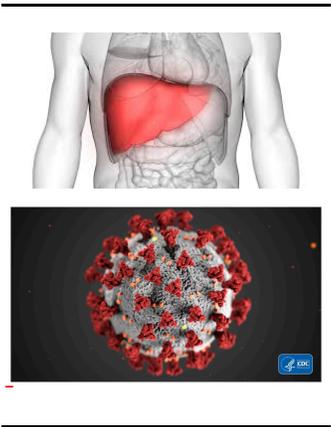




A Guide for Clinicians

Liver Involvement in SARS-CoV2 Infection/ COVID-19

In patients with chronic liver disease and liver transplant patients



In December 2019, an outbreak of a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], previously 2019-nCoV) started in Wuhan, China.² It has since then posed a global threat to human health, with the World Health Organization declaring the spread of COVID-19 as a global pandemic on the 11th of March 2020.

Although a disease primarily affecting the respiratory system through the mechanism of binding with the ACE 2 receptors in lung epithelium, there are some reports of liver test derangements in as high as 16-53% of COVID 19 patients worldwide^{1,2}.

Current evidence proposes that some of the causes for liver test abnormalities in COVID-19 may be due to the following: 1. hepatic response to the cytokine storm; 2. hepatic hypoxia and ischemia; and 3. hepatotoxicity from many of the drugs used to manage the disease. A non-peer reviewed preliminary study suggested that ACE2 receptor expression is enriched in cholangiocytes, indicating that SARS-CoV-2 might directly bind to ACE2-positive cholangiocytes to dysregulate liver function.^{1,2,4}

Patients then with underlying chronic liver disease represent a vulnerable population, particularly those with hepatitis B, liver cirrhosis, and patients on immunosuppression, i.e liver transplant recipients and those with autoimmune hepatitis. These patients are at a higher risk for contracting SARS-CoV-2 infection, may have more severe disease, and may have prolonged shedding of the virus causing increased transmission.

Comorbidity with liver disease and liver dysfunction in patients with SARS-CoV-2 infection

	Patients with SARS-CoV-2 infection	Patients with pre-existing liver conditions	Patients with abnormal liver function	Notes
Guan et al ^a	1099	23 (2.3%)	AST abnormal (22.2%), ALT abnormal (21.3%)	Elevated levels of AST were observed in 112 (18.2%) of 615 patients with non-severe disease and 56 (39.4%) of 142 patients with severe disease. Elevated levels of ALT were observed in 120 (19.8%) of patients with non-severe disease and 38 (28.1%) of 135 patients with severe disease.
Huang et al ^b	41	1 (2.0%)	15 (31.0%)	Patients with severe disease had increased incidence of abnormal liver function. Elevation of AST level was observed in eight (62%) of 13 patients in the ICU compared with seven (25%) 25 patients who did not require care in the ICU.
Chen et al ^b	99	NA	43 (43.0%)	One patient with severe liver function damage.
Wang et al ^c	138	4 (2.9%)	NA	..
Shi et al ^b	81	7 (8.6%)	43 (53.1%)	Patients who had a diagnosis of COVID-19 confirmed by CT scan while in the subclinical phase had significantly lower incidence of AST abnormality than did patients diagnosed after the onset of symptoms.
Xu et al ^b	62	7 (11.0%)	10 (16.1%)	..
Yang et al ^b	52	NA	15 (29.0%)	No difference for the incidences of abnormal liver function between survivors (30%) and non-survivors (28%).
Our data (unpublished)	56	2 (3.6%)	16 (28.6%)	One fatal case, with evaluated liver injury. ¹¹

AST= aspartate aminotransferase. ALT= alanine aminotransferase. ICU=intensive care unit.

Table: Comorbidity with liver disease and liver dysfunction in patients with SARS-CoV-2 infection

Chao Zhang, Lei Shi, Fu-Sheng Wang. Liver Injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. Published Online 04 March 2020.



The following derangements in liver function tests have so far been reported in initial descriptive studies^{1,2,4}:

- Derangements in ALT and AST have been reported in 16.1% - 53.1 % of patients.
- Abnormal levels of ALT and AST during disease progression in 14–53% of cases reported.
- GGT was found to be elevated in 54% of patients with COVID-19.
- Alkaline phosphatase is elevated in 1.8% of a small series.
- Patients with severe COVID-19 seem to have higher rates of liver dysfunction.
- Liver injury is more prevalent in severe cases than in mild cases of COVID-19.

In a study of 1099 patients with laboratory-confirmed COVID-19, 261 (23.7%) patients with COVID-19 reported having at least one comorbidity, with hypertension, diabetes, and coronary heart disease being the most common. In this study, 23 (2.1%) patients had hepatitis B infection. Severe cases were more likely to have hepatitis B infection (2.4% vs 0.6%) than non-severe cases.^{1,2}

Liver damage in mild cases of COVID-19 is often transient and can return to normal without any special treatment². The use of liver protective drugs has not been validated.

The Philippines has a significant burden of chronic liver disease, being hyperendemic for Hepatitis B. Studies estimate that about 10 million Filipinos have Hepatitis B. The number of Filipinos with Hepatitis C infection is estimated to be much less at about 400-600,000.¹ There are currently no models or registries on the number of cases of liver cirrhosis in the country.

Whether hepatitis B can aggravate the clinical course of COVID-19 remains to be seen. However, primarily when high dose steroids will be used in the treatment of COVID-19, it may be prudent to determine the HBsAg status of patients at baseline. Those who are diagnosed to have hepatitis B may need antiviral prophylaxis to prevent acute flares of hepatitis B.^{1,2}

Cirrhotic patients belong to the high-risk population, as decompensation of liver disease can be catastrophic. Liver cirrhosis is a condition of decreased immunity, decreased renal reserve, and cardiopulmonary dysfunction in advanced cases. This places these patients at a higher risk of severe COVID-19 disease.^{2,4}

The coexistence of pre-existing liver diseases such as non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, and autoimmune liver disease may lead to more severe patterns of liver injury and enzyme derangements. Monitoring of liver function and careful evaluation for drug hepatotoxicity should be done for all patients with COVID-19.^{1,2}



TRANSPLANT-SPECIFIC RECOMMENDATIONS^{3,5}

No specific reports have been made as of yet on describing the clinical course of post-liver transplant patients with COVID 19, as no such cases have been recorded as of this writing.^{3,5} However, liver transplant recipients, especially those within the first year post-transplant, and patients with autoimmune hepatitis with high levels of immunosuppression, are best assumed to be a highly vulnerable group to COVID-19. As of this time, risk factors for severe infection in this population have not been fully characterized.

GENERAL RECOMMENDATION^{3,5}

Liver transplant patients should be aware of precautions to avoid SARS-CoV-2 infection and this includes strict adherence to the preventive measures against COVID-19 recommended by the WHO.

- Many transplant recipients have medication-induced lymphopenia. Close attention should be paid to transplant patients with suspected or confirmed COVID-19 infection who are lymphopenic. Such attention may include admission (rather than care at home) and paying careful heed to oxygen saturation.

DECEASED DONORS^{3,5}

The CDC has recommended to suspend all non-essential travel by air for all people at increased risk for getting very sick from COVID-19 including transplant recipients.

- Persons who returned from China, Iran, Italy, South Korea, Vietnam, Cambodia, Laos or Myanmar or been exposed to a patient with confirmed or suspected COVID-19 within 14 days should not be accepted as a donor.
- Consider temporary suspension of the deceased donor program in a country with widespread community transmission.
- A tiered suspension plan may also be considered (i.e. deferral of more elective transplants, i.e. kidney, pancreas and heart transplantation for patients with VADs).
- There is no clear reason to suspend deceased donor transplants in countries only experiencing sporadic cases of COVID-19 cases.



LIVING-RELATED TRANSPLANTS^{3,5}

- Living donation should not be performed on either a donor or recipient who has returned from China, Iran, Italy, South Korea, Vietnam, Cambodia, Laos or Myanmar or been exposed to a patient with confirmed or suspected COVID-19 within 14 days.
- In countries with widespread community transmission, temporary suspension of the living-donor kidney and liver transplant programs should be considered.
- If transplantation is required as a life-saving procedure, it can be conducted with appropriate assessment of infection in donor and recipient and with appropriate informed consent.
- Given the paucity of data, candidates with active COVID-19 should be deferred from transplantation.
- It is recommended to have least two negative COVID-19 PCRs documented with complete symptom resolution to avoid adverse events in post-transplant as well as avoid exposure to the healthcare team.

TRANSPLANT RECIPIENTS^{3,5}

- Like all persons, transplant recipients should adhere to travel advisories issued by their respective health authorities/government bodies. This may necessitate postponing travel to China, Iran, Italy, Japan and South Korea, and other areas with high rates of community transmission.
- All patients should be educated about the importance of performing frequent hand hygiene, avoidance of crowds, and applying social distancing.

TRANSPLANT RECIPIENTS RETURNING FROM ABROAD^{3,5}

- Transplant units should be prepared to receive patients who, for various reasons, have been abroad.
 - Such patients should be housed in single rooms with an attached bathroom, and all staff attending to them should be in full PPE, until infection with COVID-19 is ruled out. Coordination is needed with other departments (eg, Radiology, Laboratory) whose services are likely needed. An effort to re-arrange schedules may be needed to permit spatial and temporal separation of patients awaiting COVID-19 “rule-out”.
 - The incubation period of the disease, the asymptomatic shedder, negative PCRs early in the course of the disease combine to make “ruling out” a very difficult task.
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SUMMARY:

1. Presence of pre-existing conditions such as non-alcoholic fatty liver disease, alcoholic liver disease or autoimmune liver disease may lead to more severe patterns of liver injury and enzyme derangements. Monitoring of liver function and careful evaluation for drug hepatotoxicity should be done for all patients with COVID-19.
2. Patients with liver cirrhosis or liver cancer may be more susceptible to severe SARS-CoV-2 infection because of their systemic immunocompromised status. Close attention must be paid to those with pre-existing conditions such as advanced liver disease, especially older patients with other comorbidities.
3. It may be prudent to test for the HBsAg status of COVID-19 patients, especially when immunosuppression is contemplated as a part of treatment.
4. In countries with widespread community transmission of COVID-19, it would be prudent to consider temporary suspension of liver transplant programs or adopting a tiered approach towards suspension, favoring more urgent life-saving transplants over elective cases.
5. The situation is fluid and rapidly-evolving, with recommendations being made on emerging, sometimes non-peer reviewed data.

Preventing transmission from an infected patient to a healthcare worker is of the essence, with careful attention to infection control precautions at the cornerstone. As more information becomes available, these recommendations shall be updated.

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