

Review Article

Liver disease in the Era of Coronavirus Disease 19 (COVID-19) pandemic

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Introduction

Coronavirus infections have caused outbreaks in humans: SARS-COV ((Severe Acute Respiratory Syndrome) and MERS-CoV (Middle East Respiratory Syndrome) resulting in significant mortality and morbidity.

A novel strain of virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China following outbreak of pneumonia in December 2019. Despite efforts at containment, this virus has now spread rapidly across most, if not all, of the world and has caused the worst world-wide pandemic since that of Spanish flu of 1918-1919. It has resulted in significant morbidity and mortality worldwide stretching already overburdened healthcare systems throughout the world.

SARS-Cov-2 belongs to Coronaviridae (CoV) family named after their "crown-like" appearance observed under electron microscopy. CoV's are subclassified into 4 genera: α -CoV, β -CoV, γ -CoV, and δ -CoV based on their phylogenetic clustering [1,2].

SARS-CoV-2 is a single, positive-stranded RNA virus belonging to β group that replicates using a virally encoded RNA-dependent RNA polymerase. SARS-CoV-2 is very similar to other SARS-COV and share the same receptor, Angiotensin converting enzyme 2 (ACE2). The crown like projections bind specifically to ACE2, which facilitates uptake into cells. Fortunately, most infected patients develop only mild symptoms (fever, tiredness and dry cough).

However, patients >65 years old, patients with cardiovascular disease, diabetes mellitus, hypertension, or chronic obstructive pulmonary disease are at increased risk for severe COVID-19 disease (Acute respiratory distress

More Information

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Submitted: 28 August 2020

Approved: 16 October 2020

Published: 20 October 2020

How to cite this article: Besur S, Begum R, Gunabushanam V, Bonkovsky HL. Liver disease in the Era of Coronavirus Disease 19 (COVID-19) pandemic. *Ann Clin Gastroenterol Hepatol.* 2020; 4: 052-057.

DOI: 10.29328/journal.acgh.1001023

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Keywords: Coronavirus infections; Abnormal liver tests; Liver transplant; Immunosuppression; viral hepatitis

Abbreviations: COVID19: Coronavirus Disease 19; SARS-CoV: Severe Acute Respiratory Syndrome; MERS-CoV: Middle East Respiratory Syndrome; CoV: Coronaviridae; ACE 2: Angiotensin Converting Enzyme 2; ULN: Upper Limit of Normal; EASL: European Association of Study of Liver disease; AASLD: American Association of Liver Disease; ACLF: Acute-on-Chronic Liver Failure; CMS: Centers for Medicare and Medicaid Services



syndrome & multiorgan failure). Men are particularly prone to more severe infection, and there is some evidence to suggest that higher levels of serum ferritin, perhaps, in part related to iron overload, which is more prevalent in men than women, may also be associated with more severe disease and outcomes [3,4]. SARS-CoV-2 can infect the liver by binding through angiotensin-converting enzyme 2 (ACE2) present cholangiocytes [5,6,7]. The effects of COVID-19 infection in patients with liver disease, pre/post liver transplantation and hepatocellular cancer remain unclear at present time. This paper aims to summarize information available so far for the management of liver disease patients in the era of COVID infection.

Abnormal liver biochemistry

Abnormal liver biochemistries have been noted in 14-



53% of patients hospitalized with COVID-19 disease [8-10]. In patients with fatal COVID-19 the incidence of liver injury is significantly higher (58% -78%) [11,12]. The elevations in liver tests are mild [1-2 times upper limit of normal (ULN)] at the time of admission in 90% of patients but often become more pronounced during hospitalization [13]. The elevations of the liver enzymes show improvement with effective treatment and acute hepatitis occurs more commonly in severe COVID-19 [9,10].

Gamma glutamyl transferase (GGT) levels are increased in severe cases but serum alkaline phosphatase (AKP) levels usually remain normal in both mild and severe cases. Abnormal liver tests could be the result of virus induced cytotoxicity or due to inflammatory response to immune mediated liver injury [14,15]. Liver biopsy findings are non-specific and show micro vesicular steatosis, mixed lobular and portal round-cell inflammatory activity, and focal hepatocyte necrosis. Liver biopsy findings suggest overactivation of T cell immune mediated liver injury rather than direct cytopathic damage from virus-specific effector cells seen in other viral respiratory infections [16]. Abnormalities in liver tests in patients without underlying liver disease could also be secondary to ischemia/hypotension, positive pressure ventilation resulting in hepatic congestion, hepatotoxic effects of drugs used to treat COVID-19 (e.g., Hydroxy Chloroquine, Tocilizumab, Baricitinib) or myositis. Thus, it is difficult to differentiate whether increases in liver biochemistries are due to SARS-CoV-2 infection or due to other causes [11,17]. Pneumonia-associated hypoxia might also contribute to liver injury or even develop into liver failure in patients with COVID-19 who are critically ill [10]. Some of the investigational therapeutic drugs like Tocilizumab, Chloroquine, Hydroxychloroquine, and Remdesivir are not contraindicated in patients with abnormal liver tests, although serum Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) levels $>5\times$ ULN may exclude patients from inclusion in trials of some investigational agents. Patients with abnormal liver chemistries can be evaluated by excluding drugs as a cause for abnormal liver chemistries, investigating to determine viral hepatitis, ischemia and congestion.

As with abnormal liver tests in most acute infectious illnesses, if ALT/AST are elevated but stable in COVID-19 patients, monitor closely; consider liver biopsy if ALT/AST $> 5\times$ ULN, if serum total bilirubin is increased and rising, or if there is evidence of developing acute liver failure with hepatic encephalopathy and INR > 1.5 . Patients with higher AST compared to ALT are at higher risk of severe COVID-19 infection and mortality.

However, even then, liver biopsy may not be wise unless results of the biopsy would be likely to affect overall management, e.g.: patients with severe pneumonia or multi-organ 'cytokine storm syndrome' are not candidates for

liver transplantation. Patients with abnormal liver tests at presentation, and particularly those with hepatocellular or mixed patterns (OR=9.04, 95% CI 3.19-25.6, $p < 0.001$) are at greater risk of progression to severe COVID-19 disease compared to those with normal liver tests [13].

Viral hepatitis

Chronic viral hepatitis (Hepatitis B & C) does not seem to affect the course or outcome of COVID-19 patients with the information available unlike SARS-CoV [18]. Patients with chronic hepatitis B and hepatitis C already on treatment should continue antivirals. Initiation of evaluation and treatment for chronic hepatitis C in patients with COVID-19 should be postponed to a later time.

Autoimmune liver disease

Patients on immunosuppression do not seem to be at increased risk of SARS-CoV-2 infection and COVID-19 disease based on data available from past and present Corona virus outbreaks.

Routine reductions in the dose of immunosuppressants is not recommended in patients with SARS-CoV-2 infection. Medication-induced lymphopenia, or bacterial/fungal superinfection are indications for immunosuppressant dose reduction with specialist supervision. In patients with Primary Biliary Cholangitis (PBC) on Ursodiol should continue medication without any change in dosing. Liver biopsy should be performed prior to diagnosing flare and making significant changes to autoimmune hepatitis treatment in COVID-19 patients [19,20].

Non-Alcoholic Fatty Liver Disease (NAFLD)/Non-Alcoholic Steatohepatitis (NASH)

Diabetes, hypertension and obesity are known risk factors for severe COVID 19. They are also commonly associated in patients with NAFLD/NASH. A recent observational study by Dong Ji et al analyzed the implication of NAFLD in COVID 19 patients at a single center in China [21]. Liver injury was observed in 75.2% patients and liver test abnormalities were predominantly hepatocellular. There was higher risk of disease progression, likelihood of abnormal liver function from admission to discharge and longer viral shedding time when compared with non-NAFLD subjects [22].

Patients with NAFLD and obesity are known to produce increased pro-inflammatory cytokines like TNF- α by adipose cells and Kupffer cells. This associated with possible derailment of functional balance between inflammation-promoting M1 macrophages and inflammation-suppressing M2 macrophages is thought to cause progression of COVID-19 in NAFLD/NASH patients [19].

Hepatocellular Cancer (HCC)

Patient with newly diagnosed HCC should be informed



about the diagnosis and treatment plan using virtual media (telephone/Video) reducing risk of exposure to SARS-CoV-2 virus. There is divergence of views between European Association of Study of Liver disease (EASL) and American Association of Liver Disease (AASLD) regarding locoregional treatments [19,20]. AASLD recommends proceeding with HCC treatments while EASL prefers postponement of therapy whenever possible. Immune checkpoint inhibitor treatment should be withdrawn and decision to continue tyrosine kinase inhibitor should be individualized [23]. Recommend early hospitalization in patients with HCC who develop COVID-19.

Compensated and decompensated cirrhosis

There is limited information regarding effects of SARS-CoV-2 on cirrhotic patients.

A recent multi center retrospective study of patients with SARS-CoV-2 infection from 37 healthcare organizations (HCOs) found increased risk of mortality in cirrhotic patients (cirrhosis (RR 4.6, 95% CI 2.6-8.3, p - value < 0.001 [24].

There is no evidence to suggest increased risk of decompensation or development of acute-on-chronic liver failure (ACLF), as has been shown for influenza infection [23]. Conversely cirrhotic patients who develop acute decompensation or ACLF should be tested for SARS-CoV-2 infection.

Routine follow-up appointments should be done using telemedicine. Spontaneous bacterial peritonitis and hepatic encephalopathy prophylaxis guidelines should be closely followed to avoid hospitalization. All cirrhotic patients should be vaccinated against *Streptococcus pneumoniae* [Pneumovax, Prevnar] and Influenza.

Routine screening for HCC and esophageal varices should be postponed to a later date to avoid inadvertent exposure to SARS-CoV-2. Esophageal varices screening can be offered to high risk patients in accordance with Baveno VI criteria. All cirrhotic patients, including those listed for liver transplant, should avoid in-person dietitian, social work assessments, liver transplant education, financial counseling and support meetings (Alcoholics Anonymous). Alternatively, telephone or video consultations should be encouraged.

Cirrhotic COVID-19 patients should not be treated with drugs that are being studied for anti-COVID-19 effects (e.g., Favipiravir/Favilavir, Camostat, Tocilizumab, Baricitinib, Remdesivir) except in the context of IRB-approved formal clinical trials.

Pre-liver transplant/listed patients

Routine inpatient liver transplant evaluations should be avoided to reduce risk of exposure to virus.

Only patients with poor short-term prognosis like those

with high MELD scores, risk of decompensation, or tumor progression should be considered for work up for liver transplantation. Centers for Medicare and Medicaid Services (CMS) categorize transplant surgery as Tier 3b ("do not postpone").

Donor and recipients should be evaluated for COVID-19 symptoms in addition to testing for SARS-CoV-2 prior to liver transplantation since there is significant false negative rates. Liver transplantation is not recommended if the donor or the recipient tests positive for SARS-CoV-2, has close contact with confirmed COVID-19 case or has traveled to high risk area within last 14 days [20].

Chest computerized tomography is done in many centers to exclude viral pneumonitis prior to liver transplantation. Potential liver transplant recipients should be informed about risk of nosocomial COVID-19 infection and restriction/prohibition of visitor access during hospital stay. Living donor transplants should be avoided whenever possible. Exposure to SARS COV-2 can be minimized by having backup recipients wait at home and accepting graft with low risk of delayed function.

Transplant surgeons and staff are at increased risk of contracting infection and they should limit travel for organ retrieval and utilize courier services for organ transport. Surgeons and staff should avoid being in the room when patient is either being intubated or extubated whenever possible to reduce risk of contracting the virus [19,20].

Post-liver transplant patients

Gown/face protection, frequent handwashing, maintaining social distancing should be followed and drainage fluids should be considered contaminated in immediate post-transplant patients. Outpatient in person follow up should be avoided by effective use of telemedicine.

Post-transplant patients should be advised against travel during the pandemic and to work from home whenever possible. Patients and their care givers should be provided with documentation for leave of absence if necessary [25].

Information available so far does not show increased risk of mortality like other corona virus epidemics (SARS/MERS). Post-transplant patients with COVID-19 have prolonged viral shedding, high viral titers hence likely more infectious [25,26].

Immunosuppression should not be changed or stopped for asymptomatic post-transplant patients without SARS-CoV-2 infection. Antimetabolites (mycophenolic acid, mycophenolate mofetil) should be stopped or reduced and calcineurin inhibitor (Cyclosporin, Tacrolimus) can be maintained in post-liver transplant patients with COVID-19 with specialist guidance [27].

Risks of nosocomial infection and mortality should be

considered prior to pursuing imaging or procedures (liver biopsy, endoscopic retrograde pancreatography). Several treatment options are being used for management of COVID-19 drug interactions should be considered before treatment initiation. Lopinavir/ritonavir and mammalian target of rapamycin (m-Tor) inhibitors should not be used concurrently because of drug-drug interactions and cyclosporine, tacrolimus levels should be closely monitored.

Hydroxychloroquine ± Azithromycin therapy requires close monitoring of immunosuppressant drug level

is required [3,27]. Patients treated with Remdesivir, Tocilizumab, Umifenovir, Favipiravir/Favilavir, Baricitinib, Camostat, Emapalumab, sofosbuvir and convalescent plasma can have minimal elevation of transaminases, liver tests should be closely monitored but medications need not be discontinued.

Impact of SARS-2-COV-2 infection on long term management of hepatology patients

SARS-2-COV-2 pandemic has caused serious disruption in

Table 1: Impact of SARS-2-COV-2 infection on Liver.

Liver Condition	Characteristics in SARS COV-2 infection	Evaluation/Management	Treatment
Liver Tests (LT)	Affects 14-53% hospitalized with COVID 19 disease AST/ALT elevations are usually 1-2 times ULN GGT levels increased in severe cases Alkaline Phosphatase normal in mild and severe cases Liver biopsy findings nonspecific (micro vesicular steatosis, mixed lobular and portal activity to focal necrosis)	LT's should be closely monitored Other causes of LT abnormalities should be considered Consider liver biopsy if AST/ALT >5 times ULN	Investigational treatments not contraindicated if AST/ALT <5 times ULN and no jaundice, no encephalopathy, no right upper quadrant pain, nausea or vomiting
Viral Hepatitis (Chronic hepatitis B & C)	Does not seem to affect the course or outcome of COVID-19 patients	Monitor LT's, albumin, INR and one-time viral load Patients on treatment for HBV, HCV with antiviral therapy should continue treatment.	Avoid initiating treatment for hepatitis C Investigational treatments for COVID-19 not contraindicated
Autoimmune liver diseases (AIH, PBC, PSC)	They do not seem to be at increased risk of SARS-CoV-2 infection and COVID-19 disease	Monitor LT's Routine reductions in the dose of immunosuppressants/ ursodiol is not recommended	Liver biopsy should be performed prior to diagnosing flare and making significant changes to autoimmune hepatitis treatment Investigational treatments for COVID-19 not contraindicated
Hepatocellular Cancer [HCC]	Patients with HCC do not seem to be at increased risk of SARS-CoV-2 infection and COVID 19 disease	Postponement of locoregional therapy whenever possible Immune checkpoint inhibitor treatment should be withdrawn	Investigational treatments for COVID-19 not contraindicated
NAFLD/NASH	Liver injury was observed in 75.2% of patients Liver test abnormalities predominantly hepatocellular Higher risk of disease progression and longer viral shedding time	Monitor LT's	Investigational treatments for COVID-19 not contraindicated
Cirrhosis (Compensated/Decompensated)	No evidence to suggest increased risk of decompensation or development of acute-on-chronic liver failure Cirrhotic patients who develop acute decompensation or ACLF should be tested for SARS-CoV-2 infection	Monitor LT's Spontaneous bacterial peritonitis and hepatic encephalopathy prophylaxis guidelines should be closely followed Vaccination against <i>Str pneumoniae</i> and Influenza Esophageal varices screening can be offered to high risk patients in accordance with Baveno VI criteria	Tocilizumab, Baricitinib are contraindicated No data available for Favipiravir/Favilavir, Camostat
Pre-Liver Transplant/Listed Patients	Cirrhotic patients who develop acute decompensation or ACLF should be tested for SARS-CoV-2 infection	Patients with high MELD scores, risk of decompensation, or tumor progression should be considered for work up for liver transplantation Liver transplantation is not recommended if the donor or the recipient tests positive for SARS-CoV-2, has close contact with confirmed COVID 19 case or has traveled to high risk area within last 14 days Living donor transplants should be avoided whenever possible	Investigational treatments determined by presence of cirrhosis
Post-Liver Transplant patients	They do not seem to be at increased risk of SARS-CoV-2 infection and COVID-19 disease	Immunosuppression should not be changed or stopped for asymptomatic post-transplant patients without SARS-COV-2 infection Antimetabolites (mycophenolic acid, mycophenolate mofetil) should be stopped or reduced and calcineurin inhibitor (Cyclosporin, Tacrolimus) can be maintained in post-liver transplant patients with COVID-19 with specialist guidance	Hydroxychloroquine ± Azithromycin therapy requires close monitoring of immunosuppressant drug level Investigational treatments can cause mild elevation of LFT

Table 2: Impact of SARS-2-COV-2 infection on Patient, Provider & Health care systems

Patient	Disruption with follow up and screening Difficulty with exercising, maintaining healthy diet Reduced access to support groups Postponement of planned procedures (Liver resection, biopsy etc) Loss of employment & medical insurance Risk of disease progression with adverse long- term implications
Provider	Failure to diagnose at earlier stage (HCC) Loss of patients for long term follow up Lack of necessary investigations in a timely manner Increased demand for follow up/procedure slots after pandemic Psychological stress from reduced health care resources and cuts
Health care systems	Increased utilization of fixed resources Anticipated loss of patient medical insurance Postponement/cancellation of planned procedures Reduced revenues that jeopardize essential programs Need to furlough or otherwise reduce staffing Adverse effects on morale

the long-term management of patients with liver disease. It is not only having serious impact on management and overall outcome of patients but is expected to have deep impact on health care systems and providers.

Routine screening for HCC and esophageal varices is being deferred. Delaying screening, elective liver resection, locoregional therapies for HCC is safe in majority of patients but may lead to diagnosis of aggressive HCC at a later stage in about 25% of patients [28].

Living donor transplants are being cancelled and deceased donor liver transplants are being offered to limited number of patients because of application of stringent prioritization criteria due to possible risk with nosocomial SARS-2-COV2, concern regarding availability of ventilators, blood products, renal replacement therapy etc. This can lead to increased wait list mortality. Angelico R et al. reported 25 % reduction in donor procurement during the first 4 weeks of the pandemic in Italy [29].

Chronic liver disease patients are at increased risk of physical deconditioning, frailty, decompensation and malnutrition because of reduction in mobility due to social distancing policies, reduced access to mental health care providers, support groups and meal delivery. Relatively easier availability of processed foods and alcohol increase risk of further decompensation. The framework that had been developed for managing patients with chronic liver disease has been disrupted during this pandemic because of issues with routine follow up, screening and missed diagnosis.

The COVID-19 pandemic is expected to result in long term disruption of world economy which may have implications regarding insurance coverage for significant section of the population. Healthcare systems may make up for the financial losses by freezing new hires, postponing new investments, making cuts in staff etc. Adverse patient outcomes because of delayed follow up, postponement of routine screening and treatment procedures along with financial challenges can add serious psychological stress to already overburdened health care providers.

Conclusion

SARS-COV-2 virus infection can affect the liver (Table 1), but it is unclear if it can cause further worsening in patients with previously existing liver disease. However, it has long term implications for patients with liver disease (Table 2) resulting in significant morbidity and mortality.

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