead to changes in drug levels of immunosuppressive medications. As yet, there are no data reporting on the clinical impact of nirmatrelvir/r in patients infected with the omicron variant. However, in vitro data suggest that nirmatrelvir/r should be effective against most COVID-19 variants currently circulating.\(^{159,160}\) There are also no data specifically for patients with CLD, transplant recipients or patients with hepatobiliary cancer. To date, reported ALT elevations are uncommon, typically mild, and are not more frequently observed with nirmatrelvir/r than with placebo.\(^{158}\) However, as both nirmatrelvir and ritonavir are metabolised in the liver by the cytochrome P450 system (largely via CYP 3A4), caution is needed in patients with advanced cirrhosis. This is consistent with well-established concerns regarding the use of similar protease inhibitors in patients with decompensated HCV-cirrhosis.\(^{161}\)

**EASL position**

- Nirmatrelvir/r can be given within 5 days of symptom onset to adults with SARS-CoV-2 infection who are at increased risk for severe COVID-19.
- Clinicians managing liver transplant recipients with SARS-CoV-2 infection who begin treatment with nirmatrelvir/r must cautiously approach calcineurin inhibitor and mTOR inhibitor dose-adjustments and drug level monitoring.
- Based on the experience with protease inhibitors in the treatment of chronic hepatitis C, nirmatrelvir/r should not be administered to patients with decompensated liver cirrhosis (CP-C) and only with caution to patients with CP-B cirrhosis if no other options exist.
- Molnupiravir can be given within 5 days of symptom onset to adults with SARS-CoV-2 infection who are at increased risk for severe COVID-19.
- Patients with CLD, including cirrhosis (including CP-B and CP-C), transplant recipients, and patients with hepatobiliary cancer can be treated with molnupiravir.
- Pregnancy is a contraindication to molnupiravir therapy.

**Molnupiravir**

Molnupiravir is an orally available antiviral agent that increases the frequency of viral RNA mutations by the viral RNA-dependent RNA polymerase and impairs SARS-CoV-2 replication in preclinical models.\(^{162}\) Molnupiravir has been shown to significantly reduce hospitalisation and/or mortality compared with placebo in non-hospitalised patients with mild/moderate COVID-19 (without supplemental oxygen requirements) and at least 1 risk factor for a severe disease course (6.8% vs. 9.7%). This equates to a relative risk reduction of 30%, absolute risk reduction of 3%, and a number needed to treat of approximately 33.\(^{160}\) In this study, therapy was initiated as early as possible and within 5 days of the onset of symptoms. The most commonly reported adverse reactions to treatment were diarrhoea (3%), nausea (2%), dizziness (1%), and headache (1%). Particular consideration should be given to the mutagenic and teratogenic potential of molnupiravir, which makes its use contraindicated during pregnancy or in women of childbearing potential not using effective contraception. No specific data have been reported on the use of molnupiravir for patients infected with the omicron variant and for patients with CLD, hepatobiliary cancer or LT recipients. As molnupiravir is a polymerase inhibitor, variants with mutations in the spike protein (e.g. omicron) should not impact its efficacy and this has been demonstrated in vitro.\(^{164,165}\) To date, there are no concerns regarding the administration of molnupiravir to patients with cirrhosis and no relevant DDIs have been reported. However, there are concerns about the potential for molnupiravir to influence the rate of SARS-CoV-2 mutation. Therefore, manufacturers are required by the FDA to establish a monitoring process using genomic databases in order to detect the emergence of treatment-related SARS-CoV-2 variants.

**Monoclonal antibodies**

Several mAbs are approved for passive immunisation of SARS-CoV-2-infected patients who are at increased risk of severe disease and are either unvaccinated or have mounted a suboptimal immune response to COVID-19 vaccination. In randomised placebo-controlled trials including non-
hospitalised patients with mild-to-moderate COVID-19 and risk factors for disease progression, the use of anti-SARS-CoV-2 mAbs (e.g. casirivimab plus imdevimab, bamlanivimab plus etesevimab or sotrovimab) has been shown to reduce the risk of hospitalisation and death. For example, hospitalisation or all-cause mortality at 28 days occurred in only 1% of patients treated with sotrovimab compared with 7% receiving placebo (6% absolute reduction and 85% relative risk reduction). However, pooled analysis of all available randomised-controlled trials indicates a low level of certainty about mAb efficacy, particularly in hospitalised individuals. This is likely due to multiple agents being included in trials and because several studies did not account for SARS-CoV-2 antibody status. The importance of this is demonstrated in the RECOVERY trial, which included 9,785 patients randomised to casirivimab and imdevimab vs. placebo. In this study, mAb use was not associated with significant differences in clinical outcomes when all patients were considered together (including those with unknown antibody status), however 28-day mortality was improved in patients who were seronegative at baseline.

Whilst cell culture studies show that the omicron variant (BA.1) is resistant to several therapeutic antibodies, the virus appears to remain sensitive to tixagevimab plus cilgavimab, or sotrovimab. This is corroborated by some preliminary human data, i.e. sotrovimab effectively prevented disease progression in omicron-infected, predominantly severely immunocompromised patients with mild-to-moderate COVID-19. However, these studies were not placebo-controlled and omicron is known to be associated with less severe COVID-19 overall. Despite this efficacy signal, the emergence of additional unique mutations in the spike protein may lead to further immune escape. For example, the omicron subvariants BA.1 and BA.2 have many differences in their mutations in the spike protein, and the difference between BA.1 and BA.2 is even greater than the difference between the original variant and, for example, the alpha variant. Therefore, it is comprehensible that in vitro data show that sotrovimab is not as effective against the BA.2 compared to earlier variants. Tixagevimab plus cilgavimab does appear to remain active against BA.2 but this combination therapy is currently only authorised for prophylactic use (as of April 2022). However, within a trial setting, the TACKLE study assessed the efficacy of tixagevimab plus cilgavimab vs. placebo given within 7 days of symptom onset in >900 outpatients with symptomatic COVID-19 and showed that active treatment reduced progression to severe COVID-19 or death (relative risk reduction 50.5%). In addition, bebtelovimab is active in vitro against most circulating omicron subvariants, but at present there are no efficacy data from placebo-controlled clinical trials. Knowledge of the predominant circulating viral variants and the immunological serostatus of the patients is therefore important when considering the use of mAbs.

Limitations associated with mAb use include the need for parenteral administration, clinical monitoring during and for ≥1-hour post-infusion, and potential hypersensitivity reactions. In addition, genetic mutations in the spike protein, which are associated with high-level resistance in vitro have been shown to occur in SARS-CoV-2-infected patients treated with mAbs (e.g. bamlanivimab and sotrovimab), particularly when viraemia persisted for a prolonged period. These data highlight the need for conscientious stewardship and post-marketing surveillance of patients treated with mAbs.

**EASL position**
- **SARS-CoV-2 Spike IgG-seronegative patients** (unvaccinated individuals or individuals without detectable serological response to vaccination) with SARS-CoV-2 infection can be treated with SARS-CoV-2-specific mAbs expected to be effective against the circulating variants and subvariants if they are at risk for severe COVID-19.
- **Treatment with SARS-CoV-2-specific mAbs** in IgG-seronegative patients should be initiated ideally within 72 hours but no longer than 7 days after symptom onset.
- In patients with early SARS-CoV-2 infection where immediate determination of spike antibody titres is not possible, SARS-CoV-2-specific mAbs can be initiated in the setting of incomplete COVID-19 vaccination or in those at risk of suboptimal vaccination responses including those with decompensated cirrhosis, liver transplant recipients, or patients on immunosuppressive therapy.

**Convalescent plasma**

Compared with placebo or standard of care, treatment with convalescent plasma has never been shown to be associated with any improvement in clinical outcomes including all-cause mortality. However, convalescent plasma is associated with a trend towards more frequent occurrence of serious adverse events and is associated with the inherent risks of transfusion-related complications.
Immunomodulatory therapies

One of the goals of immunomodulatory or anti-inflammatory therapies in hospitalised patients is to reduce the risk of a cytokine storm in the second phase of COVID-19 disease (WHO scale 5-9). Systemic corticosteroids (e.g. dexamethasone) form a cornerstone of this therapeutic approach. In addition, other immunomodulatory agents, including inhibitors of the Janus kinase (JAK)-STAT pathway and blockade of the cellular interleukin-6 (IL-6) receptor have shown promise in clinical trials.

Corticosteroids (e.g. dexamethasone)

The RECOVERY trial was the first to demonstrate a disease-modifying effect of dexamethasone in COVID-19. This trial enrolled 2,104 hospitalised patients and showed that compared to placebo, the use of oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days conferred a mortality benefit at 28 days in those who received oxygen therapy (including mechanical ventilation) but not among those requiring no respiratory support.\(^{182}\) The greatest benefit was observed in those requiring invasive ventilation. Subsequently, several other randomised-controlled trials have reported similar findings and a systematic Cochrane review concluded that there is moderate-certainty evidence that systemic corticosteroids reduce all-cause mortality in patients hospitalised with symptomatic COVID-19. There is lower certainty evidence suggesting there may also be a reduction in ventilator-free days. Currently, there is no evidence for the use of systemic corticosteroids in asymptomatic patients or non-hospitalised patients with mild disease.\(^{183}\)

COVID-19 treatment with systemic corticosteroids (dexamethasone 6 mg daily or equivalent) may increase the risk of hepatitis B reactivation in HBsAg-positive individuals, even if administered for only a few days. This risk will increase with escalating dose and exposure time. There is also a theoretical risk of reactivation in HBsAg-negative/anti-HBc-positive individuals if the immunosuppression is profound enough, either because of additional COVID-19 therapies (see below) or the cytokine milieu characteristic of COVID-19.\(^{184}\)

Therefore, monitoring of HBV markers is recommended, and prophylactic treatment should be considered according to the individual patient’s risk profile.

Janus kinase 1/2 inhibitors (e.g. baricitinib)

Baricitinib is an oral selective JAK 1/2 inhibitor (JAKI) with known anti-inflammatory properties. In the ACTT-2 study, including 1,033 patients, baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19, particularly among those receiving high-flow oxygen or non-invasive ventilation (median recovery time: 10 vs. 18 days). The 28-day mortality rate was 5.1% in the combination group and 7.8% in the control group.\(^{185}\) The COV-BARRIER study, including 1,525 participants, showed that treatment with baricitinib in addition to standard of care (including dexamethasone) had a similar safety profile to that of standard of care alone and was associated with reduced mortality (10% vs. 15%) in hospitalised patients with COVID-19.\(^{186}\)

Even in critically ill patients who required invasive mechanical ventilation or ECMO, treatment with baricitinib still appeared to reduce mortality compared with placebo (39% vs. 58%). However, this was demonstrated in an exploratory analysis of only 101 patients\(^{187}\) and most patients (84-88%) also received concurrent dexamethasone. Indeed, the combination of baricitinib with corticosteroids may have an additive or synergistic anti-inflammatory effect. A retrospective study in 197 patients with COVID-19 pneumonia showed that 30-day mortality was significantly lower in patients treated with baricitinib plus dexamethasone than with dexamethasone monotherapy (20.3% vs. 40.5%).\(^{188}\)

Increases in transaminase levels were frequently observed in clinical trials with JAKIs.

EASL position

- Convalescent plasma should not be used in patients with COVID-19.

EASL position

- Patients with COVID-19 and an oxygen requirement should be treated with dexamethasone or a total daily dose equivalent of an alternative glucocorticoid (e.g., prednisone, methylprednisolone, hydrocortisone) if not available.
- HBsAg and anti-HBc should be tested prior to corticosteroid administration.
- HBsAg-positive individuals should be tested for HBV DNA and receive NA therapy.
- HBsAg-negative/anti-HBc-positive individuals should be monitored and receive NAs if HBV DNA is detectable.
- In transplant recipients, the immunosuppressive regimen may be adapted if additional corticosteroids are used.
However, baricitinib does not have physiochemical and pharmacokinetic characteristics known to play a role in liver injury; the drug is not very lipophilic and is only minimally metabolised by CYP3A4.\(^{189}\) So far only transient and usually mild increases in liver parameters, but no clinically significant acute liver injury has been reported in the setting of COVID-19 treatment.\(^{189}\) Although, only less than 10% of baricitinib undergoes metabolisation via CYP3A4, DDIs should be considered (e.g. organic anion transporter substrate).\(^{189}\)

It is important to note that HBV reactivation with JAKI use in other clinical settings has been reported in HBsAg-positive and even in HBsAg-negative/anti-HBc-positive individuals (up to 14.9%).\(^{184,190}\)

Other JAKIs, such as ruxolitinib and tofacitinib, have also been investigated in clinical trials and have shown clinical benefit in a small number of patients.\(^{191,192}\) Importantly, ruxolitinib exhibits extensive hepatic metabolism in contrast to baricitinib.\(^{189}\)

Co-administration of JAKIs with IL-6 inhibitors (see below) should be avoided to prevent the risk of additive immunosuppression and subsequent occurrence of severe infections.

**EASL position**

- Baricitinib can be used in patients with COVID-19 requiring oxygen therapy.
- Combination of baricitinib with anti-IL6 receptor antagonist (e.g. tocilizumab) should be avoided.
- Patients with cirrhosis can also be treated with baricitinib alongside monitoring of liver parameters.
- HBsAg and anti-HBc should be tested prior to JAKI therapy.
- HBsAg-positive individuals should be tested for HBV DNA and receive NA therapy.
- HBsAg-negative/anti-HBc-positive individuals should be monitored and receive NAs if HBV DNA is detectable.
- Ruxolitinib and tofacitinib should only be considered if baricitinib is not available.

**IL-6 receptor antagonists (e.g tocilizumab)**

Tocilizumab is an intravenous recombinant humanised anti-IL-6 receptor mAb that inhibits IL-6 binding to both membrane and soluble IL-6 receptors, thereby blocking IL-6 signalling and reducing inflammation. In the RECOVERY trial, tocilizumab was shown to improve survival in hospitalised patients with severe COVID-19 pneumonia. These benefits were seen regardless of the amount of respiratory support and were additional to the benefits of systemic corticosteroids.\(^{193}\) A meta-analysis of 27 trials involving 10,930 patients\(^{194}\) has subsequently confirmed that IL-6 antagonist therapy (tocilizumab, sarilumab) is associated with a lower 28-day all-cause mortality rate than standard care or placebo (odds ratio 0.86; 95% CI 0.79-0.95). There was a non-significant increase in the rate of secondary infections at 28 days in those treated with IL-6 antagonists compared to placebo (21.9% vs. 17.6%).

In seminal studies in patients with rheumatological conditions, a high proportion (10% to 50%) of patients receiving tocilizumab experienced elevations in liver parameters, most of which were mild and transient.\(^{195}\) In in a small proportion (1-2%), ALT elevations >5x ULN may be observed, requiring temporary or permanent discontinuation of treatment.\(^{195}\) Since its approval and availability for rheumatoid arthritis, post-marketing surveillance has shown tocilizumab to be associated with rare cases of severe liver injury including jaundice.\(^{196}\) HBsAg-positive patients receiving anti-IL6 receptor monoclonal antibody treatment have a moderate to high risk of HBV reactivation. The risk of reactivation is low to moderate in HBsAg-negative/anti-HBc-positive individuals and reactivation in this setting was not associated with severe outcomes.\(^{184,196,197}\) Elevated IL-6 may downregulate CYP enzymes, thus the use of tocilizumab may lead to increased metabolism of drugs that are CYP substrates which can persist for weeks after tocilizumab discontinuation. Sarilumab is an alternative to tocilizumab\(^{198}\) but the number of patients with SARS-CoV-2 infection treated with sarilumab is limited and the evidence of efficacy for sarilumab is less extensive than for tocilizumab.

**EASL position**

- Tocilizumab may be considered in addition to dexamethasone for critically ill patients (WHO 6-9). Therapy should ideally be given within 24 h of initiation of high-flow oxygen therapy or ventilatory support.
- Patients who clinically deteriorate despite JAKI therapy (e.g. rising inflammatory markers, increasing oxygen requirements) may receive sequential therapy with an anti-IL-6 (no published data yet). Tocilizumab should not be added to JAKI treatment.
- Patients with CLD should be treated with caution and liver parameter monitoring should be performed.
- HBsAg and anti-HBc should be tested prior to tocilizumab therapy.
- HBsAg-positive individuals should be tested for HBV DNA and receive NA therapy.
Table 3. Overview of recommended therapies for SARS-CoV-2 infection.

| Antiviral therapy | Indication | Important comments and considerations for CLD and LT recipients |
|------------------|------------|---------------------------------------------------------------|
| Remdesivir (Veklury) | Prevention of severe COVID-19 in at-risk patients (within 7 days of symptom onset). | Monitoring liver parameters, eGFR. Usage in patients with an eGFR of <30 only if the potential benefits outweigh the risks. No significant DDI is expected. |
| Nirmatrelvir/ritonavir (Paxlovid) | Prevention of severe COVID-19 in at-risk patients (within 5 days of symptom onset). | Monitoring liver parameters and eGFR*, not recommended in advanced cirrhosis, caution in LT because of DDI. |
| Molnupiravir (Lagevrio) | Prevention of severe COVID-19 in at-risk patients (within 5 days of symptom onset). | Contraindicated in pregnancy and in women of childbearing potential not using effective contraception, no significant DDIs are expected. Monitoring liver parameters, eGFR*. |
| mAbs | Prevention of severe COVID-19 in at-risk patients (unvaccinated individuals or individuals without detectable serological response to vaccination). Treatment within 72 hours but no longer than 7 days after symptom onset (post exposure prophylaxis). Recommendations are based on the current knowledge of the in vitro activities of available mAbs against the circulating SARS-CoV-2 variants and subvariants. | Monitoring for hypersensitivity reactions. Consider SARS-CoV-2 variants (e.g., sotrovimab is not recommended if omicron BA.2 is dominant). Serology (antibody) assessment is not essential in immunocompromised patients. |

| Immunomodulatory therapies | Indication | Important comments and considerations for CLD and LT recipients |
|---------------------------|------------|---------------------------------------------------------------|
| Dexamethasone | Treatment of COVID-19 WHO ≥5 (oxygen demand) | Monitoring liver parameters. HBsAg/anti-HBc test, prophylactic NAs in HBsAg-positive patients, adjust immunosuppression in LT. |
| Janus kinase 1/2 inhibitor Baricitinib (Olumiant) | COVID-19 WHO ≥5 (oxygen demand) in addition to dexamethasone | Dose adjustment if eGFR <60, not recommended if eGFR is <15. Monitoring of eGFR, liver parameters. HBsAg/anti-HBc test, prophylactic NAs in HBsAg-positive patients, adjust immunosuppression in LT, no combination with anti-IL-6. |
| IL-6 receptor antagonist tocilizumab (Actemra) | COVID-19 WHO 6–9 (High-flow oxygen demand, NIV) in addition to dexamethasone | Monitoring liver parameters. HBsAg/anti-HBc test, prophylactic NAs in HBsAg-positive patients, adjust immunosuppression in LT, no combination with JAKI, contraindicated in patients with absolute neutrophil count <2,000/μL; active tuberculosis. |

DDI, drug-drug interactions; eGFR, estimated glomerular filtration rate; JAKI, Janus kinase inhibitor; LT, liver transplantation; mAbs, monoclonal antibodies; NAs, nucleos(t)ide analogues.

*Because of limited experience outside clinical trials.

**Promising medications under evaluation**

There are several additional compounds currently under investigation for use in COVID-19 which may ultimately progress through trials and into clinical practice. One promising candidate is sabizabulin, an orally bioavailable bis-indole initially developed for cancer treatment which binds to the ‘colchicine binding site’ of α- and β-tubulin and inhibits polymerisation.199 It is thought to act by preventing the formation of new leukocytes and it may inhibit the release of proinflammatory cytokines during the course of COVID-19. A multicentre phase III trial of sabizabulin in hospitalised patients with moderate-to-severe COVID-19 (WHO severity...
grade ≥4) has recently been halted prematurely due to the agent showing a clear clinical efficacy signal with a relative reduction in mortality of 55% compared to placebo (p = 0.0029) [press release: https://verupharma.com/]. However, until full publication of safety and efficacy data following peer review, we cannot make any statements about the use of this agent.

### Repurposed drugs without proven clinical efficacy
Numerous repurposed drugs with suspected antiviral or anti-inflammatory properties have been explored for the treatment of COVID-19 (Table 4). However, to date, none of these have moved into mainstream practice due to adverse safety profiles or insufficient evidence of clinical benefit.

| Medication | Comments | Study |
|------------|----------|-------|
| Lopinavir/ritonavir | Anti-retroviral therapy | No efficacy in large controlled clinical trials | 152 |
| Hydroxychloroquine | Anti-rheumatic, anti-malarial agent | No efficacy in large controlled clinical trials | 152 |
| Nitazoxanide Thiazolid | broad-spectrum antiparasitic agent | A few randomised trials showed some level of efficacy. Studies were underpowered. So far, no evidence for recommendation. | 200–202 |
| Ivermectin | Antiparasitic agent | Double-blind, randomised, placebo-controlled, adaptive platform trial with 3,515 patients (ivermectin (679 patients), placebo (679), or another intervention (2,157)): Treatment with ivermectin did not result in a lower incidence of medical admission to a hospital due to progression of COVID-19 or of prolonged emergency department observation among outpatients with an early diagnosis of COVID-19. | 203 |
| Famotidine | Selective histamine H2-receptor antagonist | Several retrospective studies have documented improved clinical outcomes in hospitalised patients, while others did not find a positive effect or even documented an association with severe COVID-19. One small randomised, double-blind, placebo-controlled trial in 55 outpatients with mild COVID-19 now showed that 80 mg famotidine accelerated the resolution of symptoms and inflammation without compromising immunity. However, the proposed mechanism of action was not antiviral but anti-inflammatory by resolution of type-I interferon elevation without impairing immunity. Based on the results of this very small study we cannot give a general recommendation for famotidine outside clinical trials. Of note, the timing of the treatment may be crucial if the proposed mechanism of action is a reduction of type-I interferon responses. This may explain different results in retrospective studies. | 204–210 |
| Fluvoxamine | Selective serotonin reuptake inhibitor and a 5-1 receptor (5-1R) agonist | Several clinical trials suggest that fluvoxamine may prevent clinical deterioration in patients with SARS-CoV-2 infection, especially when used in the early phase of infection and the full extent of hyperinflammation. The TOGETHER study in almost 1,500 patients at risk of severe COVID-19 with symptoms beginning within 7 days of the screening date showed that fluvoxamine (100 mg twice daily for 10 days) vs. placebo reduced the need for hospitalisation defined as retention in a COVID-19 emergency setting or transfer to a tertiary hospital (absolute risk reduction of 5%, and 32% relative risk reduction). | 211,212 |

### Repurposed drugs with potential immunomodulatory properties

| Medication | Comments | Study |
|------------|----------|-------|
| Inhaled budesonide | Inhaled budesonide reduced time to reported recovery in the PRINCIPLE and STOIC trials but did not significantly reduce COVID-19-related hospitalisations or deaths. Two multicentre, double-blind, randomised phase III clinical trials showed no significant benefit of inhaled and intranasal ciclesonide. | 217,218 |
| Azithromycin | Antibiotic | No efficacy in several large studies | 217,218 |
| Colchicine | Anti-inflammatory agent | No effects in large studies (e.g. RECOVERY, PRINCIPLE and COCORONA) | 219,220 |
| Interferon alfa | Early treatment, either within 5 days from the onset of symptoms or at hospital admission, confers better clinical outcomes, whereas late intervention may result in prolonged hospitalisation. | 221 |
| Interferon beta-1a | Interferon beta-1a plus remdesivir was not superior to remdesivir alone in hospitalised patients with COVID-19 and patients treated with Interferon beta-1a who required high-flow oxygen at baseline had worse outcomes. | 222 |
| Interferon lambda | Antiviral activity against SARS-CoV-2 virus in vitro. No effect of a single dose of PegIFN–γ in a small study (n = 60). | 223,224 |
| Anakinra | Recombinant human IL-1 receptor antagonist | Anakinra did not improve outcomes in 116 patients with mild-to-moderate COVID-19 pneumonia in a multicentre, open-label, randomised clinical trial (CORIMUNO-ANA-1). | 225 |
| Vitamin D | A recent Cochrane systematic review concluded that there is currently insufficient evidence to determine the benefits and harms of vitamin D supplementation as a treatment for COVID-19. | 226 |

### Table 4. Overview of selected repurposed drugs currently (3/2022) not recommended for SARS-CoV-2 infection.

| Medication | Comments | Study |
|------------|----------|-------|
| Lopinavir/ritonavir | Anti-retroviral therapy | No efficacy in large controlled clinical trials | 152 |
| Hydroxychloroquine | Anti-rheumatic, anti-malarial agent | No efficacy in large controlled clinical trials | 152 |
| Nitazoxanide Thiazolid | broad-spectrum antiparasitic agent | A few randomised trials showed some level of efficacy. Studies were underpowered. So far, no evidence for recommendation. | 200–202 |
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### Repurposed drugs with potential antiviral effects

| Medication | Comments | Study |
|------------|----------|-------|
| PegIFN-α2b | Antiviral activity against SARS-CoV-2, COVID-19. | 204 |
| PegIFN-γ | Antiviral activity against SARS-CoV-2, COVID-19. | 204 |
| Interferon alfa | Early treatment, either within 5 days from the onset of symptoms or at hospital admission, confers better clinical outcomes, whereas late intervention may result in prolonged hospitalisation. | 221 |
| Interferon beta-1a | Interferon beta-1a plus remdesivir was not superior to remdesivir alone in hospitalised patients with COVID-19 and patients treated with Interferon beta-1a who required high-flow oxygen at baseline had worse outcomes. | 222 |
| Interferon lambda | Antiviral activity against SARS-CoV-2 virus in vitro. No effect of a single dose of PegIFN–γ in a small study (n = 60). | 223,224 |
| Anakinra | Recombinant human IL-1 receptor antagonist | Anakinra did not improve outcomes in 116 patients with mild-to-moderate COVID-19 pneumonia in a multicentre, open-label, randomised clinical trial (CORIMUNO-ANA-1). | 225 |
| Vitamin D | A recent Cochrane systematic review concluded that there is currently insufficient evidence to determine the benefits and harms of vitamin D supplementation as a treatment for COVID-19. | 226 |
EASL position

- Lopinavir/ritonavir, hydroxychloroquine, azithromycin, colchicine, ivermectin, should not be used to treat SARS-CoV-2 infection.
- Currently, no recommendation can be made for the use of nitazoxanide, famotidine, budesonide or other inhaled steroids, anakinra, interferon-β/β/β, and vitamin D outside of clinical trials.
- Given the side effect profile, ease of use, low cost, and widespread availability, fluvoxamine may be used in a high-risk setting if no other medication is available to prevent severe COVID-19.

Anticoagulation

Coagulopathy is a common abnormality in patients with COVID-19 and has become established as a major driver of morbidity and mortality, particularly in patients with severe disease. As well as macro-thrombotic events, COVID-19 is associated with widespread micro-thrombosis and endothelial dysfunction contributing to multiorgan failure in the terminal phase of the disease. The dose and type of anticoagulation utilised during COVID-19 has therefore been the subject of much research attention.

In patients with critical COVID-19 requiring ICU admission, a large multiplatform randomised-controlled trial demonstrated no benefit of therapeutic dose anticoagulation compared to usual thromboprophylaxis across all major outcomes including organ support requirements, in-hospital mortality, all-cause mortality, and rates of major venous thromboembolism. However, therapeutic anticoagulation was associated with an increased risk of bleeding complications (3.8% vs. 2.3%). Similarly, the INSPIRATION trial showed no advantage of intensified prophylactic anticoagulation vs. standard prophylactic anticoagulation in terms of 30-day mortality, ECMO requirement, and development of venous thromboembolism in patients admitted to the ICU.

Conversely, among patients with COVID-19 not requiring ICU admission, an initial strategy of therapeutic dose anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support compared with usual-care thromboprophylaxis. Therapeutic anticoagulation was also superior in preventing thrombotic events but was associated with a higher rate of major bleeding compared to thromboprophylaxis (1.9% vs. 0.9%). It is postulated that improved clinical outcomes with anticoagulation in this group may be mediated through the direct anti-inflammatory and possible antiviral properties of heparins.

In the RAPID trial, which included hospitalised patients with COVID-19 and increased D-dimer, therapeutic anticoagulation was not associated with a reduction in the primary composite outcome of death, invasive ventilation, non-invasive ventilation, or ICU admission. However, the odds of mortality at 28-days were decreased and rates of major bleeding were low (0.9%). Use of direct oral anticoagulants (e.g. rivaroxaban) do not appear to improve major outcomes compared to standard thromboprophylaxis in hospitalised patients with COVID-19, but are associated with increased bleeding events. Only a small number of outpatients with mild COVID-19 have been studied to date, in whom standard thromboembolic prophylaxis showed no benefit in terms of mortality, hospitalisation, or occurrence of thrombotic events compared to placebo.

Aspirin has also been explored as a possible strategy to prevent thromboembolic events and improve patient outcomes. A systematic review including 12 studies suggested that aspirin may improve mortality in hospitalised patients with severe COVID-19. An observational cohort study of 112,269 hospitalised patients with COVID-19 showed that early aspirin use was associated with lower odds of inpatient death. However, the multiplatform RECOVERY trial found that aspirin was not associated with reductions in 28-day mortality or rates of invasive mechanical ventilation. Therefore, aspirin cannot currently be recommended in hospitalised patients with COVID-19. This also applies in the outpatient setting, where the ACTIV-4B trial showed no benefit of aspirin among individuals with symptomatic clinically stable COVID-19.

Patients with advanced CLD are at increased risk of venous thromboembolism and it is plausible that COVID-19 could further increase the risk of prothrombotic complications in such patients. Historically, there have been reservations about the use of anticoagulation in patients with advanced cirrhosis and portal hypertension because of low platelet counts or prolonged prothrombin time. However, anticoagulation in patients with cirrhosis has been shown not to be associated with an increased risk of bleeding. In a multicentre Italian study in which 80% of patients with cirrhosis and COVID-19 received thromboprophylaxis, there were no major haemorrhagic complications. Therefore, it is important that patients with cirrhosis are not excluded from anticoagulation when appropriate during the management of COVID-19.
Co-medications relevant for patients with CLD, transplant recipients, hepatobiliary cancer

Non-selective beta-blockers
Non-selective beta-blockers form a cornerstone of primary and secondary prophylaxis for variceal haemorrhage in patients with cirrhosis. Despite early concerns about the use of antihypertensives and severe COVID-19, there has subsequently been no indication that baseline use of beta-blockers is associated with an increased risk of ICU admission or death. Therefore, there is no reason for beta-blockers, including non-selective beta-blockers, to be discontinued routinely during the pandemic or following SARS-CoV-2 infection unless necessary for other clinical indications such as haemodynamic instability.

Mycophenolate mofetil
MMF use in LT recipients may have a deleterious effect in the context of COVID-19 both through precipitating more severe disease and by blunting immune responses to COVID-19 vaccination. In a nationwide study in Spain, MMF was identified as an independent predictor of mortality in LT recipients with COVID-19. This may be related to the synergistic cytotoxic effect of MMF and SARS-CoV-2 on activated lymphocytes. This negative prognostic effect was particularly evident at higher doses of MMF (>1,000 mg/day), and in patients receiving the full dose of MMF at baseline (2,000 mg/day). Withdrawal of the drug following SARS-CoV-2 infection tended to reduce COVID-19 severity. In addition, several studies have shown that patients treated with MMF are more likely to have absent or suboptimal antibody responses to COVID-19 vaccination. A study of 29 kidney transplant recipients with poor SARS-CoV-2 antibody titres after an initial vaccine course showed that immune response to a fourth dose of COVID-19 vaccination could be improved by pausing immunomodulatory therapy (e.g. MMF, azathioprine). However, larger controlled studies are required before recommendations can be made about this approach.

NAs for HBV
Population-level data from Korea have indicated that antiviral treatment with tenofovir or entecavir is associated with reduced SARS-CoV-2 positivity rate (adjusted odds ratio 0.49; 95% CI, 0.37–0.66), whilst treatment was not associated with more severe COVID-19 outcomes.
Calcineurin inhibitors
Calcineurin inhibitors (e.g. cyclosporine A, tacrolimus) have demonstrated antiviral properties against several coronaviruses in vitro including SARS-CoV and MERS-CoV. Some clinical evidence of potential benefit against SARS-CoV-2 also exists. In an open-label, non-randomised study of 209 patients with COVID-19 pneumonia, cyclosporine A in combination with glucocorticoids was associated with improved mortality compared with glucocorticoids alone. A European multicentre study of 243 LT recipients with COVID-19 also reported that tacrolimus use was associated with improved survival. A single small randomised-controlled trial of 55 patients with severe COVID-19 indicated that combination therapy with methylprednisolone and tacrolimus resulted in numerically lower all-cause mortality compared with standard treatment. However this difference was not significant and dual therapy was associated with an increased risk of secondary infections.

mTOR inhibitors
mTOR inhibitor use in renal transplant recipients has been shown to be associated with improved humoral and T-cell responses after COVID-19 vaccination. This may be linked to the immunomodulatory effect of mTOR inhibitors on memory CD8+ and CD4+ T cells which in turn promote the enhancement of memory precursor effector cells. It has also been suggested that mTOR inhibition may suppress SARS-CoV-2 replication. As such, mTOR inhibitors appear to have more potentially beneficial than detrimental effects in the context of COVID-19 and should therefore be continued.

Immune checkpoint inhibitors
Use of immune checkpoint inhibitors (ICIs) have become a mainstream treatment option for a range of cancer types including HCC. With the onset of the pandemic, it remained unclear how these agents may influence the pathogenesis of COVID-19. Whilst ICIs may theoretically enhance T-cell control of viral infections they also risk augmenting the hyperactive immune phase of COVID-19. However, several large oncology series have indicated that baseline ICI use does not negatively impact the course of COVID-19, including rates of mortality.

Prevention of SARS-CoV-2 infection and COVID-19
General public health prevention measures
General public health prevention measures (e.g. masks, social distancing, and hand hygiene) remain an important component of the population response to COVID-19. Whilst these measures are variably enforced according to local guidelines, they are likely to have a significant impact in vulnerable cohorts, especially for patients at increased risk of severe COVID-19 and those with poor vaccine responses. Factors that increase the transmissibility of the virus or affect the durability of vaccine protection should also be considered.

There should be a low threshold for adopting general public health prevention measures in vulnerable patients including patients with cirrhosis and those taking immunosuppressive medication.
COVID-19 vaccination

Available vaccine platforms and general efficacy and safety

Since the beginning of the pandemic, there has been a huge collaborative global effort to develop vaccines which protect against SARS-CoV-2 infection and the development of severe COVID-19. Four main vaccine platforms have been utilised in vaccine design: i) traditional adjuvanted vaccines, (ii) inactivated or subunit protein vaccines, (iii) viral vector vaccines, and (iv) mRNA-based vaccines. Phase III clinical trials were initially conducted when the circulating variant was mostly the initial D614G strain, which has only a minor mutation in the spike protein compared to the strain included in the vaccines. Safety and efficacy data of the range of vaccine platforms have been extensively reviewed elsewhere.3,250

By April 2022, more than half of the world’s population had received at least 1 vaccine dose, and real-world data show that vaccination is generally extremely safe and significantly reduces mortality.251 However, the initial high efficacy against infection has decreased following the emergence of new SARS-CoV-2 variants. Vaccine efficacy is particularly low against omicron infection, although fortunately it still confers considerable protection against severe COVID-19.252 Certain liver cohorts including patients with cirrhosis, ALD, NAFLD and HCC are all at risk of more severe COVID-19 (discussed earlier) and LT recipients appear more vulnerable to SARS-CoV-2 infection. Although typically excluded from initial phase III trials, these vulnerable individuals have now been vaccinated for more than a year using mRNA, viral vector and inactivated vaccines and data has emerged indicating safety253 and effectiveness254–256 in these groups. The adjuvanted protein vaccine NVX-CoV2373, Covovax, has only been approved recently and therefore real-world data in patients with liver disease is limited.

EASL position

- Vaccination is the most effective measure to prevent severe COVID-19.
- COVID-19 vaccination is recommended for all eligible patients.

Liver-related safety of COVID-19 vaccination

Acute liver injury after vaccination. All current COVID-19 vaccines are generally safe, although anaphylactic reactions (e.g. to polyethylene glycol included in mRNA vaccines), myocarditis and pericarditis (mRNA vaccines) and thromboembolic events (vector-based vaccines) may rarely occur. Other rare adverse vaccination events may only manifest once large populations have been exposed. One such observation, which was subsequently highlighted by the European Medicines Agency, was the temporal link between mRNA vaccination and acute liver injury. Establishing whether this finding represents a causal association remains the subject of ongoing studies.

Epidemiological data from a large European centre did not report an increase in new AIH diagnoses despite widespread vaccine uptake.257 However, instances of de novo AIH diagnoses despite widespread vaccine uptake.257 However, instances of de novo AIH diagnoses despite widespread vaccine uptake.257 Although typically excluded from initial phase III trials, these vulnerable individuals have now been vaccinated for more than a year using mRNA, viral vector and inactivated vaccines and data has emerged indicating safety253 and effectiveness254–256 in these groups. The adjuvanted protein vaccine NVX-CoV2373, Covovax, has only been approved recently and therefore real-world data in patients with liver disease is limited.

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Table 5. Case reports on acute liver injury after COVID-19 vaccination.

| Patient characteristics | AIH features | Treatment and outcome | Ref. |
|-------------------------|-------------|-----------------------|------|
| 35-year-old woman (third month postpartum). ALI 6 days after BNT162b1. Bili 4.8x ULN, AST 754 U/L, ALT 2,001 U/L, ALP 170 U/L. | ANA (1:1,280; homogeneous pattern), dsDNA Ab positive. IgG normal. Histology: lymphoplasmacytic and eosinophil infiltrate. | Good response to 20 mg prednisolone. | 262 |
| 76-year-old woman (Hashimoto thyroiditis and prior COVID-19 infection). Symptoms of AI started 3 days after mRNA-1273. 5 weeks after vaccination: ALT 579 U/L, ALP 124 U/L, Bili 3.3x ULN. | ANA (1:1,280, homogeneous, fine granular), SMA (1:1,280, against F-actin), anti-neutrophil cytoplasmic antibodies (titre >1:1,280, perinuclear, MPO and PR3 negative). High IgG (39.4 g/L). Interface hepatitis, plasma cells, pseudocapillaries. | Good response to 40 mg prednisolone plus azathioprine (maintenance therapy). Complete normalisation after 4 weeks. | 263 |
| 80-year-old woman (Hashimoto’s thyroiditis, granulomatous hepatitis in the past). ALI 1 week after BNT162b2. ALT 1,186 U/L, Bili 10.5x ULN, ALP 243 U/L. | No autoantibodies. Histology: eosinophil infiltrate, interface hepatitis in the portal tract with biliary injury and mild ductular proliferation | Good response to 1 mg/kg prednisolone. | 264 |
| 43-year-old woman (gingko-biloba 100 days before). 15 days (itching) after BNT162b1 and exacerbation 2 days after 2nd dose. ALT 52 U/L, ALP 162 U/L, Bili 17.5x ULN. | ANA (rim-like pattern), non-PBC AMA. IgG slightly elevated (10.96 g/L). Interface hepatitis, lobular and centrilobular inflammation. | No autoantibodies. Histology: eosinophil infiltrate, interface hepatitis in the portal tract with biliary injury and mild ductular proliferation | 265 |
| 63-year-old man (type 2 diabetes). DRB1*01:01 11:01, DQA1*01:01 05:01, and DQB1*03:01 05:01. 7 days after the first dose of mRNA-1273. ALT 1,038 U/L, ALP 192 U/L, Bili 10x ULN. | ANA present. Elevated IgG (25.1 g/L). Interface hepatitis, lymphoplasmacytic infiltrate. | Good response to 40 mg and subsequent 20 mg prednisone (but ALT, Bili declined already before start of treatment). | 266 |
| 41-year-old man (substitute hormonal therapy). 3 weeks GI symptoms after mRNA-1273. ALT 7 days after 2nd dose mRNA-1273. ALT 1,312 U/L, Bili 2.3x ULN, ALP 190 U/L. | ANA (1:80), SMA (1:40), SLA, LC1 positive. IgG elevated (20.8 g/L). Severe interface hepatitis with lymphocytes and plasma cells. | Good response to 1 mg/kg prednisolone. | 267 |
| 56-year-old woman. 6 weeks after mRNA-1273. ALT 1,701 U/L, Bili 5x ULN, ALP 298 U/L. | ANA (1:160, speckled). Normal IgG. Portal inflammation with interface hepatitis, presence of plasma cell aggregates, rosette formation, eosinophils. | Good response to budesonide (but ALT, Bili declined already before start of treatment and the kinetics did not improve during therapy). | 268 |
| 36-year-old man (Bupronfen 2 weeks prior). 26 days after ChAdOx1. ALT 1,774 U/L, Bili 1x ULN, ALP 118 U/L, Peak ALT 2,550 U/L, Bili 1.9x ULN. | ANA (1:160, speckled pattern). High IgG (35 g/L). Interface hepatitis (biopsy after start of therapy). | Adequate response to 60 mg prednisolone (24 days reported). | 269 |
| 71-year-old woman. 4 days after mRNA-1273. ALT 1,067 U/L, Bili 13.5x ULN, ALP 217 U/L. | SMA (1:2,560, anti-actin pattern). High IgG (21.77 g/L). Plasma cells, lymphocytes, eosinophils, neutrophils, interface hepatitis. | Good response to 40 mg prednisolone (but ALT, Bili declined already before start of treatment and the kinetics did not improve during therapy). | 270 |
| 57-year-old woman (Asia). First symptoms 2 weeks after CoronaVac. ALI 2 days after 2nd dose. ALT 974 U/L, Bili 13.5x ULN, ALP 217 U/L. | ANA (1:640, homogeneous pattern), anti-Sjögren syndrome antigen A. F2 fibrosis, severe lobular lymphocytic/lymphoplasmocytic infiltration, hepatic rosette formation. | Good response to prednisolone and azathioprine. | 271 |
| 65-year-old woman (JAK2 V617F-positive polycythemia vera, received IFN 2 years prior). 2 weeks after mRNA-1273. ALT 1,092 U/L, Bili 13.4x ULN, Jaundice after 5 weeks. | ANA (1:1,100, speckled pattern). IgG normal. Severe interface hepatitis and multiple confluent foci of lobular necrosis. | Good response to 60 mg prednisolone (started after jaundice occurred). | 272 |
| 40-year-old woman (history of sarcoidosis). ALT elevation 4x ULN 1 month after BNT162b2. Fluctuating ALT level for 5 months. | ANA (1:640. Elevated IgG (24 g/L). Interface necroinflammation, admixture of plasma cells. | Good response to 40 mg prednisolone. | 273 |
| 52-year-old man. 1st episode with jaundice 10 days after 1st vaccination with BNT162b1. ALT: 2,130 U/L, ALP 142 U/L, Bili 5.5x ULN, spontaneous recovery. 2nd episode 20 days after 2nd vaccination with BNT162b1. ALT 1,939 U/L, ALP 167 U/L, Bili 2x ULN. | ANA (1:200, AMA-M2 and SMA borderline. IgG normal. | Initially good response to budesonide, ALT relapse (763 U/L), prednisolone weaning. | 274 |
| 53-year-old man. 1st episode with skin erythema, abdominal pain, pruritus. 10 days after 1st vaccination with BNT162b1. ALT: 333 U/L, ALP 102 U/L, Bili normal. 2nd episode 1 month after 2nd vaccination with BNT162b1. ALT 485 U/L, AST 629 U/L, Bili 5.5x ULN, INR 1.36, Bili further increased and enchephalopathy developed. Autoantibodies negative. Elevated IgG (28.3 g/L). Histology: portal inflammation with interface activity and significant lobular necroinflammatory activity, hepatocellular rosette formation. | Initially response to steroids (32 mg/day) and antihistaminic treatment. 2nd episode: prednisolone 40 mg i.v. and plasma exchange. Living donor liver transplantation | 275 |
remains unclear whether the vaccine itself, the adjuvant, or the immune response to the vaccine may be the primary driver of liver injury. Importantly, in April 2022, the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee assessed whether vaccination with the mRNA vaccines causes AIH and concluded that the currently available evidence does not support a causal relationship between the vaccines and this condition (https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccines-safety-update-13-april-2022_en.pdf).

In conclusion, vaccine-triggered immune-mediated hepatitis is rarely reported after COVID-19 vaccination and can be accompanied by other clinical features of AIH. However, these events are extremely rare and respond well to corticosteroid treatment. Therefore, liver injury after vaccination should not represent a barrier to subsequent vaccination at the individual or population level.

Vaccine-induced thrombotic thrombocytopenia. Vaccine-induced thromboembolic event in combination with thrombocytopenia occurring between 5 and 28 days after adenoviral vector COVID-19 vaccination. VITT has mostly been associated with the ChAdOx1 nCoV-19 (Vaxzevria) vaccine but is also reported following vaccination with Ad26.COV2-S (Jcovden). Cerebral venous thrombosis is the most common (50%), followed by splanchnic vein thrombosis (30%). Hepatosplenic thrombosis has also been shown to be present in 17% of VITT cases, often occurring alongside cerebral venous thrombosis, and may be associated with more severely deranged laboratory parameters. Pulmonary emboli and arterial ischaemia have also been recognised. VITT is a rare event, occurring in 1/100,000-250,000 individuals vaccinated with an adenovirus vector platform, and shares similar hallmarks with heparin-induced thrombocytopenia, implicating an underlying immunological trigger. This is most likely mediated by antibodies to platelet factor 4 (PF4) made in response to adenovirus/PF4 complexes. Splanchnic vein thrombosis should be suspected in anybody presenting with new-onset abdominal pain and thrombocytopenia within 28 days after COVID-19 vaccination. Diagnostic work up should include D-dimer (diagnosis is typically associated with levels >2-4 mg/L), PF4 antibodies if available, and abdominal imaging. Management is with non-heparin-based anticoagulation therapy, correction of fibrinogen levels, avoiding platelet transfusions, and intravenous immunoglobulin as soon as possible after diagnosis. Patients with clinical or radiological evidence of bowel ischaemia due to portal vein thrombosis may require systemic thrombolysis, catheter-directed thrombolysis via a transjugular intrahepatic portosystemic shunt, or surgical intervention.

EASL position

- Immune-mediated hepatitis following COVID-19 vaccination is a rare event, and no causal link has yet been established. Therefore, it should not be the reason to stop further vaccination.
- Patients with signs of immune-mediated hepatitis after COVID-19 vaccination should be treated with corticosteroids.
- VITT, including splanchic and hepatosplenic thrombosis, is a rare event after COVID-19 vaccination with adenoviral vector vaccines.

Vaccine responsiveness in patients with CLD and in liver transplant recipients

Vaccine immunogenicity. Patients with CLD have been shown to have anti-SARS-CoV-2 S-spike IgG seroconversion rates of >85% following 2 vaccine doses. However, several studies have suggested that patients with cirrhosis may have a more rapid decline in antibody titres over time compared to healthy controls. In contrast, LT recipients remain at high-risk for suboptimal humoral responses to vaccination. In a prospective evaluation of patients following 2 mRNA doses or a single adenoviral vaccine, poor or undetectable antibody titres were observed in 61% of LT recipients, 23% of patients with cirrhosis, and 25% of patients with non-cirrhotic CLD (Table 6). Therefore, some countries have opted to empirically deliver a third “prime” vaccination to all SOT recipients a minimum of 1 month after the second dose. The immunological benefit of these additional vaccine doses has been investigated in some SOT cohorts. A retrospective study from France assessed anti-spike antibody responses in 396 SOT recipients (kidney, liver, lung and pancreas) following a third dose of BNT162b2 (Comirnaty) given 2 months after the second dose. The proportion of patients with detectable antibody titres increased from 41% to 68% before and after a third dose of vaccination.

In a separate study of 872 SOT recipients (including 151 LT recipients), whilst antibody levels increased more than 70-fold in patients who had already responded to the second dose, antibody levels were lower in previous non-responders. This illustrates the capacity for SOT recipients to recall memory responses following third vaccination, although this may be limited in patients with primary non-response.

Regarding cellular immunity, SOT recipients randomised to a third dose of mRNA-1273 (Spikevax) had a significant increase in polyfunctional CD4+ T cells and antibody titres compared to placebo. Similar findings have been replicated in heart and kidney transplant recipients. These
data show the capacity of third dose vaccination to augment T-cell responses in previously poor or non-responders.

**Vaccine effectiveness against initial variants.** Collectively, these immunogenicity data are corroborated by clinical effectiveness studies. For example, data from a North American cohort of patients with cirrhosis did show that infection after 1 or 2 mRNA vaccines was associated with reduced mortality compared to COVID-19 in unvaccinated individuals.294 In a large case-control study including 440 SOT recipients, vaccine effectiveness in preventing COVID-19 hospitalisations was lower compared with immunocompetent individuals, although protection was significantly improved with 3 compared to 2 mRNA vaccine doses.289

**Role of vaccination in the era of omicron predominance.** The omicron variant carries multiple spike protein mutations, has high transmissibility, but seems to lead to generally less severe COVID-19.9,30 These mutations, including within the receptor-binding domain, allow for immune escape from neutralising antibodies. However, T-cell recognition appears relatively well preserved across most SARS-CoV-2 variants.291 Including omicron.292 Boosting with a third vaccine dose substantially increases protection against omicron.293,294 Improves the breadth and magnitude of neutralising antibodies.8,294 and induces potent omicron-specific T-cell responses even in immunocompromised individuals with impaired humoral responses.295 This T-cell antigen cross-recognition290,291,296,297 may play an important role in preventing severe COVID-19. This is strengthened by the finding that third and fourth vaccine doses were associated with lower likelihood of ICU admissions and severe disease.298,299 despite only moderate levels of omicron-specific neutralising antibody response. A fourth vaccine dose in immunocompromised patients may be particularly beneficial given that many received their first vaccination dose many months earlier and are at risk of waning antibody titres. Data in kidney transplant recipients have shown a modest increase in antibody responses after the fourth dose.300 This lends weight to the potential benefit of repetitive vaccine boosters in immunocompromised patients. However, there is still insufficient evidence regarding clinical protection against severe COVID-19 in this population and the longevity of T-cell responses following multiple vaccine doses specifically in SOT recipients.

**Heterologous vaccination and consideration of previous SARS-CoV-2 infection status.** Due to variable vaccine availability, particularly during the early phases of vaccine roll-out, some individuals received heterologous ‘mix-and-match’ vaccination combinations. Subsequently, a few studies have evaluated the immunogenicity and effectiveness of these mixed immunisation regimens. In immunocompetent individuals, whilst heterologous combinations of different mRNA vaccines achieved similar immune responses, those who were primed with a viral vector or inactivated vaccine benefited from heterologous boosting with an mRNA vaccine platform. For example, in ChAdOx1 nCoV-19 primed health care workers, boosting with BNT162b2 induced significantly higher levels of spike-specific CD4+ and CD8+ T cells and higher neutralising antibody titres against multiple SARS-CoV-2 variants compared to homologous ChAdOx1-nCoV-19 vaccination.301 In another study, 458 healthy individuals primed with either mRNA-1273, BNT162b2 or Ad26.COV2-S subsequently received a heterologous booster >3 months later. Homologous boosting with Ad26.COV2-S was associated with lower humoral responses compared to other regimens, whereas heterologous boosting induced potent neutralising humoral responses. T-cell responses increased significantly after heterologous boosting, with the greatest CD8+ T-cell responses observed after any boosting of Ad26.COV2-S-primed individuals.302 T-cell responses were also higher when BNT162b2-primed individuals were heterologously boosted with Ad26.COV2-S.303 Effectiveness data from Sweden in 2021, when delta was the predominant SARS-CoV-2 variant, indicated a higher protection rate in ChAdOx1 nCoV-19 primed and mRNA-boosted individuals compared to those receiving 2 doses of ChAdOx1 nCoV-19.304 Lastly, in a large Brazilian trial (n = 1,240), individuals primed with 2 doses of CoronaVac received a third vaccine dose 6 months later with either BNT162b2, Ad26.COV2-S, ChAdOx1 nCoV-19 or homologous CoronaVac. This demonstrated that all heterologously boosted patients achieved seroconversion at 1-month with the highest antibody titres observed in those receiving BNT162b2.305 Data on the immunogenicity and clinical benefit of heterologous boosting in diseased cohorts remains limited, including in patients with CLD and LT recipients.

Multiple studies have shown that healthy individuals with previous SARS-CoV-2 infection elicit antibody and T-cell responses after a single mRNA vaccine dose which are comparable to those observed after 2 doses in those who are infection-naive.306 Furthermore, a second dose in previously infected individuals did not further increase humoral responses.307 One study compared the immune response in COVID-19 convalescents vs. matched infection-naive individuals before and after vaccination with BNT162b2.308 This showed that excellent infection-neutralising capacity against all variants of concern, including omicron, developed after either 2 vaccinations in convalescents or a third vaccination in twice-vaccinated, COVID-19-naive individuals.309 Similar findings were observed in a SOT cohort, showing higher
Table 6. Observational studies evaluating immune responses after COVID-19 vaccination in solid organ transplant recipients or patients with chronic liver disease without prior SARS-CoV-2 infection (4/2022, without claim to be exhaustive).

| Population | Vaccine | Antibody and T-cell responses after 2-dose vaccination or 3rd dose if indicated | Factors associated with a decreased humoral response | Ref |
|------------|---------|---------------------------------------------------------------------------------|-----------------------------------------------------|-----|
| **Cohorts of LTR** | | | | |
| LTR: n = 80 | | | | |
| Controls: n = 25 | | Seropositivity: 47.5% vs. 100% (anti-S1/2) | - Age (mean 63 vs. 57 years) | 226 |
| BNT162b2 | | | - Low eGFR | |
| | | | - Triple immunosuppression | |
| | | | - Treatment with high-dose glucocorticoids and MMF | |
| LTR: n = 118 | | Seropositivity 21-132 days after second dose: IgG anti-spike: 78% | - Alcohol-related liver disease before transplantation | 242 |
| BNT162b2: n = 114 | | | - MMF | |
| mRNA-1273: n = 3 | | | | |
| Ad26.COV2S: n = 1 | | | | |

**Mixed cohorts of SOTR, including at least 15 LTR**

| Population | Vaccine | Antibody and T-cell responses after 2-dose vaccination or 3rd dose if indicated | Factors associated with a decreased humoral response | Ref |
|------------|---------|---------------------------------------------------------------------------------|-----------------------------------------------------|-----|
| SOTR: n = 658 | | Seropositivity: 54% for all SOTR, 80% for LTR (anti-RBD or anti-S1) | Mixed cohort: | 227 |
| LTR: n = 129 | | | - Time since transplantation | |
| No control | | | - Antimetabolites: 43% vs. 82% | |
| BNT162b2: n = 342 | | | - No seroconversion in 40% vaccinated with mRNA-1273 vs. 51% BNT162b2 | |
| mRNA-1273: n = 207 | | | | |
| Missing: n = 9 | | Seropositivity: 71% for LTR (anti-S1 IgG or IgM) | | 319 |
| mRNA-1273 | | S-specific T-cell response: 86% for LTR (IFN-gamma ELISPOT) | | |
| LTR: n = 104 | | Seropositivity: 34.5% (n = 38/110) anti-RBD Ig, neutralising Abs in 26.9%, mostly in responders with higher anti-RBD lg levels | | 320 |
| mRNA-1273 | | T-cell responses: In 48 SOTR. 47.9% S-specific CD4 T cells. 46.2% of humoral non-responders showed CD4+ T-cell responses. Very little CD8 T-cell response detected | | |
| SOTR: n = 127 | | Seropositivity: 50% anti-SARS-CoV-2 IgG | | 328 |
| LTR: n = 58 | | | - Not reported | |
| Mostly BNT162b2 | | | | |
| SOTR: n = 396 | | Seropositivity: Before 3rd dose in 164 SOTR (41%), no data for LTR alone | | 284 |
| LTR: n = 69 | | One month after 3rd dose: 269 patients after the 3rd dose (68%); LTR: 51/69 (74%). | | |
| BNT162b2 | | Seropositivity 2 weeks to 3 months after the 2nd dose. | | 282 |
| mRNA-1273 | | LTR: anti-SARS-CoV-2 IgG in 42.5%, anti-SARS-CoV-2 anti-spike titre ≥1:50 in 39.3% | | |
| SOTR candidate: n = 241 | | | | |
| LT candidates: n = 76 | | Seropositivity: 1 month after second dose. Detectable vs. seropositive: | LTR: | 283 |
| BNT162b2: n = 50 | | - Use of 2 or more immunosuppression medications | | |
| mRNA-1273: n = 26 | | LTR: 82.2% vs. 38.7% | | |
| LTR: n = 62 | | Cirrhotic CLD: 96.2% vs. 77.2% Non-cirrhotic CLD: 95.7% vs. 75% | | |
| Cirrhotic CLD: n = 79 | | | | |
| Non-cirrhotic CLD: n = 92 | | mostly equally distributed | - Overall transplant recipient, but not for LTR | |
| BNT162b2: n = 104 | | | | |
| mRNA-1273: n = 110 | | | | |
| Ad26 single dose: n = 19 | | | | |

**Cohorts with CLD**

| Population | Vaccine | Antibody and T-cell responses after 2-dose vaccination or 3rd dose if indicated | Factors associated with a decreased humoral response | Ref |
|------------|---------|---------------------------------------------------------------------------------|-----------------------------------------------------|-----|
| Cirrhotic CLD: n = 38 | | Seropositivity: Cirrhoclid: 97.4% | Immunosuppressive treatment | 281 |
| Non-cirrhotic CLD: n = 49 | | Non-cirrhotic CLD: 87.8% | Presence of liver disease and/or cirrhosis were not correlated with either lower anti-SARS-CoV-2 antibody titres or neutralising activity | |
| Controls: n = 40 | | Controls: 100% | | |
| Mostly BNT162b2, very few mRNA-1273 | | | | |

CLD, chronic liver disease; DSA, donor-specific antibodies; eGFR, estimate glomerular filtration rate; LTR, liver transplant recipient; MMF, mycophenolate mofetil; SOTR, solid organ transplant recipient.

1. Serology performed at least 14 days after 2nd dose, if not otherwise indicated.
2. Diasonin SPA, Seropositivity at >15 AU/ml.
3. EUROMMUN enzyme immunoassay, positive cut-off of at least 1.1 AU.
4. Elecsys Anti-SARS-CoV-2 semi-quantitative, positive at ≥250 U/ml.
5. Siemens SARS- CoV-2 Total (COV2T, IgG and IgM). When COV2T positive, confirmation with Siemens SARS-CoV-2 IgG (COV2G).
6. Roche Elecsys anti- SARS-CoV-2 S enzyme immunoassay Seropositivity at 208 U/ml.
7. SARS-CoV-2 Surrogate Virus Neutralization Test assay (GenScript) cut-off for positivity at 30% neutralisation.
8. Mixed cohort: Anti-SARS-CoV-2 Spike Total Immunoglobulin (Ig) and IgG-specific assays (OrthoClinical Diagnostics, Markham, ON, Canada) were performed on the VITROS 3600 automated immunoassay analyser according to the manufacturer’s protocol.
antibody responses in previously infected vs. naïve individuals after their first vaccination.309 A small study comparing neutralising antibody responses, including those against the variant omicron, showed that even triple-vaccinated kidney and heart transplant recipients had lower neutralising antibody titres compared to previously infected and twice-vaccinated individuals.310 In summary, there is mounting evidence that previous SARS-CoV-2 infection can replace a vaccine dose in immunocompetent individuals and SOT recipients.

**EASL position**

- There is no definition of a “complete” vaccination schedule and the number of vaccines delivered should depend on local availability, individual clinical risk, and the behaviour of the prevailing SARS-CoV-2 variant.
- We currently recommend 3 doses of vaccine (or, equivalently, 3 exposures to the spike protein, which includes vaccination or SARS-CoV-2 infection).
- An additional vaccine dose may be administered on an individual basis if 3 exposures to the spike protein have occurred at short intervals (1 month between exposures, as primary vaccine series) to enhance long-term immunological memory.
- Subsequent additional doses of COVID-19 vaccine may be offered to immunocompromised patients who are at high risk for suboptimal vaccine responses, while we await further study results on immunogenicity and effectiveness.

**Absence of correlates of protection**

Despite advances in our understanding of vaccine immunogenicity, the precise immune correlates of clinical protection remain unresolved. Currently there is no established biomarker which can reliably determine whether healthy or immunocompromised individuals are protected from SARS-CoV-2 infection or severe disease. Furthermore, systemic immune responses may not translate into local immunity at the point of viral entry in the upper respiratory tract.311,312 For the initial viral variants, the magnitude of SARS-CoV-2 antibody response was positively associated with the observed collective vaccine efficacy.313 This finding was strengthened by the observation that susceptibility to SARS-CoV-2 infection tends to increase with time after vaccination in parallel with diminishing levels of total and neutralising antibody titres.315,316 Serological testing is to date the only available tool for clinicians to assess global immune responses to COVID-19 vaccination. For example, additional vaccination doses might be prioritised for patients with undetectable antibodies, particularly in those at high risk of severe COVID-19. However, it is important to note that the presence of antibodies does not preclude susceptibility to post-vaccination infection, the development of COVID-19, or the ability to transmit SARS-CoV-2.

In studies examining responses to all relevant variants, including delta and omicron, no direct correlation was found between anti-spike IgG titres and neutralising capacity. Thus, it is the quality rather than the quantity of antibodies that appears to matter most.310 Accordingly, in a study of 60 SOT recipients, many patients vaccinated with 3 doses of mRNA-1273 had undetectable omicron-specific neutralising antibodies despite positive anti-RBD (receptor-binding domain) antibodies.317 In addition, as previously discussed, SARS-CoV-2-specific T cells appear better preserved against novel viral variants.290,318 This is consistent with the clinical observation that vaccine effectiveness against symptomatic infections decreases with delta and omicron but protection against severe disease is largely maintained, as shown, for example, during the period when the delta variant was predominant.314 There are studies in SOT recipients showing that T-cell responses are detectable even in absence of antibody titres,319,320 suggesting that patients with undetectable antibodies may still be protected against severe disease. However, to date, no reliable correlation between the magnitude of T-cell response and protection against severe disease has been reported. Therefore, measurement of T-cell responses (e.g. by whole-blood interferon-γ release assays) has not yet entered into routine clinical practice321–323 and cannot be recommended at this stage.

**EASL position**

- SARS-CoV-2-specific IgG titres are not suitable to predict protection.
- Vaccine-induced T-cell responses play a role in protection against severe COVID-19. However, there is no standardised test for the reliable prediction of protection.
- A high antibody titre should not preclude completion of the COVID-19 vaccination series to achieve at least 3 exposures to the spike protein.
- Vaccine-specific antibody titres can be tested in individuals at risk for severe COVID-19 when adequate vaccine responses after at least 3 exposures to the spike protein are uncertain.
- Additional vaccine doses can be attempted if antibodies are undetectable, especially in those at risk of severe COVID-19.
Ethical considerations – vaccine hesitancy and mandatory vaccination in healthcare workers

The approach to mandatory vaccination of healthcare professionals and to the care of vaccine-hesitant transplant candidates remain contentious areas. The WHO has summarised 5 key ethical considerations in the discussion of mandatory vaccination; necessity and proportionality, sufficient supply, public confidence in science and general vaccination, and a transparent process leading to shared decision making (https://www.who.int/publications/i/item/WHO-2019-nCoV-Policy-brief-Mandatory-vaccination-2021.1). Current COVID-19 vaccines are not designed to prevent transmission, and fully vaccinated healthy individuals can still transmit SARS-CoV-2. Therefore, given the proven safety and efficacy of the vaccines, healthcare providers should be encouraged to be vaccinated.

Similarly, transplant candidates should not automatically be delisted or not considered for transplantation in the event that they refuse COVID-19 vaccination. Concerns that this stance may not be sufficient have been raised against the risk of failing to respect patient autonomy, with associated negative impacts on the patient-caregiver relationship.324 Therefore, the evidence supporting mandatory vaccination with the aim of preventing transmission to patients may not be sufficient. However, given the proven safety and efficacy of the vaccines, healthcare providers should be encouraged to be vaccinated.

The phase III PROVENT trial assessed the safety and efficacy of the mAb combination tixagevimab plus cilgavimab (Euvusheld, AstraZeneca) vs. placebo for the prevention of symptomatic COVID-19 in 5,197 unvaccinated adults with negative point-of-care SARS-CoV-2 serology tests (pre-exposure prophylaxis). Of note, the trial was conducted when the major circulating SARS-CoV-2 variants were alpha (B.1.1.7), beta (B.1.351), delta (B.1.617.2), and epsilon (B.1.429). Tixagevimab (150 mg) plus cilgavimab (150 mg) reduced the risk of developing symptomatic COVID-19 by 77%, compared to placebo. Treatment was well tolerated without safety concerns. Over 75% of participants had baseline comorbidities, which include conditions which are associated with both reduced immune responses and an increased risk of severe COVID-19.331 Tixagevimab and cilgavimab can be administered as passive immunisation (intramuscularly) every 6 months in appropriate patients, as administration of the antibodies in high-risk patients during the 183-day follow-up period reduced the incidence of symptomatic COVID-19 compared with placebo.331,332 The half-life of the antibodies has been optimised to 4-12 months due to changes in the Fc domain of IgG. Experts recommended doubling the dose to 300 mg tixagevimab plus 300 mg cilgavimab at the time when omicron BA.1 was the predominant subvariant because in vitro data have shown that BA.1 has lower susceptibility to tixagevimab plus cilgavimab.324,375,333 Updated recommendations should be reviewed here: https://www.covid19treatmentguidelines.nih.gov/overview/prevention-of-sars-cov-2/

Pre-exposure prophylaxis against SARS-CoV-2 infection

As described above, pre-emptive treatment with mAbs or antiviral drugs in the early phase of SARS-CoV-2 infection could prevent the progression to severe COVID-19. However, immediate prevention of COVID-19 in seronegative individuals after contact with infected individuals is also possible. The concept of prevention of COVID-19 in previously uninfected household contacts of infected individuals was first demonstrated with the mAb combination of casirivimab plus imdevimab.330 However, based on in vitro data, this combination is likely to be less effective against the omicron variant, whereas tixagevimab plus cilgavimab may be more effective.174,175

EASL position

- COVID-19 vaccination is strongly recommended for LT candidates and information regarding safety and efficacy of vaccines should be made available to caregivers and patients, along with an emphatic response to their concerns (e.g. motivational interview techniques).

- Pre-exposure prophylaxis of SARS-CoV-2 infection with mAbs (tixagevimab plus cilgavimab) is recommended for immunocompromised individuals (patients receiving immunosuppressive medication equivalent of >20 mg of prednisone) who are not fully vaccinated* or do not have an adequate immune response to COVID-19 vaccination.

- We suggest that patients with decompensated cirrhosis might also be considered immunocompromised and eligible for passive immunisation.
• Passive immunisation is not a replacement for active vaccination against COVID-19 and should only be used when there are important reasons not to vaccinate.

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors’ contributions
TM: Outline of the manuscript, writing of sections 1-3, review and revision of the manuscript. CSE: Outline of the manuscript, writing of section 5, review and revision of the manuscript. TB: Outline of the manuscript, writing parts in section 1-5, review and revision of the manuscript. LSB: Writing parts (liver transplantation) in sections 2,4,5, review and revision of the manuscript. MB1: Review and revision of the manuscript. MB2: Review and revision of the manuscript. MUM: Review and revision of the manuscript. RM: Review and revision of the manuscript. RJ: Review and revision of the manuscript. DS: Review and revision of the manuscript. TM: Initiation of the project, review and revision of the manuscript. MC: Organization of the project, Outline of the manuscript, writing of section 4 and parts of sections 1,2,5, review and revision of the manuscript.

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