

Review Article



Management of Patients with Liver Transplant and Chronic Liver Diseases During COVID-19 Pandemic: A Brief Review

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Abstract

The coronavirus associated disease 2019 (COVID-19) caused by the SARS-CoV-2 virus has rapidly spread all around the world and became pandemic in March 2020. Data on liver transplantation and chronic liver disease during the pandemic has remained scarce, and there is little information on whether immunosuppressed patients are at higher risk of developing severe COVID-19 infection. This review provides information for health care providers who care for patients with liver transplantation and chronic liver diseases.

Keywords: COVID-19, Liver disease, Liver transplantation

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Introduction

The COVID-19 infection was first reported in Wuhan in December 2019.¹ This infection is caused by a novel coronavirus (SARS-CoV-2) and became pandemic in March 2020.² In the previous two months, Iran has witnessed more than 88 000 patients with positive respiratory polymerase chain reaction (PCR) test and a case-fatality rate of nearly 6% as of April 24, 2020.³ The transmission of this disease occurs via human-to-human contact, and the major mode of spread is through droplets.⁴

The most common symptoms are fever, fatigue and dry cough and some present with shortness of breath, diarrhea, nausea and vomiting.^{5,6} Some preliminary data has shown that severe disease is related to older age, hypertension, diabetes mellitus and coronary artery disease.⁷

Given the presence of the angiotensin-converting enzyme-2 (ACE2) receptor in the liver and biliary epithelial cells, the liver can be a potential target for COVID-19 infection.⁸⁻¹⁰ One of the presentations of this disease is elevation of liver enzymes which is mostly seen in patients who have been admitted in the hospital with an incidence ranging from 14% to 53.1%.^{11,12} COVID-19 infection may worsen liver function in patients with underlying chronic liver diseases.¹³ The Centers for Disease Control and Prevention (CDC) has stated that patients older than 65 years, and those with liver diseases are at higher risk of

fatal disease.¹⁴

Due to the rapid spread of coronavirus infection and unknown behavior of this disease, there are debates regarding management of chronic liver diseases and patients with liver transplantation during the COVID-19 pandemic. In this review, we aimed to provide data about COVID-19 and its effects on hepatologists, liver transplant providers and their patients.

COVID-19 and Liver Diseases

In those without a history of liver disease, the COVID-19 infection and simultaneous rise in ALT or decrease in serum albumin and platelet count were associated with higher mortality rate.⁶

These laboratory data abnormalities may be due to preexisting liver disease, inflammation or hypercoagulopathy due to the SARS-CoV-2 infection. Cirrhosis as a cause of immune system dysfunction is a risk factor for infection.¹⁵

The chronic hepatitis B virus infection seems not to affect the outcome of COVID-19.⁵ The effect of chronic hepatitis (hepatitis B or C) infection on exacerbation of liver injury due to the SARS-CoV-2 infection is still unknown.¹⁶ It is recommended that treatment of hepatitis B and C should be continued in those who have already been on treatment and do not have COVID-19.¹⁷ Initiation of treatment for

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hepatitis B and C is not recommended in patients with COVID-19, unless there is a high suspicion for severe acute hepatitis.¹⁷

The effect of SARS-CoV-2 infection on clinical and biochemical course of cholestasis in patients with underlying cholestatic liver disease such as primary biliary cholangitis and primary sclerosing cholangitis is not well known with recent available data.¹²

Patients with non-alcoholic fatty liver disease or non-alcoholic steatohepatitis may be at increased risk of severe COVID-19 infection as a result of metabolic syndrome and comorbidities (hypertension, diabetes mellitus and obesity).¹⁸

In patients with autoimmune hepatitis, immunosuppressive agents should be continued unless drug side effects or severe viral infection occur. However, the impact of steroid prescription in patients with autoimmune hepatitis and COVID-19 on disease prognosis remains unclear¹² (Table 1).

Liver Transplantation and COVID-19

Before Transplantation

During a period of 23 years, 4485 liver transplantations were performed in six centers in Iran. Of these, 4106 were from deceased donors and 379 from living donors.¹⁹ Liver transplantation in the Imam Khomeini Hospital Complex affiliated to Tehran University of Medical Sciences, was started in 2002 and 1057 liver transplantations were performed until January 2020.²⁰

However, during the COVID-19 pandemic, liver transplantation is more challenging. All transplant centers should assess their local circumstances and their effect on

patients on the waiting list.

There is currently little information on the transmission of SARS-CoV-2 from organ donors, but most organ transplant centers recommend that all organ donors be tested for SARS-CoV-2 and removed from the donation list if the test is positive.²¹

A national consensus in Iran was developed by several representatives of organ transplantation teams organized by the ministry of health and medical education updated in April 21, 2020. The most important points of this consensus are:

- Liver transplantation should be performed for patients with a Model for End-stage Liver Diseases (MELD) score more than 20. Other candidates are patients with acute or acute-on-chronic liver failure. Patients with significant complications of chronic liver disease (e.g. high-grade hepatic encephalopathy, gastrointestinal bleeding or recurrent cholangitis) should be also considered for liver transplantation.
- On the day of liver transplantation, all transplant recipients should be screened for the COVID-19 infection. Medical history and physical examination, CBC with differentiation, CRP and chest CT scan and PCR test for SARS-CoV-2 should be done for all patients. A consultation with an infectious diseases specialist must be requested.
- All deceased donors should be assessed for SARS-CoV-2 by chest CT scan and PCR-based tests obtained from bronchoalveolar lavage or endotracheal sample. A consultation with an infectious diseases specialist should be performed for all organ donors.
- History of recent contact with suspected or confirmed

Table 1. Patient Care in Patients with Chronic Liver Disease and Liver Transplant during the COVID-19 Pandemic.

Patients	Considerations
Patients with compensated liver disease	<ul style="list-style-type: none"> • Use telemedicine visits as much as possible. • The risk of severe COVID-19 does not increase with viral hepatitis. • Due to comorbidities in NAFLD/NASH patients (hypertension, diabetes), the risk of severe COVID-19 may increase. • Patients with autoimmune hepatitis should not change the immunosuppressive therapy. • We can consider delaying surveillance of HCC and screening for varices.
Patients with decompensated liver disease waiting for liver transplantation	<ul style="list-style-type: none"> • Limiting liver transplantation listing to patients with MELD score more than 20 and patients with life-threatening complications. • All transplant recipients should be evaluated for COVID-19 by history and physical examination, CBC with differentiation, CRP and chest CT scan and PCR test for SARS-CoV-2 on the day of liver transplantation. • Emphasis on importance of influenza and <i>Streptococcus pneumoniae</i> vaccination. • All deceased donors should be assessed for SARS-CoV-2 by chest CT scan and PCR-based tests obtained from bronchoalveolar lavage or endotracheal sample. • Transplantation from all deceased donors with a history of serious contact with a patients with or suspected of COVID-19 in the previous 2 weeks should be canceled.
After liver transplantation	<ul style="list-style-type: none"> • Minimizing health care providers' exposure through the use of telemedicine. • Advise against reducing immunosuppression. • In patients with COVID-19, minimize the steroid dose; in the setting of lymphopenia and progressive pneumonia, discontinue azathioprine, mycophenolate and CNIs. • If using ritonavir, the dose of tacrolimus should be decreased given the strong drug-drug interaction.

MELD, Model for End-stage Liver Diseases; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CRP, C-reactive protein; CBC, complete blood count; CNIs, calcineurin inhibitors.

cases of COVID-19 in the past two weeks should be evaluated in all deceased donors and transplantation should be canceled if such a contact exists.²²

We should notify patients that the COVID-19 pandemic may increase their waiting time on the transplant list. We should also advise all potential recipients to avoid attending crowd places and keep social distance in the society. It is not necessary to ask patients to update their MELD score frequently (Table 1).

After Transplantation

Post-transplant patients should not travel during the COVID-19 pandemic and must take preventive measures like frequent hand washing, cleaning touched surfaces, avoiding large crowds and staying away from individuals who are sick.

We should conduct medical rounds with the lowest number of staff and the shortest time needed to care for patients after liver transplantation. Walk-in-clinic visits should be minimized by more frequent telecommunication, and elective procedures must be deferred.²³

Studies have shown that immune response is the basis of pulmonary injury caused by COVID-19 and immunosuppression may have a protective effect.^{24,25} Immunosuppressive drugs after liver transplantation have not been shown to be a major risk factor for mortality due to SARS (2002–2003) and MERS (2012–present).²⁵

A recent report from a liver transplant center in Italy showed that all COVID-19-related deaths pertained to patients on minimal long-term immunosuppression after liver transplantation rather than recently transplanted, fully immunosuppressed patients.²⁶ Metabolic complications after liver transplantation play a more important role than immunosuppression in the development of severe COVID-19 in patients with liver transplantation.⁵ Immunosuppression can prolong viral shedding in liver transplanted patients with COVID-19.^{23,27} Nevertheless, immunocompromised patients have higher viral titers and may be more infectious than immunocompetent individuals.²³

Due to the risk of acute rejection, we should not reduce immunosuppression, even mycophenolate mofetil, in post-transplant patients without symptoms of COVID-19. However, in post-transplant patients with COVID-19, we consider the lowest effective dose of steroid but keep it sufficient to prevent adrenal insufficiency.

In patients with lymphopenia, fever or progressive pneumonia related to COVID-19, we should consider minimizing rather than discontinuing the dose of azathioprine, mycophenolate mofetil and calcineurin inhibitors.

We can initiate high-dose immunosuppressive therapy in patients with or without COVID-19, only if there is a strong indication (e.g. acute rejection) (Table 1).¹⁷

Hepatocellular Carcinoma and COVID-19

The impact of COVID-19 on hepatocellular carcinoma is unknown. Patients with hepatocellular carcinoma are not at higher risk for severe COVID-19 related to their malignancy status.²⁸

During the COVID-19 pandemic, monitoring of HCC in patients on or off therapy and surveillance of HCC in those at risk of HCC (e.g., cirrhosis and hepatitis B) should be continued. We should discuss risks and benefits of delaying surveillance of patients, although a delay up to two months may be acceptable.

Discussion on diagnosis and treatment of HCC should be performed in a virtual tumor board with liver transplant surgeons, hepatologists and interventional radiologists and HCC treatment should not be delayed due to the COVID-19 pandemic.¹⁷

Diagnostic Procedures in Patients with Chronic Liver Disease

Endoscopic procedures are considered aerosol-generating. Physician should decide to do some procedures based on their impact on treatment. Liver biopsy may be done as a tool to rule out rejection or diagnose autoimmune hepatitis. Therapeutic paracentesis, transjugular intrahepatic portosystemic shunt and/or endoscopy for variceal bleeding, follow-up band ligation, and urgent biliary drainage for symptomatic disease such as cholangitis and sepsis could be performed.²⁹

Upper and lower endoscopy could be done but the endoscopists should wear N95 masks (as opposed to surgical masks) and use two gloves.³⁰

In pandemic conditions, screening programs for varices should also be postponed to another time.³¹

Decision for performing ERCP for post-transplant biliary strictures should be individualized based on the severity of stricture and its complications and possibility of transmission of virus to health care providers.

Liver biopsy is recommended only in patients whose treatment plan may affect prognosis as in the case of suspicious autoimmune hepatitis and increase in aminotransferases levels more than 5 times the upper limit of normal.

Generally, in patients with COVID-19, liver biopsy could be postponed because of the risk of infection and histology changes due to infection.

Pharmacologic Management of COVID-19 and Drug-drug Interactions in Patients with Chronic Liver Diseases and Liver Transplantation

There is currently no approved drug to prevent or treat COVID-19. Many investigational therapies for COVID-19 may be hepatotoxic.

Ritonavir/ Lopinavir is a strong inhibitor of CYP3A4, which is involved in the metabolism of calcineurin inhibitors, everolimus and sirolimus. Using ritonavir, the

tacrolimus dose should be decreased to 1/20 to 1/50 of baseline given the strong drug-drug interaction. Sirolimus should not be prescribed with ritonavir/ lopinavir.³²

Hydroxychloroquine (HCQ), an analogue of chloroquine with a better safety profile, has anti-SARS-CoV-2 activity *in vitro*.³³ HCQ can potentially increase the level of calcineurin inhibitors and mTOR inhibitors. So, the serum level of these agents should be monitored carefully.³³ HCQ therapy has not been associated with ALT changes and is an extremely rare cause of acute liver injury.¹⁸

Remdesivir is a nucleotide analogue with activity against SARS-CoV and MERS-CoV *in vitro*, and recently against SARS-CoV-2.^{34,35} This drug has had promising outcomes in hospitalized patients with moderate to severe COVID-19 in some studies.³⁶⁻³⁸ Remdesivir can increase aminotransferases and should be avoided in patients with ALT more than 5 times the upper limit of normal.¹⁷ There is no clinically significant interaction between remdesivir and immunosuppressive agents³² (Table 2).

In conclusion, the COVID-19 pandemic has seriously and widely affected healthcare resources throughout the world. All efforts are being made to minimize the risk of health care providers' exposure to SARS-CoV-2, so that they can provide adequate care for patients with chronic diseases, including patients with chronic liver diseases. The pandemic has affected patients waiting for liver transplantation because of the possibility of transmitting the infection from donor and donor shortage. One of the major challenges of liver transplant programs now is how to deal with the increase in mortality of patients in the waiting list due to organ shortage if the fight against COVID-19 becomes prolonged.

This article could guide physicians to help their chronic liver disease patients to reduce the impact of the COVID-19 infection on their underlying disease and give them the best care they could. This pandemic is spreading rapidly and these recommendations will need to evolve with acquisition of new data.

Authors' Contribution

MT, AM, NA and FA conceived of the presented idea. MT and VB developed the theory and performed the computations. HD and MNT verified the analytical methods. NED and AJ supervised the findings of this work. All authors discussed the results and contributed in the final manuscript.

Conflict of Interest Disclosures

The authors declare no conflict of interest.

Ethical Statement

The material has not been published in whole or in part elsewhere and this manuscript is not currently being considered for publication in another journal. All authors have been personally and actively involved in substantive work leading to the manuscript, and will hold themselves jointly and individually responsible for its content.

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Table 2. Drugs which are Used or Suggested for Management of COVID-19 and Implications for Patients with Chronic Liver Disease and Liver Transplantation

Drugs	Implications for Patients with Chronic Liver Disease and after Liver Transplantation
Hydroxychloroquine ± azithromycin	<ul style="list-style-type: none"> • Rule out G6PDD before administration. • Close monitoring of drug level for cyclosporine, tacrolimus, sirolimus and everolimus. • Acute liver injury is quite rare.
Lopinavir/ritonavir	<ul style="list-style-type: none"> • Sirolimus, everolimus should not be used. • Close monitoring of drug level for CNIs. • Should not be used in patients with decompensated cirrhosis.
Remdesivir	<ul style="list-style-type: none"> • Possible elevation of ALT. • Safer class in chronic hepatitis B, C and cirrhosis. • No drug-drug interaction with routine immunosuppressive agents.
Methylprednisolone	<ul style="list-style-type: none"> • Increases the risk of SBP and viral shedding, especially in patients with decompensated cirrhosis. • Increases the risk of HBV reactivation.

CNIs, calcineurin inhibitors; ALT, alanine aminotransferase.

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