Challenges for Liver Transplantation During Recovery From the COVID-19 Pandemic: Insights and Recommendations

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic is placing an increasing burden on liver transplant (LT) services worldwide. At the peak of the pandemic, many LT services worldwide reduced or halted their activities. With the gradual easing of lockdowns, LT teams face new challenges when restarting activities. The numbers of LTs are likely to drop in the immediate post-COVID era.

Prolonged and intermittent lockdowns are likely to lead to a shortage of supplies, especially in poor resource settings. Special attention is needed to avoid nosocomial COVID-19 infection among cirrhotic patients awaiting transplant, post-transplant patients, and members of transplant teams. LT programs may have to revise existing strategies in selecting donors and recipients for transplants.

Redesigning service provision, restructuring outpatient care, carefully screening and selecting donors and recipients, and performing LT with limited resources will have to be initiated in the post-COVID era if long-term recovery of LT services is to be expected. Costs involved with LT are likely to increase, considering the change in protocols of testing, quarantining, and interstate traveling.

This paper discusses the different elements affecting and the widespread impact of the COVID-19 pandemic on LT and strategies to minimize the impact of these factors and to adapt so LT services can meet the health care needs during this pandemic and beyond.

THE coronavirus disease 2019 (COVID-19) pandemic, while placing an increased burden, also poses enormous challenges for health care systems across the world [1]. This could negatively impact the care of patients with decompensated cirrhosis who require ongoing medical attention and potential liver transplant (LT) and care of patients after LT.

There are limited data on the impact of pre-existing cirrhosis on the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, patients with decompensated cirrhosis and recipients of LT represent vulnerable groups and are likely to be at an increased risk of disease with SARS-CoV-2 and/or a severe course of COVID-19 [2]. Thus, the challenge clinicians face is to prioritize outpatient contacts and avoid nosocomial COVID-19 infections to patients and health care providers, while maintaining standard care, including LT, for these vulnerable patients [3].

To promote the best possible care in these challenging circumstances, this paper provides clinical insights and recommendations for liver teams involved in transplantation, treating patients on waiting lists, and care of post-transplant patients. We discuss proposals for the restructuring of outpatient care, ways to minimize direct exposure to COVID-19, and advice on managing patients with decompensated liver disease on waiting lists and those following LT and resuming LT services in the period while recovering from the COVID-19 pandemic.

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The pandemic is in a different phase in each country, and the local health care system and resources also vary between states. Hence, the recommendations will have to be adapted accordingly (Table 1).

THE ECONOMIC IMPACT OF COVID-19 ON LT

Historically, health care delivery has not been significantly impacted by global recessions. The impact of COVID-19 on society is multifaceted. Prolonged lockdowns that happened across the globe have a significant bearing on the production and supply chains of medical supplies. China is the leading exporter of active pharmaceutical ingredients. The drop in supply is already affecting secondary manufacturers in countries like India, which provides low-cost drugs [4]. Even though lockdown is over, most factories will not work in their full capacity and always carry a risk of limited lockdown with possible infected cases reappearing. This may result in a shortage of vital drugs and devices used in LTs. The health-related economic impact will also be substantial in all state-funded, insurance-based, or self-funded health care deliveries [5]. Because LT is a treatment that consumes a large number of resources with a high cost, clinicians may face these specific challenges in the future. The countries with limited resources are especially at risk in terms of continuing services in their previous capacities.

INFECTION RISK WITH SARS-COV-2 AND IMPACT ON TRANSPLANT SERVICES

LTs are performed in a handful of specialized centers. The teams involved in LT are specially trained and relatively small in numbers per institution. They cannot be replaced easily. A few staff members contracting the disease or in quarantine can result in shut down of a program for weeks. Another factor that may affect the delivery of transplant services is the redeployment of transplant professionals—coordinators, theatre staff, and medical/surgical team to manage a surge in COVID-19 patients. While the transplant activities have to be suspended due to the lack of dedicated staff, these staff members are also vulnerable to high-risk exposure that may delay the transplant service provision. Hence, taking special care regarding precautions to avoid COVID-19 infection, working in small subgroups, and segregating the team taking care of immediate post-LT patients from pre-op and other patients can be recommended. In deceased donor LT, wherever possible, local teams with expertise for retrieval should be used to avoid extensive movement/travel by health care workers in LT teams.

In countries where there was community spread, the disease will be among us for a long duration. According to data from the cruise ship Diamond Princess and China National Health Commission, the percentage of asymptomatic patients could be as high as 78% [6]. There is clear evidence of virus shedding from these asymptomatic cases [7,8]. Younger children attending school are likely to be in this category [9]. When the schools reopen after the lockdowns, this group will be a challenge in pre- and post-transplant patients, especially when the extended families live with those who are awaiting or have undergone transplantation. The only possible method to overcome this is strict adherence to health care guidelines and physical distancing of this specialized group of patients.

Some countries, such as the United Kingdom, have specifically instructed vulnerable patient groups to engage in "shielding"—physical distancing advice going beyond the widely recommended social distancing to protect the patients. These groups include those who are awaiting and post-transplant patient groups. Initially recommended for 3 months from the beginning of the pandemic, with anticipated second wave of the pandemic, this is likely to extend further [10].

There is always a potential risk of patient-to-provider transmission of SARS-CoV-2, and vice versa [11]. Undiagnosed asymptomatic COVID-19 patients lurking among donors and recipients could infect transplant recipients and medical personnel. It is incumbent that all organ donor teams, transplant providers, and support staff are aware of this risk and take appropriate respiratory contact precautions. Maintaining physical distance (1-2 m), washing hands frequently (at least 20 seconds with soap), and regularly disinfecting surfaces is recommended. Avoiding hand-face contact as much as possible and avoiding close contact with individuals who may have viral infections is recommended. If contact is unavoidable, the use of an N95 mask and protective eye cover is recommended [12–14].

PATIENTS ON WAITING LISTS

COVID-19 and Cirrhosis

Currently, there are only limited data available linking underlying cirrhosis with the course of SARS-CoV-2 infection [14,15]. Patients with decompensated cirrhosis are possibly at increased risk of infection because of cirrhosis-associated immune dysfunction. The same could be true for patients after LT who receive immunosuppressive therapies.

To assess the impact of patients with cirrhosis on post-LT outcomes during the COVID-19 pandemic, Mount Sinai and the University of North Carolina launched the Surveillance Epidemiology of Coronavirus Under Research Exclusion-CIRRHOSIS (SECURE-CIRRHOSIS) registry [2]. This will help monitor and report outcomes of COVID-19 in patients with chronic liver disease (with and without cirrhosis) and post LT. At the time of submission of this article, there was a total of 254 in this cohort (cirrhosis: 151, chronic liver disease [without cirrhosis]: 62, and LT: 41). The reported morbidity with any form of decompensation among patients with cirrhosis was 38%. The reported mortality rates for the 3 groups were as follows: cirrhosis 40%, chronic liver disease (without cirrhosis) 13%, and LT 22%, indicating high mortality in this group of patients [2]. The aforementioned shielding measures, therefore, are very much helpful in protecting the vulnerable patient groups. In the United Kingdom, patients have been informed explicitly via telephone to remind them about shielding, in addition to the

Table 1. Summary of Key Recommendations

Practice	Suggested Change
Protecting members of health care teams	• Split transplant teams into smaller subgroups that work separately • Minimize the direct contact with patients • Screen for COVID-19 before major procedures • Address the psychological impact and impact of deskilling of health care workers during lockdown
Pretransplant care	• Develop strategies to separate pretransplant patients mixing with general patients in the hospitals • Use telemedicine as much as possible
Organ donation	• Commence live donation when infrastructure completely recovers • Include screening and laboratory testing for COVID-19 in the donor assessment checklist
Liver transplantation	• Revise strategies of patient selection considering possible organ shortage • Pay attention to the change of costs involved with transplants • Develop strategies to overcome traveling restrictions for medical requirements
Follow-up	• Require minimum hospital visits after transplant • Prepare for potential shortages of drugs, devices, and supplies

Abbreviation: COVID-19, coronavirus disease 2019.

government letters asking them to do so. Furthermore, a checklist questionnaire is used by the transplant coordinators when a suitable graft is made available for a particular recipient before the patient is asked to travel to the hospital. This questionnaire is about possible contacts' presence or absence of any constitutional symptoms suggestive of COVID-19. This prescreening method would alleviate the impact a possible cancellation of the transplant on the patient, if the patient is deemed positive for COVID-19 [10].

Shielding and physical distancing of vulnerable, sick patients for extended times also may have detrimental effects. This could have adverse effects on the physical prehabilitation, and patients are likely to be both physically and psychologically weak when they are finally called in for transplantation. Shielding may not be practical in patients with chronic encephalopathy who needs continued care and support.

Outpatient Care and Reduction of Direct Exposure

The management and surveillance of patients with advanced liver disease on LT waiting lists and those receiving immunosuppressive treatment for LT is often performed in larger units or centers. These institutions, however, are currently also COVID-19 hotspots, thus potentially putting these vulnerable patients at risk of nosocomial infections. In addition, hospital staff face challenges such as long working hours and even reduced staffing because of COVID-19 quarantining. It seems appropriate to limit the number of face-to-face contacts for patients at risk of a more severe course of COVID-19 infection [16]. Therefore, promoting telemedicine in the outpatient setting, prioritizing outpatient visits, and avoiding nosocomial dissemination of the virus, while maintaining standard care for patients who require immediate medical attention is recommended [17]. In addition, exposure to medical staff should be minimized wherever possible.

These considerations require the adaptation of standard operating procedures for outpatient care, including remodeling waiting areas to allow sufficient distance between patients, reducing waiting times, and encouraging patients to wait outside wherever possible and eventually be contacted by phone. Prescreening patients for high-risk exposure or symptoms, checking body temperature of the patient on arrival, keeping patients at an appropriate distance from each other, and providing hand sanitization facilities should be practiced in conducting a LT clinic for those needing face-to-face consultations.

Technical solutions are available to enable remote physician-patient interactions, which can be helpful during the pandemic [18]. Health authorities should be urged to equip hospitals with such systems to care for and guide patients needing to be protected from a potentially harmful infection in the hospital setting.

Patients With Decompensated Liver Disease

Care should be maintained according to guidelines but with minimal exposure to medical staff, by using telemedicine and consultation by phone and remote blood test work-up, wherever possible or required to avoid face-to-face consultation and hospital admission [16–18].

Testing for SARS-CoV-2 in patients with acute decompensation or acute-on-chronic liver failure should be included. Consent for diagnostic and therapeutic procedures related to transplantation should include the potential risk of nosocomial COVID-19 [19]. Depending on available resources, screening for varices by esophagogastroduodenoscopy should be reserved for patients at risk of variceal bleeding, such as patients with a history of variceal bleeding or signs of significant portal hypertension (ascites, thrombocyte count $<100{,}000/\mu L$). Noninvasive risk assessment for the presence of varices should be applied for stratification (thrombocyte count or Baveno VI) [19]. Guidelines on prophylaxis of spontaneous bacterial peritonitis and hepatic encephalopathy should be closely followed to prevent decompensation and avoid admission [19].

Selection of Patient and Work-up for Transplants

The selection of new patients for LT will be a challenge in the future. LT activities and turnover of cases are likely to fall during and after the COVID-19 era [20]. The selection

criteria for LT will have to be restrategized. Listing for transplantation should be initially restricted to patients with poor short-term prognosis including those with acute liver failure or acute-on-chronic liver failure, a high Model for End-Stage Liver Disease (MELD) score (including exceptional MELDs) and hepatocellular carcinoma at the upper limits of the Milan criteria, as transplantation activities/organ donations will likely be reduced in many countries and areas [21,22]. Patients with lower MELD who are likely to survive without a transplant until the transition period is passed are best managed medically. Similarly, the selection of patients with extended criteria or patients after downstaging the disease with hepatocellular carcinoma needs rethinking. Living-donor transplantations should be considered on a case-by-case basis.

In new patients who are being worked up, reducing the in-hospital LT evaluation program to the strictly necessary is recommended to shorten the in-hospital stay and also reduce the number of consultations in other departments/clinics (eg, cardiac, respiratory, renal, dental, nutrition and psychiatric consultations can be done in local outpatient settings). It is essential that LT centers continuously assess and adapt to their local situation and its impact on patients included in transplant waiting lists.

ORGAN DONATION

There will be a reduction in organ recovery because of COVID-19-related limitations on institutional resources and the potential risk of donor-derived disease transmission [23,24]. SARS-CoV-2 routine testing by real-time, reverse transcription polymerase chain reaction (rRT-PCR) on samples collected by nasal swabs, should be performed on 2 consecutive days (at least 1 day apart) if possible, before living donor transplantation in both donors and recipients, acknowledging that negative testing cannot completely rule out infection [25–27]. Always screen potential donors for exposure (no contact history with suspected or confirmed COVID-19 patients, no residence history or travel history in an endemic area, and no history of residence or travel in an endemic area for persons in close contact over the past 28 days) and clinical features (no fever or respiratory symptoms over the past 28 days) compatible with COVID-19 [28].

Due to incomplete sensitivity of rRT-PCR (89%), consider the use of alternatives to polymerase chain reaction (PCR)-based testing such as chest radiography or CT [29]. Avoid deceased and living organs retrieved from donors within endemic or high prevalence areas. If a living donor has been within an endemic area, wait at least 14 days (presumed incubation period) for symptom development before proceeding with a donation [28].

LIVER TRANSPLANT CANDIDATES

Inform the patients and their caregivers about the potential impact of the COVID-19 pandemic on their waiting time on the transplant list [25]. Screen potential recipients for COVID-19 as the same outlined for recipients [28]. Screening for potential exposure of features of COVID-19 should be done before they are called in from home for transplantation due to availability of acceptable organs. Routine testing by rRT-PCR on samples collected by nasal swabs should be performed. What is encouraging at present is the development and availability of rapid PCR diagnostics that can return a result within 90 minutes, and transplant programs have been advised to use these techniques in candidates before the surgery. This may be more relevant in deceased donor transplants. Encourage recipients to arrive at the hospital by private transport and be accompanied by only 1 relative. The recommendation of waiting 14 days if the candidate traveled through an endemic area is current but subject to change [28]. Also, consider accepting only grafts with a low risk of delayed graft function to minimize complications and postoperative lengths of stay. Avoid transplanting and immunosuppressing someone with developing or active COVID-19 disease.

TRANSPLANTATION SURGERY

As long as the donor and recipient are negative for COVID-19, the surgery itself does not require additional use of protective wear. However, at minimum, because of the risk of having false-negative PCR in a low-risk patient, it is advisable to use essential protection during aerosol-generating procedures like intubation [21,22].

Different units might take different timespans to recover from the impact they experienced during the height of the disease. This could be carefully considered by the centers performing a high volume of living-donor LT. Considering the complexity of the surgery and the donor risks, centers should wait until their routine services and infrastructure are returned.

There are many centers globally offering LT for international patients. Even though most of the programs are pressed to restart LT services, international patients may face many drawbacks. Traveling from one country to another may require a mandatory quarantine period and travel restrictions. Providing facilities for accompanying family members could be demanding. These centers will have to look into these aspects before restarting their services. There will likely be a shortage in the supply of blood products because of restricted blood donations and population mobility caused by COVID-19. This may adversely affect LT services [30].

There will also likely be some psychological costs to the transplant teams. These professionals who function with high demand, which is a part of their normal life, have had their normal daily routines disrupted. This may lead to poor morale among the team members. The prolonged absence of routine transplants also carries the risk of deskilling the junior staff and residents.

The need for changing existing infrastructure and adding new infrastructure, as well as the need for additional testing and use of personal protective equipment required for LT,

will likely add to the cost of transplantation. These additional cost factors will adversely impact the health care systems where LT services are free, and the recipient and families by increasing the financial burden on them where transplantation is not free.

POST-TRANSPLANT PATIENTS

The actual impact of the virus in post-LT patients is unclear. According to data from Milan, Italy, out of 640 post-transplant patients, 1.4% (n = 8) contracted the disease. Of these, 6 had a milder form, and 2 required noninvasive ventilation [31]. According to data from Lombardy, Italy, out of 111 long-term LT survivors, 2.7% (n = 3) died [32]. There is conflicting emerging data from the SECURE-CIRRHOSIS registry that LT recipients were acquiring acute SARS-CoV-2 infection and carrying significant mortality (22%) [2]. Recipients are apt to become infected postoperatively because of compromised immunity and increased hospital stays.

In the absence of precise data, utmost care needs to be taken to avoid contracting the disease. Uninfected recipients should take respiratory precautions by wearing masks and washing their hands frequently and thoroughly. They should avoid crowded places and always practice physical distancing. Respiratory isolation and supportive therapy are the first-line treatment for people who contract COVID-19. This is true for transplant recipients as well. Although there is no proven effective antiviral treatment, the field is rapidly evolving.

Maintain care according to guidelines, but consider minimal exposure to medical staff, by using telephone consultation wherever possible or required to avoid long journeys of early post-transplant patients to the hospital. In stable patients, perform remote blood test workup utilizing local laboratory testing (including drug levels).

We currently advise against the pre-emptive reduction of immunosuppressive therapy. Stopping patients' medications increases the risk of acute cellular rejection in LT. Treatment would require admission to over-crowded hospitals and stronger immunosuppressive therapy during this pandemic. Therefore, post-transplant immunosuppressive therapy should continue as usual [25,33]. The reduction should be considered only under special circumstances (eg, medication-induced lymphopenia, or bacterial/fungal superinfection in case of severe COVID-19) after consultation of a specialist.

CONCLUSIONS

The COVID-19 pandemic is placing an increasing burden on and halting LT services worldwide. There is a growing challenge for transplant teams to restart activities, avoid nosocomial COVID-19 infections to patients and health care providers, and maintain standard LT care for their patients. Redesigning service provision, restructuring outpatient care, screening donors and recipients, and cautiously resuming LT services will have to be initiated in the period while recovering from the COVID-19 pandemic if long-term recovery of services is to be expected. As this pandemic will not end in the near future, continuous use and modification of the above measures should be practiced in LT units globally.

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