

Principles of Care for Patients with Liver Disease During the Coronavirus Disease 2019 (COVID-19) Pandemic: Position Statement of the Saudi Association for the Study of Liver Disease and Transplantation

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In December 2019, a novel coronavirus was identified in patients in Wuhan, China. The virus, subsequently named severe acute respiratory syndrome coronavirus-2, spread worldwide and the disease (coronavirus disease 2019 or COVID-19) was declared a global pandemic by the World Health Organization in March 2020. Older adults and individuals with comorbidities have been reported as being more vulnerable to COVID-19. Patients with chronic liver disease (CLD) have compromised immune function due to cirrhosis and are more susceptible to infection. However, it is unclear if patients with CLD are more vulnerable to COVID-19 and its complications than other populations. The high number of severe cases of COVID-19 has placed an unusual burden on health systems, compromising their capacity to provide the regular care that patients with CLD require. Hence, it is incredibly crucial at this juncture to provide a set of interim recommendations on the management of patients with CLD during the current COVID-19 outbreak.

Coronavirus disease 2019 (COVID-19) is a pulmonary disease caused by a recently identified betacoronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).^{1,2} The genome of SARS-CoV-2 is about 80% identical to that of severe acute respiratory syndrome coronavirus (SARS-CoV) and 50% identical to Middle East respiratory syndrome coronavirus (MERS-CoV).³⁻⁵ COVID-19 has spread rapidly worldwide; in March 2020, the disease was declared a global pandemic by the World Health Organization (WHO), with more than two million people infected as of April 17th, 2020,⁶ of whom over 149,000 have died.⁷ Even though the current reported case-fatality rate (CFR) of COVID-19 is lower than the CFRs of infections caused by SARS-CoV and MERS-CoV,^{6,7} substantially more people have now died as a result of SARS-CoV-2-related complications than from any of the other two viruses.⁸

Despite the fact that the vast majority of patients present with mild or no symptoms, SARS-CoV-2 infection can lead to severe respiratory distress, which can be fatal, particularly in older adults or those with comorbidities.⁶⁻⁹ There is an urgent need to understand which factors can affect the prognosis of the disease: in a summary of 72314 cases reported in China, the CFR calculated for the whole population was 2.3%. However, in those aged 70–79 years and 80 years or older, the CFRs were 8.0% and 14.8%, respectively.¹⁰ Similarly, in patients with comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, or cancer, the CFRs were higher than that of the general population. Whether those with liver disease are at a higher risk of a worse outcome due to COVID-19 remains to be fully understood. Nevertheless, these patients represent a potentially vulnerable population who may require special care.¹¹ The Saudi Association For The Study of Liver Disease and Transplantation (SASLT) is committed to the care of patients with liver disease and decided to urgently initiate a task force to address all medical issues experienced by these patients during the COVID-19 pandemic. In this position statement, we present an updated series of facts and interim recommendations relevant to physicians responsible for the care of patients with liver disease during the ongoing pandemic.

COVID-19 and preexisting liver disease

It is currently unclear if preexisting liver disease is a risk factor for a worse prognosis in patients with COVID-19. In a cohort study from China, 32.1% of individuals who reported a preexisting hepatitis B virus (HBV) infection progressed to a severe form of COVID-19, compared to 15.7% in those who did not.¹² In another study, the opposite was reported; patients with HBV infection were less likely to progress to a severe form of the disease.¹³ It was also observed that levels of transaminases, alkaline phosphatase and gamma-glutamyl transpeptidase tended to be elevated in COVID-19 patients who required care in an intensive care unit and in those presenting with severe disease.^{13,14} Low serum albumin levels are also a predictor of COVID-19 severity.¹⁵

In patients with chronic liver disease (CLD), issues of concern are the following: the viral entry receptor, angiotensin-converting enzyme 2 (ACE2), is expressed in the liver,¹⁶ and its expression is upregulated in the cirrhotic liver.^{17,18} Cholangiocytes, in particular, appear to be the main expressers of ACE2, suggesting that they can be infected by SARS-CoV-2.¹⁹ Previous lessons from SARS-CoV (which also enters host cells via the ACE2 receptor) provide some preliminary in-

sight: SARS-CoV has been detected by polymerase chain reaction in several organs other than the lung, including the liver.^{20,21} Another concern is that SARS-CoV infection could aggravate liver injury in patients with preexisting hepatitis,¹⁵ but the evidence is limited. Importantly, infection with the respiratory virus influenza A was shown to lead to hepatic decompensation in patients with cirrhosis.²² Whether similar phenomenon can also occur in patients with CLD upon infection with SARS-CoV-2 remains to be understood and should not be entirely disregarded as a potential occurrence during the ongoing COVID-19 pandemic. Another possible concern is systemic immunosuppression as a result of cirrhosis. It is relatively well established that cirrhosis impairs the role of the liver in the maintenance of systemic immune homeostasis, as reviewed extensively by Albillos et al.²³ In turn, this can contribute to a worse outcome from bacterial and viral infections in patients with advanced liver disease.^{24,25} This is cause for caution, but not necessarily for alarm, since it is unclear whether immunosuppression is a risk factor for a worse outcome. In fact, it might even prove to be beneficial in some cases, in which mortality might occur primarily due to severe inflammation characterized by a “cytokine storm” event.²⁶

The increasing number of reported cases of COVID-19 in patients with liver disease and the recently established registries for patients with liver diseases who are infected with COVID-19 (SECURE-Cirrhosis²⁷ and COVID-HEP²⁸) should help us understand the interplay between SARS-CoV-2 and the liver. Further, these data will allow us to establish the impact of COVID-19 infection on patients with liver disease and understand four key open questions: First, does COVID-19 have a more severe course and a worse prognosis in patients with preexisting liver conditions? Second, does it lead to decompensation in patients with an impaired liver reserve and compromised immune function as a result of cirrhosis? Third, can the infection lead to direct viral injury of liver or bile duct cells? Fourth, can it promote viral reactivation in patients with chronic viral hepatitis? Until those questions are resolved, it is better to exert maximum caution to minimize the chance of potential exposure of patients with CLD to SARS-CoV-2. Furthermore, the hepatotoxicity of drugs used to treat COVID-19 should be taken into account, particularly in patients with liver disease.

Minimizing exposure in patients who require continual treatment

The care of patients with CLD is traditionally done at clinics of hospitals with a low admission threshold since

the clinical course of these patients tends to deteriorate rapidly. During the ongoing pandemic, many hospitals have to provide care for patients with COVID-19. As a result, healthcare workers (HCW) frequently become infected, and in-person contact with HCWs represents an additional risk of nosocomial infection for patients with CLD. Therefore, two factors must be weighed when deciding on the provision of care for patients with CLD: how beneficial is the patient's visit to clinics for receiving medical care and how significant is the risk of exposure to COVID-19. In turn, this depends on the patient's specific underlying disease and the current number of active COVID-19 cases at the clinic.

Apart from using telemedicine as a substitute for face-to-face medical care for the majority of patients, many clinics and hospitals need to adapt their *modus operandi* to accommodate social distancing requirements. For example, the number of patients in waiting rooms should be minimized and the distance between them maximized. Patient-staff contact must be reduced as much as possible to protect both HCW and patients. Hospital leadership should make telemedicine and remote communication equipment available, ensuring that any measures implemented do not prevent older adults with low technical proficiency from receiving medical care. While teleconferences are of great value, those with a lower degree of computer literacy might not be able to easily take advantage of those systems. Traditional methods (such as a phone) should still be available to ensure the maintenance of patient-physician contact. Patients should also be adequately informed of the implementation of these measures, to avoid confusion and unnecessary trips to clinics and hospitals.

Recommendations for patients with chronic liver disease

All patients

- In patients with CLD, we suggest that all non-urgent medical visits be postponed until the outbreak is under control.
- Routine tests should be held, whenever possible, in locations that are not potential or known COVID-19 hotspots.
- Telemedicine should be adopted as much as it is reasonably possible.
- Monitor and question patients for signs of COVID-19 before admission to the clinic/hospital and promote the use of personal protective equipment (PPE).
- Avoid hosting multiple patients in waiting rooms. Define and enforce strict arrival times and ensure ap-

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propriate distancing between different patients and staff members.

Non-alcoholic fatty liver disease

- While liver disease per se has not been established as a risk factor, it is important to consider that patients with non-alcoholic fatty liver disease often present with metabolic disorders that are risk factors for severe COVID-19, such as obesity, diabetes mellitus, and hypertension.^{29,30} Therefore, patients with non-alcoholic fatty liver disease should be considered as vulnerable patients.

Compensated cirrhosis

- Opt to delay any routine screenings or surveillance procedures. Consider avoiding invasive screening methods for variceal bleeding in low-risk patients, as recommended by the Baveno VI consensus.³¹

Viral hepatitis

- All patients with chronic HBV on antiviral therapy should be maintained on antiviral therapy.
- The treatment of patients with hepatitis C virus (HCV) should not be postponed.
- Provide patients with an extra supply of medications (both as a precaution against an anticipated delay in medication shipping and as a way to reduce the need for travel). Overall, this measure should increase compliance and minimize the interruption of antiviral therapy, reducing the development of viral resistance and improving the outcome of their condition.
- Potential interactions between any drugs used in the treatment of COVID 19 and those used in HBV and HCV therapies should be taken carefully into consideration.
- Certain biological therapy agents such as tocilizumab (interleukin-6 receptor blocker) could be promising in the treatment of COVID-19, according to certain studies.^{32,33} However, they can potentially lead to flare-ups of inactive HBV. This could result in further deterioration of liver function and decompensation in patients with advanced fibrosis or cirrhosis.
- HBV serology (surface antigen, surface antibody, and core antibody) should be performed before starting any biological therapy.

Autoimmune liver disease

- A reduction of immunosuppressive medication is generally discouraged and should only be done in special conditions on a case-by-case basis (e.g. drug-induced cytopenia or superinfection).
- In patients with confirmed or suspected COVID-19,

liver enzymes might be elevated due to infection.¹³

¹⁴ Therefore, we strongly recommend that suspected disease flare is confirmed by biopsy. However, if there is a strong suspicion of autoimmune hepatitis, empiric treatment may be initiated without histological confirmation at the standard treatment dose.

Recommendations for patients with decompensated liver disease

All patients

- All essential care must be maintained, but any medical evaluations and discussions that do not require physician-patient contact should be held remotely. Establish institutional policies to determine which patients must be personally examined and which ones can be examined remotely, and transmit them clearly to patients.
- Before admission, call patients to inquire about recent travel history, contact with confirmed cases of COVID-19, or symptoms of COVID-19. Encourage patients to check their body temperature at home. Follow instructions of the Saudi Center for Disease Control and Prevention for suspected cases based on clinical or epidemiological risk factors.
- Limit the number of visits of patients undergoing evaluation for liver transplant by focusing on those who would benefit more from immediate transplantation (i.e. those with a poor short-term prognosis). Create and enforce protocols to ensure that the admitted patients spend as little time as possible in the institution, without compromising the evaluation.³⁴
- When possible, physically separate areas that can potentially be visited by patients with COVID-19 from "COVID-19-free" areas, and direct patients with liver disease to COVID-19-free areas.
- Advise current patients against traveling, especially to areas with a high incidence of COVID-19.
- Communicate adequately with existing patients and inform them of the procedures to obtain prescription refills or new medications. Hospital pharmacies should implement procedures that allow them to continue supplying medication to patients.
- Encourage vaccination against *Streptococcus pneumoniae* and influenza.
- Provide an Arabic document/notice to the patient (and a companion, if necessary) that justifies the need for travel to the health care facility during the curfew period.
- Test patients for SARS-CoV-2 as a potential cause of new decompensation upon hospital admission.

Patients listed for transplantation

- To minimize the chance of SARS-CoV-2 infection, both donor and recipient should be tested for the presence of the virus and assessed for symptoms. However, due to the potential for false negatives, especially early in the course of the infection, consent forms should mention the possibility of nosocomial SARS-CoV-2 infection.

Hepatocellular carcinoma (HCC)

Locoregional therapy and systemic treatments should be maintained, as any interruption or delay can have severe negative consequences. Evaluation for liver transplantation should be continued, keeping in mind that some transplant programs might experience longer waiting times, especially those involving organ transplants from living donors. In those cases, the centers may modify their current treatment protocols for HCC based on their capacity and priorities. This requires decisions to be made on a case-by-case basis, in consultation with multidisciplinary teams. As for other patients, any medical evaluations and discussions that do not require physician-patient contact should be held remotely.

General recommendations

- Evaluate and discuss with the patient the benefits and risks of delaying HCC surveillance and diagnostic tests.
- Patients with an incidental liver lesion <1 cm have a low risk of disease progression in the short-term. As such, consider avoiding immediate evaluation with further imaging procedures or liver biopsy.
- In those infected (or suspected of infection) with COVID-19, HCC surveillance should be deferred until recovery (for those with confirmed COVID-19) or until the patient has tested negative (for those with suspected disease), as a way to minimize the risk of infection for HCWs.
- Surveillance imaging tests can likely be safely delayed for 1–2 months, on average. If a longer delay is expected, consider using risk models or biomarkers (which should be further validated in future studies) to identify those patients at the highest risk of HCC to prioritize testing.
- For patients with early-stage HCC, consider using locoregional or systemic treatments as a bridging therapy while awaiting liver transplantation.
- Switch patients on systemic therapy for HCC from intravenous drugs to orally administered formulations to decrease the number of hospital visits.

Liver-specific diagnostic procedures

General recommendations

- Postpone all non-urgent procedures. Examples of procedures that should not be postponed include biopsy to diagnose autoimmune liver disease or to exclude graft rejection, follow-up band ligation and endoscopy for patients with variceal bleeding, and transjugular intrahepatic portosystemic shunt. Therefore, each patient should be individually assessed, and the decision should consider the consequences if a procedure or needed treatment is delayed.

Endoscopy

Endoscopic procedures are considered an aerosol-generating procedure, which can generate potentially infectious aerosols if the patient is infected with COVID-19.³⁵ Therefore, these procedures should be carried out under airborne precautions, where all HCWs wear full PPEs including N95 masks and double gloves. A negative pressure room should be used; if not available, a room with a portable high-efficiency particulate air (HEPA) filter is preferred. The number of HCWs present during the procedure should be minimized as a way to avoid transmission from patient to staff (or vice-versa).

- In patients with confirmed or suspected COVID-19, interventions should be limited to medical emergencies such as gastrointestinal bleeding and bacterial cholangitis.
- In patients proven negative for SARS-CoV-2 infection, esophagogastroduodenoscopy should only be performed in those at high risk of variceal bleeding. Other non-invasive methods for assessing the risk of variceal bleeding should be used (Baveno VI consensus).³¹ Endoscopic retrograde cholangiography for stent replacement or dilatation should be decided on a case-by-case basis, considering the risk/benefit of performing the procedure and taking into account the risk of nosocomial infection.

Ultrasound

- In patients proven negative for SARS-CoV-2 infection, the decision to perform HCC surveillance with ultrasound should be made on a case-by-case basis, depending on the results of an individual risk assessment and the availability of resources and medical personnel. Priority should be given to patients presenting with risk factors for HCC such as advanced cirrhosis, elevated alpha-fetoprotein levels, or unexplained decompensation of liver disease.

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Biopsy

- In patients proven negative for SARS-CoV-2 infection, the decision to perform liver biopsies should be made on a case-by-case basis, depending on the results of an individual risk assessment, on the availability of resources and medical personnel, and the indication for histopathological evaluation. Priority should be given to those with very high levels of transaminases of unknown cause and to those with liver masses that might indicate malignancy.
- Liver biopsy can be deferred in patients with stable chronic liver disease or mildly elevated liver enzymes, as the risks of the procedure outweigh the benefits. Several reports suggest that the SARS-CoV-2 viral entry receptor ACE2 is expressed in cholangiocytes,¹⁷⁻¹⁹ so there is a risk of spreading the infection.

Inpatients

We have focused on recommendations applicable to outpatients as a way to minimize the number of liver patients who will be infected with the virus. However, many patients with CLD may require inpatient care during the current outbreak for reasons such as acute decompensation, graft rejection, or other complications.

General recommendations

- Test patients for COVID-19 on admission to the hospital.
- Whenever possible, patients with liver disease should be hospitalized in areas physically separated from COVID-19 patients.
- Since HCWs can potentially spread the virus from infected to non-infected patients, interaction between patients and staff should be minimized. Consider providing patients with tablets or devices that can enable remote communication.
- Conduct medical rounds with as few personnel as possible without compromising the quality of care.
- Discourage in-person multidisciplinary meetings and consultations.
- Limit the number of visits that inpatients may receive.
- Minimize the number of procedures that inpatients are required to undergo; verify if the procedures are essential for diagnostic purposes before requesting them.
- Before discharge, discuss and educate patients on how to follow precautions to avoid infection with SARS-CoV-2, and communicate how to proceed with post-discharge follow-up meetings using telemedicine.

Drugs therapy in patients with COVID-19 and liver disease

SARS-CoV-2 is a highly infectious virus,³⁶ so regardless of preventive measures, many patients with preexisting liver disease will be at a high risk for infection.¹³ While there is no widely accepted treatment, many antiviral drugs and vaccines are currently undergoing clinical trials.³⁷ The pandemic is a rapidly evolving situation, and hundreds of clinical trials are ongoing globally. Since updates are available on an almost daily basis, we recommend following the recommendations present in

the guidelines published by the Infectious Diseases Society of America on the treatment and management of patients with COVID-19.³⁸

Before starting any drug for COVID-19, we recommend checking for potential hepatotoxic effects at "LiverTox"³⁹ and drug interactions at "HEP drug interactions".⁴⁰ In **Table 1**, we have briefly summarized special considerations that apply to patients with CLD on drugs currently being considered in trials for the treatment of COVID-19, along with studies of these drugs in patients with COVID-19.⁴¹⁻⁶³

Table 1. Selected drugs that have been repurposed for the treatment of COVID-19 and special considerations for patients with liver disease.

Drug	Mechanism of action	Special considerations	References
Remdesivir	Nucleotide analog; inhibits viral RNA polymerases	Can raise aminotransferase levels. ⁴¹ No relevant drug interactions expected. ⁴²	41, 43
Lopinavir-ritonavir	Inhibitors of HIV-1 protease and host cytochrome P450 3A4. ⁴⁴	Interacts with immunosuppressive drugs (mTOR and calcineurin inhibitors). ⁴² Low risk of hepatotoxicity in patients with liver disease. ⁴⁵ Avoid using in patients with decompensated cirrhosis.	15, 46-47
Hydroxychloroquine	Inhibits autophagy and lysosomal acidification; ⁴⁸ prevents viral entry <i>in vitro</i> . ⁴⁹	Interacts with immunosuppressive drugs (mTOR and calcineurin inhibitors). ⁴² No conclusive evidence for its efficacy, but has a low-risk profile. ^{50,51} QTc prolongation has been reported. Frequently used in combination with azithromycin. ⁵⁰ Do not use in patients with G6PD deficiency.	48-52
Favipiravir	Influenza virus RdRP inhibitor. ⁵³	Can raise aminotransferase levels. No data are available for patients with cirrhosis.	54
Corticosteroids	Inhibit the production of proinflammatory cytokines. ⁵⁵	Not recommended by the WHO. ⁵⁶ The risk of co-infections might increase in patients with decompensated cirrhosis. Possibility of HBV activation; consider general antimicrobial prophylaxis.	57
Baricitinib	JAK1 and JAK2 inhibitor; also inhibits AAK1; might prevent viral entry. ⁵⁸	Can result in lymphopenia; might negatively affect the outcome of COVID-19. ⁵⁹ Possibility of HBV activation; consider general antimicrobial prophylaxis. Not recommended for those with hepatic impairment.	58-60
Tocilizumab	Interleukin-6-receptor inhibitor; blocks signal transduction and cytokine storm. ^{61,62}	Can cause clinically apparent liver injury with jaundice. Can potentially lead to flare-ups of inactive HBV. Mild or transient worsening of HCV infection also reported. ⁶³	61-63

Abbreviations: AAK1: AP2-associated protein kinase 1; G6PD: glucose-6-phosphate dehydrogenase; HIV: human immunodeficiency virus; JAK: Janus kinase; mTOR: mammalian target of rapamycin; QTc: Corrected QT Interval; RdRP: RNA-dependent RNA polymerase; RNA: Ribonucleic acid.

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