

WGO Guidance for the Care of Patients With COVID-19 and Liver Disease

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Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the least deadly but most infectious coronavirus strain transmitted from wild animals. It may affect many organ systems. Aim of the current guideline is to delineate the effects of SARS-CoV-2 on the liver. Asymptomatic aminotransferase elevations are common in coronavirus disease 2019 (COVID-19) disease. Its pathogenesis may be multifactorial. It may involve primary liver injury and indirect effects such as “bystander hepatitis,” myositis, toxic liver injury, hypoxia, and preexisting liver disease. Higher aminotransferase elevations, lower albumin, and platelets have been reported in severe compared with mild COVID-19. Despite the dominance of respiratory disease, acute on chronic liver disease/acute hepatic decompensation have been reported in patients with COVID-19 and preexisting liver disease, in particular cirrhosis. Metabolic dysfunction-associated fatty liver disease (MAFLD) has a higher risk of respiratory disease progression than those without MAFLD. Alcohol-associated liver disease may be severely affected by COVID-19—such patients frequently have comorbidities

including metabolic syndrome and smoking-induced chronic lung disease. World Gastroenterology Organization (WGO) recommends that interventional procedures such as endoscopy and endoscopic retrograde cholangiopancreatography should be performed in emergency cases or when they are considered strictly necessary such as high risk varices or cholangitis. Hepatocellular cancer surveillance may be postponed by 2 to 3 months. A short delay in treatment initiation and non-surgical approaches should be considered. Liver transplantation should be restricted to patients with high MELD scores, acute liver failure and hepatocellular cancer within Milan criteria. Donors and recipients should be tested for SARS-CoV-2 and if found positive donors should be excluded and liver transplantation postponed until recovery from infection.

Key Words: COVID-19 disease, liver disease, chronic viral hepatitis, metabolic dysfunction-associated liver disease, autoimmune liver diseases, hepatocellular carcinoma, liver transplantation

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The World Health Organization (WHO) declared a global pandemic of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on March 11, 2020, barely 10 weeks after the WHO's Country Office in the People's Republic of China identified a media statement on cases of “viral pneumonia” in Wuhan, People's Republic of China. By mid-July 2020, more than 14 million confirmed cases of coronavirus disease 2019 (COVID-19) had been reported worldwide, and nearly 600,000 deaths.

Many of us feel overwhelmed by the increased demands that this pandemic has imposed on all facets of our health care systems and personal work. It has become clear that COVID-19 is a multisystem disease but effects of SARS-CoV-2 on different organ systems remain poorly understood as do the effects of COVID-19 in the presence of pre-existing conditions. In addition, health care has been very severely affected by the severe restrictions on resources and access to health care arising from pandemic and the need to control the spread of disease. Over the last few months, every specialty has had to re-evaluate the care of their patients and implement emergency procedures in the face of local and systemic constraints. There is no single, universal approach to this global emergency and so health care providers from around the world are collaborating to develop and share evidence or expertise-informed, resource-sensitive guidance relevant to their areas of clinical practice. Recognizing the impact of the COVID-19 pandemic on the

management of patients with liver disease, the Hepatology Special Interest Group of the World Gastroenterology Organization (WGO) has produced this document to summarize its current assessment of how best to manage liver disease in the context of the COVID-19 pandemic, acknowledging that local circumstances will determine which recommendations can, realistically, be implemented.

SARS-CoV-2, the coronavirus strain that causes COVID-19, is 1 of 3 strains which have been transmitted from wild animals leading to disease in humans.¹ The reported mortality rate for COVID-19 is 5% compared with rates of 10% for SARS (severe acute respiratory syndrome, caused by SARS-CoV) and 35% for MERS (the Middle East respiratory syndrome, caused by MERS-CoV). However, although it is less deadly, SARS-CoV-2 is much more infectious than SARS-CoV or MERS-CoV; by mid June 2020, more than 14 million COVID-19 cases had been reported worldwide, compared with 2519 MERS cases between 2012 and January 2020² and 8422 SARS cases reported during the 2003 epidemic,³ with no subsequent reported cases.

The median incubation period for COVID-19 is 4 days (interquartile range, 2 to 7 d); it mainly affects the respiratory system, the most common symptoms being fever, cough, and dyspnea.¹ In some cases, patients may present with gastrointestinal (GI) symptoms such as diarrhea, nausea, and vomiting. On admission to hospital, chest computed tomography findings of ground-glass opacity are observed in more than half of patients and lymphocytopenia in more than 80%. Definite diagnosis is made by reverse-transcription polymerase chain reaction detection of SARS-CoV-2 RNA in nasal or nasopharyngeal swap specimens.

LIVER ABNORMALITIES IN COVID-19

Asymptomatic elevated liver biochemistries are common, reported in 14% to 76% of COVID-19 cases; elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most common abnormalities with raised γ -glutamyl transferase (GGT) levels in up to 50% and slightly raised bilirubin in 10% of cases; alkaline phosphatase (ALP) is typically normal.⁴⁻⁶

Significantly higher ALT and AST levels are reported in severe COVID-19 but the increases are mild and do not exceed 3 times the upper limit of normal. Serum AST was >40 IU/L in 52% of patients who died, but only in 16% patients who recovered.⁷ AST is more frequently elevated compared with ALT. Lower platelet counts and albumin levels are seen in those with more severe disease; 65% of deceased but only 14% of recovered patients had albumin levels <32 g/L. However, low albumin levels are in general not linked to liver failure. Acute-on-chronic liver failure (ACLF) reported for the influenza virus,⁸ had not been reported for SARS-CoV-2 infection until recently. However, in 2 retrospective studies, ACLF was reported in 12% and 28% of patients with baseline compensated cirrhosis.^{9,10} COVID-19 was associated with liver injury and increased 30-day mortality in both studies. However, chronic liver disease (CLD) without cirrhosis was not associated with increased mortality.⁹

Acute hepatitis has been reported as a presenting feature of COVID-19 in a patient with HIV on therapy and normal prior liver tests; viral screen was negative and typical fever with chest x-ray changes developed 18 hours after admission.¹¹ However, further data are required before

recommending routine SARS-CoV-2 testing in patients with acute hepatitis.

PATHOGENESIS OF LIVER ABNORMALITIES IN COVID-19

It is unlikely that SARS-CoV-2 directly causes primary liver injury⁴⁻⁷ but the mechanisms by which SARS-CoV-2 affects the liver are not well defined. Direct viral cytopathic effects have been described with SARS and MERS but there are few data on COVID-19. Postmortem studies report moderate microvascular steatosis with mild lobular and portal activity but no obvious inflammatory cell infiltration or typical liver cell necrosis.¹² Liver biopsy in an infant who developed COVID-19 postliver transplant showed moderate acute hepatitis with prominent clusters of apoptotic hepatocytes, lobular lymphohistiocytic inflammation, mild steatosis, and mild to moderate acute cellular rejection but no viral inclusions.¹³ However, ultrastructural examination from 2 COVID-19 patients identified typical, spike structure coronavirus particles in the cytoplasm of hepatocytes accompanied by massive hepatic apoptosis, some binuclear hepatocytes and scanty CD4⁺ and CD8⁺ lymphocytes that were considered indicative of a typical viral infection.¹⁴

A proposed mechanism of direct liver injury is by direct cytotoxicity from viral replication in liver cells. However, the cell entry receptor of SARS-CoV-2, angiotensin converting enzyme 2 receptor (ACE2),¹⁵ which is highly expressed in alveolar epithelial cells of the lung and the GI tract, is expressed only in 2.6% of hepatocytes. In contrast, although ACE2 is expressed on 58% of bile duct cells,¹⁶ ALP, a marker of bile duct injury appears to be the least-affected of the liver enzymes. Thus, it remains unclear whether SARS-CoV-2 plays a direct role in producing liver injury.⁵⁻⁷

ACE2 receptors are expressed on vascular endothelial cells but, although there are reports of increased vascular diseases in COVID-19 including peripheral arterial disease¹⁷ and thromboembolism including pulmonary microthromboses in critically-ill patients,¹⁸⁻²¹ the American Society of Hematology considers that the true incidence of venous thromboembolism has not been established in COVID. It remains to be seen if thromboembolic events are secondary to severe illness or if there is a specific link between COVID-19 infection and thromboembolic events. With respect to COVID-19-associated liver disease, ACE2 receptor expression is reported to be low in the liver vascular endothelium and endotheliitis has not been noted in post-mortem liver biopsies.²²

Systemic viral infections can cause transient elevation in transaminases as a result of general immune activation due to circulating cytokines without significant liver injury ("bystander hepatitis").²³ In 1 study, serum concentrations of proinflammatory and anti-inflammatory cytokines, including interleukin (IL)-2R, IL-6, TNF- α , and IL-10, were increased in the most severe COVID-19 cases and were markedly higher than in moderate cases, suggesting that cytokine storms might be associated with disease severity.²⁴ However, in the absence of a confirmed relationship between cytokine changes and hepatic injury, it is hard to conclude that abnormal liver tests in COVID-19 indicate "bystander hepatitis" and other mechanisms should, therefore, be considered.

Raised transaminases may indicate drug-induced liver injury,^{5,6} but they may also be due to myositis, reported

TABLE 1. A Step-wise Approach in COVID-19 Patients Suspected to Have Hepatobiliary Disease

Determine cause(s)
COVID-19 infection per se
Complication of COVID-19 or treatment
Sepsis
Hypoxic injury and/or ventilator complications
Drugs including antibiotics and experimental therapy
Pre-existing liver disease that may not have been diagnosed (HAV, HBV, HCV, HEV, MAFLD, alcohol-related liver disease, autoimmune liver disease, other)
Concomitant medical problems
Examples: Common bile duct obstruction (stones)
Malignancy of liver or biliary tract
Ascites
Thrombosis (Budd-Chiari, portal vein thrombosis)
Exclude nonhepatic causes of abnormal liver tests
Determine need for further evaluation and urgency of intervention
Conservative approach is the rule
No invasive procedure
Defer further imaging, use bedside ultrasound if needed
Exceptions
Findings that may determine disease outcome <i>and if</i> diagnosed/treated have major implications
Examples: Ascitic tap: decompensated cirrhosis vs. malignancy and rule out infection
Ultrasonography: common bile duct obstruction—stones vs. mass
Liver biopsy: autoimmune hepatitis? Can we treat without biopsy?
EGD for upper GI hemorrhage

EGD indicates esophagogastroduodenoscopy; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; GI, gastrointestinal; MAFLD, metabolic dysfunction-associated fatty liver disease.

commonly in COVID-19, characterized by AST > ALT and a raised creatinine kinase. Hypoxic ischemic liver injury is another possible cause of raised transaminases, particularly in the context of a COVID-related myocarditis.

SHOULD ALL PATIENTS WITH COVID-19 GET A SET OF LIVER TESTS DONE?

In the absence of underlying liver disease, outpatients with COVID-19 managed by home quarantine do not require routine liver tests. Inpatients should have baseline liver tests, including ALT, AST, GGT, ALP, and bilirubin. Liver enzymes should be monitored as COVID-19

TABLE 3. WGO Recommendations Regarding the General Approach to Patients With Liver Disease in the Era of COVID-19

In this COVID-19 era, routine outpatient testing of liver biochemistry is not recommended
In patients with elevated ALT or AST, rule out viral hepatitis. This may be particularly important in developing countries, as patients may not have been tested before
Routine investigation to exclude other etiologies should take into consideration local context and availability
Routine imaging is not recommended unless it will alter management

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.

progresses; if available, platelets, albumin, ferritin, and C-reactive protein should also be monitored in severe cases.

Additional blood tests, including viral hepatitis serology, should be considered to exclude other causes, depending on the local context and available resources. Routine imaging is not recommended unless it is likely to change the management of the patient.

New onset liver test abnormalities during admission in COVID-19 patients should be managed in the same way as in COVID-19-negative patients, with particular consideration for excluding drug-induced liver injury especially given the large number of alternate therapies used promoted by social media, such as ingestion of disinfectants. Patients with abnormal liver tests should not be excluded from receiving investigational agents to treat COVID-19, but close monitoring is recommended. Routine liver biopsy is not recommended.

After analysis of findings, assessment should include the urgency of implementation of any recommendations (Table 1). Test results need to be interpreted in the context of the patient's illness (Table 2). WGO recommendations for a general approach to patients with liver disease in the era of COVID-19 are shown in Table 3.

LIVER COMORBIDITIES AND COVID-19

Regardless of diagnosis, all patients with CLD should be counseled about general protective measures, including frequent hand washing, social distancing, and wearing a face mask when going out.

Chronic Hepatitis B and C

It is not yet known whether SARS-CoV-2 causes liver injury, directly or indirectly,^{4,25} despite a report of 3 cases of

TABLE 2. Interpretation of Liver Test Results in COVID-19 Patients

Test	Comments
Hypoalbuminemia	Common in patients with systemic inflammatory response, may also be suggestive of acute hepatic decompensation/ACLF in patients with pre-existing liver cirrhosis
Prolonged INR or thrombopenia	Spontaneous coagulopathy/DIC may be present in 1/3 of sick patients ^{15,21} Thromboembolic events likely common. ACLF may be a possibility
High transaminases or bilirubin (> 3×ULN)	Not typical for COVID-19, however in patients with pre-existing liver disease (cirrhosis) may indicate ACLF
Anemia	GI bleeding: ulcer? Variceal hemorrhage?
Imaging	Chest-CT often done in some places: Could it help to assess liver/biliary tract disease? If indicated do US but avoid unnecessary imaging including US (not formally investigated)
GI symptoms including diarrhea	Common

ACLF indicates acute-on-chronic liver failure; CT, computed tomography; DIC, disseminated intravascular coagulation; GI, gastrointestinal; US, ultrasound; INR, international normalized ratio.

viral hepatitis during the original SARS-1 outbreak.²⁶ Similarly, little is known about the independent contribution of chronic viral hepatitis B virus (HBV), with or without hepatitis D, and chronic hepatitis C virus (HCV) to outcomes in persons infected by SARS-CoV-2. A study early in the COVID-19 epidemic in China, where the prevalence of chronic HBV is high, found no evidence that chronic HBV infection increased adverse outcomes in persons with COVID-19.⁴ The Centers for Disease Control and Prevention in the United States reported that 1% of hospitalized persons with COVID-19 has underlying liver disease²⁷ but there were no data on the etiology of the liver disease. Nevertheless, it is highly likely that persons with chronic HBV or HCV and advanced fibrosis or cirrhosis would be at greater risk of adverse outcomes if they were to develop COVID-19. As pointed out earlier in this review, 2 studies have now clearly shown that COVID-19 may lead to acute hepatic decompensation and ACLF and is associated with increased 30-day mortality in patients with baseline cirrhosis.^{9,10}

As a general recommendation, all persons with chronic viral hepatitis who develop COVID-19 should have blood tests for AST, ALT, bilirubin; if any of these is elevated, hepatitis B surface antigen and anti-hepatitis C antibody (reflexed to HCV RNA if positive) testing should be performed. If there is evidence of chronic viral hepatitis, liver tests should be monitored frequently during hospitalization. For patients with compensated liver disease, noninvasive fibrosis markers may be used to assess for advanced liver disease (fibrosis) or cirrhosis; cirrhotic patients need close follow-up due to risk of ACLF. Patients with decompensated cirrhosis should be further assessed with Child-Pugh and model for end-stage liver disease (MELD) scores.

A rise in transaminases should be evaluated carefully in a person who acquires COVID-19 on a background of chronic viral hepatitis. If the person also had a liver transplant, the change may be due to COVID-19 disease rather than rejection of the transplanted liver. If the person is receiving antiviral therapy for hepatitis B they should continue their medications, as the changes could be due to the immunologic response to COVID-19 or to a flare of the HBV infection. An HBV DNA level should be done and if low (<2000 IU/mL) or undetected, the flare may be considered a manifestation of COVID-19.

In the case of HCV infection, persons who are taking HCV direct acting antiviral (DAA) medications should continue these drugs without interruption. In contrast, interferon treatment for either HBV or HCV should be held as interferon is a potent cytokine and the severity of COVID-19 manifestations appears to be related, at least in part, to a SARS-CoV-2-induced cytokine storm. In view of this, it may be prudent to delay starting interferon therapy for chronic HBV until the COVID-19 pandemic is over.

There is no evidence that HBV or HCV oral antiviral drugs have any additional adverse effects in persons with chronic viral hepatitis who acquire COVID-19 disease. However, for persons with active HCV infection who are not yet on DAA, it would be prudent to delay therapy until after their recovery from COVID-19 disease if there is no suspicion of advanced liver disease.

It is possible that some HBV and HCV antiviral medications, such as sofosbuvir,²⁸ tenofovir, and ribavirin may have therapeutic activity against SARS-CoV-2 but, although clinical trials are underway,²⁹ there is no current evidence of clinical benefit.

In conclusion, more data are needed to determine if persons with chronic hepatitis B or C without cirrhosis are

TABLE 4. WGO Recommendations for Patients With Chronic Hepatitis B and C in the Era of COVID-19

It is unknown if patients with chronic hepatitis B and C, may be more susceptible to liver damage from SARS-CoV-2 or whether patients with chronic HCV or HBV infection have a greater risk or not of severe disease after acquiring COVID-19. However, patients with cirrhosis have a poorer prognosis including acute hepatic decompensation and development of ACLF
In low income countries assessment for COVID-19 should include blood tests for AST, ALT, and if any are elevated, patients should be tested for HBsAg and anti-HCV (reflexed to HCV RNA if positive)
Treat those diagnosed with HBV or HCV with DAAs, at least those with signs indicative of advanced liver disease
Do not stop antiviral medications for HBV or HCV in patients who present with COVID-19
Provide 90-d supplies instead of 30-d supplies for HBV oral antiviral drugs and have a full course of DAA medications to complete HCV treatment if this has been started
Avoid procedures during the COVID-19 illness that could put others at risk such as liver US or other advanced imaging unless there is a clinical suspicion

ACLF indicates acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct acting antiviral; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; US, ultrasonography; WGO, World Gastroenterology Organisation.

at increased risk of adverse outcomes if they acquire COVID-19. However, patients with chronic viral hepatitis and advanced fibrosis or cirrhosis are at risk of more severe outcomes; they should, therefore, self-isolate to minimize the risk of developing COVID-19. Persons receiving DAA for hepatitis C or tenofovir or entecavir for HBV should continue antiviral therapy to prevent viral rebound and a subsequent hepatitis flare. These persons should, also, ensure that they have sufficient antiviral medications, so that they do not run out during the pandemic.

General WGO recommendations for patients with chronic hepatitis B and C are given in Table 4.

Metabolic Dysfunction-associated Fatty Liver Disease (MAFLD)

The diagnosis of MAFLD, formerly called non-alcoholic fatty liver disease, is based on evidence of hepatic steatosis and 1 of the following 3 criteria: overweight/obesity, type 2 diabetes mellitus, or metabolic dysregulation.³⁰ Untreated MAFLD may progress to steatohepatitis, fibrosis and cirrhosis and, ultimately, hepatic decompensation and hepatocellular carcinoma (HCC).³¹

Many MAFLD patients have risk factors such as obesity, associated with a greater risk for respiratory infections. For example, a nested case control study reported MAFLD in 36% of 561 patients with community-acquired pneumonia and a 30-day pneumonia mortality of 17% in MAFLD patients compared with 5.8% in those without MAFLD. This association was stronger in patients with advanced hepatic fibrosis.³²

The association between MAFLD and respiratory infections begs the questions of whether MAFLD patients have a greater risk of acquiring COVID-19 and whether MAFLD patients with COVID-19 have a different prognosis.

Risk of Acquiring COVID-19

It is unknown whether MAFLD patients have a greater risk of acquiring COVID-19 although it is speculated that

they may be more vulnerable because SARS-CoV-2 enters the cell through the ACE2 receptor which is upregulated in liver injury and MAFLD; thus, MAFLD and ACE inhibitor therapy may increase susceptibility to COVID-19.³³

Interestingly MAFLD increases viral shedding time (17.5 ± 5.2 vs. 12.1 ± 4.4 d, $P < 0.0001$) compared with patients without MAFLD. Thus, MAFLD patients are infectious for ~5 days longer.³⁴

Different COVID-19 Prognosis

The effect of MAFLD on COVID-19 outcomes is difficult to establish, independent of the effects of the other manifestations of metabolic syndrome. A cohort study of 202 patients in China reported that patients with MAFLD ($n = 76$) had a higher risk of respiratory disease progression than those without MAFLD (44.7% vs. 6.6%) and a higher likelihood of abnormal liver biochemistry during admission (11.1% vs. 70%).³⁴ However, in another cohort study of 66 MAFLD patients, obese (body mass index > 25 kg/m²) patients ($n = 45$) had a greater risk than nonobese patients of a severe COVID-19 disease course [unadjusted odds ratio = 5.77; 95% confidence interval (95% CI), 1.19-27.91; $P = 0.029$] and the risk remained significant even after adjusting for age, sex, smoking, diabetes, hypertension, and dyslipidemia.³⁵ A systematic review and meta-analysis (20 articles, 4062 participants) reported that patients with a high body mass index and a combination of metabolic risk factors were more likely to develop critical illness with increased risks related to diabetes mellitus (3.04; 95% CI, 2.01-4.60), hypertension (2.31; 95% CI, 1.68-3.18), and coronary heart disease (2.76; 95% CI, 1.39-5.45).³⁶ Another cohort study reported that MAFLD patients with increased noninvasive liver fibrosis scores (FIB-4 score) are at higher likelihood of having severe COVID-19 illness.³⁷

WGO recommendations for patients with MAFLD in the COVID-19 area are shown in Table 5.

Autoimmune Liver Disease

Autoimmune Hepatitis (AIH)

AIH is typically confirmed with liver biopsy but, to minimize hospital-based invasive procedures during the pandemic, some experts recommend empiric therapy (corticosteroids +/- azathioprine) for patients with elevated ALT, positive autoantibodies and elevated immunoglobulin G levels, once other liver diseases have been excluded.³⁸ However, the AASLD expert panel warned against

presuming that elevated liver tests in AIH patients are due to a disease flare without biopsy confirmation.³⁹

AIH patients on immunosuppression may be at higher risk of acquiring infection and should be prioritized for SARS-CoV-2 testing when presenting with fever, upper respiratory tract symptoms, or atypical symptoms such as diarrhea or loss of smell and taste.^{39,40} It is not recommended that immunosuppressive therapy be reduced in stable AIH patients as this could lead to disease flares that ultimately would require higher doses of corticosteroids to control.^{39,40} It is important that these patients receive pneumococcus and influenza vaccinations.⁴⁰ This latter recommendation should encompass not just autoimmune liver diseases but all liver diseases.

Early reports from the United States suggest that immune-compromised patients account for 6% of hospitalized patients and 9% of those admitted to intensive care unit.²⁷ Emerging evidence and past experiences with SARS and MERS does not suggest that immunosuppressed patients with COVID-19 are at higher risk of severe pulmonary disease.⁴¹ A series of 150 cases from Wuhan, China suggests that corticosteroids might exacerbate COVID-19-associated lung injury, leading experts to recommend against their use.⁴²

Therefore, if AIH patients on corticosteroids develop COVID-19, high doses of prednisone should probably be avoided, recognizing that stress doses may be necessary to avoid adrenal insufficiency.³⁹ However, the situation is even more complex giving the potential contribution of cytokine storm in the pathogenesis of COVID-19 and the recently reported beneficial effect of dexamethasone in COVID-19 (see the Therapies under investigation for COVID-19 and potential hepatotoxicity section). Patients with COVID-19 may develop lymphopenia and, if this is associated with fever or worsening respiratory status, it may be appropriate to monitor lymphopenia and reduce the doses of azathioprine or mycophenolate mofetil.³⁹

Cholestatic Liver Diseases

It is not clear if patients with primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC), without underlying cirrhosis, are at increased risk of COVID-19 or if the virus worsens chronic cholestatic liver disease.²⁵ PBC patients should continue usual treatment, including ursodeoxycholic acid and second-line agents (eg, obeticholic acid or bezafibrate). During the pandemic, HCC surveillance should be deferred³⁹ as should endoscopic surveillance for varices in early stage disease with nonselective β -blockers being a preferred management strategy.⁴³ Magnetic resonance cholangiopancreatography in PSC patients should be used only if it is likely to change management (eg, suspected cholangiocarcinoma or dominant stricture in PSC).³⁹ Fever and worsening liver tests may indicate COVID-19 but they should, also, prompt blood cultures, broad spectrum antibiotic therapy, noninvasive imaging, and consideration of endoscopic retrograde cholangiopancreatography for possible ascending cholangitis.

Some WGO recommendations for the management of patients with autoimmune liver diseases in the COVID-19 era are listed in Table 6.

Alcohol-associated Liver Disease (ALD)

It has been proposed that ALD patients may be among the groups affected most severely by the COVID-19 pandemic⁴⁴ for several reasons: (i) their depressed immune function makes them susceptible to viral and bacterial infections,⁴⁵ (ii) they commonly have comorbidities including obesity and metabolic syndrome, (iii) they are often unable to

TABLE 5. WGO Recommendations for the Management of Patients With Metabolic Dysfunction-associated Fatty Liver Disease in the COVID-19 Era

The identification and monitoring of patients with metabolic disease to identify MAFLD stage and grade is pivotal during and after the COVID-19 crisis
Patients with MAFLD have a number of risk factors such as obesity diabetes mellitus which may translate to a higher mortality from respiratory illnesses, including COVID-19
Patients with MAFLD had a higher risk of respiratory disease progression than those without MAFLD
Counseling of MAFLD patients to change lifestyle with a focus to curtail risk factors (such as obesity) that predict a poor prognosis of COVID-19 is encouraged

MAFLD indicates metabolic dysfunction-associated fatty liver disease; WGO, World Gastroenterology Organization.

TABLE 6. WGO Recommendations for the Management of Autoimmune Liver Diseases in the COVID-19 Era

During the pandemic, follow-up of stable patients with AIH should be done with phone consultation or tele-health where available

Patients with AIH should be prioritized for SARS-CoV-2 testing when presenting with symptoms

It is not recommended to lower immunosuppressive therapy in stable patients with AIH in an attempt to reduce the risk of contracting the infection

However, if patients with COVID-19 develop lymphopenia, consider lowering the doses of azathioprine or mycophenolate mofetil

In new patients presenting with features of AIH, it is best to avoid liver biopsy during the pandemic, and starting empiric therapy can be recommended

If AIH patients on corticosteroids develop COVID-19, high doses of prednisone should be avoided, keeping in mind that stress doses may be needed

AIH indicates autoimmune hepatitis; WGO, World Gastroenterology Organization.

attend regular visits with providers, (iv) social isolation can cause psychological decompensation and increased drinking or relapse drinking, (v) they are often smokers with chronic respiratory disease. As a result, ALD patients may be at higher risk for severe COVID-19 infection,⁴⁴ they may be unwilling to adopt COVID-19 prevention measures and they may not seek medical care until they are critically ill; unfortunately, these behaviors may become even more entrenched as ALD patients' alcohol consumption increases in COVID-related isolation. Finally, ALD patients and others should be warned, unequivocally, that alcohol consumption does not provide any protection, whatsoever, against COVID-19. There are reports, from around the world, of people drinking alcohol in the false belief that it will prevent COVID-19⁴⁶ and, tragically, in Iran, some 180 people died in March 2020 after consuming "moonshine" or industrial alcohol, containing methanol, to prevent COVID-19.

Patients with severe alcoholic hepatitis probably should not receive standard corticosteroid treatment, particularly in areas of high COVID-19 prevalence.⁴⁴ As pointed out before we use the wording "probably" as steroids at some stages of the infection may even be beneficial. More data are definitely needed. Other than this, the treatment of ALD is based on ameliorating the social effects of COVID-19 on ALD patients and trying to ensure that they maintain appropriate, safe access to health care resources.

WGO recommendations are shown in Table 7.

PRACTICAL ASPECTS OF CARING FOR CLD PATIENTS DURING COVID-19

Following CLD During COVID-19

CLD patients make extensive use of the health system for in-person visits, laboratory tests, and diagnostic imaging and their responses are conflicted by the risks of staying at home and missing important clinical care or of attending health care institutions and risking infection by SARS-CoV-2. To date, specialist society recommendations have, necessarily, been based on expert opinion^{39,40} to guide physicians as they deal with the complex effects of COVID-19 in CLD, balancing the risks of treatment in patients at risk of COVID-19, the risks of undertreatment in patients with advanced or progressive

TABLE 7. WGO Recommendations for the Management of CLD in General and Patients With Alcoholic Liver Disease in Particular in the COVID-19 Era

Patients with stable, compensated liver diseases should postpone medical visits and routine labs. Telemedicine or phone visits should be encouraged in such cases

In low income countries telemedicine or phone visits may not be possible. Outpatient visits may be used to differentiate patients with compensated vs. decompensated liver disease

In high-moderate income countries outpatient visits should be limited to those with high MELD scores

In persons with decompensated cirrhosis who have complications that need laboratory monitoring such as ascites management, visits for blood draw and clinical evaluation may be needed but should be kept to a minimum

Telemedicine approaches should take into account patients with alcohol use disorder and such patients should be approached

Routine prescriptions should be sent by mail and should be given to cover extended durations

Patients with any liver disease should be encouraged to receive pneumococcus and influenza vaccinations

Treatment of severe alcoholic hepatitis with corticosteroids should be decided and followed on a case by case basis. Whenever possible patients should be hospitalized

Liver biopsies should be restricted to cases in which it becomes unavoidable in order to make a definitive diagnosis

Hospitalizations, if needed, should be as short as possible, preferably in private rooms: keep doors closed and windows open, limit medical and nursing staff

SARS-CoV-2 testing should be done in patients who present with acute decompensation of CLD, or acute-on-chronic liver failure

CLD indicates chronic liver disease; MELD, model for end-stage liver disease; WGO, World Gastroenterology Organization.

CLD, and the risks of iatrogenic COVID-19 in patients exposed to the health care system.⁴⁷

In general, patients with stable, compensated CLD should postpone routine testing and use telemedicine or telephone visits, whenever possible.^{39,40,48,49} Further, these patients should receive pneumococcus and influenza vaccinations.⁴¹ WGO recommendations for the management of CLD patients in the COVID-19 era are shown in Table 7.

Performing Procedures During COVID-19

CLD patients, particularly those with advanced or decompensated cirrhosis, often require therapeutic or prophylactic interventions. Whenever possible, noninvasive risk assessment should be performed to triage patients and identify those who should definitely undergo a procedure. There is general agreement that procedures should not be performed in CLD patients except for urgent or life-threatening conditions; nonurgent or elective procedures should be postponed but reviewed periodically to ensure that the patient's condition remains stable.

Human-to-human transmission of SARS-CoV-2 occurs mainly through respiratory secretions and aerosols but it can, also, be transmitted by feces and environmental surfaces.^{50–52} The goal of performing procedures for CLD patients during the current pandemic is to provide appropriate, necessary care while minimizing the transmission of SARS-CoV-2 to and from patients and health care providers.

Endoscopy

The risk of transmission for patients can be minimized by screening patients at entry to detect possible SARS-CoV-

2 infection, minimizing exposure in waiting and recovery areas, and ensuring disinfection of equipment and the endoscopy room.

Endoscopy is, generally, a high-risk procedure that exposes health care providers to respiratory and/or GI fluids⁵² and upper endoscopy, an aerosol-generating medical procedure, poses greater risks than lower endoscopy.

To minimize the risk to endoscopy personnel, they should always follow appropriate hand washing and personal protective equipment (PPE) usage protocols, including the use of N95 masks, double gloves, hairnets, waterproof gowns, and protective eyewear.^{53–55} If possible, procedures should be performed in a negative pressure room for patients who are known or are very likely to be COVID-19 positive.⁵⁴

Guidance regarding the use of PPE, particularly in resource restrained countries, has been issued by WGO.⁵⁶

For CLD patients, the indications for urgent or emergency endoscopic procedures relate to the management of active GI tract bleeding, biliary sepsis, or pancreatitis.

Variceal banding should be performed for high-risk patients (who had been assessed in the pre-COVID era) with large varices and red spots, recent variceal bleeding, signs of significant portal hypertension (large volume ascites, thrombocytopenia $< 100 \times 10^9/\text{mL}$), or with signs of active bleeding (hematemesis or melena).^{40,57} Endoscopic screening for varices in patients with cirrhosis should be deferred.

The indications for endoscopic retrograde cholangiopancreatography should be reviewed by experts to identify cases of cholangitis, acute biliary pancreatitis, sepsis, or high suspicion of cholangiocarcinoma^{40,53,57,58} that require intervention; nonurgent procedures should be deferred and reviewed regularly in case the patient's status changes. Noninvasive procedures should be the default unless intervention is clearly needed.

Paracentesis

Although there are no reports of SARS-CoV-2 in peritoneal fluid, paracentesis should be performed with appropriate PPE and the patient should wear a surgical mask. Paracentesis is, rarely, an urgent or emergency procedure, unless it is performed for suspected spontaneous bacterial peritonitis, for evaluating spontaneous bacterial peritonitis treatment response at day 3 or for refractory, large volume ascites.

Transjugular Intrahepatic Portosystemic Shunt

There are no reported cases of transjugular intrahepatic portosystemic shunt insertion in COVID-19 patients but it is a risky, time-consuming procedure, which may require hospital admission and, thus, it should only be performed in life-threatening cases of refractory variceal bleeding.⁵⁷

WGO recommendations on performing procedures during the COVID-19 era are shown in Table 8.

Therapies Under Investigation for COVID-19 and Potential Hepatotoxicity

Currently, there are no drugs approved for COVID-19 although many are under investigation. When considering COVID-19 therapy, CLD patients are at high risk of adverse events from drug toxicities due to impaired liver function (ie, Child-Pugh B/C cirrhosis)⁴⁰ or from drug-drug interactions, especially in liver transplant patients receiving immunosuppressive therapies with calcineurin inhibitors (cyclosporine or tacrolimus) or mTOR inhibitors (sirolimus or everolimus) that require close monitoring.

TABLE 8. WGO Recommendations for Performing Procedures During the COVID-19 Era

Interventional procedures, such as endoscopy and ERCP, should not be performed in patients with CLD unless they are strictly necessary, such as those with high-risk varices or cholangitis
Pure screening of gastric and esophageal varices in patients with stable cirrhosis should be rescheduled
Endoscopy should always be performed using appropriate PPE. Please see recent WGO guidance on use appropriate use of PPE
Ensuring proper disinfection of equipment and the endoscopy room, minimize exposure in waiting and recovery areas and triage patients at entry, using well-trained staff is of extreme importance to ensure patient safety
Clinicians should consider screening all patients undergoing endoscopy using a rapid COVID-19 test before the procedure
In resource poor settings, pooled RT-PCR for SARS-CoV-2, as a screening measure before endoscopy, may be used to reduce costs
TIPS insertion should only be performed in life-threatening cases of refractory variceal bleeding

CLD indicates chronic liver disease; ERCP, endoscopic retrograde cholangiopancreatography; PPE, personal protective equipment; RT-PCR, reverse-transcription polymerase chain reaction; WGO, World Gastroenterology Organization.

Remdesivir is a nucleoside analog that is approved in the United States for emergency use for COVID-19. It is a viral RNA polymerase inhibitor that inhibits SARS-CoV-2 in vitro.⁵⁹ Case reports of benefit in COVID-19⁶⁰ were confirmed in a recent double-blind placebo-controlled randomized study in 1063 patients.⁶¹ There is no experience so far in patients with cirrhosis but experience with nucleoside analogs in chronic hepatitis B and C suggests that remdesivir may be safer than other drug classes.⁴⁰ Liver toxicity with ALT elevation is a possible adverse event. No relevant drug-drug interactions are expected.⁶²

Chloroquine and hydroxychloroquine interfere with the ACE2 receptor and act as an endosomal acidification fusion inhibitor. Initial reports that hydroxychloroquine, with azithromycin, reduced viral load in COVID-19 patients have not been confirmed⁶³ although a recent retrospective multicenter observational study reported that patients receiving hydroxychloroquine, with or without azithromycin, had higher survival rates than patients receiving neither drug.⁶⁴ Still, it is currently recommended by WHO that their use should be restricted to clinical trials for postexposure prophylaxis only. The use of chloroquine and hydroxychloroquine should prompt exclusion of G6PD deficiency, review of drug-drug interactions, especially for immunosuppressive drugs, close monitoring of drug levels of calcineurin or mTOR inhibitors,⁶² and monitoring for severe QT prolongation. Hepatotoxicity due to hydroxychloroquine has been described but is rare.⁶⁵

Lopinavir/ritonavir are protease inhibitors approved for second-line HIV treatment but they have no proven efficacy in severe COVID-19.⁶⁶ Because of well-documented interactions with immunosuppressive drugs, calcineurin inhibitor drug levels monitoring is recommended, while mTOR inhibitors should not be coadministered.⁶² Patients with decompensated cirrhosis should not be treated, based on the experience with protease inhibitors in HCV. The risk of lopinavir-associated hepatotoxicity in patients with very advanced liver disease is low.⁶⁷

Tocilizumab is a humanized monoclonal antibody against IL-6 receptor that suppresses the cytokine release syndrome observed in COVID-19. Rises in ALT are

frequent but clinically apparent liver injury with jaundice is rare.⁶⁸ It can cause HBV reactivation⁶⁹ and it should not be used in decompensated cirrhosis.⁴⁰

Favipiravir is a guanine analog that is an RNA-dependent RNA polymerase (RdRp) inhibitor, approved for influenza in Japan. Studies have revealed that favipiravir showed better treatment outcomes in COVID-19 patients in terms of their disease progression and viral clearance.⁷⁰ ALT and AST elevation is a possible side effect, whereas no data in cirrhosis are available.⁴⁰

Sofosbuvir, a nucleotide analog that inhibits HCV RdRp, essential for viral replication, and acts as a chain terminator,⁷¹ was originally approved for HCV. It binds to SARS-CoV-2 RdRp in vitro²⁸ and may, therefore, be effective, with or without ribavirin, for COVID-19. On the basis of experience with chronic hepatitis, including decompensated cirrhosis, sofosbuvir is safe for CLD patients although ribavirin may cause severe hemolytic anemia.⁴⁰

Convalescent plasma shows a potential therapeutic effect with low risk in severe COVID-19⁷² but there is no experience with its use CLD patients who have COVID-19 patients.⁴⁰

Dexamethasone, 6 mg daily for up to 10 days, reduced 28-day mortality, the primary outcome, compared with standard of care (21.6% vs. 24.6%, $P < 0.001$) in a randomized, controlled, open-label trial performed in over 6000 patients at 176 hospitals in the United Kingdom.⁷³ There are no specific concerns regarding the use of dexamethasone in CLD patients.

WGO recommendations on management and safety of COVID-19 disease with investigational drugs are shown in Table 9.

MANAGEMENT OF COMPLICATIONS OF LIVER DISEASE DURING THE COVID-19 PANDEMIC

Screening and Treatment of HCC

HCC is the fifth most common tumor, globally, and the second most common cause of cancer-related death⁷⁴; in contrast to most common cancers, HCC incidence and mortality rates continue to rise.^{75,76}

Routine HCC surveillance can be postponed for 2 to 3 months but probably no longer for patients with stable, fully compensated cirrhosis, high-risk HBV or MAFLD.^{39,40} Patients with cirrhosis and a suspect nodule or elevated AFP should continue surveillance imaging exams.⁷⁷

All patients being evaluated for HCC must first be screened for COVID-19^{39,77,78}; if possible, patients should not be seen in person before an initial telemedicine or

telephone interview, a review of all previous relevant records and imaging and a full multidisciplinary team (MDT) review. The optimal standard of care is an MDT to provide expertise in transplant surgery, hepatology, oncology, body image and interventional radiology, pathology, psychology or psychiatry and social work^{39,78} and, in the era of COVID-19, infectious disease specialists, pulmonologists are especially critical, along with pharmacologists/pharmacists, to care for these very complex patients. MDT care has been shown to increase survival as compared with non-MDT care.⁷⁹ However, we do recognize that in many parts of the world such an MDT is difficult to bring together, in particular, considering the increased work load of infectious disease specialists and pulmonologists. It may hence suffice to consult them whenever deemed clinically necessary.

COVID-19-negative patients should be managed according to local protocols with additional steps to minimize COVID-19 exposure, including the use of telemedicine visits and minimal intervention therapies and the avoidance of strategies requiring anesthesiologists, surgeons, interventional radiologists, or infusion therapies, to reduce risks to patients and care givers and avoid diversion of resources from the care of severely-ill COVID-19 patients.^{39,78}

COVID-19-positive HCC patients may, reasonably, be monitored closely for 1 to 2 months with AFP and imaging while determining the course of their COVID-19 disease before starting HCC therapy, unless there is, already, extensive tumor burden or multiple lesions. Many COVID-19 patients will resolve their infection in a matter of weeks. The effects of HCC on COVID-19 severity and of COVID-19 on HCC progression are not known but the slow median doubling time of HCC and the reported resolution of COVID-19 in a matter of weeks for many patients support a rationale for short delays in HCC treatment⁸⁰ and radiologic surveillance, given other COVID-19-related demands on health care institutions.³⁹

Nonsurgical treatment approaches are recommended in most cases to reduce stress and risks to patients and staff in the OR and intensive care unit.^{39,78} Depending on local availability, transarterial chemoembolization, transarterial radioembolization, radiofrequency ablation, or stereotactic body radiation therapy would be the first line of therapy^{39,78}; transarterial radioembolization may be preferable for COVID-19 patients who require urgent therapy to reduce the potential effects of that chemoembolization-related immunosuppression on recovery from COVID-19. If these first-line therapies are unavailable, ultrasound-guided percutaneous ethanol injection is an appropriate temporizing measure.⁸¹ The WGO Global Guidelines provide additional details of resource-relevant approaches to the management of HCC.⁸²

In the absence of published reports on chemotherapy or immunotherapy in the presence of COVID-19 to prolong life in advanced HCC, no recommendations are possible. The International Liver Cancer Association suggests that oral tyrosine kinase inhibitors may be preferred for patients with advanced HCC requiring systemic therapy to minimize nosocomial exposure during infusion regimens.⁷⁸

The ultimate therapy for HCC remains liver transplantation if available and appropriate, recognizing that the COVID-19 pandemic may reduce access. As for HCC treatment, transplantation may, reasonably, be delayed to allow resolution of the patient's COVID-19 disease.

WGO recommendations for screening and treatment of HCC in the COVID-19 era are shown in Tables 10 and 11.

TABLE 9. WGO Recommendations of Investigational Drugs for the Management of COVID-19

No recommendation can be currently made with regards to treatment of COVID-19, as there are no drugs approved for COVID-19, although many are under investigation
Evolving treatment data should be thoroughly evaluated by experts, bearing in mind issues of efficacy, safety, local access, and affordability
So far, favorable data have been reported for remdesivir, favipiravir, and dexamethasone
Abnormal liver tests should not be a contraindication to using COVID-19 experimental therapies if needed

WGO indicates World Gastroenterology Organization.

TABLE 10. WGO Recommendations on Screening and Treatment of HCC During the COVID-19 Era

Routine HCC surveillance can be postponed for 2-3 mo in patients who are otherwise stable
All patients being evaluated for the diagnosis and management of HCC must first be screened for COVID-19
It is recommended to include ID specialists and pulmonologists in the multidisciplinary team for HCC care, especially during the COVID-19 pandemic
In patients with concomitant COVID-19, the slow median doubling time supports a rationale for a short delay in initiating treatment for the HCC
Nonsurgical treatment approaches are recommended in most cases, depending on local availability. Percutaneous ethanol injection can be a viable option in low-middle income countries, when other options are not available
Preferable use of oral tyrosine kinase inhibitors is recommended, to avoid nosocomial exposure associated with receiving infusion regimens
Delaying transplant to allow the COVID-19 to resolve is preferred, if possible

HCC indicates hepatocellular carcinoma; WGO, World Gastroenterology Organization.

Liver Transplantation

COVID-19 is affecting all aspects of hepatology, including the quality of care.⁴⁷ Liver transplantation is particularly challenging because it must consider risks to both the donor and the recipient. General guidance should be supported by hospital-specific transplant policies to optimize resource utilization and limit risks to patients and providers.

Experience with transplantation for COVID-19 patients is very limited; 2 COVID-positive HCC patients survived liver transplantation and recovered despite prolonged post-operative courses and infectious complications after increased immunosuppression for rejection episodes.^{39,83} Liver transplantation in COVID-19-positive patients remains a last choice until effective COVID-19 treatments are available and should be undertaken only after careful discussion by the MDT, the patient and the patient's family.

TABLE 11. WGO Recommendations for Liver Transplantation in the Era of COVID-19

Listing for liver transplantation should be restricted to patients with a poor short-term prognosis such as patients with high MELD score, acute liver failure or liver cancer within Milan criteria
LDLT for patients with high MELD score and acute liver failure may be considered in areas of the world where LDLT represents the majority of transplantations done. Access to LDLT will need to be dynamically assessed as locations begin to reopen
Testing organ donors for the presence of virus is recommended, and those that are positive should be ineligible for donation
Recipients should be screened for SARS-CoV-2 by rapid PCR testing. If found positive transplantation may be postponed until after recovery from SARS-CoV-2 infection
PTIS regimens should not be changed. However, in patients diagnosed with COVID-19, reduction of PTIS should be considered

LDLT indicates living donor liver transplantation; MELD, model for end-stage liver disease; PCR, polymerase chain reaction; PTIS, posttransplantation immunosuppression.

Preliver Transplantation

Patients being considered for liver transplantation are at risk not only during evaluation but, also, if evaluation is delayed. Investigations should, therefore, follow clinical guidelines for transplantation while limiting exposure to COVID-19 by the use of telemedicine or telephone visits; in-person visits should be restricted to urgent issues such as new symptoms or test results indicating decompensation. In the post-COVID-19 era, pretransplantation evaluation may also need to acknowledge and accommodate the effects of COVID-19 on patients' adherence to management recommendations, particularly for ALD patients.

High MELD/Acute

Evaluation for liver transplantation is traditionally encouraged when patients meet minimal listing criteria, have unmanageable advanced liver disease or have liver cancer within Milan criteria. However, the COVID-19 pandemic is expected to affect organ availability and peritransplant risk so the decision to evaluate must balance the patient's prognosis, age and comorbidities against the need for testing and the risk of SARS-CoV-2 exposure. Individuals with a poor short-term prognosis requiring prompt transplantation should continue to be evaluated and listed. This applies for patients with high MELD and acute hepatic failure and, also, for liver cancer patients who must be listed so that they can start accruing time and points which render them more competitive for transplantation.

Elective procedures, including living donor liver transplantation (LDLT), have generally been deferred for all but pediatric indications.³⁹ However, where LDLT constitutes the majority of transplantations, it may be considered in selected transplantation centers for patients with high MELD score and acute liver failure. Access to LDLT will need to be dynamically assessed as locations begin to reopen. The COVID-related risk to the donor engaging in medical care in a COVID environment needs to be considered.

There are few data regarding transmission of SARS-CoV-2 through transplant. Potential donors should be tested for COVID-19, those who are positive being ineligible to donate.^{41,84} Recipients should be screened with rapid COVID-19 polymerase chain reaction testing before surgery although the results may mislead or contribute to delays. A computed tomography chest without contrast can be performed to look for typical opacities if a potential recipient is symptomatic.⁸⁴

Postliver Transplant

Routine posttransplant monitoring should continue, but in-person visits should be minimized. All patients should be encouraged, strongly, to practise hand washing and social distancing, including telework options. Posttransplant immune suppression is not reported to be a risk factor for mortality with SARS-CoV-2 although more data are needed. Prophylactic reduction in immunosuppression is not recommended but immune suppressed patients who develop COVID-19 should reduce immunosuppression to the lowest levels, especially if more than 6 months have elapsed since transplantation.⁴⁰

WGO recommendations for liver transplantation in the COVID-19 era are shown in Table 11.

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