Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Management of patients with liver derangement during the COVID-19 pandemic: an Asia-Pacific position statement

Grace Lai-Hung Wong, Vincent Wai-Sun Wong, Alex Thompson, Jidong Jia, Jinlin Hou, Cosmas Rinaldi Adithya Lesmana, Adityo Susilo, Yasuhito Tanaka, Wah-Kheong Chan, Ed Gane, Arlinking K Ong-Go, Seng-Gee Lim, Sang Hoon Ahn, Ming-Lung Yu, Teerha Piratvisuth, Henry Lik-Yuen Chan, on behalf of the Asia-Pacific Working Group for Liver Derangement during the COVID-19 Pandemic

Lancet Gastroenterol Hepatol 2020; 5: 776–87

Published Online June 22, 2020 https://doi.org/10.1016/S2468-1253(20)30190-4

Department of Medicine and Therapeutics, and Medical Data Analytic Centre, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (G L-H Wong MBChB, Prof V W-S Wong MBChB, Prof H L-Y Chan MD); **Department of Gastroenterology, St Vincent's Hospital Melbourne, University of Melbourne, Melbourne, VIC, Australia** (A Thompson MBBS); **Liver Research Centre, Beijing Friendship Hospital, Capital Medical University, Beijing, China** (Prof J Jia MD); **Hepatology Unit and Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China** (Prof J Hou MD); **Department of Gastroenterology** (C R A Lesmana MD) **and Division of Tropical Medicine and Infection, Department of Internal Medicine** (A Susilo MD), **Dr Cipto Mangunkusumo National General Hospital, Universitas Indonesia, Jakarta, Indonesia; Department of Virology and Liver Unit, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan** (Prof Y Tanaka MD); **Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia** (Prof W-K Chan PhD); **New Zealand Liver Transplant Unit, Auckland City Hospital, University of Auckland, Auckland, New Zealand** (Prof E Gane MD); **Department of Gastroenterology, Metropolitan Medical Center, Manila, Philippines** (A K Ong-Go MD); **Department of Medicine, National University of Singapore, Singapore** (Prof S-G Lim MBBS);

The COVID-19 pandemic has spread rapidly worldwide. It is common to encounter patients with COVID-19 with abnormal liver function, either in the form of hepatitis, cholestasis, or both. The clinical implications of liver derangement might be variable in different clinical scenarios. With growing evidence of its clinical significance, it would be clinically helpful to provide practice recommendations for various common clinical scenarios of liver derangement during the COVID-19 pandemic. The Asia-Pacific Working Group for Liver Derangement during the COVID-19 Pandemic was formed to systematically review the literature with special focus on the clinical management of patients who have been or who are at risk of developing liver derangement during this pandemic. Clinical scenarios covering the use of pharmacological treatment for COVID-19 in the case of liver derangement, and assessment and management of patients with chronic hepatitis B or hepatitis C, non-alcoholic fatty liver disease, liver cirrhosis, and liver transplantation during the pandemic are discussed.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel zoonotic coronavirus that can cause an acute respiratory illness in humans, known as COVID-19.[1] COVID-19 is a global health problem not only because of the rapid human-to-human transmission but also because of its consequences on social life, economics, and infrastructures.[2] SARS-CoV-2 has spread rapidly, resulting in more than 7·27 million infections and 413 000 deaths worldwide as of June 11, 2020.[3] There have been more than 600 000 reported cases in the Asia-Pacific region (including the South-East Asia and Western Pacific regions defined by WHO) as of May 5, 2020.

Abnormal liver function, or liver derangement, either in the form of hepatitis, cholestasis, or both, can be observed in patients with COVID-19. In an early report from China, raised serum alanine aminotransferase (ALT) was reported in 28 (28%) of 99 patients with COVID-19 and increased total bilirubin was reported in 18 (18%).[4] The frequency and severity of liver dysfunction increases with the severity of COVID-19. In early SARS-CoV-2 infection, liver function tests are normal or minimally elevated. Liver histology shows microvascular steatosis, syncytial multinuclear hepatocytes, and mild lobular and portal activity.[5] Electron microscopy shows mitochondrial swelling, endoplasmic reticulum dilatation, glycogen depletion, and impaired cell membranes. These microscopic and ultrastructural features are all co-incident with the direct cytopathic effect of SARS-CoV-2 on the hepatocyte. In the severe acute respiratory syndrome (SARS) epidemic, severe acute respiratory syndrome coronavirus (SARS-CoV) viral particles and positive strand RNA with replicative intermediates were detected within hepatocytes, consistent with hepatocyte infection.[6] Evidence suggests that SARS-CoV-2 also replicates within hepatocytes.[7] Hepatocytes and cholangiocytes express the ACE2 receptor necessary for cell entry.[8] The minimal increase in aminotransferases and absence of marked lobular necroinflammation suggests that liver injury induced by SARS-CoV-2 is mild.

Although severe liver dysfunction has been described in patients with severe COVID-19, it is likely to be caused by other factors such as sepsis-associated cholestasis, ischaemic hepatitis from hypoxaemia and hypotension, and drug-induced liver injury. Many of the drugs being used in severe cases of liver dysfunction are associated with hepatotoxicity, including those used to treat SARS-CoV-2 infection such as remdesivir, lopinavir, and ritonavir. Additionally, exacerbation or reactivation of underlying chronic liver disease must be considered in any patient with chronic viral hepatitis or non-alcoholic fatty liver disease (NAFLD). There is evidence that SARS-CoV-2 might aggravate liver injury in patients with chronic viral hepatitis.[9] Importantly, drug-induced liver injury during the treatment of SARS-CoV-2 infection should not be ignored.

Almost 10% of the estimated 5 billion people living in the Asia-Pacific region have chronic viral hepatitis.[10] The increasing prevalence of NAFLD in the region further increases the probability of coexistence of COVID-19 and liver diseases.[11] Furthermore, inadequate infrastructure and insufficient health-care personnel trained in liver diseases are important issues that also need to be addressed in the Asia-Pacific region. Therefore, chronic liver diseases are prevalent in Asia-Pacific region and it is important to consider the potential impact of COVID-19 on patients with underlying liver disease.[12]

This Rapid Review presents the recommendations of the Asia-Pacific Working Group for Liver Derangement during the COVID-19 Pandemic. This position statement focuses on the clinical management of patients who have been or who are at risk of developing liver derangement during the COVID-19 pandemic and does not cover specific management of patients with COVID-19. Regional hepatology associations have developed position papers to inform physicians on the care of patients with liver disease

during the COVID-19 pandemic.[13–15] These position papers provide general high-level recommendations on institutional arrangement and care principles for patients attending clinic and hospitals. Some recommendations, including telemedicine and decentralisation of care, might not apply in some parts of the Asia-Pacific region. In this position statement, developers from the Working Group formulated a list of questions of discrete clinical scenarios that physicians are facing in their daily practice. The recommendations in this position statement are based on specific clinical scenarios and will supplement other regional position papers on COVID-19.

Methods

This position statement was developed in compliance with the Institute of Medicine, Hong Kong, standards for trustworthy position statement, and uses the Grading of Recommendation Assessment, Development, and Evaluation approach (appendix p 1). In this approach, the quality of evidence (ie, certainty in evidence) is rated as A (high), B (moderate), or C (low) on the basis of the domains of precision, directness, consistency, and risk of bias and publication bias. The Working Group based its recommendations on the quality of evidence, balance of benefits and harms, patients' values and preferences, and clinical context. Recommendations are graded as 1 (strong), which apply to most patients with minimal variation, or as 2 (weak), which apply to most patients whose values and preferences are consistent with the course of action (appendix p 1).

The specific questions and scenarios specified for evaluation by the Working Group, as well as the grading before and after voting, are shown in the appendix (pp 2–5). A methodologist moderated and facilitated the process of question development. Multiple systematic reviews of the literature were searched to support the recommendations in this position statement. Members of the Working Group did a systematic review of the literature on specified domains of interest, thereby allowing them to provide recommendations on different aspects of the clinical assessment and management of patients with COVID-19 and liver diseases. By multiple electronic communications, the Working Group finalised evidence summaries, and the final grading of evidence and recommendations were determined by majority vote. The basis of recommendations are purely on consensus and some of them with low quality or certainty of evidence rated as C are not based on evidence, but are instead based on consensus as the evidence is currently insufficient.

Management of liver derangement in patients with COVID-19

Scenario 1: should off-label pharmacological treatment for COVID-19 be continued in the case of liver derangement?

In patients with abnormal liver function, differential diagnoses include COVID-19 itself, ischaemic hepatitis, sepsis, drug-induced liver injury, and underlying causes of liver disease. In the Asia-Pacific region, where the prevalence of viral hepatitis is high, investigation of abnormal liver function should be tailored to the clinical presentation but should include serological tests for viral hepatitis (statement 1A; table 1). In regions with a low prevalence of viral hepatitis, it is reasonable to monitor liver function panel and to investigate underlying causes of liver disease if liver function tests fail to normalise within a reasonable time frame, arbitrarily from 8 weeks to 12 weeks of diagnosis.

At present, there is no registered drug for the treatment of COVID-19.[16] However, the US Food and Drug Administration issued an emergency use authorisation for the investigational antiviral drug remdesivir for the treatment of suspected or confirmed COVID-19 in hospitalised patients with severe disease on May 1, 2020.[17] Interferons, lopinavir–ritonavir, ribavirin, and chloroquine or hydroxychloroquine are available in most places in the Asia-Pacific region but are registered for other indications; whereas, nucleoside analogues (remdesivir and galidesivir), monoclonal antibodies and interleukin (IL)-6 receptor blockers (eg, tocilizumab), convalescent plasma, hyperimmune γ globulin, or vaccines are not yet approved at the time of writing. Even after approval, the availability of drugs in countries in the Asia-Pacific region is likely to be variable. Although some drugs might appear promising in preclinical studies or early clinical experience, efficacy has not yet been supported in phase 2 and 3 clinical trials. For example, lopinavir–ritonavir have been widely used for the treatment of COVID-19 because of preliminary evidence suggesting therapeutic benefits in patients with SARS.[18] However, the drug did not improve clinical outcomes or increase viral clearance in a randomised controlled trial of 199 patients with SARS-CoV-2 infection and hypoxia.[19] Although COVID-19 treatment is often used in the short term, because COVID-19 is a potentially life-threatening acute illness, the risk–benefit ratio should be considered in the decision-making process. Off-label COVID-19 therapies might be used with caution and close monitoring in patients with abnormal liver function (statement 1B; table 1).

Table 2 lists the drugs that have been used for the treatment of COVID-19 and their associated liver safety. It is important to note that liver derangement might be due to drug-induced liver injury, underlying medical disease, or concomitant medications. In patients who do not have COVID-19, elevation in concentrations of serum ALT or aspartate aminotransferase (AST) has been described in individuals receiving interferon, lopinavir–ritonavir, tocilizumab, or remdesivir.[20–22] Isolated cases of severe liver injury in patients with COVID-19 have also been reported rarely.[23] The drugs, particularly corticosteroids, might also cause indirect liver injury through reactivation of underlying liver diseases such as chronic hepatitis B virus (HBV) infection.[24]

Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea (Prof S H Ahn MD); **Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan** (Prof M-L Yu MD); **and Department of Gastroenterology, NKC Institute of Gastroenterology and Hepatology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand** (T Piratvisuth MD)

Correspondence to:
Prof Henry Lik-Yuen Chan, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China
hlychan@cuhk.edu.hk

See **Online** for appendix

	Recommendation statements	Quality of evidence	Strength of recommendation
1A	Patients with COVID-19 and persistent liver derangement should have standard investigations for liver diseases; the choice of investigations would depend on the clinical presentation and pattern of liver injury but should involve at least serological tests for viral hepatitis	C	1
1B	Patients with abnormal liver function should be closely monitored when using off-label lopinavir–ritonavir, chloroquine, hydroxychloroquine, and tocilizumab, preferably monitored in the setting of clinical trials	C	1
1C	Off-label treatment for COVID-19 should be withheld in the case of moderate-to-severe (ie, category 2–3) liver injury	C	1
2A	Clinicians should test liver function in hospitalised patients with COVID-19	C	1
2B	The optimal interval for liver tests is uncertain; however, it would be reasonable to monitor liver tests twice weekly in patients on potentially hepatotoxic medication, patients with pre-existing liver disease, and more frequently in any patients with abnormal liver function	C	2
3A	Patients with COVID-19 and liver derangement should have investigations for the underlying cause, including screening for common liver diseases (eg, viral hepatitis); there is no evidence to support routine screening for chronic liver diseases in patients with normal liver tests	B	1
3B	Screening for other causes of liver disease might wait until abnormal liver function persists beyond recovery of COVID-19	C	2
4A	If systemic corticosteroids or other potent immunosuppressants (eg, tocilizumab) are used as COVID-19 therapy for 7 days or longer, screening for HBsAg is recommended; antiviral therapy for HBV should be initiated to avoid HBV reactivation and hepatitis flare in patients with known HBV infection	B	1
4B	Antiviral therapy for HBV newly diagnosed at the time of presentation with COVID-19 should be started according to the existing international guidelines	A	1
4C	Concomitant use of tenofovir disoproxil fumarate or tenofovir alafenamide with lopinavir–ritonavir is relatively contraindicated as drug concentration of tenofovir might be increased; tenofovir might be temporarily switched to entecavir during the use of lopinavir–ritonavir in the absence of entecavir resistance	B	1
4D	Do not stop oral nucleoside antiviral therapy for HBV at the time of COVID-19 to avoid the risk of HBV reactivation and clinical flare	B	1
5A	Concomitant use of protease inhibitor-containing DAA regimens for hepatitis C virus with lopinavir–ritonavir is contraindicated	A	1
5B	DAAs should be continued if being taken at the time of COVID-19 diagnosis, unless drug–drug interactions would be problematic or patients are in critical condition	B	1
5C	If clinically significant drug–drug interactions with COVID-19 therapies are present, DAAs should be deferred until after COVID-19	A	1
5D	Drug–drug interactions between some new COVID-19 therapies and DAAs should be closely monitored as data are scarce	C	1
6A	Have heightened awareness of adverse clinical outcomes in patients with NAFLD who have COVID-19, especially if they have diabetes	C	1
6B	Blood pressure and glycaemic control should be monitored and managed in patients with NAFLD who have COVID-19	C	2
7A	Prioritise resources to continue usual surveillance imaging (with or without tumour markers) in patients who need hepatocellular carcinoma surveillance the most (eg, patients with cirrhosis or high hepatocellular carcinoma risk scores)	B	1
7B	An arbitrary delay of 3 months in patients with relatively low risk of hepatocellular carcinoma is reasonable and might be necessary if COVID-19 outbreaks are ongoing in the region	C	2
8A	Patients with hepatocellular carcinoma who have COVID-19 should have their hepatocellular carcinoma treatment deferred until after recovery from COVID-19	C	2
8B	Bridging transarterial chemoembolisation, radiofrequency ablation, or systemic chemotherapy might be considered in selected patients with hepatocellular carcinoma who have COVID-19 when surgical resection is deferred	C	2
9A	Postponement of elective upper gastrointestinal endoscopic examination for variceal screening in patients with no history of gastrointestinal bleeding until a COVID-19 outbreak is under control is reasonable, and might be necessary if COVID-19 outbreaks are ongoing in the region	C	1
9B	Non-invasive tools (eg, Baveno VI criteria, platelet-to-liver stiffness measurement ratio, liver and spleen stiffness measurement) might be used to identify patients who are at high risk of having clinically significant varices	B	1
9C	Endoscopic eradication of oesophageal varices should be done following a variceal bleed	A	1
9D	In the case that emergency or urgent upper endoscopy is warranted in suspected or confirmed cases of COVID-19, it should be done under a negative-pressure room when available with strict isolation precautions, and all endoscopy personnel should wear appropriate personal protective equipment, including N95 respirator and waterproof protective gown	B	1
10A	Reduce the number of patients coming to transplantation clinic per session for assessment; only assess patients with hepatocellular carcinoma or patients with high MELD scores who are likely to benefit from immediate liver transplantation listing	C	1
10B	Telehealth should be available to most transplantation centres	C	2
10C	Clear instruction to patients awaiting liver transplantation to maintain physical distancing and to not travel during the COVID-19 pandemic	B	1
10D	All potential donors (cadaveric and live donors) and recipients should be tested for SARS-CoV-2 RNA and transplantation will only proceed with negative donors to negative recipients	B	1
11A	Check for any drug–drug interactions if COVID-19 therapies are needed in patients after transplantation	A	1
11B	It is not necessary to reduce immunosuppression or stop mycophenolate mofetil for asymptomatic patients after transplantation	B	1
11C	Patients or their caregivers with COVID-19 symptoms should not visit the liver transplantation clinic	B	1
11D	All patients after transplantation should avoid an unnecessary outpatient visit; an arbitrary delay of 3 months is reasonable and might be necessary if COVID-19 outbreaks are ongoing in the region	B	1

(Table 1 continues on next page)

	Recommendation statements	Quality of evidence	Strength of recommendation
(Continued from previous page)			
11E	Emphasise well known prevention measures to patient after transplantation: frequent hand washing, cleaning frequently touched surfaces, staying away from large crowds, staying away from individuals who are ill, etc.	B	1
12A	In patients with known decompensated cirrhosis, decisions about intensive care unit support should be made on a case-by-case basis, taking into account baseline liver function, previous episodes of liver decompensation, and transplantation eligibility	C	2
12B	Spontaneous bacterial peritonitis in patients with COVID-19 and decompensated cirrhosis should be treated with broad-spectrum antibiotics with no drug–drug interactions with the COVID-19 therapies	C	2

Quality of evidence (ie, certainty in evidence) is rated as high (A), moderate (B), or low (C) on the basis of the domains of precision, directness, consistency, and risk of bias and publication bias. Strength of recommendations are graded as strong (1), which apply to most patients with minimal variation, or as weak (2), which apply to most patients whose values and preferences are consistent with the course of action. HBV=hepatitis B virus. DAA=direct-acting antiviral. NAFLD=non-alcoholic fatty liver disease.

Table 1: **Recommendation statements on the management of patients with liver derangement during COVID-19 pandemic**

Because liver derangement is common in COVID-19, the difficulty in establishing the diagnosis of drug-induced liver injury poses a clinical dilemma. The Working Group suggest following established guidelines to manage suspected cases of drug-induced liver injury.[25] In the case of elevated ALT, AST, or both, standard investigations should be done to rule out other liver diseases such as acute or chronic viral hepatitis and autoimmune liver diseases. For the sake of infection control, clinicians should avoid sending patients with COVID-19 to another area or facility for liver imaging, unless there are clinical symptoms and signs of biliary pathology. Bedside ultrasonography can be done to look for cirrhosis, hepatocellular carcinoma, and biliary pathology. If bedside ultrasonography does not provide high-quality imaging, proper imaging at the radiology department with adequate infection control could be arranged in an emergency situation (eg, ruptured hepatocellular carcinoma, acute cholangitis, or cholecystitis). Routine FibroScan examination should be deferred. The severity of liver injury might be classified according to the recommendations by the US Drug-Induced Liver Injury Network or International Drug-Induced Liver Injury Expert Working Group (appendix p 6).[9,26] As the benefits of off-label treatments are uncertain, in the case of moderate-to-severe liver injury (ie, ALT >5 times upper limit of normal [ULN] or alkaline phosphatase [ALP] >2 times ULN, and total bilirubin >2 times ULN or presence of coagulopathy or clinical decompensation) it would be reasonable to stop the drug (statement 1C; table 1). If the treatment for COVID-19 is given in a clinical trial, the management of liver derangement should follow the study protocol.

Scenario 2: should all patients with COVID-19 have liver function checked routinely?

Liver derangement is common in patients with COVID-19. It is reported that 16–53% of patients had elevated ALT and AST during the course of illness (appendix p 7).[4,27–32] In general, patients with liver derangement tend to have severe COVID-19. It is important to note that clinically significant abnormalities of liver function tests with hepatic decompensation are rare.

There are different reasons for liver derangement in COVID-19. Although SARS-CoV-2 binds ACE2 with high affinity and ACE2 is present in the biliary system,[33] the normal concentrations of serum alkaline phosphatase in most patients with COVID-19 suggests that this is not an important mechanism underlying the association with liver derangement.

By contrast, most cases of liver derangement will reflect either underlying chronic liver disease, sepsis-related cholestasis and inflammatory changes, or hepatotoxicity from concomitant medications. Because liver derangement might contraindicate particular medications, it is necessary to monitor liver tests in hospitalised patients with COVID-19, although the optimal interval for liver tests is unknown (statements 2A and 2B; table 1). It is important to note that the current data on liver derangement in patients with COVID-19 were derived from cohorts of hospitalised patients. The frequency and severity of liver injury in asymptomatic patients or in individuals with mild symptoms is unknown.

Scenario 3: should all patients with COVID-19 be routinely screened for common chronic liver diseases on the basis of local prevalence?

Asia has a high prevalence of chronic hepatitis B, chronic hepatitis C, alcohol-related liver disease, and NAFLD.[10,34,35] In the case of abnormal liver function, investigations for acute and chronic liver diseases according to the clinical presentation and local epidemiology would clarify the clinical picture and facilitate management. In some cases, notably chronic viral hepatitis, specific treatment of underlying liver disease might also improve liver tests. Routine testing for HBV was recommended in all individuals born in the Asia-Pacific region before the introduction of universal neonatal vaccination. Routine testing for HCV was recommended in individuals with a history of injecting drug use, blood transfusion, or organ transplantation before the introduction of donor screening. Otherwise, there is no evidence to support

	Risk of liver injury	Safety in hepatic impairment
Immunomodulators		
Interferon alfa	ALT might increase to >2 times ULN in >25% of patients with chronic viral hepatitis; jaundice and decompensation rare but reported	Contraindicated in decompensated liver disease
Interferon beta	ALT might increase to >3 times ULN in 10% of patients; jaundice and decompensation rare but reported	Not specified
Corticosteroids	Risk of HBV reactivation; could trigger or worsen non-alcoholic steatohepatitis	No evidence of increased toxicity in hepatic impairment
Antivirals		
Favipiravir	<10% of patients might have self-limiting ALT elevation	Not specified
Lopinavir–ritonavir	ALT might increase to >5 times ULN in 5% of patients; jaundice and decompensation rare but reported	Increased risk of hepatotoxicity in patients with chronic liver diseases, ALT elevation, or hepatic decompensation
Remdesivir	Mild ALT elevation to >2 times ULN; mild-to-moderate AST elevation to >3–4 times ULN	Not specified
Ribavirin	ALT elevation uncommon when used in isolation	No evidence of increased toxicity in hepatic impairment
Nitazoxanide	Uncommon	Safety in hepatic impairment not studied
Antimalarials		
Chloroquine	ALT elevation in <5% of patients	Not specified but chloroquine is known to concentrate in the liver; should be used with caution in patients with hepatic disease or alcohol misuse, or in conjunction with known hepatotoxic drugs
Hydroxychloroquine	ALT elevation in <5% of patients	Should be used with caution in patients with hepatic disease or alcohol misuse, or in conjunction with known hepatotoxic drugs
Monoclonal antibody		
Tocilizumab	ALT elevation in >20% of patients; ALT increase to >5 times ULN in <1% of patients	Safety in patients with hepatic impairment and cytokine release syndrome has not been formally studied

ALT=alanine aminotransferase. ULN=upper limit of normal. HBV=hepatitis B virus. AST=aspartate aminotransferase.

Table 2: **Drugs used for the treatment of COVID-19 and their liver safety**

routine screening for chronic liver diseases in patients with persistently normal liver tests (statement 3A; table 1).

Causes of liver disease other than chronic viral hepatitis and NAFLD might only account for less than 10% of chronic liver diseases in the region.[11] Therefore, screening for uncommon causes not previously diagnosed (eg, autoimmune hepatitis, haemochromatosis, Wilson's disease, etc) might be done only if the abnormal liver function persists beyond recovery of COVID-19 (statement 3B; table 1).

Management of patients with underlying liver disease

Scenario 4: should patients with COVID-19 and chronic HBV infection have antiviral therapy for HBV that started when liver derangement developed? What are the risks of drug–drug interactions of medications for chronic liver diseases and the pharmacological treatment for COVID-19?

Patients with chronic liver disease might be susceptible to liver damage from some coronavirus infections, including Middle East respiratory syndrome (MERS) and SARS.[36] It is not clear whether such patients are also susceptible to liver damage from SARS-CoV-2 infection. Some studies from China report a lower prevalence of HBV infection in patients hospitalised with COVID-19 than in the general population.[28] In patients with chronic HBV infection who develop SARS-CoV-2 superinfection, elevation of serum aminotransferase concentrations might be secondary to chronic hepatitis B.[4] Systemic high-dose corticosteroid and tocilizumab have been advocated for treatment of patients with COVID-19 who are critically ill.[29,37] This regimen might cause HBV reactivation, hepatitis flare, and acute liver failure in patients with chronic HBV infection. Therefore, screening for HBsAg is recommended, and antiviral prophylaxis with nucleoside analogues is recommended in all patients with severe COVID-19 who test positive for HBsAg during corticosteroid therapy (statement 4A; table 1).[38]

It would be reasonable to initiate antiviral therapy for HBV newly diagnosed at the time of presentation with COVID-19 when patients fulfil the treatment criteria recommended by international guidelines—namely, HBV DNA above 2000 IU/mL, ALT more than ULN (European Association for the Study of the Liver recommendations)[39] or 2 times ULN (Asian Pacific Association for the Study of Liver and American Association for the Study of Liver Diseases recommendations),[40,41] or compensated or decompensated cirrhosis with detectable HBV DNA (statement 4B; table 1).

Current first-line nucleoside analogues have excellent long-term safety.[42] Hence, if patients do not exactly fulfil the treatment criteria or are in the grey zone (eg, ALT mildly elevated to 1–2 times ULN), it is reasonable to start antiviral therapy as long as the patients accept

	Elbasvir–grazoprevir	Glecaprevir–pibrentasvir	Sofosbuvir–velpatasvir	Sofosbuvir–velpatasvir–voxilaprevir	Sofosbuvir–daclatasvir	Tenofovir disoproxil fumarate	Tenofovir alafenamide	Entecavir
Immunomodulators								
Interferon alfa	NA	NA	NA	NA	No clinically significant effect	NA	NA	No clinically significant effect
Interferon beta	NA	NA	NA	NA	NA	NA	NA	NA
Corticosteroids	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect
Antivirals								
Favipiravir	NA	NA	NA	NA	NA	NA	NA	NA
Lopinavir–ritonavir	Potentially increased exposure of the comedication; contraindicated	Potentially increased exposure of the comedication; contraindicated	No clinically significant effect	Potentially increased exposure of the comedication; contraindicated	No clinically significant effect	Potentially increased exposure of the comedication	Potentially increased exposure of the comedication	No clinically significant effect
Remdesivir	NA	NA	NA	NA	NA	NA	NA	NA
Ribavirin	No clinically significant effect	No clinically significant effect	No clinically significant effect	NA	No clinically significant effect	NA	NA	No clinically significant effect
Nitazoxanide	NA	NA	NA	NA	NA	NA	NA	NA
Antimalarials								
Chloroquine	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect
Hydroxychloroquine	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect
Monoclonal antibody								
Toclizumab	NA	NA	NA	NA	NA	NA	NA	NA

NA=not available.

Table 3: **Potential drug–drug interactions between COVID-19 therapies and direct-acting antiviral therapy for the treatment of chronic hepatitis C or oral nucleoside analogues for the treatment of chronic hepatitis B**

long-term treatment. Drug–drug interactions might occur between agents used to treat COVID-19 and treatments for HBV. It would be advisable to check the potential drug–drug interactions with reliable online platforms (eg, the Liverpool Drug Interaction Group).

In general, there are no major drug–drug interactions between the therapeutic options for COVID-19 and nucleoside analogues for HBV that lead to absolute contraindication. Coadministration of lopinavir–ritonavir and tenofovir disoproxil fumarate might increase the concentration of tenofovir by 32–51%, whereas coadministration of lopinavir–ritonavir and tenofovir alafenamide might increase the concentration of tenofovir by 275–316%.[43] Therefore, there might be increased risk of renal impairment. No dose adjustment of tenofovir disoproxil fumarate or tenofovir alafenamide fumarate is recommended, but close monitoring of renal function and for adverse reactions associated with tenofovir is required. Alternately, tenofovir disoproxil fumarate or tenofovir alafenamide fumarate might be switched to entecavir during use of lopinavir–ritonavir (statement 4C; table 1).

Virological or biochemical relapse occur in a substantial proportion of patients with chronic hepatitis B after stopping oral antiviral drugs.[44,45] Given that stopping nucleoside analogues might lead to HBV reactivation and clinical flare,[46] it is not advisable to halt such treatment in patients with COVID-19 (statement 4D; table 1).

Scenario 5: what are the potential drug–drug interactions between direct-acting antiviral (DAA) therapy for chronic HCV infection and pharmacological treatment for COVID-19?

Table 3 summarises the drug–drug interactions between COVID-19 therapies and DAAs. Concomitant use of protease inhibitor-containing DAA regimens (elbasvir–grazoprevir, glecaprevir–pibrentasvir, and sofosbuvir–velpatasvir–voxilaprevir) with lopinavir–ritonavir might increase the drug concentrations of protease inhibitor and, hence, risk of ALT elevations because lopinavir is a potent OATP1B (SLCO1B1) inhibitor. Therefore, concomitant use of these three DAA regimens with lopinavir–ritonavir is contraindicated (statement 5A; table 1). Use of chloroquine, hydroxychloroquine, and ribavirin is generally safe as no obvious drug–drug interactions have been reported.

As most COVID-19 therapies do not have considerable drug–drug interactions with DAAs, DAAs should be continued to maximise the sustained virological response rate (statement 5B; table 1). Premature cessation of DAA therapy might reduce this rate from nearly 100% to 74%.[47]

For more on the **Liverpool Drug Interaction Group** see https://www.covid19-druginteractions.org

Any use of COVID-19 therapies in patients who are receiving DAAs should be closely monitored for potential adverse events. Because hepatitis flare related to HCV following DAA termination is very rare,[48] DAA might be withheld or terminated prematurely if there are problematic drug–drug interactions, or if patients are in critical condition (eg, under positive pressure ventilation or intubated) (statement 5C; table 1).

Data for some new COVID-19 therapies are insufficient, either because the therapies are relatively new (eg, remdesivir or tocilizumab), or because there are no studies of concomitant use of DAAs in combination with existing therapies (eg, interferon). As such, their use in patients also receiving DAAs should be closely monitored (statement 5D; table 1).

Scenario 6: what are the precautions and treatments recommended for patients with NAFLD?

Patients with NAFLD might have metabolic comorbidities such as type 2 diabetes, hypertension, and obesity, putting them at increased risk of a severe course of COVID-19 (statement 6A; table 1). Although studies specifically looking into the clinical course of COVID-19 in patients with NAFLD are pending, diabetes has been repeatedly found to be associated with admission to the intensive care unit, mechanical ventilation, or death.[28] A study from China reporting use of CT scan showed that fatty liver was associated with increased risk of severe and critical illness among patients with COVID-19 aged younger than 60 years.[49] Furthermore, patients with NAFLD might be more susceptible to drug-induced liver injury.[26]

Both hyperglycaemia and hypoglycaemia have been reported in patients with diabetes diagnosed with COVID-19.[50] Although the optimal amount of glycaemic control in patients with critical COVID-19 is a matter of debate, it would be prudent to avoid hypoglycaemia and severe hyperglycaemia as they have been associated with inhospital mortality. On the basis of existing data, it is reasonable to aim for a blood glucose target of 10 mmol/L (180 mg/dL).[51] Additionally, although patients with NAFLD commonly have hypertension, shock can occur in patients with severe COVID-19. Monitoring and timely adjustment of medications for these metabolic disorders are likely to reduce the risk of adverse outcomes (statement 6B; table 1).

Scenario 7: how should hepatocellular carcinoma surveillance be done during the COVID-19 pandemic?

Hepatocellular carcinoma is the fifth most common cancer in men and the ninth most common in women worldwide.[52] This type of cancer has a high mortality rate and represents the third most frequent cause of death from cancer globally (782 000 deaths in 2018).[52] Regular surveillance can facilitate early detection of hepatocellular carcinoma that is still manageable by curative treatment, leading to improved survival.[53] As resources are scarce in the COVID-19 pandemic, in terms of staffing and scanning sessions, resources should be prioritised to continue usual surveillance imaging in patients who are most in need of hepatocellular carcinoma surveillance (statement 7A; table 1).

However, there should be a balance between the risk of being infected with SARS-CoV-2 and the risk of hepatocellular carcinoma while attending facilities for hepatocellular carcinoma surveillance. Efforts should be made to minimise risk of COVID-19 exposure; for example, community-based radiology is recommended where available to reduce the risk of iatrogenic exposure. In hospitals or regions with high prevalence of COVID-19, it is reasonable to delay planned hepatocellular carcinoma screening by 3 months because, although hepatocellular carcinoma surveillance every 6 months is recommended, hepatocellular carcinoma surveillance every year also provides benefits with no difference in overall survival.[54] Furthermore, because of the shortage of health-care resources and staffing, some non-urgent health-care services might be cancelled or delayed to facilitate reallocation to urgent services during the COVID-19 pandemic.[55] Therefore, it would be reasonable and necessary to have an arbitrary delay, probably around 3–6 months, if there is substantial community transmission of SARS-CoV-2 in the region (statement 7B; table 1).

Scenario 8: how should patients with hepatocellular carcinoma be managed during the COVID-19 pandemic?

Detailed discussions about hepatocellular carcinoma management during the COVID-19 pandemic have been discussed by various oncology societies.[56,57] Because most patients with COVID-19 recover within 3–4 weeks,[28] it would be reasonable to defer treatment of hepatocellular carcinoma for a few weeks after the recovery of COVID-19 (statement 8A; table 1).

Among the various treatment methods for hepatocellular carcinoma, surgical resection would be affected the most during the COVID-19 pandemic. On one hand, the demand to expand ventilation capacity for patients with COVID-19 has resulted in a shortage of anaesthetists to support surgery and other procedures such as ablation, which require a general anaesthetic. On the other hand, spreading SARS-CoV-2 aerosol by general anaesthesia in patients with confirmed or undiagnosed COVID-19 might pose a risk to health-care personnel in the operating theatre. Bridging therapy with transarterial chemoembolisation, radiofrequency ablation, or systemic chemotherapy might be offered in place of potentially curative interventions (statement 8B; table 1). Coupling this therapy with close monitoring, such as imaging and α-fetoprotein, should be used to reduce the risk of patients progressing beyond criteria for transplantation, resection, or ablation.

Scenario 9: how should variceal screening be done during the COVID-19 pandemic?

During the COVID-19 pandemic, various groups have advocated to defer non-urgent, elective endoscopic

examinations.[58,59] Upper gastrointestinal endoscopy is likely to be a high-risk procedure because respiratory and gastric secretions might contain high viral loads of SARS-CoV-2. Upper gastrointestinal endoscopy can induce aerosol spreading of COVID-19 due to blowing air and suction through the nose and throat. However, variceal bleeding is a potentially life-threatening complication in patients with liver cirrhosis.[60] Patient outcome would be much poorer if patients developed variceal bleeding and presented as an endoscopic emergency, compared with elective prophylactic band ligation of varices.[61] Similar to hepatocellular carcinoma surveillance, there should be a balance between the risk of variceal bleeding and the risk of getting COVID-19 during the process of variceal surveillance. Furthermore, the risk of infecting health-care personnel in the endoscopy suite, nosocomial outbreaks, and short supply of personal protective equipment should all be considered. Hence, it would be reasonable and necessary to have an arbitrary delay, probably up to 3 months, if COVID-19 outbreaks are ongoing in the region. We recommend that elective upper gastrointestinal endoscopic examination for variceal screening is postponed in patients with no history of gastrointestinal bleeding until the COVID-19 outbreak is under control, and postponement might be necessary if COVID-19 outbreaks are ongoing in the region (statement 9A; table 1).

To reduce the risk of nosocomial outbreaks and usage of personal protective equipment, non-invasive assessments such as Baveno VI criteria,[62] platelet-to-liver stiffness measurement ratio,[63] liver stiffness measurement, and spleen stiffness measurement with transient elastography have been widely studied and found to have good predictive value to identify patients who have clinically significant varices[64] and who are at risk of future variceal bleeding (statement 9B; table 1).[65] Patients with cirrhosis might first undergo transient elastography examination. Such a strategy might be able to reduce the need for at least 50% of endoscopic examinations,[38,62] thus saving many sets of personal protective equipment and reducing the risk of infecting endoscopy personnel.

Endoscopic eradication of oesophageal varices should be done following a variceal bleed (statement 9C; table 1). Although variceal eradication would usually last for 6–12 months after repeated band ligation, oesophageal variceal recurrence after variceal eradication might occur at a median time of 13·4 months.[66] Prophylactic coverage of non-selective β blockers for patients at high risk might be an alternative if screening cannot be arranged.[67]

For patients with suspected, probable, or confirmed COVID-19, endoscopy should only be done for emergency or urgent indications, with strict isolation precautions and ideally in a negative-pressure room (statement 9D; table 1). As some endoscopy units might not have a negative-pressure room, the procedure can be done in a venue outside of the endoscopy centre (eg, with negative pressure in the operation theatre or in a room with improved ventilation).[58]

Scenario 10: what are the special arrangements and precautions in patients needing liver transplantation during the COVID-19 pandemic?

The well established risk factors of severe illness among patients with COVID-19 include individuals aged older than 60 years with advanced frailty.[68] Other comorbidities associated with worse outcome include congestive heart failure, chronic lung disease, diabetes, hypertension, renal failure, and liver failure. Patients with either acute liver failure or decompensated cirrhosis have a poor outcome following SARS-CoV-2 infection.[9] However, it is not yet known whether recipients of liver transplant without comorbidities are at greater risk of developing severe COVID-19 than are non-transplant patients. Early reports have highlighted the importance of paying attention to long-term liver transplant patients with metabolic comorbidities.[69,70] Immunosuppression per se does not appear to affect the natural history of SARS-CoV-2 infection. Theoretically, immunosuppression could prevent progression to COVID-19 through cytokine downregulation. Steroids and hydroxychloroquine have been used in the most critically ill patients with COVID-19 in intensive care, albeit with minimal success because these patients often have irreversible sepsis or multiorgan failure. To reduce the risk of COVID-19 in patients with advanced liver disease, priority should be given to individuals who need liver transplant urgently—namely, patients with hepatocellular carcinoma or high MELD scores (statement 10A; table 1).[71]

Telehealth home monitoring has been found to be feasible and useful in recipients of liver transplant;[72] therefore, it should be available to most transplantation centres and expanded to patients before transplantation if telehealth facilities are available in some parts of the Asia-Pacific region (statement 10B; table 1).[73]

Considering that SARS-CoV-2 can be transmitted from asymptomatic individuals, including children, patients awaiting liver transplantation should strictly adopt physical distancing or not travel during the COVID-19 outbreak (statement 10C; table 1).[74]

Both organ donors and recipients might be at risk of incubating asymptomatic or active COVID-19 through contact with a patient who has had the infection or by community and hospital exposure during the outbreak.[75] Unrecognised COVID-19 in recipients of organ donation considerably increases the risk of severe immune suppression and infection after transplantation, which might lead to multisystem organ damage or death.[76] The donor with unidentified SARS-CoV-2 infection might also spread the virus to multiple recipients. Patients who develop COVID-19 after transplantation might have prolonged fever, lymphopenia, poor recovery of liver function, and prolonged detectability of SARS-CoV-2.[77] Thus, strict screening guidance for recipients and donors of organ transplants needs to be developed to help to reduce further transmission (statement 10D; table 1).

	Anti-thymocyte globulin	Azathioprine	Belatacept	Ciclosporin	Mycophenolate mofetil	Sirolimus	Tacrolimus
Immunomodulators							
Interferon alfa	NA	Potentially increased exposure of the comedication	NA	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect
Interferon beta	NA	Potentially increased exposure of the comedication	NA	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect
Antivirals							
Favipiravir	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect
Lopinavir–ritonavir	No clinically significant effect	No clinically significant effect	No clinically significant effect	Potentially increased exposure of the comedication	Potentially increased exposure of the comedication; potentially decreased exposure of the comedication	Potentially increased exposure of the comedication; contraindicated	Potentially increased exposure of the comedication
Remdesivir	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect
Ribavirin	No clinically significant effect	Potentially increased exposure of the comedication	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect
Nitazoxanide	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect	No clinically significant effect
Antimalarials							
Chloroquine	No clinically significant effect	No clinically significant effect	No clinically significant effect	Potentially increased exposure of the comedication	No clinically significant effect	Potentially increased exposure of the comedication	Potentially increased exposure of the comedication
Hydroxychloroquine	No clinically significant effect	No clinically significant effect	No clinically significant effect	Potentially increased exposure of the comedication	No clinically significant effect	Potentially increased exposure of the comedication	Potentially increased exposure of the comedication
Monoclonal antibody							
Toclizumab	No clinically significant effect	No clinically significant effect	No clinically significant effect	Potentially decreased exposure of the comedication	No clinically significant effect	Potentially decreased exposure of the comedication	Potentially decreased exposure of the comedication

NA=not available.

Table 4: **Potential drug–drug interactions between COVID-19 therapies and immunosuppressive agents**

Scenario 11: what are the special arrangements and precautions in managing patients after transplantation during the COVID-19 pandemic?

Table 4 summarises the drug–drug interactions between COVID-19 therapies and immunosuppressive agents commonly used in liver transplantation. Drug–drug interactions might occur between agents that are metabolised via cytochrome P450 enzymes (eg, ciclosporin, sirolimus, and tacrolimus; statement 11A; table 1). Lopinavir–ritonavir are potent inhibitors of CYP3A4, which is involved in the metabolism of calcineurin inhibitors, sirolimus, and tacrolimus. If lopinavir–ritonavir are used, we recommend that tacrolimus dosage is reduced to 2–5% of baseline because of drug–drug interactions.

Azathioprine, ciclosporin, and mycophenolate mofetil are commonly used immunosuppressive agents in patients after transplantation with no or minimal drug–drug interactions with COVID-19 therapies (statement 11B; table 1).[78]

Transplant recipients aged older than 60 years and immunosuppressed patients are more likely to acquire SARS-CoV-2 infection.[70] Innate immune response might be the main driver for lung injury due to COVID-19; therefore, immunosuppression might possibly protect patients with COVID-19 from severe illness.[78] To date, data do not suggest that immunosuppression after transplantation is a risk factor for mortality associated with SARS (2003–04) or MERS (2012–present).[78] Nonetheless, immunosuppression might prolong viral shedding in patients with COVID-19 after transplantation.[76] Patients with COVID-19 symptoms should not be evaluated in the liver transplantation clinic. The clinic visit should be deferred for at least 14 days, and medication refill should be offered to avoid acute withdrawal of immunosuppressive therapy (statement 11C; table 1).

If clinical evaluation of a patient with suspected or even confirmed COVID-19 after transplantation is deemed necessary, use of an outpatient clinic or a site dedicated for this purpose with adequate personal protective

equipment provided to the health-care personnel might be considered. There is evidence showing the spread of COVID-19 from asymptomatic patients;[79] therefore, if community COVID-19 outbreaks are ongoing in the region, after transplantation all patients should avoid unnecessary outpatient visit and arbitrarily delay their visit to a time when community outbreak is mostly under control (statement 11D; table 1).

Appropriate preventive measures remain the cornerstone of avoiding infection with COVID-19 (statement 11E; table 1).[80]

Scenario 12: should patients with decompensated cirrhosis be sent to the intensive care unit if they develop respiratory failure due to COVID-19?

Presence of cirrhosis is an established risk factor of severe illness among patients with COVID-19.[68] From the real-world combined data from SECURE Cirrhosis and COVID-Hep in April, 2020, which included 82 patients with cirrhosis (43 decompensated cirrhosis), a third of patients with cirrhosis died. Nearly two-thirds of the patients who died were not taken to the intensive care unit before their death.[80] It is generally understandable and justifiable to give priority to maximising the number of patients who might survive treatment (statement 12A; table 1).[55]

To date, there is no study looking into the specific management approach for patients with COVID-19 who develop spontaneous bacterial peritonitis. Spontaneous bacterial peritonitis occurred in eight (3%) of 259 patients with cirrhosis who developed COVID-19, which is the largest cohort of patients with cirrhosis and COVID-19 published to date.[9] However, no specific management exists for patients with COVID-19 who develop spontaneous bacterial peritonitis (statement 12B; table 1).

Future perspectives

Because COVID-19 is a new disease, much more data are needed to improve our understanding of its impact on the liver and of the appropriate management of patients with liver diseases. As liver impairment is a common observation among patients with COVID-19, basic investigations on the causes of liver disease, including viral hepatitis serology tests, should be done in all future patients with COVID-19, particularly in the Asia-Pacific region where HBV is prevalent. With new antiviral drugs being developed for COVID-19, the potential drug–drug interactions and liver toxicity must be thoroughly evaluated. Recommendations might need to be updated when a vaccine for COVID-19 becomes available, and safety and efficacy of such a vaccine has to be proven in patients with advanced liver disease and in recipients of liver transplant.

Contributors

GL-HW, VW-SW, and HL-YC were responsible for the study concept and design, and for setting up the clinical scenarios and first draft of recommendation statements. All authors were responsible for crucial review of current literature relevant to the recommendation statements, voting for the recommendation statements, the drafting, and crucial revision of the manuscript for important intellectual content.

Declaration of interests

GL-HW has served as an advisory committee member for Gilead Sciences and Janssen; a speaker for Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen, and Roche; and reports grants from Gilead Sciences. VW-SW has served as an advisory committee member for Sagiment Biosciences (formerly 3V-BIO), AbbVie, Allergan, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Janssen, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, TARGET-NASH, and Terns; a speaker for Bristol-Myers Squibb, Echosens, Gilead Sciences, and Merck; and reports grants from Gilead Sciences. AT has served on advisory boards for Gilead, AbbVie, Merck, BMS, Roche, Bayer, and Eisai; received speaker fees from Gilead, AbbVie, Merck, BMS, and Eli Lilly; and reports institutional grants from Gilead, AbbVie, and Merck. S-GL is an advisor for AbbVie, Roche, Gilead, Arbutus, Springbank, Abbott, and Kaleido Biosciences; a speaker for Gilead, AbbVie, and Abbott; and reports research support from Gilead, Abbott, Roche, Sysmex, Fibronostics, and Merck. M-LY has served as a consultant of AbbVie, Abbott, Ascletis, BMS, Gilead, Merck, and Roche; was a speaker of AbbVie, Abbott, BMS, Gilead, Merck, and Ipsen; and reports grants from Abbott, Bristol-Myers Squibb, Gilead, and Merck. TP has served as a speaker for Bristol-Myers Squibb, Gilead Sciences, Bayer, Abbott, Eisai, Mylan, MSD, Ferring; and reports grants from Gilead Sciences, Roche Diagnostic, Janssen, Fibrogen, and Vir. HL-YC is an advisor for AbbVie, Aptorum, Arbutus, Hepion, Intellia, Janssen, Gilead, GlaxoSmithKline, GRAIL, Medimmune, Merck, Roche, Vaccitech, VenatoRx, and Vir Biotechnology; and a speaker for Mylan, Gilead, and Roche. All other authors declare no competing interests.

References

1 Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; **382:** 727–33.

2 WHO. WHO Director-General's remarks at the media briefing on COVID-19 outbreak on 18 February 2020. Feb 18, 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-covid-19-outbreak-on-18-february-2020 (accessed March 18, 2020).

3 WHO. Coronavirus disease 2019 (COVID-19): situation report–104. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200503-covid-19-sitrep-104.pdf?sfvrsn=53328f46_2 (accessed May 4, 2020).

4 Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395:** 507–13.

5 Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8:** 420–22.

6 Chau TN, Lee KC, Yao H, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. *Hepatology* 2004; **39:** 302–10.

7 Mallapaty S. Why does the coronavirus spread so easily between people? *Nature* 2020; **579:** 183.

8 Zhang H, Li HB, Lyu JR, et al. Specific ACE2 expression in small intestinal enterocytes cause gastrointestinal symptoms and injury after 2019-nCoV infection. *Int J Infect Dis* 2020; **96:** 19–24.

9 Moon AM, Webb GJ, Aloman C, et al. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: preliminary results from an international registry. *J Hepatol* 2020; published online May 21. DOI:10.1016/j.jhep.2020.05.013.

10 The Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol* 2018; **3:** 383–403.

11 Sarin SK, Kumar M, Eslam M, et al. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol* 2020; **5:** 167–228.

12 Chinese Digestion Association, Chinese Medical Doctor Association, Chinese Society of Hepatology, Chinese Medical Association. The protocol for prevention, diagnosis and treatment of liver injury in coronavirus disease 2019. *Chin J Hepatol* 2020; **28:** 217–21 (in Chinese).

13 American Association for the Study of Liver Diseases. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. May 14, 2020. https://www.aasld.org/sites/default/files/2020-05/AASLD-COVID19-ClinicalInsights-May142020-FINAL.pdf (accessed May 15, 2020).

14 APASL Covid-19 Task Force, Lau G, Sharma M. Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations. *Hepatol Int* 2020; published online May 23. DOI:10.1007/s12072-020-10054-w.

15 Boettler T, Newsome PN, Mondelli MU, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep* 2020; **2:** 100113.

16 Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov* 2020; **19:** 149–50.

17 Sagonowsky E. Gilead's remdesivir scores emergency FDA nod in COVID-19 days after big data reveal. May 1, 2020. https://www.fiercepharma.com/pharma/gilead-s-remdesivir-scores-emergency-fda-nod-covid-19-days-after-big-data-reveal (accessed on May 15, 2020).

18 Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; **59:** 252–56.

19 Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med* 2020; **382:** 1787–99.

20 Bijlsma JWJ, Welsing PMJ, Woodworth TG, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. *Lancet* 2016; **388:** 343–55.

21 Palacios R, Vergara S, Rivero A, et al. Low incidence of severe liver events in HIV patients with and without hepatitis C or B coinfection receiving lopinavir/ritonavir. *HIV Clin Trials* 2006; **7:** 319–23.

22 Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med* 2020; **382:** 2327–36.

23 Sun J, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. *Liver Int* 2020; **40:** 1278–81.

24 Sonneveld MJ, Murad SD, van der Eijk AA, de Man RA. Fulminant liver failure due to hepatitis B reactivation during treatment with tocilizumab. *ACG Case Rep J* 2019; **6:** e00243.

25 Andrade RJ, Aithal GP, Björnsson ES, et al. EASL clinical practice guidelines: drug-induced liver injury. *J Hepatol* 2019; **70:** 1222–61.

26 Fontana RJ, Seeff LB, Andrade RJ, et al. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology* 2010; **52:** 730–42.

27 Fan Z, Chen L, Li J, et al. Clinical features of COVID-19-related liver damage. *Clin Gastroenterol Hepatol* 2020; **18:** 1561–66.

28 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; **382:** 1708–20.

29 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395:** 497–506.

30 Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020; **20:** 425–34.

31 Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ* 2020; **368:** m606.

32 Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8:** 475–81.

33 Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020; **367:** 1260–63.

34 Li J, Zou B, Yeo YH, et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999–2019: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2019; **4:** 389–98.

35 The Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol* 2017; **2:** 161–76.

36 Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020; **40:** 998–1004.

37 Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. *Lancet* 2020; **395:** 683–84.

38 Wong GL, Yuen BW, Chan HL, et al. Impact of dose and duration of corticosteroid on the risk of hepatitis flare in patients with chronic hepatitis B. *Liver Int* 2019; **39:** 271–79.

39 Lampertico P, Agarwal K, Berg T, et al. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67:** 370–98.

40 Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10:** 1–98.

41 Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67:** 1560–99.

42 Wong GL, Seto WK, Wong VW, Yuen MF, Chan HL. Review article: long-term safety of oral anti-viral treatment for chronic hepatitis B. *Aliment Pharmacol Ther* 2018; **47:** 730–37.

43 HEP Drug Interactions. Interaction checker. https://www.hep-druginteractions.org/checker (accessed April 15, 2020).

44 Chong CH, Lim SG. When can we stop nucleoside analogues in patients with chronic hepatitis B? *Liver Int* 2017; **37** (suppl 1)**:** 52–58.

45 Wong GL, Chan HL, Yuen BW, et al. The safety of stopping nucleos(t)ide analogue treatment in patients with HBeAg-negative chronic hepatitis B. *Liver Int* 2020; **40:** 549–57.

46 Seto WK, Hui AJ, Wong VW, et al. Treatment cessation of entecavir in Asian patients with hepatitis B e antigen negative chronic hepatitis B: a multicentre prospective study. *Gut* 2015; **64:** 667–72.

47 Marshall MC, Herrera JL. Lack of patient compliance in real-world practice negatively affects sustained viral response rates to direct acting agent therapy for hepatitis C. *Dig Dis Sci* 2018; **63:** 3228–32.

48 Huang CF, Yu ML. Unmet needs of chronic hepatitis C in the era of direct-acting antiviral therapy. *Clin Mol Hepatol* 2020; published online March 19. DOI:10.3350/cmh.2020.0018.

49 Zhou YJ, Zheng KI, Wang XB, et al. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: a multicenter preliminary analysis. *J Hepatol* 2020; published online April 26, 2020. DOI:10.1016/j.jhep.2020.04.027.

50 Zhou J, Tan J. Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. *Metabolism* 2020; **107:** 154216.

51 Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360:** 1283–97.

52 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68:** 394–424.

53 Wong GL, Wong VW, Tan GM, et al. Surveillance programme for hepatocellular carcinoma improves the survival of patients with chronic viral hepatitis. *Liver Int* 2008; **28:** 79–87.

54 Wang JH, Chang KC, Kee KM, et al. Hepatocellular carcinoma surveillance at 4- vs 12-month intervals for patients with chronic viral hepatitis: a randomized study in community. *Am J Gastroenterol* 2013; **108:** 416–24.

55 Emanuel EJ, Persad G, Upshur R, et al. Fair allocation of scarce medical resources in the time of Covid-19. *N Engl J Med* 2020; **382:** 2049–55.

56 American Society of Clinical Oncology. COVID-19 patient care information. https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19 (accessed May 15, 2020).

57 International Liver Cancer Association. Management of HCC during COVID-19: ILCA guidance. https://ilca-online.org/management-of-hcc-during-covid-19-ilca-guidance (accessed May 15, 2020).

58 Chiu PWY, Ng SC, Inoue H, et al. Practice of endoscopy during COVID-19 pandemic: position statements of the Asian Pacific Society for Digestive Endoscopy (APSDE-COVID statements). *Gut* 2020; **69:** 991–96.

59 Lui RN, Wong SH, Sánchez-Luna SA, et al. Overview of guidance for endoscopy during the coronavirus disease 2019 pandemic. *J Gastroenterol Hepatol* 2020; **35:** 749–59.

60 Poordad FF. Presentation and complications associated with cirrhosis of the liver. *Curr Med Res Opin* 2015; **31:** 925–37.

61 Sung JJ. Treatment of variceal bleeding. *Curr Treat Options Gastroenterol* 2003; **6:** 171–80.

62 de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: report of the Baveno VI Consensus workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; **63:** 743–52.

63 Petta S, Sebastiani G, Bugianesi E, et al. Non-invasive prediction of esophageal varices by stiffness and platelet in non-alcoholic fatty liver disease cirrhosis. *J Hepatol* 2018; **69:** 878–85.

64 Wong GLH, Kwok R, Hui AJ, et al. A new screening strategy for varices by liver and spleen stiffness measurement (LSSM) in cirrhotic patients: a randomized trial. *Liver Int* 2018; **38:** 636–44.

65 Wong GL, Liang LY, Kwok R, et al. Low risk of variceal bleeding in patients with cirrhosis after variceal screening stratified by liver/spleen stiffness. *Hepatology* 2019; **70:** 971–81.

66 Zheng J, Zhang Y, Li P, et al. The endoscopic ultrasound probe findings in prediction of esophageal variceal recurrence after endoscopic variceal eradication therapies in cirrhotic patients: a cohort prospective study. *BMC Gastroenterol* 2019; **19:** 32.

67 Gattini D, Cifuentes LI, Torres-Robles R, Gana JC. Sclerotherapy versus beta-blockers for primary prophylaxis of oesophageal variceal bleeding in children and adolescents with chronic liver disease or portal vein thrombosis. *Cochrane Database Syst Rev* 2020; **1:** CD011659.

68 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395:** 1054–62.

69 Bhoori S, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol* 2020; **5:** 532–33.

70 Belli LS, Duvoux C, Karam V, et al. COVID-19 in liver transplant recipients: preliminary data from the ELITA/ELTR registry. *Lancet Gastroenterol Hepatol* 2020; published online June 4. https://doi.org/10.1016/S2468-1253(20)30183-7.

71 Fix OK, Hameed B, Fontana RJ, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. *Hepatology* 2020; published online April 16. DOI:10.1002/hep.31281.

72 Ertel AE, Kaiser TE, Abbott DE, Shah SA. Use of video-based education and tele-health home monitoring after liver transplantation: results of a novel pilot study. *Surgery* 2016; **160:** 869–76.

73 Serper M, Cubell AW, Deleener ME, et al. Telemedicine in liver disease and beyond: can the COVID-19 crisis lead to action? *Hepatology* 2020; published online April 10. DOI:10.1002/hep.31276.

74 Stein RA. COVID-19 and rationally layered social distancing. *Int J Clin Pract* 2020; published online March 14. DOI:10.1111/ijcp.13501.

75 Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; **323:** 1061–69.

76 Kumar D, Manuel O, Natori Y, et al. COVID-19: a global transplant perspective on successfully navigating a pandemic. *Am J Transplant* 2020; published online March 23. DOI:10.1111/ajt.15876.

77 Qin J, Wang H, Qin X, et al. Perioperative presentation of COVID-19 disease in a liver transplant recipient. *Hepatology* 2020; published online March 27. DOI:10.1002/hep.31257.

78 D'Antiga L. Coronaviruses and immunosuppressed patients: the facts during the third epidemic. *Liver Transpl* 2020; **26:** 832–34.

79 Gandhi M, Yokoe DS, Havlir DV. Asymptomatic transmission, the achilles' heel of current strategies to control Covid-19. *N Engl J Med* 2020; **382:** 2158–60.

80 COVID-Hep Registry and Secure-Cirrhosis Registry. First combined weekly update–13 Apr 2020. https://covid-hep.net/img/combined_weeklyupdate_20200413.pdf (accessed April 15, 2020).