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# Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper



Tobias Boettler,<sup>1</sup> Philip N. Newsome,<sup>2,3</sup> Mario U. Mondelli,<sup>4</sup> Mojca Maticic,<sup>5,6</sup> Elisa Cordero,<sup>7</sup> Markus Cornberg,<sup>8,9</sup> Thomas Berg<sup>10,\*</sup>

## Summary

The coronavirus disease 2019 (COVID-19) pandemic poses an enormous challenge to healthcare systems in affected communities. Older patients and those with pre-existing medical conditions have been identified as populations at risk of a severe disease course. It remains unclear at this point to what extent chronic liver diseases should be considered as risk factors, due to a shortage of appropriate studies. However, patients with advanced liver disease and those after liver transplantation represent vulnerable patient cohorts with an increased risk of infection and/or a severe course of COVID-19. In addition, the current pandemic requires unusual allocation of healthcare resources which may negatively impact the care of patients with chronic liver disease that continue to require medical attention. Thus, the challenge hepatologists are facing is to promote telemedicine in the outpatient setting, prioritise outpatient contacts, avoid nosocomial dissemination of the virus to patients and healthcare providers, and at the same time maintain standard care for patients who require immediate medical attention.

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## Introduction

Coronavirus disease 2019 (COVID-19) is caused by the recently identified coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Symptoms associated with COVID-19 are mostly fever, tiredness and dry cough. Some patients also develop symptoms including shortness of breath, aches, nasal congestion, sore throat, anosmia and ageusia. Nausea, vomiting and diarrhoea occur less frequently.<sup>1</sup> While symptoms remain mild throughout the course of infection in the majority of patients, older patients were identified to be at higher risk of a fatal disease course, with hypertension, diabetes and coronary heart disease being the most frequent comorbidities in these cohorts.<sup>2,3</sup>

## COVID-19 and the liver

While pre-existing liver disease is not specifically listed in the published cohort studies, elevated alanine aminotransferase (ALT) levels, reduced platelet counts and reduced albumin levels at the time of admission have been associated with higher mortality,<sup>2</sup> although not all of these alterations are independent risk factors. It remains unclear at this time whether these laboratory test alterations are a sign for pre-existing liver diseases in patients with a more severe course of infection, whether they rather reflect liver damage caused by the virus itself, or whether they mirror a severe inflammatory response (hypoalbuminemia) with

disseminated intravascular coagulation (thrombocytopenia). Possibly, patients with advanced chronic liver disease are at increased risk of infection due to cirrhosis-associated immune dysfunction.<sup>4</sup> The same could be true for patients after liver transplantation and possibly those with autoimmune liver diseases who receive immunosuppressive therapies.

However, currently, there are only limited data available linking underlying liver diseases with the course of SARS-CoV-2 infection and there are many open questions (Box 1). Chronic hepatitis B virus infection for example, which is more prevalent in China than Europe, does not appear to affect the outcome of COVID-19.<sup>1</sup> In addition, although there is no proof for this assumption, immunosuppression may even provide some protection from immunopathology, which appears to contribute to lung damage in cases with more severe manifestations of the disease.<sup>5,6</sup> These may be associated with a macrophage activation syndrome in the context of a hyperinflammatory syndrome characterised by a cytokine storm with multi-organ failure.<sup>7</sup> On the other hand, systemic viral infections are often associated with transient elevations of transaminases which may reflect general immune activation or inflammation caused by circulating cytokines without compromising liver function, a phenomenon called “bystander hepatitis”. This may also be the case in patients with COVID-19

Received 25 March 2020;  
received in revised form 31  
March 2020; accepted 31  
March 2020; available online  
2 April 2020

<sup>1</sup>Department of Medicine II, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany; <sup>2</sup>National Institute for Health Research, Birmingham Biomedical Research Centre at University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; <sup>3</sup>Centre for Liver & Gastrointestinal Research, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK; <sup>4</sup>Division of Infectious Diseases and Immunology, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; <sup>5</sup>Clinic for Infectious Diseases and Febrile Illnesses, University Medical Centre Ljubljana, Slovenia; <sup>6</sup>Faculty of Medicine, University of Ljubljana, Slovenia; <sup>7</sup>Department of Medicine, University of Seville, Clinical Unit of Infectious Diseases University Hospital Virgen del Rocío, Institute of Biomedicine, Sevilla, CSIC, Spain; <sup>8</sup>Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; <sup>9</sup>Centre for Individualised Infection Medicine (CIIM), Hannover, Germany; <sup>10</sup>Division of Hepatology, Clinic and Polyclinic for Gastroenterology, Hepatology, Infectious Diseases, and Pneumology, University Hospital Leipzig, Leipzig, Germany.

\* Corresponding author.  
Address: University Hospital Leipzig, Department of Internal Medicine, Liebigstraße 18, D-04103 Leipzig, Germany; Tel.: +49 341/97-12200, fax: +49 341/97-12209.  
E-mail address: [Thomas.Berg@medizin.uni-leipzig.de](mailto:Thomas.Berg@medizin.uni-leipzig.de) (T. Berg)



### Box 1. Open questions for liver-related basic/translational research regarding COVID-19.

- Hepatobiliary and gastrointestinal tracts as a hub for viral trafficking via liver and biliary excretion into the gastrointestinal tract
- Influence of immunosuppression on course of COVID-19
- Cirrhosis-associated immune dysfunction and emergence of protective immunity
- Innate and adaptive immune activation or exhaustion in COVID-19 and their impact on chronic liver disease
- Risk of SARS-CoV-2 induced hepatic decompensation/ACLF or graft rejection

ACLF, acute-on-chronic liver failure; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

where liver failure has not been specifically reported, even in the most severe and fatal courses of disease.<sup>1,2</sup> However, signs of liver dysfunction may occur in critically ill patients with COVID-19,<sup>8</sup> as reviewed in.<sup>9,10</sup> Whether patients with cirrhosis and COVID-19 are at increased risk of decompensation or development of acute-on-chronic liver failure (ACLF), as has been shown for influenza infection,<sup>11</sup> remains to be determined. SARS-CoV-2 may also directly infect liver cells as the receptor of the virus, angiotensin-converting enzyme 2 (ACE2),<sup>12</sup> has been shown to be expressed on cholangiocytes,<sup>13,14</sup> which may explain cases of viral shedding into the faeces.<sup>15,16</sup> How far observations from Asian cohorts can be transferred to European populations remains to be determined, but it appears unlikely that SARS-CoV-2 infection causes liver damage to an amount that substantially contributes to the overall disease burden.

Aside from the direct implications of liver disease on the course of COVID-19 or vice versa, there are several additional aspects that require attention. The current pandemic and the amount of available information – including misinformation and rumours – result in uncertainties and concerns among patients but also healthcare providers. While the threat that COVID-19 poses should not be underestimated, it remains important to maintain care of patients with chronic liver disease and to identify potential ways to prioritise care of these patients in times of limited healthcare resources.

### Considerations for patients with chronic liver disease and patients after liver transplantation

The recommendations provided here address the specific characteristics of patients with liver disease and are meant to provide additional guidance for the care of these patients. General recommendations and guidelines with regards to prevention, diagnosis and treatment of COVID-19 from local authorities should be adhered to.

### Outpatient care

The management and surveillance of patients with advanced liver disease and those receiving immunosuppressive treatment is often performed in larger units or centres. These institutions, however, are currently also COVID-19 hotspots, thus, potentially putting outpatients with chronic liver diseases at risk of nosocomial infections. In addition, hospital staffs face challenges such as long working hours and even reduced staffing because of

COVID-19 quarantining. Therefore, several factors have to be considered by hepatologists who provide care for these vulnerable patients. Clearly, prioritisation criteria need to be defined for outpatient contacts. The general and specific recommendations provided here (Fig. 1) cannot comprehensively cover all patient cohorts and are not backed up by datasets. Moreover, the precise management of these patients strongly depends on the local COVID-19 burden. In case of COVID-19 in patients with more advanced chronic liver disease, we recommend admission for inpatient care depending on the presence of certain risk factors, which is discussed in more detail in a separate section.

### Reduction of direct exposure

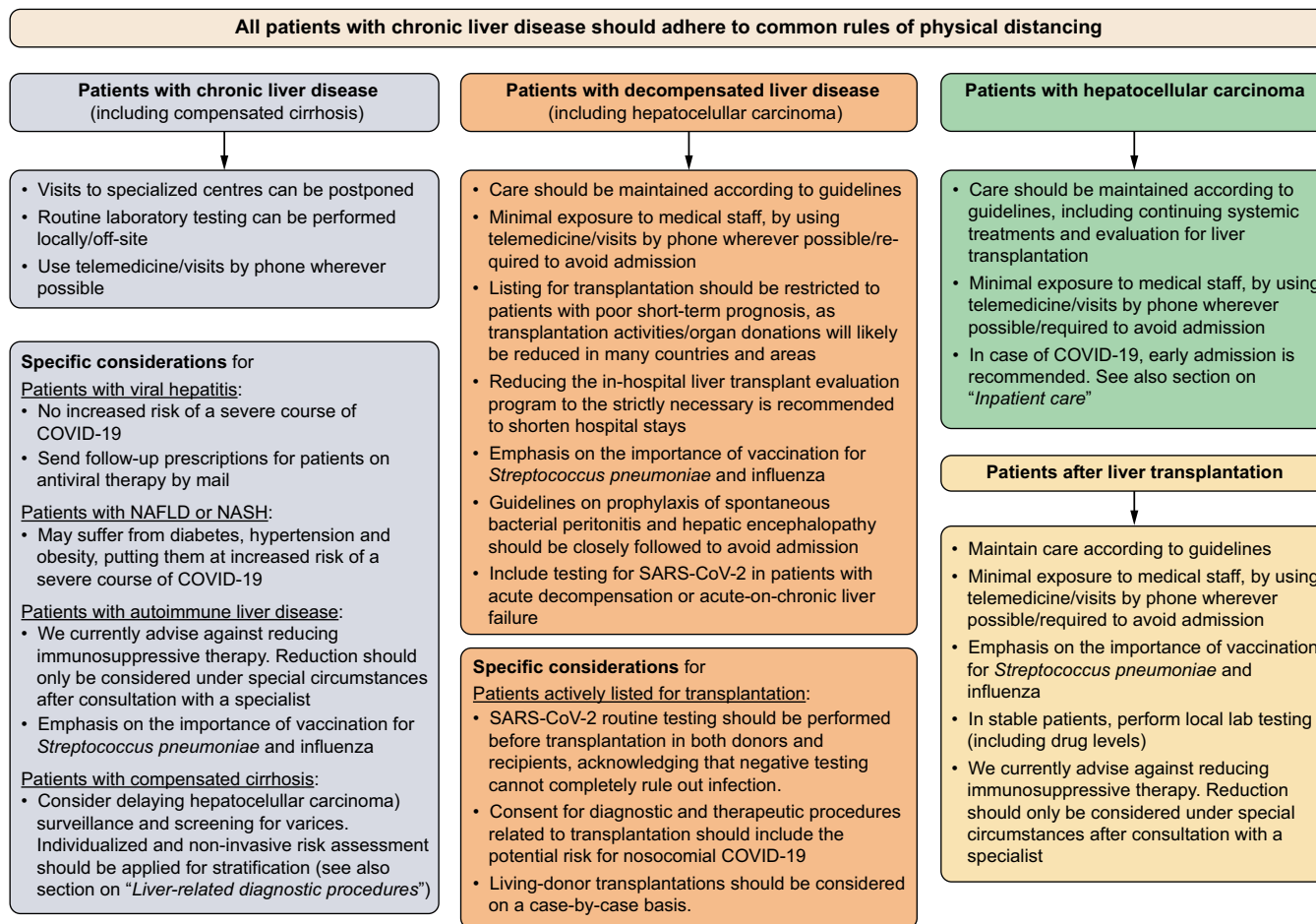
Physical distancing has been suggested and/or officially implemented in multiple countries across the globe to prevent dissemination of SARS-CoV-2. This measure aims to prevent a rapid increase in SARS-CoV-2 infections in the general population with the overall goal of minimising the number of patients with a severe course of COVID-19 at any one time, enabling healthcare providers to maintain medical/intensive care of these patients. At the same time, vulnerable patient cohorts should be protected from individuals with potential SARS-CoV-2 exposure or infection. Thus, in these patients, the benefits of maintaining patient care have to be weighed against the risk of infection. These considerations require adaptation of standard operating procedures for outpatient care, including remodelling of waiting areas to allow sufficient distance between patients, reduction of waiting times and encouraging patients to wait outside wherever possible and eventually be contacted by phone. In addition, exposure to medical staff should be minimised wherever possible.

Face-to-face contact is the basis for the physician-patient relationships and allows physicians to quickly assess the overall condition of the patient. However, due to the amount of individual contacts, physicians are at risk of infection and subsequently also dissemination of the virus. Thus, it seems appropriate to also limit the amount of face-to-face contacts for patients at risk of a more severe course of infection. Technical solutions are available to enable remote physician-patient interactions and their benefits have already been discussed in the context of the COVID-19 pandemic.<sup>17</sup> Health authorities should be urged to equip hospitals with such systems not only to attend to COVID-19 patients who stay in quarantine at home but also to care for patients that need to be protected from a potentially harmful infection and guide them through the pandemic, explaining the future treatment/management strategies/plan and provide advice concerning general prevention measures. The current pandemic clearly underlines the importance of making these technical solutions available to health care providers in order to be better prepared for situations like these in the future.

### Patients with compensated liver disease

#### General considerations

- Visits to specialised centres can be postponed.
- Use telemedicine or visits by phone wherever possible.
- Routine laboratory testing can be performed locally, e.g. through primary care physician, and its frequency needs careful individual risk-benefit considerations.



**Fig. 1. Flow chart for the prioritisation of patient care in patients with chronic liver disease.** The individual management of these patients strongly depends on the local COVID-19 burden and officially implemented rules and regulations. In some countries and areas, maintenance of standard care might not be able and transplantation activities might be reduced. COVID-19, coronavirus disease 2019; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

### Specific considerations

- Chronic viral hepatitis does not appear to increase the risk of a severe course of COVID-19.<sup>1</sup> Use telemedicine/local laboratory testing for follow-up visits in patients under antiviral therapy, send follow-up-prescriptions by mail.
- Patients with non-alcoholic fatty liver disease (NAFLD) or steatohepatitis (NASH) may suffer from metabolic comorbidities such as diabetes, hypertension and obesity putting them at increased risk of a severe course of COVID-19.
- 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 case of severe COVID-19) after consultation of a specialist.
- Emphasis on the importance of vaccination for *Streptococcus pneumoniae* and influenza.
- In patients with compensated cirrhosis, consider delaying hepatocellular carcinoma (HCC) surveillance and screening for varices. Non-invasive risk assessment for the presence of varices should be applied for stratification (thrombocyte count or Baveno VI).<sup>18</sup> See also section on “[liver-related diagnostic procedures](#)”.

### Patients with decompensated liver disease

#### General considerations

- Care should be maintained according to guidelines but consider minimal exposure to medical staff, by using telemedicine/visits by phone wherever possible/required to avoid admission.
- Listing for transplantation should be restricted to 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, as transplantation activities/organ donations will likely be reduced in many countries and areas.
- Reducing the in-hospital liver transplant evaluation program to the strictly necessary is recommended to shorten the in-hospital stay and also reduce the number of consultations in other departments/clinics (i.e. ophthalmologic, dermatologic, dental, neurologic consultations can be done in local outpatient settings).
- Emphasis on the importance of vaccination for *Streptococcus pneumoniae* and influenza.

- Guidelines on prophylaxis of spontaneous bacterial peritonitis and hepatic encephalopathy should be closely followed to prevent decompensation and avoid admission.
- Include testing for SARS-CoV-2 in patients with acute decompensation or ACLF.

#### Specific considerations for patients actively listed for transplantation

- SARS-CoV-2 routine testing should be performed before transplantation in both donors and recipients, acknowledging that negative testing cannot completely rule out infection.
- Consent for diagnostic and therapeutic procedures related to transplantation should include the potential risk of nosocomial COVID-19.
- Living-donor transplantations should be considered on a case-by-case basis.

#### Patients with hepatocellular carcinoma

- Care should be maintained according to guidelines including continuing systemic treatments and evaluation for liver transplantation, but consider minimal exposure to medical staff, by using telemedicine/visits by phone wherever possible/required to avoid admission.
- In case of COVID-19, early admission is recommended. See also section on “inpatient care”.

#### Patients after liver transplantation

- Maintain care according to guidelines, but consider minimal exposure to medical staff, by using telemedicine/visits by phone wherever possible/required to avoid admission.
- Emphasis on the importance of vaccination for *Streptococcus pneumoniae* and influenza.
- In stable patients: perform local laboratory testing (including drug levels).
- We currently 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 of a specialist.<sup>19</sup>

#### Liver-related diagnostic procedures

##### Endoscopy

*Patients without COVID-19:* Depending on available resources, screening for varices by esophagogastroduodenoscopy (EGD) should be reserved for patients at risk of variceal bleeding, such as patients with a history of variceal bleeding or signs of significant portal hypertension (ascites, thrombocyte count <100,000/ $\mu$ l). Non-invasive risk assessment for the presence of varices should be applied for stratification (thrombocyte count or Baveno VI).

Endoscopic retrograde cholangiography (ERC) for dilatation or stent replacement in patients after liver transplantation or patients with primary sclerosing cholangitis should be performed after careful individual risk-benefit considerations, including risk for nosocomial SARS-CoV-2 infection depending on local COVID-19 burden.

*Patients with COVID-19:* Endoscopic procedures are associated with an increased risk of disseminating SARS-CoV-2. During EGD or 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, indications for

endoscopic procedures in patients with COVID-19 should be limited to emergencies such as gastrointestinal bleeding, bacterial cholangitis or other life-threatening conditions.

##### Ultrasound (HCC surveillance)

*Patients without COVID-19:* HCC surveillance can 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, such as patients with elevated alpha-fetoprotein levels, advanced cirrhosis, chronic hepatitis B, NASH/diabetes *etc.*, may be prioritised if resources are limited.

*Patients with COVID-19:* HCC surveillance should be deferred until after recovery.

##### Liver biopsy

*Patients without COVID-19:* Recommendations strongly depend on the local COVID-19 burden and the individual indication for histological assessment.

Biopsy should be deferred in patients with

- NAFLD or chronic viral hepatitis (for grading/staging)
- mildly elevated transaminases (e.g. ALT <3 $\times$  the upper limit of normal [ULN]) of unknown aetiology

Biopsy should be performed in patients with

- strongly elevated transaminases (e.g. ALT >5 $\times$  ULN) of unknown aetiology (in case of suspected autoimmune liver disease, treatment without histological diagnosis can be considered based on individual risk-benefit considerations)
- liver masses suspicious of malignancy

*Patients with COVID-19:* Liver biopsy should be deferred in most patients as

- treatment/care for COVID-19 outweighs diagnosis of co-existing liver disease
- systemic inflammation associated with COVID-19 will obscure aetiology-specific histologic characteristics
- liver biopsy may represent a risk for viral transmission (although the virus has so far not been detected in liver tissue, the expression of its receptor on cholangiocytes suggests that the virus might be present in the liver as well).

#### Collaboration with local health care providers and primary care physicians

The necessity to reduce travel and limit visits to specialised centres is a challenge for liver disease patients and local health care providers alike. In order to facilitate decentralised care for these patients, close collaborations between specialised hepatologists and local health care providers is required. This pertains to several factors such as communication of immunosuppressive target levels in patients after liver transplantation, management of patients with severe ALT elevations of unknown aetiologies and others. Thus, we recommend that specialised centres provide easily accessible contact information for local health care providers to facilitate fast and uncomplicated collaboration for the benefit of patients with liver diseases.

**Table 1. Selected repurposed drugs that have been suggested/discussed for the treatment of COVID-19 and considerations for patients with liver disease or after liver transplantation.**

| Drug  | Mechanism of action, rationale for COVID-19  | Considerations for patients with liver diseases or after liver transplantation  |
|---|--|---|
| Remdesivir  | <ul style="list-style-type: none"> <li>• NUC/viral RNA polymerase inhibitor (completed phase III for Ebola treatment)</li> <li>• Inhibits SARS-CoV-2 <i>in vitro</i><sup>24</sup></li> <li>• Case reports with COVID-19<sup>26</sup></li> </ul>  | <ul style="list-style-type: none"> <li>• No relevant drug-interactions expected<sup>34</sup></li> <li>• No experience in liver cirrhosis but a NUC might be safer than other drug classes based on experience with NUCs in chronic hepatitis B and C</li> <li>• Liver toxicity (↑ALT) possible</li> </ul>   |
| Chloroquine/<br>Hydroxychloroquine <sup>35</sup><br>±<br>azithromycin | <ul style="list-style-type: none"> <li>• Interference with the cellular receptor ACE2<sup>24</sup></li> <li>• Endosomal acidification fusion inhibitor</li> <li>• Generally used for treatment of malaria and amoebiasis</li> <li>• <i>In vitro</i> and <i>in vivo</i> data<sup>32,36</sup></li> </ul>                                     | <ul style="list-style-type: none"> <li>• Exclude G6PD deficiency before application</li> <li>• Drug-interactions with immunosuppressive drugs: close monitoring of drug level is required for cyclosporine, tacrolimus, sirolimus, everolimus<sup>34</sup></li> <li>• Hydroxychloroquine therapy has not been associated with ALT abnormalities and is an extremely rare cause of clinically apparent acute liver injury (LiverTox).</li> </ul>   |
| Lopinavir/ritonavir   | <ul style="list-style-type: none"> <li>• Lopinavir/ritonavir are approved PIs for HIV</li> <li>• <i>In vitro</i> data, experience in patients with SARS, case reports with COVID-19<sup>37</sup></li> <li>• No proven efficacy <i>in vivo</i> in severe COVID-19<sup>28</sup></li> <li>• Many centres have discontinued its use</li> </ul> | <ul style="list-style-type: none"> <li>• Known and well-studied drug-interactions with immunosuppressive drugs. mTOR inhibitors (sirolimus, everolimus) should not be co-administered, close monitoring of drug level are required for calcineurin-inhibitors (cyclosporin, tacrolimus)<sup>34</sup></li> <li>• Data for patients with liver cirrhosis exist<sup>38</sup></li> <li>• The risk of lopinavir-associated hepatotoxicity in patients with very advanced liver disease is low</li> <li>• Based on experience with PIs in HCV, patients with decompensated cirrhosis should not be treated</li> </ul> |
| Tocilizumab   | <ul style="list-style-type: none"> <li>• Humanised mAb targeting interleukin-6 receptor</li> <li>• Treat cytokine release syndrome observed in COVID-19<sup>7</sup></li> </ul>   | <ul style="list-style-type: none"> <li>• ALT elevations are frequent but clinically apparent liver injury with jaundice seem to be rare<sup>39</sup></li> <li>• Patients with decompensated cirrhosis should not be treated</li> <li>• Consider risk of HBV reactivation<sup>40</sup></li> </ul>  |
| Methylprednisolone (steroids)   | <ul style="list-style-type: none"> <li>• Corticosteroids bind nuclear receptors to dampen proinflammatory cytokines</li> <li>• Mostly used in patients with septic shock</li> <li>• Currently NOT recommended by WHO<sup>41</sup></li> </ul>   | <ul style="list-style-type: none"> <li>• The risk of other infections (<i>e.g.</i> SBP) and viral shedding may increase in patents with decompensated liver cirrhosis</li> <li>• Consider antimicrobial prophylaxis</li> <li>• Consider risk of HBV reactivation</li> </ul>   |
| Convalescent plasma<br>Umifenovir (Arbidol)*                          | <ul style="list-style-type: none"> <li>• Case reports with COVID-19<sup>42</sup></li> <li>• May inhibit viral entry into target cells and stimulate the immune response, used to treat influenza in some countries<sup>31</sup></li> </ul>   | <ul style="list-style-type: none"> <li>• No experience in patients with chronic liver disease</li> <li>• Possible drug interactions between arbidol and CYP3A4 inhibitors and inducers<sup>43</sup></li> <li>• Potentially metabolised in liver and intestines in humans. Caution in patients with liver cirrhosis</li> </ul>   |
| Favipiravir/favilavir*  | <ul style="list-style-type: none"> <li>• Guanine analogue, RNA-dependent RNA polymerase (RdRp)- inhibitor, approved for influenza in Japan</li> <li>• Preliminary results from a study with 80 COVID-19 patients<sup>31</sup></li> </ul>   | <ul style="list-style-type: none"> <li>• Metabolised by aldehyde oxidase and xanthine oxidase. CYP450 isoenzymes are not involved in the metabolism</li> <li>• Elevation of ALT and AST possible.</li> <li>• No data in cirrhosis available</li> </ul>  |
| Sofosbuvir*<br>maybe combination<br>with ribavirin                    | <ul style="list-style-type: none"> <li>• Nucleotide analogue, RdRp-inhibitor</li> <li>• Approved for treatment of chronic hepatitis C</li> <li>• <i>In vitro</i> data show binding to SARS-CoV-2 RdRp<sup>44</sup></li> </ul>  | <ul style="list-style-type: none"> <li>• Good experience in patients with chronic hepatitis C including patients with decompensated cirrhosis</li> <li>• For drug-interaction details see<sup>45</sup></li> <li>• Ribavirin may cause severe haemolytic anaemia</li> </ul>  |
| Baricitinib*  | <ul style="list-style-type: none"> <li>• Janus kinase inhibitor, might interrupt endocytosis of the virus and intracellular assembly of virus particles<sup>46</sup></li> <li>• Could affect both inflammation and cellular viral entry</li> </ul>   | <ul style="list-style-type: none"> <li>• Associated with transient and usually mild elevations of ALT<sup>47</sup></li> <li>• Patients with decompensated cirrhosis should not be treated</li> </ul>  |
| Camostat*   | <ul style="list-style-type: none"> <li>• Blocks serine protease TMPRSS2 <i>in vitro</i> which is required for S protein priming<sup>48</sup></li> <li>• Licensed in Japan for treatment of chronic pancreatitis</li> </ul>   | <ul style="list-style-type: none"> <li>• Patients with chronic viral hepatitis and cirrhosis are excluded from clinical trial for chronic pancreatitis.<sup>49</sup></li> <li>• Drug-interactions unknown</li> </ul>  |

(continued on next page)

Table 1 (continued)

| Drug        | Mechanism of action, rationale for COVID-19  | Considerations for patients with liver diseases or after liver transplantation   |
|-------------|--|--|
| Emapalumab* | <ul style="list-style-type: none"> <li>• mAb targeting interferon-gamma</li> <li>• Treat cytokine release syndrome observed in COVID-19<sup>7</sup></li> <li>• Approved for haemophagocytic lymphohistiocytosis</li> <li>• Clinical trial for COVID-19 planned<sup>50</sup></li> </ul> | <ul style="list-style-type: none"> <li>• Associated with mild and transient ALT elevations typically arising a few weeks after start of treatment</li> <li>• Risk of reactivation of tuberculosis, pneumocystis jirovecii, herpes zoster</li> <li>• Risk of HBV reactivation may be lower</li> </ul> |
| Anakinra*   | <ul style="list-style-type: none"> <li>• Interleukin 1 receptor antagonist</li> <li>• Clinical trial for COVID-19 planned<sup>50</sup></li> </ul>  | <ul style="list-style-type: none"> <li>• Minimal hepatic metabolism</li> </ul>   |

This list is not intended to give treatment recommendations. The evidence to use these drugs is low. Multiple RCTs for the above-mentioned drugs and some other drugs are ongoing in patients with SARS-CoV-2 infection.

ACE2, angiotensin-converting enzyme 2; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; NUC, nucleoside analogue; Pls, protease inhibitors; RdRp, RNA-dependent RNA polymerase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

\*These drugs are listed to include the most frequently discussed agents for COVID-19. These drugs may lack clinical efficacy, and some have been considered based on *in vitro* observations or their mode of action.

### Inpatient care

Many patients with chronic liver disease will continue to require inpatient care during the COVID-19 crisis for decompensation, cholangitis, rejection or other complications. General measures to prevent SARS-CoV-2 exposure and infection will be of utmost importance for these patients. Depending on the local infrastructure, implementation of COVID-19-clean wards or hospitals is warranted. However, based on the local COVID-19-burden, a sharp separation of “clean” and “dirty” wards/hospitals may not be sustainable, although recent evidence provides somewhat reassuring data regarding the absence of environmental contamination with SARS-CoV-2 RNA of inanimate surfaces outside patient rooms.<sup>20</sup> Wherever possible, patients with chronic liver disease requiring inpatient care for non-COVID-19 causes should be admitted to COVID-19-clean wards or hospitals. As these institutions may not be able to provide specialised hepatology-care, similar to our recommendations on outpatient care, we recommend that specialised centres provide easily accessible contact information to facilitate immediate hepatology consultations.

However, due to the contagiousness of the virus, patients with underlying liver disease will become infected and will subsequently require inpatient care for COVID-19. With regards to nosocomial-infections, recent observations from Spain that compared patient characteristics between patients with community-acquired influenza and nosocomial-acquired influenza could not detect a significant difference between these cohorts with regards to underlying chronic liver disease.<sup>21</sup> Whether these observations will also hold up in the context of the COVID-19 pandemic remains to be proven. Until further evidence emerges, we recommend that patients with chronic liver disease and COVID-19 are admitted for inpatient care if they have additional risk factors for a more severe COVID-19 course like hypertension, diabetes or obesity, cirrhosis, HCC or a post-transplant status.

### Treatment considerations for COVID-19

Although there are currently no drugs approved for SARS-CoV-2, several repurposed drugs have been tested in recent weeks and many of them are still under investigation (see Table 1).<sup>22</sup> Remdesivir acts as an adenosine-analogue that induces RNA chain termination and was initially developed as an antiviral agent against Ebola.<sup>23</sup> It has recently been shown to inhibit a clinical isolate of SARS-CoV-2 *in vitro*<sup>24</sup> and to reduce disease

severity of the related MERS-CoV-infection in a non-human primate model *in vivo*.<sup>25</sup> In addition, several reports have suggested clinical efficacy in patients suffering from COVID-19.<sup>26,27</sup> Clinical trials are ongoing to further evaluate efficacy in affected patients. Although ritonavir-boosted lopinavir showed some antiviral effect on SARS-CoV-2 *in vitro*, a recently published clinical trial in patients with severe COVID-19 showed no effect *in vivo* compared to no treatment.<sup>28</sup> Other drugs currently under evaluation include chloroquine phosphate or hydroxychloroquine.<sup>29</sup> Chloroquine has shown antiviral efficacy against SARS-CoV-2 *in vitro* through interference with the ACE2-receptor mediated endocytosis and is widely used in the treatment of patients with severe COVID-19 as monotherapy, but also in combination with azithromycin.<sup>24,30–32</sup> The administration of any of these compounds to infected patients will remain an individual decision as efficacy and optimal timing remain to be clarified. However, with regards to patients with chronic liver disease, possible adverse events have to be kept in mind. This is particularly important with respect to drug-interactions in patients with certain immunosuppressive therapies where drug levels of cyclosporine, tacrolimus, sirolimus or everolimus will have to be closely monitored. In addition, patients with impaired liver function are at high risk of drug toxicities, *i.e.* in patients with Child-Pugh B/C cirrhosis. Table 1 summarises some considerations with regards to potential toxicities in these patients. It is also important to stress that all the drugs currently under investigation are not approved for SARS-CoV-2. However, given that early initiation of antiviral therapy is known to blunt the course of influenza, it is reasonable to assume that early treatment initiation might also be beneficial to prevent severe pneumonia in COVID-19. Thus, in patients with liver disease and risk factors for a severe course of the disease, we recommend inclusion into early antiviral treatment programmes or clinical trials that might be active at different centres.

### General considerations for patients with chronic liver disease and COVID-19

- Consider early admission according to the presence of additional risk factors and inclusion in clinical trials and (experimental) antiviral therapy of COVID-19 following local guidelines (see Table 1 for guidance with regards to CLD)
- Prevent acetaminophen overdosing (2–3 g/day is considered safe in patients with cirrhosis without active alcohol consumption<sup>33</sup>)

- Do not administer non-steroidal anti-inflammatory drugs in patients with cirrhosis and portal hypertension<sup>33</sup>
- See also section on “liver-related diagnostic procedures” for recommendations on endoscopy, HCC surveillance and liver biopsy

### Specific considerations for patients with chronic liver disease and COVID-19

- In patients with decompensated cirrhosis, treatment for cirrhosis-associated complications such as portal hypertension,

ascites, hepatic encephalopathy, spontaneous bacterial peritonitis etc. should be continued.

- In patients with HCC, locoregional therapies should be postponed whenever possible and immune-checkpoint inhibitor therapy temporarily withdrawn. The decision on whether to continue (reduced dose) kinase inhibitors in non-severe COVID-19 should be taken on a case-by-case basis.
- In patients after liver transplantation, dose adjustment of calcneurin- and/or mTOR- inhibitors might be required depending on the antiviral therapy initiated (Table 1).

### Abbreviations

ACE2, angiotensin-converting enzyme 2; ACE-I, angiotensin-converting enzyme inhibitor; ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; EGD, esophagogastroduodenoscopy; ERC, endoscopic retrograde cholangiography; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NUC, nucleoside analogue; PIs, protease inhibitors; RdRp, RNA-dependent RNA polymerase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULN, upper limit of normal.

### Conflicts of interest

Dr Berg reports grants, personal fees and non-financial support from Gilead. Dr Boettler reports consultancy fees from Gilead. Dr Cornberg reports personal fees from Gilead. All other authors report no conflicts of interest.

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

### Acknowledgement

We thank Benjamin Maasoumy for critically reviewing the manuscript and providing valuable comments.

### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2020.100113>.

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Author names in bold designate shared co-first authorship

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