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Title:

Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic

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1. Introduction/Abstract

During the early stages of the COVID-19 pandemic, EASL and ESCMID published a position paper to provide guidance for physicians involved in the care of patients with chronic liver disease. In the meantime, many countries and healthcare systems have been, or are still overwhelmed by the pandemic, significantly impacting on the care of this group of patients, whilst others have started to return towards their usual routine. In addition, many studies have been published focusing on how COVID-19 may affect the liver and how pre-existing liver diseases might influence the clinical course of COVID-19. While many aspects remain poorly understood, it has become increasingly evident that pre-existing liver diseases and liver injury during the course of the disease have to be kept in mind when caring for patients with COVID-19. Thus, this review should serve as an update on the previous position paper summarizing the evidence for liver disease involvement during COVID-19 and also provide some recommendations on how to return to routine care wherever possible.

2. Pre-existing liver disease as risk factor for COVID-19

Patients with chronic liver diseases *per se* do not appear to be over-represented in cohorts of patients with COVID-19 where they represent less than 1% of reported cases [1, 2]. These observations suggest that patients with chronic liver disease are not at increased risk of contracting SARS-CoV-2. However, risk of infection and/or risk for severe course of COVID-19 may be different depending on the nature of the chronic liver disease and the presence or absence of advanced fibrosis or cirrhosis. We will therefore summarize current evidence for different liver diseases regarding the risk for SARS-CoV-2 infection and for a severe course of COVID-19.

Metabolic-dysfunction associated fatty liver disease (MAFLD)

Obesity represents a significant risk factor for a severe course of COVID-19 [3, 4] with severe pneumonia being particularly increased in obese men [3]. While the precise mechanisms driving this association remain unclear, it has been postulated that adipose tissue may serve both as a viral reservoir and also an immunological hub for the inflammatory response [5]. Similarly, other metabolic syndrome elements such as hypertension and diabetes are commonly observed in patients with severe COVID-19 [6]. As metabolic dysfunction-associated fatty liver disease (MAFLD, previously known as non-alcoholic fatty liver disease, NAFLD) [7] and non-alcoholic steatohepatitis (NASH) are closely associated with these metabolic comorbidities, it is of relevance to identify whether presence of MAFLD specifically predisposes to a more severe

course of COVID-19. A retrospective cohort of 202 patients with COVID-19 demonstrated an association between MAFLD and disease progression defined as deteriorating dyspnoea, hypoxia or radiological findings whilst in hospital [8]. This additional risk has been observed even in younger patients with MAFLD [9] and in the absence of type 2 diabetes [10] and interestingly, patients with MAFLD also appear to have a longer duration of viral shedding [8]. Within patients with MAFLD, non-invasive fibrosis scores appear to correlate with higher likelihood of developing severe COVID-19 illness, irrespective of metabolic comorbidities [11], however, genetic polymorphisms implicated in the development and progression of NASH do not appear to be associated with severe disease [12, 13]. In addition, transcriptional activity of genes relevant for SARS-CoV-2-infection has not been found to be increased in liver-tissues of MAFLD patients [14]. Larger analyses are needed to determine whether MAFLD is an independent risk factors for a poor prognosis in COVID-19 or whether the reported effects are due to the presence of confounding factors.

Chronic viral hepatitis

In contrast to metabolic liver disease, little or no evidence has emerged to suggest that the presence of chronic viral hepatitis affects the COVID-19 disease course. Data from both an international registry and from a multicenter cohort study in Italy on COVID-19 outcomes in patients with chronic liver disease include patients with viral hepatitis (23%-37%). However, despite both studies demonstrating associations between severity of liver disease and poor outcome, it remains unknown whether the presence of chronic viral hepatitis influences prognosis [15, 16].

Autoimmune hepatitis

In the previous position paper, we advised against the withdrawal of established immunosuppressive therapy in patients with autoimmune liver disease [17] and a panel of experts on autoimmune liver disease have subsequently given similar recommendations [18]. While there is still little evidence to demonstrate that immunosuppressive therapy *per se* predisposes to SARS-CoV-2 infection, a handful of observational studies have suggested an association between corticosteroid use and a more severe COVID-19 disease course [19-23]. The potential implications of these observations are discussed below in more detail. Further data are needed to determine whether the specific risk of COVID-19 is increased in patients with autoimmune hepatitis and the influence of steroids and/or other immunosuppressive medications on outcome (see also Box 1).

Cirrhosis

Patients with liver cirrhosis are at increased risk for infections and associated complications due to cirrhosis-associated immune dysfunctions, which is particularly important for patients with decompensated cirrhosis. A recent case-series from China reported that from 21 consecutive patients with pre-existing cirrhosis, 5 did not survive SARS-CoV-2-infection [24] and specifically patients with Child-Pugh class C cirrhosis were more likely to suffer a fatal course of COVID-19 [24, 25]. Another case series from Italy documented 50 patients with cirrhosis and COVID-19; 26% of these patients presented with MELD ≥ 15 , increasing from 13% at the last documented visit prior to SARS-Cov-2 infection. The 30 day mortality was 34%, with end-stage-liver disease considered as the cause of death in only 5 patients (29%) whilst respiratory failure due to COVID-19 accounted for death in 12 patients (71%) [15]. These data are in line with observations from a European registry that reported the outcome of 103 patients with cirrhosis - nearly 40% died with patients with Child-Pugh class C cirrhosis at the highest risk for a fatal course of COVID-19 (63%, n= 27) [16]. Similarly, multicentre hospital coding data in the USA demonstrated a significantly higher risk of mortality from COVID-19 in patients with chronic liver disease compared to those without, with the highest risk found in those with cirrhosis [26]. However, these data did not have a contemporaneous comparison group of patients with cirrhosis presenting with acute decompensation without COVID-19. Recently, a prospective multicentre study compared outcomes between patients with cirrhosis and COVID-19 (n=37), cirrhosis alone (n=127) and COVID-19 alone (n=108). Although rates of mortality or transfer to hospice in patients with cirrhosis and COVID-19 was greater than COVID-19 alone (30% vs 13%, p=0.03) there was no significant difference from cirrhosis alone (30% v. 20%; p=0.11). The presence of acute-on-chronic liver failure (ACLF) was also similar in the two cirrhosis groups (29.7% vs 22.8%) as was mortality in ACLF patients (55% v. 36%; p=0.25) although the number of cases was small [27]. Taken together, currently it is difficult to conclude that the occurrence of COVID-19 in cirrhosis patients increases the risk of developing ACLF or mortality compared with those patients that decompensate with cirrhosis due to other reasons. However, the mortality of cirrhosis patients with COVID-19 is markedly greater than those that do not have cirrhosis.

Liver Transplantation (LT) recipients

The clinical course of COVID-19 in immunosuppressed transplant recipients may differ from those in non-immunosuppressed patients [28]. Indeed, while hepatocellular injury, as

1 characterized by elevated serum aminotransferases, appears to be relatively less prevalent,
2 acute kidney injury is more common in transplant recipients with COVID-19, possibly due to the
3 use of calcineurin inhibitors [28]. These findings will need confirmation in larger case series;
4 however, in line with the general risk factors for severe COVID-19, elderly patients with
5 comorbidities are among those with the highest risk within the cohort of transplant recipients
6 [28, 29]. Early reports from Italy described low mortality rates in transplant recipients < 5% [20,
7 30], however subsequent analyses have reported mortality rates in liver and other solid organ
8 transplant recipients at around 25% [28, 31-34]. The results of a prospective European study
9 from 19 transplant centres were recently reported [35] including 57 LT recipients with confirmed
10 SARS-CoV-2 infection. Overall and in-hospital case-fatality rates were 12% and 17%
11 respectively, which are similar to the expected mortality for patients with severe COVID-19
12 infection. Five of the 7 patients who died had an underlying history of cancer. Taken together
13 the currently available data do not support the notion that transplantation or specific
14 immunosuppressive regimens significantly affect the risk for a severe course of COVID-19 but
15 those with underlying cancer may require special attention [28, 31, 35].

17 **3. Liver injury secondary to COVID-19**

18 Deranged liver biochemistry of varying degrees is common in patients with COVID-19, being
19 found in 19-76% of cases [36-41]. Most of these studies report a predominantly hepatocellular
20 pattern of liver injury with elevated serum aminotransferases (rarely > 5 x upper limit of normal)
21 although cholestatic or mixed patterns of liver injury have also been reported. Importantly, this
22 appears to occur to a similar degree in patients with and without pre-existing liver disease [26]
23 and has also been documented in pregnant women in association with increased levels of pro-
24 inflammatory cytokines [42]. To what extent this liver injury is derived from the direct effect of
25 SARS-CoV-2, as opposed to a secondary phenomenon caused by the broader disease course
26 of COVID-19 remains to be elucidated. SARS-CoV-2 infection of hepatocytes with subsequent
27 mitochondrial disturbance and apoptosis has been suggested [41], but requires confirmatory
28 testing particularly since single cell RNA sequencing has shown relatively sparse hepatocyte
29 expression of the receptors necessary for viral uptake [43]. Similarly, direct infection of
30 cholangiocytes via angiotensin-converting enzyme 2 (ACE2) has been posited as a potential
31 mechanism for intrinsic liver injury [44] but requires further investigation. Given the profound
32 multi-systemic involvement of COVID-19, particularly in the severe and critical forms of disease,
33 liver injury is likely to be multifactorial with contributions from systemic inflammation, intrahepatic
34 immune activation, microvascular thrombosis, hepatic congestion, perturbations of the gut-liver-

axis as well as drug toxicity [45-48]. The prognostic significance of deranged biochemistry in COVID-19 remains unresolved [49]; some groups have demonstrated a strong correlation with duration of hospitalisation, organ failure and intensive care unit admission [37, 41, 50] whilst others have failed to observe any significant associations with outcome [39, 40].

4. Recommendations for the management of patients with chronic liver disease

General recommendations

In the aftermath of COVID-19 at its peak, there was an urgent need to anticipate and plan for the wave of liver disease yet to come. This will be characterised by emergent hepatic decompensation, increased dropouts from transplant waiting lists and a vast back-log of deferred hospital visits and testing [51]. Clinicians and their institutions should therefore be proactive in structuring their services to tackle these challenges and strive to resume standard-of-care for patients with liver disease wherever possible. Equally, it is important to embrace innovative technologies and methods of practice developed during the pandemic which may continue to be of benefit to patients (e.g. telemedicine use, remote monitoring) [52]. Combining standard of care with novel ideas will help to mitigate against longer term consequences of the pandemic including missed diagnosis, incomplete HCC screening, and progressive liver disease. Furthermore, in light of accumulating evidence that baseline liver disease severity is associated with poor outcomes from COVID-19 [15, 16], treatment of underlying liver disease may represent one of the most important strategies to protect patients from the adverse effects of any future SARS-CoV-2 infection. This in turn will further reduce the burden on healthcare systems and allow more rapid return towards gold standard hepatology practice (Fig 1). The epidemiology of COVID-19 has proven unpredictable, but the burden of disease is likely to expand and shrink episodically within populations for some time to come. The approach to patient care must therefore be personalised and flexible, balancing national dynamics of SARS-CoV-2 infection, the local resource availability, and the severity of each individual patient's underlying liver disease. Lastly, with time, it will be important to resume clinical trial enrolment wherever possible to allow the field to advance despite unprecedented global events.

Specific recommendations

MAFLD

- Patients should be made aware of potential adverse metabolic and hepatic consequences of social isolation including more sedentary lifestyles and increased consumption of processed foods.
- Preventing liver disease progression through intensive lifestyle intervention, including nutritional guidance, weight loss advice, and diabetes management may help prevent the development of a severe disease course with future SARS-CoV-2 infection.
- Treatment of arterial hypertension should continue in accordance with existing guidelines. There is currently no evidence showing that angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) increase the risk of SARS-CoV-2 infection or the risk of developing severe complications or death from COVID-19 [53].
- Early admission should be considered for all patients with MAFLD who become infected with SARS-CoV-2.

Viral hepatitis

- Continue treatment of chronic hepatitis C virus (HCV) and chronic hepatitis B virus (HBV) if already receiving treatment.
- Use telemedicine/local laboratory testing for follow-up visits in patients receiving antiviral therapy, send follow-up-prescriptions by mail and supply extended prescription supplies including full course of direct acting antiviral (DAA) medications to complete HCV treatment if this has been initiated. However, patients with poor compliance with medications should be considered for directly observed treatment protocols.
- In patients without COVID-19, treatment for HCV and HBV should be initiated according to general guidelines [54, 55].
- Given the unknown impact of interferon alpha on systemic inflammation associated with COVID-19, alternative agents should be considered when initiating treatment for patients with HBV during the COVID-19 pandemic.
- In patients with COVID-19, initiation of treatment for HBV and HCV is usually not warranted and should be deferred until recovery from COVID-19.
- In patients with COVID-19 in whom there is evidence of high disease activity (flare) or clinical suspicion for severe acute HBV hepatitis, a decision to initiate antiviral therapy should be made on a case-by-case basis in consultation with a specialist.

- In patients with chronic, occult or resolved HBV and COVID-19 receiving corticosteroids, tocilizumab or other immunosuppressive agents, consider the use of antiviral therapy to prevent viral flare or reactivation.
- Continue to work towards the WHO goal of eliminating viral hepatitis by 2030 by trying to adapt the cascade-of-care to the new coronavirus situation and make modifications for safe delivery of services according to the local requirements.

Alcohol associated liver disease

- Chronic alcohol consumption may increase susceptibility of acute respiratory distress syndrome (ARDS) secondary to SARS-CoV-2 infection [56].
- Social isolation can lead to new or increased alcohol consumption [57] and an increase in alcohol related admissions including new hepatic decompensation should be anticipated during and after periods of physical distancing.
- Clinicians and institutions should therefore implement pre-emptive strategies such as patient outreach and telephone alcohol liaison and cessation services.
- Whilst introducing corticosteroids has shown benefit in the treatment of hospitalised patients with COVID-19 requiring respiratory support [58], concerns remain that patients who are already taking higher doses of corticosteroids may be more susceptible to severe COVID-19 [19, 59]. These concerns must be considered when initiating corticosteroids as a treatment for patients with severe alcoholic hepatitis.
- Clinicians should be aware of circulating false online misinformation regarding the protective effects of alcohol against SARS-CoV-2 leading to previous instances of deliberate excess consumption [60].

Autoimmune liver disease

- In patients with autoimmune liver disease, we currently advise against reducing immunosuppressive therapy to prevent SARS-CoV-2 infection. Reductions should only be considered under special circumstances (e.g. medication-induced lymphopenia, or bacterial/fungal superinfection in cases of severe COVID-19) after consultation with a specialist.
- Whilst introducing corticosteroids has shown benefit in the treatment of hospitalised patients with COVID-19 requiring respiratory support [58], concerns remain that patients who are already taking higher doses of corticosteroids may be more susceptible to SARS-CoV-2 infection and severe COVID-19 [19, 59]. To minimise systemic glucocorticoid exposure we

therefore recommend considering budesonide as a first-line agent to induce remission in patients without cirrhosis who have a flare of autoimmune hepatitis [61].

- In patients treated with corticosteroids who develop COVID-19, corticosteroid dosing should be sufficient to prevent adrenal insufficiency. Addition of, or conversion to dexamethasone should only be considered in patients with COVID-19 who require hospitalisation and respiratory support [58].
- There remains a paucity of data to make specific recommendations for patients with primary biliary cholangitis, primary sclerosing cholangitis and IgG4-related disease.
- All patients should receive vaccination for *Streptococcus pneumoniae* and influenza

Cirrhosis

- Patients with cirrhosis are particularly vulnerable to both the consequences of SARS-CoV-2 infection and to the adverse effects of delayed or altered standard of care during the COVID-19 pandemic.
- Every effort should be made to resume the best standard of care for patients with cirrhosis according to guidelines [62] wherever possible.
- Patients with cirrhosis who are infected with SARS-CoV-2 are at high risk of new or worsening hepatic decompensation, severe COVID-19 and death [15, 16].
- All patients with new or worsening hepatic decompensation or acute-on-chronic liver failure (ACLF) should be prioritised for SARS-CoV-2 testing even in the absence of respiratory symptoms [16].
- In those with cirrhosis who are admitted for reasons other than COVID-19, particular effort should be made to manage these patients in a designated non-COVID-19 ward, preferably in a side-room, in order to reduce the risk of nosocomial SARS-CoV-2 infection.
- Guidelines on prophylaxis of spontaneous bacterial peritonitis, gastrointestinal haemorrhage, and hepatic encephalopathy should be closely followed to prevent decompensation and avoid admission [62].
- Early admission should be considered for all patients with cirrhosis who become infected with SARS-CoV-2.
- Because of the potential of circulatory dysfunction, in particular in the pulmonary circulation associated with COVID-19 [63], the use of vasoconstrictor therapy, which is known to increase pulmonary pressure and decrease cardiac output, should be considered with great caution among critically ill patients with cirrhosis and COVID-19.

- Rapid clinical deterioration in patients with advanced liver disease and COVID-19 should prompt consideration of a symptoms-based approach using palliative care guidelines [64].
- All patients should receive vaccination for *Streptococcus pneumoniae* and influenza.

Liver transplant (LT) candidates

- Patients on the LT waiting list with decompensated cirrhosis are at high risk of severe COVID-19 and death following SARS-CoV-2 infection.
- We therefore recommend LT centers aim to restore transplantation services following the peak of the COVID-19 epidemic wherever possible.
- In centers with ongoing resource limitations, LT should be prioritized for patients with poor short-term prognosis including those with acute/acute-on-chronic liver failure (ALF/ACLF), high model for end-stage liver disease (MELD) score (including exceptional MELDs) and HCC at the upper limits of the Milan criteria.
- The risk of SARS-CoV-2 transmission via liver transplantation remains unknown [65] and therefore we currently recommend to test all donors for SARS-CoV-2 infection by RT-PCR and recommend against using livers from SARS-CoV-2 infected donors [66].
- We encourage LT centres to develop and improve local and global risk stratification pathways for LT donors and recipients incorporating a combination of clinical history, chest radiology, and SARS-CoV-2 testing [67] and ethical considerations regarding transplantation activities and allocation [68].
- Measures should be taken to reduce the risk of SARS-CoV-2 infection in the peri-transplantation period. In areas of high disease burden, a COVID-19 free pathway through transplantation should be implemented including strict social isolation for waiting list patients, telephone screening for symptoms and exposures before admission, and perioperative management in a designated clean ICU and post-LT ward [69].
- Consent for diagnostic and therapeutic procedures related to transplantation should include the potential risk of nosocomial COVID-19.
- LT candidates should be made aware that infection with SARS-CoV-2 in patients undergoing major surgery is associated with an increased risk of severe COVID-19 and death [70].
- Living-donor transplantations should be considered on a case-by-case basis and include careful risk stratification of donor and recipient incorporating a combination of clinical history, chest radiology, and SARS-CoV-2 testing.

LT recipients

- We advise against reduction of immunosuppressive therapy to prevent SARS-CoV-2 infection. Reduction should only be considered under special circumstances (e.g. medication-induced lymphopenia, or bacterial/fungal superinfection in case of severe COVID-19) after consultation with a specialist.
- Clinicians must be aware of the high reported rates of fear and anxiety regarding COVID-19 in LT recipients and the barrier this may pose to compliance with immunosuppressive medication and attendance at scheduled medical visits [71].
- Drug levels of calcineurin inhibitors and mechanistic Target of Rapamycin (mTOR) inhibitors should be closely monitored when they are administered together with drugs such as hydroxychloroquine, protease inhibitors or alongside new trial drugs for COVID-19 as they emerge.
- Early admission should be considered for all LT recipients who develop COVID-19
- Risk factors for a severe course of COVID-19 in LT recipients may include underlying malignancy, sarcopenia, graft dysfunction and metabolic comorbidities. However, the individual contributions of these factors require further clarification.
- All patients should receive vaccination for *Streptococcus pneumoniae* and influenza.

Hepatocellular carcinoma (HCC)

- The specific risk of COVID-19 in patients with hepatocellular carcinoma remains undefined.
- However, mortality from COVID-19 in cancer patients appears to be determined by age, gender, and comorbidities as opposed to the use of cytotoxic chemotherapy or other anticancer treatment [72].
- Care should be maintained according to guidelines including continuing systemic treatments and evaluation for liver transplantation.
- Multidisciplinary HCC boards should continue to function remotely and provide treatment recommendations
- Full HCC surveillance should resume where possible. Where resources remain limited, patients with increased risk, such as patients with elevated alpha-fetoprotein levels, advanced cirrhosis, chronic hepatitis B, NASH/diabetes etc should be prioritised in conjunction with the use of published HCC risk stratification scores.

5. Liver-related diagnostic procedures

Endoscopy

Endoscopic procedures are associated with an increased risk of disseminating SARS-CoV-2. During esophagogastroduodenoscopy (EGD) or endoscopic retrograde cholangiography (ERC), spreading of virus-containing droplets can occur. In addition, shedding of the virus in the faeces increases the risk of dissemination during colonoscopy. Thus, depending on the local COVID-19 burden, we recommend SARS-CoV-2 testing prior to endoscopic procedures in all patients. In patients who test negative and in areas with low COVID-19 burden, EGD - to screen for and treat varices - and ERC - for duct dilatation or stent replacement in patients after liver transplantation or patients with primary sclerosing cholangitis - should not be delayed.

In patients with COVID-19, indications for endoscopic procedures should be limited to emergencies such as gastrointestinal bleeding and bacterial cholangitis.

Ultrasound (HCC surveillance)

HCC surveillance should only be deferred based on available resources (including availability of therapeutic options in case of HCC diagnosis) at the centre and the individual risk assessment. Patients with increased risk (e.g. patients with elevated alpha-fetoprotein levels, advanced cirrhosis, chronic hepatitis B, HCV-related cirrhosis (even after cure), NASH/diabetes) should be prioritised if resources are limited.

In patients with COVID-19, HCC surveillance can be deferred until after recovery.

Liver biopsy

In areas with low COVID-19 burden, liver biopsies should be performed as indicated, including grading/staging for MAFLD and chronic viral hepatitis and histological assessment of elevated transaminases of unknown aetiology. In areas with high COVID-19 burden or limited availability of resources, biopsy should be prioritised in patients with severely elevated transaminases of unclear cause (e.g. ALT >5x upper limit of normal), suspected transplant rejection and liver masses suspicious of malignancy.

In patients with COVID-19, liver biopsy may be performed based on the individual indication for histological assessment. It has to be considered that treatment/care for COVID-19 may outweigh the diagnosis of co-existing liver disease and that systemic inflammation associated

with COVID-19 is likely to obscure aetiology-specific histologic characteristics. As discussed above, liver function test abnormalities are common in patients with COVID-19 particularly with more severe disease and routine liver biopsy in this context is not required.

6. Liver specific considerations in the pharmacological management of COVID-19

The targeted management of COVID-19 is a rapidly evolving field with a plethora of new or repurposed medications constantly shifting in and out of favour. In Europe alone there are currently over 200 registered COVID-19 specific drug trials [73]. This number will no doubt continue to increase as we learn more about the pathophysiology of the disease. It is beyond the scope of this updated position paper to comprehensively review the potential therapeutic options for COVID-19. While some interventions, such as infusion of convalescent plasma or favipiravir (recently approved in India) show encouraging signals of efficacy, little is known with regards to liver-specific side effects or contraindications. However, for some therapeutic agents there are liver-specific considerations which we will discuss. Hepatologists must be mindful of the secondary effects these drugs may have on the liver and continually evaluate the specific risks and benefits conferred to their patients with underlying liver disease.

Remdesivir

Remdesivir is an adenosine-analogue that induces RNA chain termination and was initially developed as an antiviral agent against Ebola. It has emerged as a promising treatment candidate against COVID-19 being shown to reduce the duration of symptoms when used early in the disease course [74, 75]. Despite preclinical investigations demonstrating reversible aminotransferase elevations [76], use of remdesivir in controlled trials has not demonstrated a significant impact on liver function tests compared with placebo. In the largest randomised control trial to date, Beigel et al demonstrated no difference in rates of aminotransferase elevation between patients taking remdesivir compared with placebo (4% v. 5.9%) [74]. Similarly, Wang et al also showed comparable rates of elevated transaminases between remdesivir and placebo groups [77]. Both trials excluded patients with baseline ALT or AST >5x upper limit of normal and Wang et al. also excluded patients with cirrhosis. Should remdesivir ultimately move into mainstream use, caution should therefore be exercised in patients with advanced liver disease or with severe baseline derangements in liver biochemistry, but otherwise transaminase elevations do not appear to occur over and above what may be

1 expected as part of the typical disease course of COVID-19. Remdesivir is approved for the
2 treatment of COVID-19 in several European countries.

3 4 Tocilizumab

5 Interleukin-6 (IL-6) appears to be a key driver of the “cytokine storm” leading to significant lung
6 and other organ damage in cases of severe COVID-19. Tocilizumab, a humanized monoclonal
7 antibody targeting IL-6 has therefore been postulated to counter this dysregulated inflammation
8 and has shown promise in retrospective series of COVID-19 by reducing the need and duration
9 of organ support [78]. The liver side effect profile of tocilizumab is well established due to its
10 widespread use in rheumatoid arthritis and other auto-inflammatory conditions. Mild serum
11 aminotransferase elevations are common and are usually self-limiting and asymptomatic [79],
12 however, progressive jaundice requiring liver transplantation has been reported [80]. Rarely,
13 tocilizumab has been associated with Hepatitis B virus reactivation [81] and therefore HBV
14 serology should form part of routine pre-treatment work-up.

15 16 Corticosteroids

17 There seems to be a dichotomous relationship between corticosteroids and COVID-19. Whilst
18 patients already taking corticosteroids may be at increased risk of adverse outcomes from
19 COVID-19, those with established severe disease seem to paradoxically benefit from
20 corticosteroid introduction. In patients with inflammatory bowel disease, the use of
21 corticosteroids has been associated with intensive care unit admission, ventilator requirement
22 and/or death [19]. Similarly, patients on maintenance glucocorticoids for rheumatological
23 conditions have an increased rate of hospitalisation following SARS-CoV-2 infection [59]. As
24 yet, small case series have been unable to draw definitive conclusions regarding the risks
25 posed by corticosteroid use in patients with autoimmune hepatitis or after liver transplantation
26 [31, 34]. In these patients, the risks of hepatitis flares or graft rejection must be weighed against
27 the potential risks of developing severe COVID-19. Currently, we advise against routine
28 reduction of immunosuppression in AIH or LT recipients, including the use of steroids if
29 required. Corticosteroids however do appear to be a viable treatment option for patients with
30 severe COVID-19 requiring respiratory support. In June 2020, the RECOVERY [58] trial
31 reported that dexamethasone reduced deaths by one-third in ventilated patients and by one fifth
32 in patients receiving supplemental oxygen. It is likely that this agent will be increasingly used in
33 the management of severe COVID-19 including in patients with pre-existing chronic liver
34 disease.

Anticoagulation

Patients with advanced liver disease are at increased risk of venous thromboembolism [82]. Similarly, coagulopathy is a common abnormality in patients with COVID-19 and has emerged as a major driver of morbidity and mortality, particularly in patients with severe disease. Hospitalised patients with COVID-19 have alarmingly high rates of venous thromboembolic disease with an observed incidence of 20% at day 7, and 42% at day 21 despite thromboprophylaxis [83]. As well as macro-thrombotic events, COVID-19 is also associated with widespread micro-thrombosis and endothelial dysfunction contributing to multiorgan failure in the terminal phase of the disease [84, 85]. The role of anticoagulation in patients with COVID-19 has therefore been extensively investigated and has been shown to improve outcomes in severe COVID-19 [86], although unified risk stratification models and treatment thresholds have yet to emerge. Given that both advanced liver disease and COVID-19 are both associated with a hypercoagulable state, it reasons that SARS-CoV-2 infection in patients with cirrhosis may yield a cumulative risk of prothrombotic complications. We therefore suggest that in this scenario patients should be deemed at particularly high risk of thromboembolic events. Whilst historically there have been reservations about the use of anticoagulation in patients with cirrhosis and portal hypertension, systematic review has demonstrated no excess of bleeding events in anticoagulated patients with cirrhosis and portal vein thrombosis [87]. Furthermore, anticoagulation may have antifibrotic properties [88] and even confer a survival advantage in patients with cirrhosis [89]. Further reassurance is provided by a recent multicentre Italian study in which 80% of patients with cirrhosis and COVID-19 received thromboprophylaxis without any evidence of major haemorrhagic complications [15]. Whilst thromboprophylaxis, typically with low molecular weight heparin (LMWH), should form part of standard of care for all patients with cirrhosis admitted to hospital, it remains to be determined whether patients with COVID-19 and cirrhosis should receive early treatment with enhanced or therapeutic anticoagulation.

Box 1.

Open questions for liver related basic/translational research regarding COVID-19

- Risk factors for increased mortality in patients after liver transplantation
- Role of pre-existing immune activation (e.g. in cirrhosis or MAFLD/obesity) in exacerbating COVID-19 outcomes

- Identification of central hubs for SARS-CoV-2 dissemination within the GI-tract and fat tissues
- Involvement of liver endothelium in promoting SARS-CoV-2 dissemination
- Identification of direct and indirect effects of SARS-CoV-2 on hepatocytes/cholangiocytes
- COVID-19 as a trigger for ACLF and decompensation in cirrhotic patients
- COVID-19 induced thrombophilia as a contributor to progressive liver disease

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Figure legends

Fig. 1

Liver disease progression and poor outcomes from SARS-CoV-2 infection are closely associated. There must therefore be a concerted effort to resume standard of care and restore hepatology/transplantation services in order to improve patient outcomes.

Fig. 2

Summary of recommendations.

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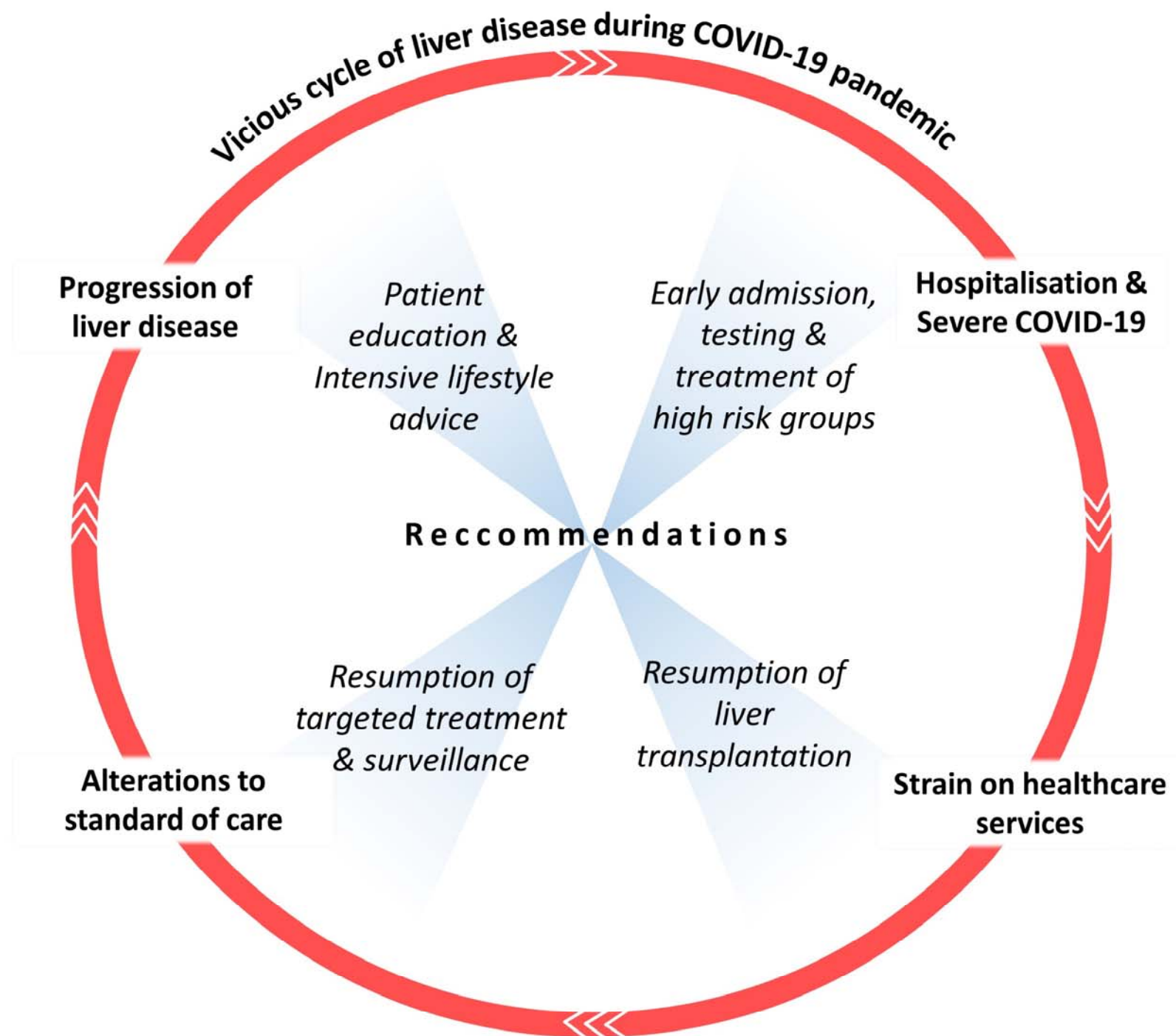
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Figure 1



All patients with chronic liver disease should adhere to common rules of physical distancing

Metabolic-dysfunction associated fatty liver disease (MAFLD)

- Patients should be made aware of potential adverse metabolic and hepatic consequences of social isolation including more sedentary lifestyles and increased consumption of processed foods.
- Preventing liver disease progression through intensive lifestyle intervention, including nutritional guidance, weight loss advice, and diabetes management may help prevent the development of a severe disease course with future SARS-CoV-2 infection.
- Treatment of arterial hypertension should continue in accordance with existing guidelines. There is currently no evidence showing that angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) increase the risk of SARS-CoV-2 infection or the risk of developing severe complications or death from COVID-19.
- Early admission should be considered for all patients with MAFLD who become infected with SARS-CoV-2.

Viral hepatitis

- Continue treatment of chronic hepatitis C virus (HCV) and chronic hepatitis B virus (HBV) if already receiving treatment.
- Use telemedicine/local laboratory testing for follow-up visits in patients receiving antiviral therapy, send follow-up-prescriptions by mail and supply extended prescription supplies including full course of direct acting antiviral (DAA) medications to complete HCV treatment if this has been initiated. However, patients with poor compliance with medications should be considered for directly observed treatment protocols.
- In patients without COVID-19, treatment for HCV and HBV should be initiated according to general guidelines
- Given the unknown impact of interferon alpha on systemic inflammation associated with COVID-19, alternative agents should be considered when initiating treatment for patients with HBV during the COVID-19 pandemic.
- In patients with COVID-19, initiation of treatment for HBV and HCV is usually not warranted and should be deferred until recovery from COVID-19.
- In patients with COVID-19 in whom there is evidence of high disease activity (flare) or clinical suspicion for severe acute HBV hepatitis, a decision to initiate antiviral therapy should be made on a case-by-case basis in consultation with a specialist.
- In patients with chronic, occult or resolved HBV and COVID-19 receiving corticosteroids, tocilizumab or other immunosuppressive agents, consider the use of antiviral therapy to prevent viral flare or reactivation.
- Continue to work towards the WHO goal of eliminating viral hepatitis by 2030 by trying to adapt the cascade-of-care to the new coronavirus situation and make modifications for safe delivery of services according to the local requirements

Autoimmune liver disease

- In patients with autoimmune liver disease, we currently advise against reducing immunosuppressive therapy. Reductions should only be considered under special circumstances (e.g. medication-induced lymphopenia, or bacterial/ fungal superinfection in cases of severe COVID-19) after consultation with a specialist.
- Whilst introducing corticosteroids has shown benefit in the treatment of hospitalised patients with COVID-19 requiring respiratory support, concerns remain that patients who are already taking higher doses of corticosteroids may be more susceptible to SARS-CoV-2 infection and severe COVID-19. To minimise systemic glucocorticoid exposure we therefore recommend considering budesonide as a first-line agent to induce remission in patients without cirrhosis who have a flare of autoimmune hepatitis.
- In patients treated with corticosteroids who develop COVID-19, corticosteroid dosing should be sufficient to prevent adrenal insufficiency. Addition of, or conversion to dexamethasone should only be considered in patients with COVID-19 who require hospitalisation and respiratory support.
- There remains a paucity of data to make specific recommendations for patients with primary biliary cholangitis, primary sclerosing cholangitis and IgG4-related disease.
- All patients should receive vaccination for Streptococcus pneumoniae and influenza

Alcohol related liver disease

- Chronic alcohol consumption may increase susceptibility of acute respiratory distress syndrome (ARDS) secondary to SARS-CoV-2 infection.
- Social isolation can lead to new or increased alcohol consumption and an increase in alcohol related admissions including new hepatic decompensation should be anticipated during and after periods of physical distancing.
- Clinicians and institutions should therefore implement pre-emptive strategies such as patient outreach and telephone alcohol liaison and cessation services.
- Whilst introducing corticosteroids has shown benefit in the treatment of hospitalised patients with COVID-19 requiring respiratory support, concerns remain that patients who are already taking higher doses of corticosteroids may be more susceptible to severe COVID-19. These concerns must be considered when initiating corticosteroids as a treatment for patients with severe alcoholic hepatitis.
- Clinicians should be aware of circulating false online misinformation regarding the protective effects of alcohol against SARS-CoV-2 leading to previous instances of deliberate excess consumption.

Hepatocellular carcinoma

- The specific risk of COVID-19 in patients with HCC remains undefined.
- However, mortality from COVID-19 in cancer patients appears to be determined by age, gender, and comorbidities as opposed to the use of cytotoxic chemotherapy or other anticancer treatment.
- Care should be maintained according to guidelines including continuing systemic treatments and evaluation for LT
- Multidisciplinary HCC boards should continue to function remotely and provide treatment recommendations
- Full HCC surveillance should resume where possible. Where resources remain limited, patients with increased risk, such as patients with elevated alpha-fetoprotein levels, advanced cirrhosis, chronic hepatitis B, NASH/diabetes, should be prioritised in conjunction with the use of published HCC risk stratification scores.

Liver transplant candidates

- Patients on the LT waiting list with decompensated cirrhosis are at high risk of severe COVID-19 and death following SARS-CoV-2 infection. We therefore recommend LT centers aim to restore transplantation services following the peak of the COVID-19 epidemic wherever possible.
- In centers with ongoing resource limitations, LT should be prioritized for patients with poor short-term prognosis including those with acute liver failure, ACLF, high MELD score (including exceptional MELDs) and HCC at the upper limits of the Milan criteria.
- The risk of SARS-CoV-2 transmission via liver transplantation remains unknown and therefore we currently recommend against using livers from SARS-CoV-2 infected deceased donors.
- We encourage LT centres to develop and improve local and global risk stratification pathways for LT donors and recipients incorporating a combination of clinical history, chest radiology, and SARS-CoV-2 testing and ethical considerations regarding transplantation activities and allocation.
- Measures should be taken to reduce the risk of SARS-CoV-2 infection in the peri-transplantation period. In areas of high disease burden, a COVID-19 free pathway through transplantation should be implemented including strict social isolation for waiting list patients, telephone screening before admission, and perioperative management in a designated clean ICU
- Consent for procedures related to transplantation should include the potential risk of nosocomial COVID-19 and LT candidates should be made aware that infection with SARS-CoV-2 in patients undergoing major surgery is associated with an increased risk of severe COVID-19.
- Living-donor transplantation should be considered on a case-by-case basis and include careful risk stratification of donor and recipient.

Liver transplant recipients

- LT recipients with underlying malignancy are a particular risk of mortality if infected with COVID-19 and need to be recognised as a group at high risk.
- We advise against reduction of immunosuppressive therapy. Reduction should only be considered under special circumstances (e.g. medication-induced lymphopenia, or bacterial/fungal superinfection in case of severe COVID-19) after consultation with a specialist.
- Clinicians must be aware of the high reported rates of fear and anxiety regarding COVID-19 in LT recipients and the barrier this may pose to compliance with immunosuppressive medication and attendance at scheduled medical visits.
- Drug levels of calcineurin inhibitors and mechanistic Target of Rapamycin (mTOR) inhibitors should be closely monitored when they are administered together with antiviral drugs.
- Early admission should be considered for all LT recipients who develop COVID-19
- All patients should receive vaccination for Streptococcus pneumoniae and influenza.

Cirrhosis

- Patients with cirrhosis are particularly vulnerable to both the consequences of SARS-CoV-2 infection and to the adverse effects of delayed or altered standard of care during the COVID-19 pandemic.
- Every effort should be made to resume the best standard of care for patients with cirrhosis according to guidelines wherever possible.
- Patients with cirrhosis who are infected with SARS-CoV-2 are at high risk of new or worsening hepatic decompensation, severe COVID-19 and death.
- All patients with new or worsening hepatic decompensation or acute-on-chronic liver failure (ACLF) should be prioritised for SARS-CoV-2 testing even in the absence of respiratory symptoms.
- In those with cirrhosis who are admitted for reasons other than COVID-19, particular effort should be made to manage these patients in a designated non-COVID-19 ward.
- Guidelines on prophylaxis of spontaneous bacterial peritonitis, gastrointestinal haemorrhage, and hepatic encephalopathy should be closely followed to prevent decompensation and avoid admission.
- Early admission should be considered for all patients with cirrhosis who become infected with SARS-CoV-2.
- Because of the potential of circulatory dysfunction, the use of vasoconstrictor therapy, which is known to increase pulmonary pressure and decrease cardiac output, should be considered with great caution among critically ill patients with cirrhosis and COVID-19.
- Rapid clinical deterioration in patients with advanced liver disease and COVID-19 should prompt consideration of a symptoms-based approach using palliative care guidelines.
- All patients should receive vaccination for Streptococcus pneumoniae and influenza