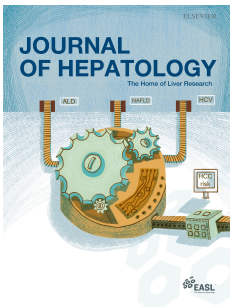

Impact of COVID-19 on the liver and on the care of patients with chronic liver disease, hepatobiliary cancer, and liver transplantation: an updated EASL position paper

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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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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.
TB: 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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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 transmissible [4] and resistant to neutralization by antibodies induced by current vaccine platforms or following SARS-CoV-2 infection [7,8]. 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 optimized [14]. Despite these caveats, this position paper seeks to review all the available data, comprehensively summarize the liver-specific effects of SARS-CoV-2 infection, and highlight important care considerations for patients with COVID-19 and chronic liver disease, hepatobiliary cancer, and previous liver transplantation.

1. 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 during the course of COVID-19 occurring in 10-65% of individuals [15]. These abnormalities are usually characterized 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 signaling, ischemia, and drug toxicity. Alongside this 'bystander' hepatitis there is also likely to be direct liver injury via SARS-CoV-2 infection of hepatocytes. Multimodal investigation 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 disease severity and outcome [17–19] 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 COVID-19 patients who were hospitalized 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 [19]. The time taken for complete normalization of liver biochemistry has not been systematically investigated but persisting abnormalities following complete recovery from COVID-19 may indicate undiagnosed pre-existing chronic liver disease.

EASL position

- Liver parameters (including AST, ALT, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) and bilirubin should be regularly assessed during hospitalization 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. This is most likely of multifactorial origin with contributions by the systemic inflammatory response, drug induced liver injury, hypoxia, microvascular hepatic thrombosis, as well as possible direct viral infection of hepatocytes [15]. In contrast, cholestasis, characterized 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* [20]. However, over the course of the pandemic several case series have reported delayed-onset and progressive cholestasis 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 chronic Liver Disease (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 which 4 (44%) subsequently developed features of secondary sclerosing cholangitis (SSC) defined by bile duct irregularities and strictures on magnetic resonance cholangiopancreatography (MRCP) [21]. 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 [21]. Similarly, in a single-center North American study, 12 patients admitted to ICU with severe COVID-19 subsequently developed delayed onset cholestasis (ALP >3x ULN) with associated MRCP abnormalities [22]. This clinical picture was present in <0.6% of all patients hospitalized 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 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 [21,22]. These cholestatic complications also appear more frequent and pronounced in patients with pre-existing CLD [23]. 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. 70% of these SSP patients had NAFLD/NASH, 90% were treated with ursodeoxycholic acid, all patients had severe COVID-19 requiring ICU admission with an overall mortality of 50%.

Notably in both European series, >90% of patients who developed severe cholestasis or SSP were exposed to ketamine as an anesthetic agent on ICU [21,23]. This contrasts with no ketamine use in an influenza cohort who developed relatively little SSP [21]. Whilst recreational ketamine misuse has been associated with cholangiopathy [24,25], acute biliary injury in the context of critical illness is less well recognized. 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 [26,27].

Critical illness-SSC (CI-SSC) has long been recognized as a distinct pathological entity typically developing after burns, polytrauma, complex surgery, hypovolemic shock or other life-threatening disease including influenza-associated acute respiratory distress syndrome (ARDS) [28,29]. However, it is a rare condition, with only 200 cases reported in the literature over the last 2 decades [30]. Whether SSC observed in the context of COVID-19 constitutes a distinct clinical entity or simply reflects a continuum of CI-SSC remains unclear. However, the relatively high prevalence of cholangiopathy following critical COVID-19 may implicate SARS-CoV-2-specific biliary tropism and injury.

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 assess for secondary sclerosing cholangitis.
- Where possible, ketamine may be avoided as a sedating agent in CLD patients with critical COVID-19 who require ICU admission.

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 (SLE) [32]. De novo autoimmunity following SARS-CoV-2 infection is also well recognized, manifesting in a range of clinical phenomena including SLE, immune thrombocytopenic purpura, Guillain-Barré syndrome, and autoimmune/autoimmune-like hepatitis (AIH) [33]. Mechanistically, this could be related to viral-induced molecular mimicry [31] resulting in the development of new-onset autoantibodies targeting traditional autoantigens or cytokines [34].. To date, at least six cases of AIH following COVID-19 have been reported including one case of overlap with primary biliary cholangitis (PBC) [35–39] (**Table 1**). In each case, a diagnosis of AIH was made based on characteristic laboratory parameters including elevated transaminases, immunoglobulin G (IgG), and the presence of associated autoantibodies. Liver biopsy was performed in three patients, all of whom demonstrated typical histological features of AIH, including lymphoplasmacytic inflammation and interface hepatitis. Most cases occurred within one month of mild COVID-19 and responded well to immunosuppressive therapy. Beyond these isolated reports, the broader population 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 SMA and ANA 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

- *De novo* autoimmune hepatitis may rarely occur following SARS-CoV-2 infection.
- Routine monitoring for this condition in all patients recovering from COVID-19 is not required.

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, hospitalized [35]	ALT 264 IU/L Bili 1.6 mg/dL IgG 2,260 mg/dL ANA 1/80	Not performed	20 days	Prednisolone + Azathioprine (Relapsed after discontinuation)
72 years, female, hospitalized [35]	ALT 640 IU/L Bili 11.2 mg/dL IgG 4250 mg/dL SMA + 1/640	Not performed	2 days	Prednisolone + tacrolimus
54 years, male, mild [36]	ALT 1238 IU/L Bili 25mg/dL IgG 3151mg/dL ANA+ 1:2560 SMA+ 1:45	Portal & lobular inflammation, plasma cell infiltrate, interface hepatitis	1 month	Prednisolone
60 years, female, mild [37]	ALT 1433 IU/L Bili 11.7 mg/dL IgG 2775 mg/dL ANA+ 1:320 SMA+ 1:80	Lobular lymphoplasmacytic infiltration, interface hepatitis	0 days	'Induction therapy' + Azathioprine
57 years, male, mild [38]	ALT 106 IU/L Bili 2.1 mg/dL IgG 4049 mg/dL SMA+ AMA+ Anti-dsDNA+	Not performed	1 month	No immunosuppression
40 years, female, mild [39]	ALT 1300 IUU/L Bili 22 mg/dL IgG 2190 mg/dL ANA+	Portal and lobular inflammation, plasma cell infiltrate	1 month	Prednisolone

ALT; alanine transferase, Bili; bilirubin, IgG; immunoglobulin G,SMA; smooth muscle antibody, ANA; antinuclear antibody, AMA; anti-mitochondrial antibody, dsDNA; double-stranded DNA.

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

Chronic liver disease 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 hospitalized CLD patients across 29 countries, with case fatality 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 COVID-19 patients without CLD after matching for age and comorbidity. Outcome data in CLD patients across 21 North American institutions also found decompensated cirrhosis as an independent risk factor for death [46]. High rates of COVID-19 mortality in cirrhosis, ranging between 20-30%, have also been replicated in an exclusively Asian registry [47] and in several multicenter 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 CLD patients in North America further emphasized the negative impact of advanced liver disease at a population level, with cirrhosis being associated with a 2.38 x adjusted hazard of mortality 30-days following 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 hospitalization and death related to COVID-19 in patients coded as having cirrhosis [52]. These findings do contrast with one 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 hospitalization in patients with COVID-19 after vaccination [55].

It is important to recognize 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 hospitalization 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 (HE), 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 [45,48]. Presentation with gastrointestinal symptoms is more frequent in patients with cirrhosis than matched controls [45] and is associated with a worse disease trajectory [46]. This is already a well-recognized phenomena within the general population [57] and is thought to be secondary to greater gut permeability and systemic inflammation. Historic studies have shown a >30-fold increase in ACE2 receptor expression in cirrhotic versus healthy livers, suggesting that patients with cirrhosis may be uniquely susceptible to SARS-CoV-2 mediated hepatic dysfunction [58]. In addition, Wanner et al. have shown clear evidence of specific SARS-CoV-2 hepatotropism, further implicating the ability of the virus to trigger decompensation in patients with pre-existing CLD [16]. Acute-on-chronic liver failure (ACLF) following SARS-CoV-2 infection is also well-recognized, being reported in up to 12%-50% [45,47–49] of decompensating patients. In this context, several scoring models have been applied with the prognostic value of CLIF-C ACLF score and CLIF organ failure scores appearing to outperform MELD, NACSELD, and Child-Pugh 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 HE, and coagulopathy [15]. 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 CLD versus non-CLD patients [51]. In addition, this study introduced the concept of limited ‘therapeutic effort’ for patients with cirrhosis and alcohol-related liver disease, both of which 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 [42,60]. Balancing the costs and benefits of ICU admission in severely unwell patients with cirrhosis has remained a consistent clinical challenge for decades [61], which may have become acutely unmasked during the COVID-19 pandemic.

EASL position

- Patients with chronic liver disease with or without cirrhosis do not appear at increased risk of SARS-CoV-2 infection. However, those with cirrhosis are at high risk of COVID-19 related mortality.

- Liver disease severity is a strong predictor of developing severe COVID-19 and preventing liver disease progression may protect patients from the adverse effects of future SARS-CoV-2 infection.
- Limited data are available on the impact of viral variants and COVID-19 vaccination on the clinical course of SARS-CoV-2 infection in patients with CLD.
- SARS-CoV-2 infection can precipitate new or worsening acute hepatic decompensation and ACLF in patients with cirrhosis.
- Patients with cirrhosis and SARS-CoV-2 infection often present without typical respiratory symptoms but subsequently deteriorate with the predominant cause of death being COVID-19 respiratory failure.
- Limitations of access to care, including invasive ventilation, may contribute to adverse outcomes in hospitalized patients with cirrhosis and COVID-19. Consequently, every effort must be made to facilitate access to intensive care units when appropriate.

Alcohol-related liver disease (ALD)

The immunomodulating effects of alcohol are well recognized [62,63], with increased alcohol consumption known to predispose to a range of septic insults including community acquired bacterial and viral pneumonias [64]. A history of harmful alcohol use also appears to increase susceptibility to acute respiratory distress syndrome (ARDS), a hallmark of severe COVID-19, in critically ill patients with sepsis [65]. Both registry data and multicenter studies have identified alcohol-related liver disease (ALD) as being independently associated with COVID-19 mortality after controlling for important co-factors including baseline liver disease severity [45,46,51]. However, alcohol consumption in patients with CLD, categorized as either social drinking or current daily drinking, was not associated with all-cause mortality compared to abstinence in a multivariable model [46]. The precise mechanisms through which ALD negatively impacts on prognosis in COVID-19 remains 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 [51]. The strength of this negative association exceeded that observed with any other individual co-morbidity or category of Charlson comorbidity index, suggesting that mortality in hospitalized 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) [66] 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 alcohol related liver disease 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 CLD of other etiology.

Non-alcoholic fatty liver disease (NAFLD)

The impact of NAFLD on COVID-19 outcomes has been closely scrutinized due to its association with well-established risk factors for severe COVID-19 including obesity, type 2

diabetes (T2D), cardiovascular disease, and hypertension [42]. 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 [67–69], which is corroborated by interval meta-analyses of epidemiological studies [70,71]. 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 non-alcoholic steatohepatitis (NASH) [72]. In addition, obese patients with biopsy proven NAFLD have upregulation of ACE2 in liver, subcutaneous, and visceral adipose tissue compared to obese non-NAFLD controls [73]. 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 [74,75]. In addition, there appears to be a lack of association between gene variants associated with NAFLD (PNPLA3, TM6SF2, MBOAT7, GCKR) and severe COVID-19 [76,77]. Indeed, one study from the UK biobank even reported a possible protective immunomodulatory effect of the PNPLA3 rs738409 G allele [77], although this was not replicated following targeted PNPLA3 genotyping in 383 consecutive Sicilian patients with COVID-19 [78]. Separate independent analyses using two-step Mendelian randomization techniques have also failed to identify a causal relationship between NAFLD and COVID-19 susceptibility and severity [79,80]. This approach attempts to overcome confounding by using genetic variants as instrument variables to draw causal inferences between risk factors and health outcomes [79]. In summary, from a pure 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 contributed to by the presence of other high-risk co-morbidities.

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 including the use of maintenance corticosteroids and thiopurines in patients with rheumatoid conditions and inflammatory bowel disease, respectively [81,82]. Conversely, the disease course in those on immunosuppression following solid organ transplantation appears comparable to non-immunosuppressed individuals [83,84]. A large-scale European survey of 1752 individuals with autoimmune hepatitis (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 significant increased risk of severe disease [85]. Subsequently, in an international cohort of 70 patients with AIH and COVID-19, of which 86% were immunosuppressed, no differences were found in the rates of adverse outcomes including hospitalization, ICU admission, and death compared to those with other causes of CLD [86]. 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 hospitalization 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 medication. Similar findings were concurrently reported in a multi-center cohort of 110 AIH patients who also had comparable outcomes to other liver disease types [87]. However, a larger retrospective study from the same group including 254 AIH patients with COVID-19 did indicate that baseline treatment with systemic glucocorticoids (median dose 5 mg/day) or azathioprine (median dose 75 mg/day) were associated with more severe COVID-19 [88] after adjusting for age, sex, comorbidities, and presence of cirrhosis. Data for patients with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are limited. One Nationwide study in Spain did observe a higher cumulative incidence of hospitalization and mortality in patients with PBC compared with the general population although interpretations are limited by the lack of adjustment for co-morbidities [89].

EASL position

- Patients with autoimmune hepatitis on immunosuppression do not appear to be at a higher risk of SARS-CoV-2 infection or COVID 19 related mortality.
- However, baseline use of glucocorticoids or azathioprine may be associated with more severe COVID-19; yet, discontinuing, or reducing the dose of these agents should only occur following careful assessment of all risks and benefits.

Chronic viral hepatitis

Several studies have investigated the clinical impact of co-existing chronic hepatitis B (HBV) or chronic hepatitis C virus (HCV) infection with SARS-CoV-2. A large territory-wide retrospective cohort study in Hong Kong [90] 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 biochemistry abnormalities during COVID-19 were the same across groups. Notably, 73 treatment-naïve patients with chronic HBV were started on HBV-targeted nucleoside analogues (NA) 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 NA, 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 [91]. Furthermore, in those with COVID-19 the proportion of patients with chronic HBV was lower than the general population after adjusting for co-morbidities and socioeconomic status, indicating that patients with HBV may be less susceptible to SARS-CoV-2 infection [91]. It has been suggested that this protective effect is mediated through the use of antiviral treatment including tenofovir and entecavir, which have been shown to be associated with a reduced rate of SARS-CoV-2 positivity [91,92]. Similar protective effects have also been reported in HIV-positive patients receiving tenofovir as part of antiretroviral therapy [93]. NA may have some immunomodulatory effects and possibly may have some specific antiviral properties against SARS-CoV-2 as postulated in pilot studies and pre-clinical models [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 [91].

Analysis from a large American Veterans dataset demonstrated that a greater proportion of HCV-positive patients (n=975) with COVID-19 were hospitalized 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 [97]. Two subsequent single-center studies have indicated adverse outcomes in patients with co-existing HCV and SARS-CoV-2 including ICU admission and mortality, particularly in those with elevated HCV RNA levels [98,99]. However, interpretations are limited by small sample size and lack of adjustment for the presence of cirrhosis. The repurposing of DAA therapy for use against COVID-19 has been investigated but results remain contentious (discussed below) [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.

Hepatobiliary cancer

Accurate risk stratification of patients with malignancy and COVID-19 has remained challenging due to high rates of comorbidity and heterogeneity in cancer type, stage, and treatment modality. Nonetheless, patients with malignancy do appear to be more susceptible overall to SARS-CoV-2 infection and death from COVID-19 [42,52]. Data related specifically to patients with hepatobiliary cancer are limited. In a large prospective UK cancer cohort, 95 patients were coded as having 'non-colorectal digestive malignancy' of which 29% died following SARS-CoV-2 infection [103]. In a multicenter North American study of patients with CLD and COVID-19, patients with hepatocellular carcinoma (HCC) (n=22) had an all-cause mortality of 52%, approximately 7-fold higher than in patients without HCC, although whether cause of death was related to COVID-19 or HCC complications remains unclear [46]. This equated to HCC being an independent risk factor for COVID-19 mortality even after controlling for the presence of cirrhosis (hazards ratio 3.31 [1.53–7.16]). Within this HCC cohort 8 (36.4%) had received locoregional therapy and 2 (9.1%) had received immunotherapy. Conversely, international registry data including 48 patients with HCC failed to show an independent association with death [45]. At present, there are no data providing risk estimates for adverse COVID-19 outcomes in patients with cholangiocarcinoma.

EASL position

- Patients with hepatocellular carcinoma may have an increased risk of mortality following SARS-CoV-2 infection.

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 the general population [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 [106] (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 [83]. 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 [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 [104], calcineurin inhibitors (e.g. tacrolimus, ciclosporin) and mTOR inhibitors may have a favourable impact on disease course [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 recipients are variable. However, gastrointestinal symptoms including diarrhoea appear more frequent, particularly in patients receiving mycophenolate mofetil (MMF) [83,107,113]

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 co-morbidities, non- or hypo-responsiveness to COVID-19 vaccination (details in section 5) and immunosuppression.
- In liver transplant recipients with COVID-19, a dose reduction or temporary discontinuation of antimetabolites (e.g. azathioprine or MMF) may be considered.

3. Effects of the COVID-19 pandemic on incidence and management of chronic liver diseases

Impact on harmful alcohol use and alcohol-related liver disease

COVID-19 has had a vast collateral impact on the incidence and severity of alcohol use disorder and alcohol-related liver disease (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 [114–117]. This was corroborated by retail and e-commerce statistics reflecting huge surges in alcohol purchasing by up to 400% [118]. In addition, 17% of abstinent individuals with a history of alcohol use disorder were found to relapse to drinking under lockdown conditions [119]. These behaviors are likely to have been triggered by heightened anxiety, social isolation, deteriorating mental health, and disruption to alcohol support services [15,114]. 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 [120]. 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 (AH) was found to have doubled during the pandemic compared to the previous two years (22.1/10,000 admissions vs. 11.6/10,000 admissions; $p<0.001$) [121]. 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 [120]. Alcohol consumption during the pandemic has also heavily influenced liver transplantation programs with ALD now accounting for 40% of transplant listings in North America, more than NASH and HCV combined [122]. 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 MELD-Na scores in patients with ALD [122]. 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 [123]. 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 [124]. 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 [125,126], which is also a key consideration in the EASL Lancet Liver Commission [127].

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 non-alcoholic fatty liver disease

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 calory intake, and reduced physical activity during periods of enhanced social distancing [128–130]. This appears to have translated into an increased prevalence of obesity during the pandemic, particularly in pediatric and adolescent populations. According to figures from the Centers for Disease Control and Prevention (CDC), among a cohort of 432,302 individuals aged 2-19 years, the rate of increase in body mass index (BMI) approximately doubled during the pandemic compared to the period preceding it [131]. 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 [132]. Paradoxically, a study of primary care practices in the UK observed a 70% decrease in the rate of type 2 diabetes (T2D) diagnoses in the initial months following the onset of the pandemic reflecting reduced testing and limited population engagement with health services [133]. This subsequently normalized throughout 2020 and there are concerns that a rebound in the incidence of type 2 diabetes mellitus and severity of diabetic complications may be imminent [134]. 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.

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

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 [135]; however, many of these programs were significantly affected by the pandemic and newly diagnosed cases of HBV and HCV declined in many countries [136–138], profoundly impacting meticulously planned elimination strategies and policies [139]. A modeling study has predicted that a delay of just one 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 [140]. Nevertheless, SARS-CoV-2 testing requirements and the rollout of mass vaccination campaigns offered a unique opportunity to approach large parts of the population and offer screening for viral hepatitis [141,142]. Although several groups have successfully seized this opportunity [143], efforts to meet the WHO goal of viral elimination should continue without further delay.

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 programs are strongly encouraged.

Changes in the standard of care and adherence to surveillance programs

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 esophageal varices) for selected patient cohorts in order to reduce the likelihood of nosocomial infections and to respond to the re-allocation of healthcare resources [1]. Even this transient interruption of surveillance programs and standard care was anticipated to impact patients for years to come [144]. Indeed, numbers 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 [145]. 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 [146]. More than 80% of European centers had to change their clinical practices because diagnostic procedures, screening programs, curative and/or palliative treatments, and liver transplant programs were affected by lockdown measures [147].

EASL position

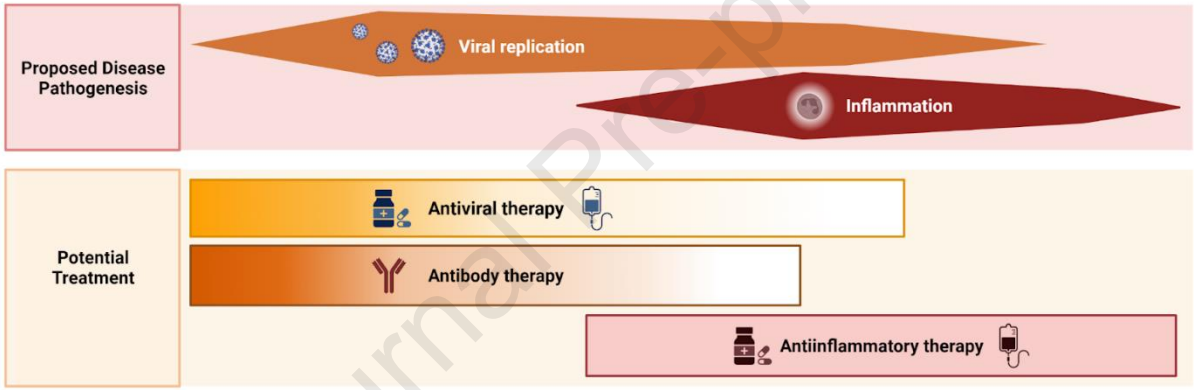
- The pandemic profoundly altered the standard of care within hospitals and the outpatient setting. All efforts should be made to return to these standards and resume and improve surveillance programs in order to reduce the backlog of deferred care for the future.

4. Treatment of COVID-19 in patients with chronic liver disease, transplant recipients and patients with hepatobiliary carcinoma

General concepts of COVID-19 treatment

The pathogenesis of COVID-19 is mainly determined by two 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 characterized 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.

Figure 1: Therapy concepts according to disease stage (Figure adapted from [148].



Antiviral therapies

Direct antiviral approaches aim to inhibit viral replication by interacting with key proteins or other structures necessary for viral replication whereas viral neutralizing monoclonal antibodies (mAbs) have the ability to 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 (RdRp) of coronaviruses and has demonstrated potent activity against SARS-CoV-2 *in vitro* and in animal models [149]. In the ACTT-1 study, which included 1062 hospitalized patients with COVID-19 and evidence of lower respiratory tract infection, those randomized to receive 10 days of remdesivir recovered more rapidly than those receiving placebo (median recovery time 10 vs. 15 days). All-cause mortality estimates by day 29 were 11.4% in the remdesivir group and 15.2% in the placebo group [150]. There were no differences in clinical outcomes observed between those treated with either 5- or 10-days of remdesivir [151]. Despite improved recovery times in ACTT-1, the clinical benefit of remdesivir in hospitalized patients with COVID-19

remains controversial. The Solidarity trial, which assessed multiple repurposed antiviral drugs using data across 405 institutions in 30 countries, showed no clinical benefit of remdesivir versus standard of care [152]. Nevertheless, other real-world data have indicated remdesivir to be associated with improved survival among COVID-19 patients [153]. 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 [154]. This is corroborated by the DisCoVeRy study which showed no clinical benefit of remdesivir in hospitalized patients who required oxygen support and had been symptomatic for >7 days [155]. Conversely, the PINETREE study showed that early introduction of 3-days treatment with remdesivir in high-risk non-hospitalized patients with symptoms <7 days appeared safe and resulted in an 87% lower risk of hospitalization or death compared to placebo [156]. 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%) [150] although most trials have excluded patients with baseline ALT >5 ULN. There are no specific drug interaction concerns with the use of remdesivir.

EASL position

- Remdesivir should not be used in symptomatic patients with invasive ventilation.
- For hospitalized patients with COVID-19 pneumonia and requiring oxygen therapy or noninvasive 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 available alternative options.
- Remdesivir can be given preemptively within 7 days of symptom onset to patients with SARS-CoV-2 infection who are at increased risk for 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 [157]. In a phase 2-3 study including 2,246 patients, nirmatrelvir/r given as early as possible and within 5 days of symptom onset, significantly reduced hospitalization and/or death rates compared with placebo in non-hospitalized patients with mild/moderate COVID-19 (without supplemental oxygen requirements) and at least one risk factor for a severe disease course (7.0% vs. 0.8%) This equates to a relative risk reduction of 88.9% if onset within 3 days, and 87.8% within 5 days [158]. The most common adverse events reported during treatment with nirmatrelvir/r versus placebo were dysgeusia (5.6% vs. 0.3%) and diarrhea (3.1% vs. 1.6%) [158]. Numerous clinically relevant drug-drug interactions (DDI) must be considered with the use of nirmatrelvir/r due to ritonavir inhibition of CYP450 enzymes [156]. Websites to check the DDI are available (https://www.covid19-druginteractions.org/checker, https://www.fda.gov/media/155050/download). This is particularly important for solid organ transplant 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 metabolized 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

Molnupiravir is an orally available antiviral agent that increases the frequency of viral RNA mutations by the viral RNA-dependent RNA polymerase (RdRp) and impairs SARS-CoV-2 replication in preclinical models [162]. Molnupiravir has been shown to significantly reduce hospitalization and/or mortality compared with placebo in non-hospitalized patients with mild/moderate COVID-19 (without supplemental oxygen requirements) and at least one 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 [163]. 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 diarrhea (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. There are currently no specific molnupiravir data reported for patients infected with omicron 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 DDI 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.

EASL position

- 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.

Monoclonal Antibodies

Several monoclonal antibodies (mAb) are approved for passive immunization 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 randomized placebo-controlled trials including non-hospitalized patients with mild to moderate COVID-19 and risk factors for disease progression, the use of anti-SARS-CoV-2 mAb (e.g. casirivimab plus imdevimab [166], bamlanivimab plus etesevimab [167] or sotrovimab [168] have been shown to reduce the risk of hospitalization and death. For example, hospitalization 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) [168]. However, pooled analysis of all available RCTs indicates a low level of certainty about mAb efficacy, particularly in hospitalized individuals [169]. 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 9785 patients randomized to casirivimab and imdevimab versus 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 [170].

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 [7]. 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 [171,172]. However, these studies were not placebo-controlled and omicron is known to be associated with less severe COVID-19 overall [173]. Despite this efficacy signal, the emergence of additional unique mutations in the spike protein may lead to further immune escape [174]. 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 [175] but this combination therapy is currently only authorized for prophylactic use (as of April 2022) [175]. However, within a trial setting, the TACKLE study assessed the efficacy of tixagevimab plus cilgavimab versus placebo in >900 outpatients with symptomatic COVID-19 for ≤7 days and showed that active treatment reduced progression to severe COVID-19 or death (relative risk reduction 50.5%) [176]. In addition, Bebtelovimab is active *in vitro* against most circulating omicron subvariants [177], 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 monoclonal antibodies.

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 spike which are associated with high-level resistance *in vitro* have been shown to occur in SARS-CoV-2-infected patients treated with mAb (e.g. bamlanivimab [178] and sotrovimab [179]), particularly when viremia persisted for a prolonged period. These data highlight the need for conscientious stewardship and post-marketing surveillance of patients treated with mAb.

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 monoclonal antibodies expected to be effective against the circulating variants and subvariants if they have a risk for severe COVID-19.
- Treatment with SARS-CoV-2-specific monoclonal antibodies in IgG seronegative patients should be initiated ideally within 72 hours but no longer than 7 days of symptom onset.
- In patients with early SARS-CoV-2 infection where immediate determination of spike antibody titers is not possible, SARS-CoV-2-specific monoclonal antibodies 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 [180]. 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 [181].

EASL position

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

Immunomodulatory therapies

One of the goals of immunomodulatory or anti-inflammatory therapies in hospitalized 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 2104 hospitalized 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 RCTs have reported similar findings and a systematic Cochrane review concluded that there is moderate-certainty evidence that systemic corticosteroids reduce all-cause mortality in patents hospitalized 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-hospitalized 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 by 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.

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 NA if HBV DNA is detectable.
- In transplant recipients, the immunosuppressive regimen may be adapted if additional corticosteroids are used.

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 1033 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 noninvasive ventilation (median recovery time: 10 vs 18 days). The 28-day mortality was 5.1% in the combination group and 7.8% in the control group [185]. The COV-BARRIER study including 1525 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 hospitalized 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].
Increase in transaminase levels was frequently observed in clinical trials with JAKI. 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 metabolized 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 metabolization via CYP3A4, DDI should be considered (e.g. OAT 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 JAKI 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 JAKI with IL6 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 NA 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 humanized anti-IL-6 receptor monoclonal antibody that inhibits IL-6 binding to both membrane and soluble IL-6 receptors, thereby blocking IL-6 signaling and reducing inflammation. In the RECOVERY trial, tocilizumab was shown to improve survival in hospitalized patients with COVID-19 with severe 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 compared to standard care or placebo summary (OR, 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 parameter, most of which were mild and transient [195]. In in a small proportion (1-2%), ALT elevations >5 x 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 rarely associated with 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 withwith 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 24h 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 chronic liver disease 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.
- HBsAg negative / anti-HBc positive individuals should be monitored and receive NA if HBV DNA is detectable.
- Tocilizumab should be used with great caution in patients whose immune system is severely suppressed (i.e., transplant recipients). The safety of using tocilizumab plus a corticosteroid in immunocompromised patients is unknown. DDI should be evaluated.
- Sarilumab can be used if tocilizumab is not available or not feasible to use.

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 polymerization [199]. This mechanism of action is suggested to prevent the formation of new leukocytes and may inhibit the release of proinflammatory cytokines during the course of COVID-19. A multicenter phase III trial of sabizabulin in hospitalized patients with moderate-to-severe COVID-19 (WHO

severity grade ≥4) has recently been halted prematurely due to the agent showing 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.

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

Therapy	Non-hospitalized WHO 1-3	Hospitalized without oxygen demand WHO 4	Low flow oxygen demand WHO 5	High flow oxygen or NIV/CPAP WHO 6	Invasive ventilation, ECCMO WHO 7-9
Antivirals*	*	*	***	***	
mAbs**	**	**			
Dexamethasone					
JAKI***			***	***	***
Anti-IL6***				***	Continuation if initialed at WHO 6

Color code: grey: inconclusive (data lacking), red: not indicated, dark green: indicated (strong recommendation), light green: indicated (weak recommendation)

* 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 ≤3 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

Table 3. Overview of recommended therapies for SARS-CoV-2 infection.

Medication and dose	Indication	Important comments and considerations for CLD and LT recipients
Antiviral therapy		
Remdesivir (Veklury) 200 mg on day 1 followed by 100 mg on days 2 and 3 (intravenous).	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) 300 mg (2 tablets) / 100 mg (1 tablet) twice daily for 5 days (per os)	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) 800 mg (4 tablets) twice daily for 5 days (per os)	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 DDI is expected. Monitoring liver parameters, eGFR#
Monoclonal Antibodies **Sotrovimab (Xevudy)** 500 mg (intravenous) **Bebtelovimab** 175 mg (intravenous) **Tixagevimab / Cilgavimab (Evusheld)** 150 mg / 150 mg or 300 mg / 300 mg (intramuscular) – *only approved for pre-exposure prophylaxis*	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 of symptom onset (post exposure prophylaxis). Recommendations are be 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		
Dexamethasone 6 mg Dexamethasone for 10 days (per os or intravenous)	Treatment of COVID-19 WHO ≥5 (oxygen demand)	Monitoring liver parameters, HBsAg/anti-HBc test, prophylactic NA in HBsAg positive, adjust immunosuppression in LT
Janus kinase 1/2 inhibitor Baricitinib (Olumiant) 4 mg per day for 14 days (per os)	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 NA in HBsAg positive, adjust immunosuppression in LT, no combination with anti-IL-6
IL-6 receptor antagonist Tocilizumab (Actemra) 8 mg/kg (<65 kg = 400 mg, up to 90 kg = 600 mg, >90 kg = 800 mg) as a single dose (intravenous).	COVID-19 WHO 6-9 (High flow oxygen demand, NIV) in addition to dexamethasone	Monitoring liver parameters, HBsAg/anti-HBc test, prophylactic NA in HBsAg positive, adjust immunosuppression in LT, no combination with JAKI, contraindicated in patients with absolute neutrophil count <2000/µl; active tuberculosis

 # because of limited experience outside clinical trials, eGFR = , LT = liver transplantation, DDI = drug-drug interactions, NA = nucleos(t)ide analogue, JAKI = Janus kinase inhibitor, mAbs = monoclonal antibodies

Repurposed drugs without proven clinical efficacy

Numerous repurposed drugs with suspected antiviral or anti-inflammatory properties have been explored in 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.

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

Medication	Comments	Study
Repurposed drugs with potential antiviral effects		
Lopinavir/ritonavir Anti-retroviral therapy	No efficacy in large controlled clinical trials	[152]
Hydroxychloroquine Anit-rheumatic, anti-malarial agent	No efficacy in large controlled clinical trials	[152]
Nitazoxanide Thiazolid broad-spectrum antiparasitic agent	A few randomized trials showed some level of efficacy. Studies were underpowered. So far, no evidence for recommendation.	[200–202]
Ivermectin Anti-parasitic agent	Double-blind, randomized, placebo-controlled, adaptive platform trial with 3515 patients (ivermectin (679 patients), placebo (679), or another intervention (2157)): 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 hospitalized patients, while others did not find a positive effect or even documented an association with severe COVID-19. One small randomized, 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 of the retrospective studies.	[204–210]
Fluvoxamine Selective serotonin reuptake inhibitor and a σ-1 receptor (S1R) 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 with almost 1500 patients with risk for severe COVID-19 and symptoms beginning within 7 days of the screening date showed that fluvoxamine (100 mg twice daily for 10 days) versus placebo reduced the need for hospitalization 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		
Inhaled budesonide	Inhaled budesonide reduced time to reported recovery in the PRINCIPLE and STOIC trials but did not significantly reduce COVID-19-related hospitalizations or deaths. Two multicenter, double-blind, randomized phase 3 clinical trials showed no significant benefit of inhaled and intranasal ciclesonide.	[213–216]
Azithromycin Antibiotic	No efficacy in large in several studies	[217,218]

Colchicine, Anti-inflammatory agent	No effects in large studies (e.g. RECOVERY, PRINCIPLE and COLCORONA)	[219,220]
Interferon alfa	Early treatment, either within five days from the onset of symptoms or at hospital admission, confers better clinical outcomes, whereas late intervention may result in prolonged hospitalization.	[221]
Interferon beta-1a	Interferon beta-1a plus remdesivir was not superior to remdesivir alone in hospitalized 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 PEG-IFN lambda 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 multicenter, open-label, randomized 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 of 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 alfa, interferon beta or interferon lambda, 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 utilized during COVID-19 has therefore been subject of much research attention.

In patients with critical COVID-19 requiring ICU admission, a large multiplatform RCT 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 (VTE). However, therapeutic anticoagulation was associated with an increased risk of bleeding complications (3.8% vs. 2.3%) [230]. Similarly, the INSPIRATION trial showed no advantage of intensified prophylactic anticoagulation versus standard prophylactic anticoagulation in terms of 30-day mortality, ECMO requirement, and development of VTE in patients admitted to the ICU [231].

Conversely, among COVID-19 patients 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 [232]. In the RAPID trial which included hospitalized patients with COVID-19 and increased D-dimer, therapeutic anticoagulation was not associated with a reduction in the primary composite outcome or death, invasive, or non-invasive ventilation. However, the odds of mortality at 28-days was decreased and rates of major bleeding were low (0.9%) [233]. Use of direct oral anticoagulants (e.g. rivaroxaban) do not appear to improve major outcomes compared to standard thromboprophylaxis in hospitalized patients with COVID-19, but are associated with increased bleeding events [234]. 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, hospitalization, or occurrence of thrombotic events compared to placebo [235,236].

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 hospitalized patients with severe COVID-19 [237]. An observational cohort study of 112,269 hospitalized patients with COVID-19 also showed that early aspirin use was associated with lower odds of inpatient death [238]. However, the multiplatform RECOVERY trial found that aspirin was not associated with reductions in 28-day mortality or rates of invasive mechanical ventilation [239]. Therefore, aspirin cannot currently be recommended in hospitalized 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 [235].

Patients with advanced CLD are at increased risk of venous thromboembolism [240], so it is plausible that combination with COVID-19 may lead to a cumulative risk of prothrombotic complications. 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 cirrhotic patients has been shown not to be associated with an increased risk of bleeding [241]. In a multicenter Italian study in which 80% of patients with cirrhosis and COVID-19 received thromboprophylaxis, there were no major hemorrhagic complications [48]. Therefore, it is important that patients with cirrhosis are not excluded from anticoagulation when appropriate during the management of COVID-19.

EASL position

- Hospitalized patients with COVID-19 should receive standard thromboembolic prophylaxis with low-molecular-weight (LMW) heparin or fondaparinux in the absence of contraindications.
- Therapeutic dose anticoagulation, preferably with LMW or unfractionated heparin,

may be considered in hospitalized non-intensive care patients with COVID-19 and increased venothromboembolic risk (e.g. D-dimers ≥ 2 mg/l), taking into account renal function and bleeding risk. In ICU patients, therapeutic anticoagulation is not recommended without a specific indication (e.g., pulmonary embolism). Intermediate-intensity anticoagulation is not recommended.

- Patients with cirrhosis are at high risk of thrombotic complications and should not be excluded from anticoagulation therapy.

Co-medications relevant for patients with CLD, transplant recipients, hepatobiliary cancer

Nonselective beta blockers (NSBB)

NSBB form a cornerstone of primary and secondary prophylaxis for variceal hemorrhage 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 [242]. Therefore, there is no reason for beta-blockers, including NSBB, to be discontinued routinely during the pandemic or following SARS-CoV-2 infection unless necessary for other clinical indications such as hemodynamic instability.

EASL position

- Both selective and non-selective beta blockers should not be discontinued due to SARS-CoV-2 infection unless there are other clinical reasons to do so (e.g. hemodynamic compromise).

HBV nucleos(t)ide analogues (NA)

Population level data from Korea have indicated that antiviral treatment with tenofovir or entecavir is associated with reduced SARS-CoV-2 positivity rate (aOR 0.49; 95% CI, 0.37–0.66), whilst treatment was not associated with more severe COVID-19 outcomes [91].

EASL position

- NA therapy should not be discontinued or withheld due to SARS-CoV-2 infection.

Direct acting antiviral agents (DAA) against HCV

There are no reported concerns about DAA therapy in patients with COVID-19. Small clinical studies and one meta-analysis initially suggested that sofosbuvir-based therapies may even have clinical benefit in the case of COVID-19 [102], although this has not been replicated in other systematic analyses [101].

EASL position

- Following SARS-CoV-2 infection, planned initiation of DAA therapy can be postponed until after COVID-19 has resolved.
- DAAs should not be discontinued routinely following SARS-CoV-2 infection in those who are already established on therapy.
- Drug-drug interactions should be considered in patients on DAA therapy before starting antiviral or immunomodulatory treatment for COVID-19.

Mycophenolate mofetil

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 [104]. 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 [104]. 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 [242,243]. A study of 29 kidney transplant recipients with poor SARS-CoV-2 antibody titers after an initial vaccine course showed that immune response to a fourth dose of COVID-19 vaccination could be improved by pausing antimetabolite therapy (e.g. MMF, azathioprine) [244]. However, larger controlled studies are required before recommendations can be made about this approach.

EASL position

- In severe COVID-19, dosing of mycophenolate mofetil may be reduced or discontinued.
- Patients taking mycophenolate mofetil are less likely to respond to COVID-19 vaccination.

Calcineurin inhibitors

Calcineurin inhibitors (e.g. cyclosporine A, tacrolimus) have demonstrated antiviral properties against several coronaviruses *in vitro* including SARS-CoV and MERS-CoV [245,246]. Some clinical evidence of potential benefit against SARS-CoV-2 also exists. In an open-label, nonrandomized study of 209 patients with COVID-19 pneumonia, cyclosporine A in combination with glucocorticoids was associated with improved mortality compared with glucocorticoids alone [109]. A European multicenter study of 243 LT recipients with COVID-19 also reported that tacrolimus use was associated with improved survival [113]. A single small randomized 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 [111].

EASL position

- Calcineurin inhibitors should not be routinely modified following SARS-CoV-2 infection (exception: see statement on nirmatrelvir/r).
- Adjustment of the calcineurin inhibitor dose should be considered if corticosteroids are used for the treatment of COVID-19.

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 [247]. 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 [112]. As such, mTOR inhibitors appear to have more potentially beneficial than detrimental effects in the context of COVID-19 and should therefore be continued.

EASL position

- mTOR inhibitors should not be routinely modified following SARS-CoV-2 infection (exception: see statement on nirmatrelvir/r).

Immune check-point inhibitors (ICI)

Use of immune check-point inhibitors 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 ICI 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 [248,249].

EASL position

- The COVID-19 pandemic should not prevent or delay the initiation or continuation of ICI when clinically indicated.
- ICI may be suspended upon diagnosis of SARS-CoV-2 infection until COVID-19 has resolved.

5. 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 (https://www.covid19treatmentguidelines.nih.gov/overview/prevention-of-sars-cov-2/).

EASL position

- 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 utilized 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 has received at least one vaccine dose, and real-world data show that the 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 infection with omicron, 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 a more severe COVID-19 (see section 2) 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 safety [253] and effectiveness [254–256] in these groups. The adjuvanted protein vaccine NVX-CoV2373, Covovax, has only been approved recently and therefore real-world data in liver patients 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 (EMA), was the temporal link between mRNA vaccination and acute liver injury (ALI). Establishing whether this finding represents a causal association remains subject of ongoing studies.

Epidemiological data from one large European center did not report an increase in new AIH diagnoses despite widespread vaccine uptake [257]. However, instances of *de novo* AIH-like liver injury occurring in close proximity to COVID-19 vaccination have been reported in the literature and selected cases are presented in **Table 5**. ALI was mostly observed in association with mRNA platforms, but cases have also been described for vector-based vaccines (e.g. case 9). Many of these presentations displayed typical features of AIH including the presence of autoantibodies, increased IgG levels, and classical histological changes on liver biopsy (**Table 5**). Significant clinical heterogeneity exists between cases with a spectrum of liver biochemical abnormalities described ranging from mild ALT elevations to severe jaundice. Typical cases often had a past medical history of autoimmune disease suggesting that AIH may have become unmasked by COVID-19 vaccination [269]. Similar to the AIH-like phenomena rarely observed after COVID-19, most of the cases of liver injury after vaccination are self-limiting or respond well to treatment with corticosteroids [258]. In some patients, steroids could already been stopped and no relapse occurred [258]. However, relapses or worsening of hepatitis have also been reported after revaccination with a second dose of vaccine, but the clinical picture seems to improve in most cases with steroid administration (cases 4 and 6). However, in one case, fulminant hepatitis was reported after a second vaccination (case 15) [259]. The risk of relapse associated with the use of an alternative vaccine platform remains to be determined and the decision to offer a repeat vaccination following vaccine-related liver injury should consider individual risk for severe COVID-19.

The pathogenetic mechanisms leading to hepatitis after COVID-19 vaccination have not been fully elucidated and it is difficult to establish a definite causality between COVID-19 vaccination and hepatitis. However, in a patient with two episodes of hepatitis with jaundice occurring after the first and second doses of mRNA vaccine, highly activated CD8+ T-cells with SARS-CoV-2 specificity were detected in the liver as part of a CD8+ T-cell-dominant immune infiltrate that differed from classical AIH (case 14) [260]. This suggests that different forms of immune phenomena may contribute to these selected cases of vaccine-associated hepatitis. Drug-induced liver injury (DILI) remains an important differential diagnosis [261], and it is notable that certain cases describe hepatic eosinophilic and neutrophilic infiltrates reminiscent of DILI [268]. However, it 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 EMA's Pharmacovigilance Risk Assessment Committee (PRAC) 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 barrier to initial vaccination both at an individual and population level.

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

#	Patient characteristics	AIH features	Treatment and Outcome	Ref.
1	- 35-year-old woman (third month postpartum) - ALI 6 days after BNT162b1 - Bili 4.8 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]
2	- 76-year-old woman (Hashimoto thyroiditis and prior COVID-19 infection) - Symptoms of ALI started 3 days after mRNA-1273 - 5 weeks after vaccination: ALT 579 U/L, ALP 124 U/L, Bili 3.3 ULN	- ANA (1:1,280, homogeneous, fine granular), SMA (1:1,280, against F-actin), anti-neutrophil cytoplasmic antibodies (titer >1:1280, perinuclear, MPO and PR3 negative) - High IgG (39.4 g/L) - interface hepatitis, plasma cells, pseudorosettes	- Good response to 40 mg prednisolone plus azathioprine (maintenance therapy) - Complete normalization after 4 weeks	[263]
3	- 80-year-old woman (Hashimoto's thyroiditis, glomerulonephritis in the past) - ALI 1 week after BNT162b2 - ALT 1,186 U/L, Bili 10.5 ULN, ALP 243 U/L	- ANA (1:160, speckled pattern) - High IgG (3,500 mg/dl) - Interface hepatitis with moderate lymphoplasmacytic infiltrate	- Good response to 1 mg/kg prednisolone	[264]
4	- 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 192 U/L, Bili 17.5 ULN	- no autoantibodies - Histology: eosinophil infiltrate, interface hepatitis in the portal tract with biliary injury and mild ductular proliferation	- Good response to 1 mg/kg methylprednisolone - Complete normalization after 8 weeks	[265]
5	- 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 10 ULN	- ANA (rim-like pattern), non-PBC AMA - IgG slightly elevated (19.96 g/L) - interface hepatitis, lobular and centrilobular inflammation	- Good response to 40 mg and subsequent 20 mg prednisone (but ALT, Bili declined already before start of treatment)	[266]
6	- A 47-year-old man - ALI 3 days after the first dose of mRNA-1273 - ALT 1,048 U/L, ALP 229 U/L, Bili 9.5 ULN - Exacerbation after 2nd dose - ALT 1,084 U/L, Bili 17.8 ULN	- ANA, - elevated IgG (25.1 g/L), - interface hepatitis, lymphoplasmacytic infiltrate	- Spontaneous decline of ALT after the first episode, worsening after re-exposure (ALT 332 U/L, Bili to 3.5 ULN) - Good response to 40 mg prednisolone after the second episode	[267]
7	- 41-year-old woman (substitutive hormonal therapy) - 3 weeks GI symptoms after mRNA-1273 - ALI 7 days after 2nd dose mRNA-1273 - ALT 1,312 U/L, Bili 2.3 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	[268]
8	- 56-year-old woman - 6 weeks after mRNA-1273	- ANA (1:160, speckled) - normal IgG	- Good response to budeosonide (but	[269]

	- ALT 1,701 U/L, Bili 5 ULN, ALP 298 U/L	- portal inflammation with interface hepatitis, presence of plasma cell aggregates, rosette formation, eosinophils	ALT, Bili declined already before start of treatment and the kinetic did not improve during therapy)	
9	- 36-year-old man (Ibuprofen 2 weeks prior) - 26 days after ChAdOx1 - ALT 1,774 U/L, Bili 1 ULN, ALP 118 U/L - Peak ALT 2,550 U/L, Bili 1.9 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)	[270]
10	- 71-year-old woman - 4 days after mRNA-1273 - ALT 1,067 U/L, Bili 13.5 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 kinetic did not improve during therapy)	[271]
11	- 57-year-old woman (Asia) - First symptoms 2 weeks after CoronaVac, ALI 2 days after 2nd dose - ALT 974 U/L, Bili 13.5 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	[272]
12	- 65-year-old woman (JAK2 V617F-positive polycythemia vera, received IFN 2 years prior) - 2 weeks after after mRNA-1273 - ALT 1,092 U/L, Bili 1.14 ULN - Jaundice after 5 weeks	- ANA (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)	[273]
13	- 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	[274]
14	- 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 5.5 ULN, spontaneous recovery - 2nd episode 20 days after 2nd vaccination with BNT162b1 - ALT 1,939 U/L, ALP 167 U/L, Bili 2 ULN,	- ANA 1:200, AMA-M2 and SMA borderline - IgG normal	- Initially good response to budeosonide, ALT relapse (763 U/l), prednisolone weaning	[260]
15	- 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 one month after 2nd vaccination with BNT162b1 - ALT 485 U/L, AST 629 U/L, Bili 5.5 ULN, INR 1.36, Bili further increased and encephalopathy 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: Prednolone 40mg i.v. and plasma exchange - Living donor liver transplantation	[259]

Abbreviation: ALI (acute liver injury), ALP (alkaline phosphatase), Bili (bilirubin), ALT (alanine aminotransferase), GI (gastrointestinal), SMA (smooth muscle antibodies), ANA (antinuclear antibodies), SLA (soluble liver antigen antibodies), LC1 (liver cytosol antibodies), IFN (Interferon treatment)

Vaccine-induced thrombotic thrombocytopenia (VITT)

VITT is defined as a thromboembolic event in combination with thrombocytopenia occurring between 5 and 28 days after adenoviral vector COVID-19 vaccination [275]. 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 vascular bed involved (50%), followed by splanchnic vein thrombosis (SVT) (30%) [276]. Hepatosplenic thrombosis has also been shown to be present in 17% of VITT cases, often

occurring alongside CVT, and may be associated with more severely deranged laboratory parameters [277]. Pulmonary emboli and arterial ischemic are also recognized. VITT is a rare event, occurring in 1/100,000-250,000 individuals vaccinated with an adenovirus vector platform [278] 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 [279]. SVT 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 ischemia due to portal vein thrombosis may require systemic thrombolysis, catheter directed thrombolysis via a transjugular intra-hepatic portosystemic shunt (TIPS) [280], 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.
- Vaccine-induced thrombotic thrombocytopenia (VITT) including splanchnic 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 two vaccine doses [281]. However several studies have suggested that patients with cirrhosis may have a more rapid decline in antibody titers over time compared to healthy controls [281,282]. In contrast, LT recipients remain at high-risk for suboptimal humoral responses to vaccination. In a prospective evaluation of patients following two mRNA doses or a single adenoviral vaccine, poor or undetectable antibody titers were objectified in 61% of LT recipients, 23% of cirrhosis patients, and 25% of patients with non-cirrhotic CLD [283] (**Table 6**). Therefore, some countries have opted to empirically deliver a third “prime” vaccination to all solid organ transplant 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 two months after the second dose. The proportion of patients with detectable antibody titers increased from 41% to 68% before and after a third dose of vaccination [284]. 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 [285]. 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 randomized to a third dose of mRNA-1273 (Spikevax) had a significant increase in polyfunctional CD4+ T-cells and antibody titers compared to placebo [286]. Similar findings have been replicated in heart and kidney transplant recipients [287,288]. 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 one or two mRNA vaccines was associated with reduced mortality compared to COVID-19 in unvaccinated individuals [254]. In a large case-control study including 440 SOT recipients, vaccine effectiveness in preventing COVID-19 hospitalizations was lower compared with immunocompetent individuals, although protection was significantly improved with three compared to two 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 [9,10]. These mutations, including within the receptor-binding domain (RBD), allow for immune escape from neutralizing antibodies. However, T-cell recognition appears relatively well preserved across most SARS-CoV-2 variants [290] including omicron [291,292]. Boosting with a third vaccine dose substantially increases protection against omicron [252,293], improves the breadth and magnitude of neutralizing antibodies [8,294], and induces potent omicron-specific T cells responses even in immunocompromised individuals with impaired humoral responses [295]. This T-cell antigen cross-recognition [290,291,296,297] 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 neutralizing 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 titers. 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 immunization 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 neutralizing antibody titers against multiple SARS-CoV-2 variants

compared to the 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 neutralizing 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 two doses of ChAdOx1 nCoV-19 [304]. Lastly, in a large Brazilian trial (n=1240), individuals primed with two doses of CoronaVac received a third vaccine six months later with either BNT162b2, Ad26.COV2-S, ChAdOx1nCoV-19 or homologous CoronaVac. This demonstrated that all heterologously boosted patients achieved seroconversion at 1-month with highest antibody titers 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 two 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 versus matched infection-naive individuals before and after vaccination with BNT162b2 [308]. This showed that excellent infection-neutralizing capacity against all variants of concern, including omicron, developed after either two vaccinations in convalescents or a third vaccination in twice-vaccinated, COVID-19-naive individuals [308]. Similar findings were observed in a SOT cohort, showing higher antibody responses in previously infected versus naïve individuals after their first vaccination [309]. A small study comparing neutralizing antibody responses, including those against the variant omicron, showed that even triple-vaccinated kidney and heart transplant recipients had lower neutralizing antibody titers 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 behavior of the prevailing SARS-CoV-2 variant.
- We currently recommend three doses of vaccine (or, equivalently, three 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 three 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, awaiting 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 individual 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 [314] in parallel with diminishing levels of total and neutralizing antibody titers [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 prioritized 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 titers and neutralizing capacity. Thus, it is the quality rather than the quantity of antibodies that appears to matter most [308]. Accordingly, in a study of 60 SOT recipients, many patients vaccinated with three doses of mRNA-1273 had undetectable omicron-specific neutralizing antibodies despite positive anti-RBD 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 titers [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-gamma release assays) have not yet entered into routine clinical practice [321–323] and cannot be recommended at this stage.

EASL position

- SARS-CoV-2 specific IgG titer are not suitable to predict protection.
- Vaccine induced T cell responses play a role in protection of severe COVID-19. However, there is no standardized test for the reliable prediction of protection.

- A high antibody titer should not preclude completion of the COVID-19 vaccination series to achieve at least three exposures to the spike protein.
- Vaccine-specific antibody titers can be tested in individuals at risk for severe COVID-19 when adequate vaccine responses after at least three exposures to the spike protein are uncertain.
- Additional vaccine doses can be attempted if antibodies are undetectable, especially in persons at risk for severe COVID-19.

Ethical considerations – vaccine hesitancy and mandatory vaccination in healthcare workers

The approach to mandatory vaccination of health-care professionals and to the care of vaccine-hesitant transplant candidates remain two contentious areas. The WHO has summarized five key ethical considerations in the discussion of mandatory vaccination; necessity and proportionality, sufficient proofs regarding safety, efficacy and effectiveness, sufficient supply, public confidence in science and general vaccination, and a transparent process leading 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, 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.

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 reflect a wider risk of poor compliance with other important health messages must be balanced against the risk of failing to respect patient autonomy, with associated negative impacts on the patient-caregiver relationship [324]. Therefore, we propose that patients who decline COVID-19 vaccination should be informed about vaccine safety and efficacy using motivational interview-based techniques [325] in order to maintain a healthy therapeutic relationship. In addition, we recommend a psychological evaluation to rule out potential future problems with overall adherence. Finally, lack of COVID-19 vaccination should not be a reason to exclude people who are otherwise motivated and comply with the measures associated with transplantation.

EASL position

- COVID-19 vaccination is strongly recommended for liver transplant candidates and information regarding safety and efficacy of vaccines should be made available to caregivers and patients and to empathically respond to their concerns (e.g. motivational interview techniques).

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**
LTR: n=80 Controls: n=25 BNT162b2	Seropositivity: 47.5% vs 100% (anti-S1/2[1])	- Age (mean 63 vs 57 years) - Low eGFR - Triple immunosuppression - Treatment with high dose glucocorticoids and MMF	[326]
LTR: n=118 BNT162b2 n=114 mRNA-1273 n= 3 Ad26.COV2.S n=1	Seropositivity 21-132 days after second dose: IgG anti-spike[2]: 78%	- Alcohol related liver disease before transplantation - MMF	[242]
- Mixed cohorts of solid organ transplant recipients, including at least n=15 liver transplant recipients			
SOTR n=658 **LTR n=129** no control BNT162b2 n=342 mRNA-1273 n= 207 missing n=9	Seropositivity 54% for all SOTR, 80% of LTR (anti-RBD[3] or anti-S1[2])	Mixed cohort: - Time since transplantation - Anti-metabolites: 43% vs 82% - No seroconversion in 40% vaccinated with mRNA-1273 vs 51% BNT162b2	[327]
SOTR N=104 **LTR n=58** mRNA-1273	Seropositivity: 71% LTR (anti-S1 IgG or IgM[4]) S-specific T cell response (IFN-gamma ELISpot) LTR: 86%	- Hypogammaglobulinemia - Vaccination during the first year after transplantation - High-dose MMF	[319]
SOTR N=127 **LTR n=15** no control mRNA-1273	Seropositivity: 34.5% (n=38/110) anti-RBD Ig[5], neutralizing Abs[6] in 26.9%, mostly in responders with higher anti-RBD Ig levels T-cell responses (n=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	- MMF - Higher Tacrolimus trough - No-LTR	[320]
SOTR: n=367 **LTR n=58** Mostly BNT162b2	Seropositivity: 50% anti-SARS-CoV-2 IgG [7]	- Not reported	[328]
396 SOTR **LTR n=69** BNT162b2	Seropositivity: Before 3rd dose 164 SOTR (41%), no data for LTR alone[7] One month after 3rd dose: 269 patients after the 3rd dose (68%) LTR: 51/69 (74%)	- Immunosuppressive treatment	[284]
SOTR n=1163 **LTR n=274** mRNA vaccines SOT candidate n=241 **LT candidates n=76** BNT162b2 n=50 mRNA-1273 n=26	Seropositivity 2 weeks to 3 months after the 2nd dose LT Cand: 100%, LTR: anti-SARS-CoV-2 IgG: 42.5%[8] anti-SARS-CoV-2 anti-spike titer ≥1:50 39.3%	- Overall transplant recipient, - but not for LTR	[329]
LTR: n=62 Cirrhotic CLD n=79 Non-cirrhotic CLD n=92 BNT162b2 n=104 mRNA-1273 n=110 Ad26 single dose n=19 mostly equally distributed	Seropositivity: 1 month after second dose: Detectable[5] vs Seropositive[3] LTR: 82.2% vs 38.7% Cirrhotic CLD 96.2% vs 77.2% Non-cirrhotic CLD 95.7% vs 75%	LTR - Use of 2 or more immunosuppression medications - Vaccination with single dose Ad26	[283]
Cirrhotic LD N=38 Non- Cirrhotic LD n=49 Controls n=40 mostly BNT162b2, very few mRNA-1273	Seropositivity: Cirrhotic LD: 97.4%[2] Non- Cirrhotic LD: 87.8%[2] Controls 100%[2]	- Immunosuppressive treatment - Presence of liver disease and/or cirrhosis were not correlated with - either lower anti-SARS-CoV-2 antibody titers or neutralizing activity	[281]

*SOTR: Solid Organ Transplant Recipient, LTR: Liver Transplant recipient, LD: Liver disease, MMF: Mycophenolat-Mofetil, eGFR: estimated glomerular filtration rate, DSA: Donor-specific antibodies *serology performed at least 14 days after 2nd dose, if not otherwise indicated*
1: DiaSorin S.p.A, Seropositivity at >15 AU/mL; 2:
2: EUROIMMUN enzyme immunoassay, positive cutoff of at least 1.1 AU
3: Elecsys® Anti-SARS-CoV-2 semi-quantitative, positive at ≥250 U/ml
4: Siemens SARS- CoV-2 Total (COV2T, IgG and IgM). When COV2T positive, confirmation with Siemens SARS-CoV-2 IgG (COV2G
5: Roche Elecsys anti– SARS-CoV-2 S enzyme immunoassay Seropositivity at ≥0.8 U/ml
6: SARS-CoV-2 Surrogate Virus Neutralization Test (SVNT) assay (GenScript) cut-off for positivity at 30% neutralization
7: SARS-CoV-2 total antibodies enzyme-linked immunosorbent assay test (Beijing Wantai Biological Pharmacy Enterprise) (around 80% of patients)
8: Qualitative 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 analyzer according to the manufacturer's protocol

Pre-exposure prophylaxis against SARS-CoV-2 infection

As described above, preemptive treatment with mAb 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 monoclonal antibody combination 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].

The phase III trial PROVENT assessed the safety and efficacy of the monoclonal antibody combination tixagevimab plus cilgavimab (Evusheld, AstraZeneca) versus 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 immunization (intramuscularly) every six 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 optimized to 4-12 months due to changes in the Fc domain of IgG. Experts recommended double the dose of 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 [174,175,333]. Updated recommendations should be reviewed here; https://www.covid19treatmentguidelines.nih.gov/overview/prevention-of-sars-cov-2/

EASL position

- Pre-exposure prophylaxis of SARS-CoV-2 infection with monoclonal antibodies (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 be also considered immunocompromised and eligible for passive immunization.
- ** Passive immunization 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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