Saudi Association for the Study of Liver Diseases and Transplantation position statement on liver transplantation during the COVID-19 pandemic

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Abstract The World Health Organization (WHO), on March 11th 2020, upgraded the status of the novel coronavirus disease (COVID-19) from epidemic to pandemic. Over two million individuals have been infected with SARS-CoV-2, the virus causing COVID-19, and as of April, 14th 2020, there were over 5000 confirmed cases in Saudi Arabia (SA). Many countries, including SA, have imposed major restrictions on travel, and everyday life, and the implications of these necessary changes are being felt in liver transplant (LT) centers in SA. Concerns remain that there is an increased risk for individuals over 65 years of age, with underlying medical conditions, or for those who are immunocompromised. Therefore, the Saudi Association for the Study of Liver Diseases and Transplantation (SASLT) established an urgent task force to launch a statement that can be utilized by LT centers as a guidance in the management of patients with advanced liver disease from the time of LT listing to the post-operative care of transplanted patients.

Keywords: Cirrhosis, COVID-19, liver transplant

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RATIONALE FOR A POSITION STATEMENT

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first described in China, is the cause of a rapidly spreading illness, Coronavirus Disease 2019 (COVID-19), affecting hundreds of thousands of people worldwide, and has clearly become the most serious public health threat of recent times.^[1] The lower airway

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is the primary target of the infection and pneumonia is always present in patients with severe COVID-19.^[1] Since the outbreak grew to a pandemic, several liver transplant (LT) centers worldwide have raised concerns regarding the feasibility and desirability of performing LT due to donors' and recipients' safety for living donor liver

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transplant (LDLT) programs.^[2] In addition, the possibility of developing COVID-19 in immunocompromised patients post-LT remains a source of considerable concern.^[2] On this fluid backdrop, where opinions differ considerably, owing to the disease's ambiguity and a lack of clear information of its impact on transplantation, the Saudi Association for the Study of Liver Diseases and Transplantation (SASLT) assembled an expert panel of transplant-related specialties to develop consensuses. We believe that these consensuses can be used by LT transplant programs as a guidepost in approaching LT during the COVID-19 pandemic. As transplant and infectious disease specialists, we deem it crucial to carefully balance costs and benefits in performing LT during a COVID-19 outbreak. It must be understood that the SASLT statement is our position on an arguable viewpoint, where each jurisdiction may develop their own polices, adapted and individualized to the local circumstances. Moreover, the recommendations contained herein remains the Position of the authors and the SASLT board, and is not intended to be a guideline document, which in turn is generally evidence-based.

COVID-19

Coronaviruses are single-stranded RNA viruses that belong to the family Coronaviridae.^[3] The virus is transmitted via respiratory droplets, close contact with infected patients or touching contaminated surfaces.^[4-7] The median incubation period is estimated to be around 5 days. However, majority of patients became symptomatic within 12 days of exposure.^[7,8] Most symptomatic patients present with fever, dry cough and myalgia.^[8,9] Likewise, majority of patients presented with leukopenia and lymphopenia on admission.^[1] In addition, abnormality in hepatic function test was observed in 20-30% of patients and chest imaging was abnormal in the vast majority of reported cases.^[8,9] The gold standard test for diagnosis is polymerase chain reaction (PCR). The sensitivity of PCR testing is different based on the sample source and the timing of infection.^[4,10] The sensitivity from lower respiratory samples ranged from 75% for sputum to 93% for bronchoalveolar lavage. Oropharyngeal and nasopharyngeal swabs sensitivity were 32% and 63%, respectively.^[10] Presence of viremia was variably reported in different studies among patients who were infected with COVID-19.^[7] Due to the wide range of sensitivity of the PCR-based tests, the Saudi Ministry of Health currently recommends lower respiratory samples for PCR testing in patients who fulfil the Ministry of Health criteria for any suspected cases of COVID-19 [Table 1].

LIVER TRANSPLANT PROGRAMS IN COVID-19 PANDEMIC

Several LT programs in SA have decreased or temporarily suspended their transplant activity until further notice, due to the widespread development of COVID-19 within the country. The compromising burden of COVID-19 on the healthcare system has been observed in several countries such as China, Singapore, and Italy.^[1,11,12] It is important to emphasize that overall 10-16% of positive cases with COVID-19 would require hospitalization, and 5-12% intensive care admission.^[1,11,12] As a result, healthcare systems are expected to become increasingly overwhelmed, and patients with advanced liver disease that are normally well-managed may find themselves slipping into states of medical distress requiring hospitalization or even intensive care. Likewise, decisions to proceed with organ donation and transplantation is predicated on hospital capacity and resource considerations, and it is understood that it may be affected by provincial and facility incidence and severity of COVID-19.

Several societies have recommended that transplant programs should make a case-by-case evaluation when

Table 1: Definition of COVID-19 suspected case*	
Clinical presentation	Epidemiological link
1. Patient with acute respiratory illness (sudden onset of at least one of the following: fever or recent history of fever, cough or shortness of breath) and in the 14 days prior to symptom onset has at least one of the four epidemiological links	Had a history of travel abroad or Travel to an identified high-risk area in the Kingdom or A close physical contact prior to symptom onset with a confirmed COVID-19 case or Working in or attended a healthcare facility where patients with confirmed COVID-19 are admitted.
 2. Adult patient with severe acute respiratory illness (intensive care unit admission, adult respiratory distress syndrome, adult respiratory distress syndrome or CURB-65 score ≥3 points) and all the following conditions fulfilled: a) Testing for influenza and MERS-CoV are negative. b) Clinical assessment indicating that the patient is not improving and has no clear underlying causes 	Not required

*Suspected case definition needs to fulfill one of the above criteria

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assessing the convenience of carrying out a transplantation based on the availability of resources such as an intensive care unit bed, operating room, and adequate number of healthcare providers that would include anesthesiologists, nurses, transplant coordinators and physicians.^[13-15] Such decisions need to be taken in the context of the risk/benefit ratio of exposing an immunocompromised patient to COVID-19 versus the need for timely transplantation.

Most LT transplant programs in North America are deceased donor-driven programs while LDLT is performed only in cirrhotic patients with low model for end-stage liver disease/Na (MELD-Na) score. Patients with low MELD-Na scores have lower mortality rates from liver disease. Therefore, most transplant centers in North America have decreased or suspended their LDLT activity, in the anticipation that the expected marginal delays would not greatly impact mortality rates for listed patients. In addition, several cadaveric LT programs in North America and Europe would initiate LT workup if the patient's MELD-Na score is close to the median MELD-Na score for transplantation in their jurisdiction. For instance, certain centers in Ontario, Canada would initiate LT workup if the patient's MELD-Na score is 25 since the median MELD-Na score for transplantation in the province of Ontario is 25. However, these regulations would not be applicable in SA as most LT activities are based on living donors. A total of 1071 LTs were performed in Saudi Arabia from 2010-2016. Among those, 703 (65%) were LDLT.^[16] Each center in SA has its own wait-list and registry database for LT. Therefore, it is difficult to estimate the national median MELD-Na at the time of listing or transplantation in SA. In addition, the cadaveric donor allocation system is center-based in SA. Each LT center receives a cadaveric organ in turns. Once a particular LT center receives a cadaveric donor, it is utilized to identify a matched donor in the center's waitlist which may result in LT for non-urgent cases with low MELD-Na.

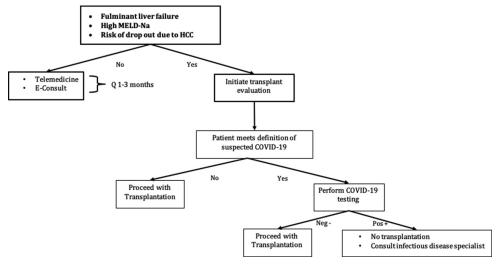
It is important to acknowledge that the mortality rate from COVID-19 is lower than the mortality rate from end-stage liver disease with a high MELD score, fulminant liver failure, and hepatocellular carcinoma. In COVID-19, the greatest mortality risk of 6% observed in the upper age stratum is dwarfed by the 90-day MELD-based mortality (MELD score 20, 19.6%; 30, 52.6%; and 40, 71.3%).^[1,17] Conversely, a high COVID-19 (upper age stratum) mortality of 6% is comparable only to end-stage liver disease patients' mortality at a relatively low MELD score of 15.^[1,17] Nonetheless, it worthy to note that the time horizons for COVID-19 and MELD scores do not align perfectly. Clearly then, the risk/benefit ratio would favour proceeding with LT in patients with the high risk of mortality in the short term.

Recommendations

- LT evaluation for deceased and living donors should be considered in urgent cases (e.g., patient with fulminant liver failure, high risk of drop-out from LT list due to hepatocellular carcinoma, and high MELD-Na). Algorithm for liver transplant evaluation during COVID-19 pandemic is shown in Figure 1.
- 2. Hospital resources for cadaveric and living donor liver transplant programs must be evaluated on a weekly basis, where it may impact on the feasibility to proceed with transplantation.

RECIPIENT ASSESSMENT

Patients with advanced liver disease are generally immunocompromised and at higher risk of infection.^[18]



Hence, careful assessment of patients with advanced liver disease is required during transplant evaluation, which in turn may require frequent and in-person clinic visits. In addition, recipients who are on the LT wait-list should be evaluated frequently for symptoms related to COVID-19. Likewise, these patients should be evaluated for hepatic decompensations i.e., hepatic encephalopathy or worsening MELD-Na scores which could be due to COVID-19. However, during this ongoing pandemic, such in-person clinic visits may broaden the COVID-19 exposure in these patients with potentially poor outcomes. As such, due consideration must be given to virtual clinics, tele-medicine or electronic consultations. All potential recipients with a confirmed COVID-19 diagnosis should have the surgery put on hold until further assessment by transplant infectious disease specialists. This also applies to LT candidates with close contact to a confirmed case of COVID-19, or those residing in an epidemic area with COVID-19. The definition of close contact to a confirmed case of COVID-19 is listed in Table 2. Additional information and clarity regarding LT recipient evaluation during the COVID-19 pandemic can be found on the Saudi Society for Organ Transplantation (SCOT) website.[19]

Recommendations

- 1. LT programs must develop a policy to decide which LT candidate needs to be seen in person in the clinic.
- 2. Consideration must be given to virtual clinics, telemedicine or electronic consultations as alternative options for non-urgent cases.
- 3. All potential LT recipients should be provided with preventive measures for COVID-19, listed in Table 3.
- 4. Consider evaluating liver disease patients with new onset encephalopathy or worsening MELD-Na scores for COVID-19.

DONOR ASSESSMENT

There is no clear guidance on evaluating organ donors for COVID-19 and there are no cases to date to suggest possible donor-related transmission of the virus. However, given the limited experience with the virus, and a lack of comprehensive understanding of its pathogenicity, this clearly does not obviate the risk of viral transmission. For deceased donors, much of the prevailing opinion, and based on the position of SCOT, testing for COVID-19 should be done prior to harvesting.^[19] In the event that the test is positive, the donor would be declined from donation as there is not sufficient evidence to suggest that surgery can be performed safely in the absence of efficacious antiviral agents. Other potentially high-risk donor groups

Table 2: Definition of close contact of COVID-19

- Health care associated exposure, including providing direct care for COVID-19 patients, working with health care workers infected with COVID-19, visiting patients or staying in the same close environment of a COVID-19 patient.
- Working together in close proximity or sharing the same classroom environment with a COVID-19 patient.
- Traveling together with COVID-19 patient in any kind of transportation.
- Living in the same household as a COVID-19 patient.

are those from geographical areas in the Kingdom with a large number of cases, or in situations of testing unavailability or prior lack of information about definitive epidemiological risk. In these situations, we recommend adhering to SCOT recommendations while discussing cases on an individualized basis. For living donors, individuals must be evaluated for COVID-19 symptoms.

Obviously, individuals with a confirmed diagnosis of COVID-19 should be excluded from donation. Likewise, individuals with close contact to a confirmed case of COVID-19, or those residing in an epidemic area with COVID-19 should not proceed with donor evaluation until further assessment is performed by an infectious disease specialist. Additional information and clarity regarding living donor evaluation during the COVID-19 pandemic can be found on the SCOT website.^[19]

Recommendations

- All deceased and living donors should be evaluated for COVID-19 and all positive donors with COVID-19 should be denied donation for LT.
- 2. Living donor's safety comes first prior to initiating donor work-up. However, LDLT can be performed if the donor's healthcare would not be compromised due to the COVID-19 outbreak.

Table 3: General recommendations for liver transplant recipients

- Avoid contact with sick people.
- Wash your hands frequently and thoroughly with soap and hot water, or approved hand gel sanitizer for at least 20 sec, especially after touching common surfaces or other people, even when they don't appear to be sick.
- Avoid touching your nose, eyes, and mouth as much as possible.
- Seek medical attention from your health care provider for any fever, cough, cold symptoms, or difficulty breathing.
- If you haven't already, get your flu shot.
- Social distancing is critical. Avoid social gatherings of more than 10 people and work from home if possible.
- Unnecessary travel is medically inadvisable, but particularly to areas/venues/locations with large crowds.
- If sick, check with your doctor or transplant coordinator for advice on management of your medications.

PEDIATRIC LIVER TRANSPLANT DURING COVID-19 PANDEMIC

Over the decades, pediatric liver transplantation has been a major success, and is now an established therapeutic entity. The use of innovative surgical techniques has allowed the application of LT even to very young infants with excellent outcomes. However, there remains a veritable gap between the number of patients suitable for LT and the number of donated human livers and hence, LRLT has emerged as an alternative to cadaveric LT. In SA, the organ shortage as well as organ quality is considered a great limitation for using cadaveric livers to treat end-stage liver disease in children. Therefore, the justification for the use of livingrelated organs is quite acceptable, considering that it is the most accessible method to save the lives of these children.

The paediatric end-stage liver disease (PELD) score and the MELD-Na for adults were developed simultaneously to create an integrated system of deceased donor liver allocation based on the severity of chronic liver disease.^[20] Unfortunately, PELD/MELD-Na scores are not applicable in paediatric liver transplantation in SA where centers remain dependent on living donors regardless of their scores. In addition, pediatric LT programs in SA have their own waitlists for LT. Therefore, the median MELD-Na/PELD scores cannot be estimated. However, from our experience in patients with familial and metabolic liver diseases, which are the major drivers of LT in our population, the 30-day mortality is a very significant endpoint even with low PELD score as in some familial and metabolic liver diseases i.e. progressive familial intrahepatic cholestasis type 3 and glycogen storage disease type 4.

Available reports to date show that paediatric patients with COVID-19 generally develop mild to moderate symptoms. ^[21,22] Suggested reasons include children having a more active innate immune response, healthier respiratory tracts because they have not been exposed to as much cigarette smoke and air pollution as adults, and fewer underlying disorders. A more vigorous immune response in adults may also explain a detrimental immune response that is associated with acute respiratory distress syndrome.^[23]

To date, there is no single reported case of COVID-19 in immunosuppressed pediatric LT patients. The largest paediatric hepatology and LT centre in Bergamo located in the "red zone" of the Italian outbreak, highlighted that unlike common viral agents (such as Adenovirus, Rhinovirus, Norovirus, Influenza, Respiratory Syncytial Virus), coronaviruses have not caused a more severe disease in immunosuppressed LT patients. For this family of viruses the host innate immune response appears to be the main driver of lung tissue damage during infection. These findings suggest that in this setting an immunocompromised host may potentially be protected by a weaker immune response against the virus.^[2] However, more data is required before we can draw a firm conclusion.

Recommendations

- 1. Paediatric liver transplantations from cadaveric donors can be continued during the COVID-19 outbreak.
- 2. Paediatric liver transplantation from living donors should be considered in the following cases:
 - A. Acute liver failure
 - B. Liver tumors
 - C. Unresectable hepatoblastoma (without active extra hepatic disease)
 - D. Decompensated liver disease with life expectancy less than 4 weeks based on clinical conditions and on liver function.

POST-LIVER TRANSPLANT MANAGEMENT

Outcome of COVID-19 infection in the liver-transplanted patient is unclear. However, immunocompromized individuals are more likely to develop unfavorable outcomes when infected with various pathogens.^[24] D'Antiga et. al. from Italy reported their LT program experience in immunosuppressed patients during the COVID-19 outbreak.^[2] They have not observed severe or life-threatening conditions in post-LT patients. In addition, there are three reported cases of successful recovery from COVID-19 pneumonia, one in renal and two in heart transplant patients, with long-term immunosuppression.^[25,26] Nevertheless, infected transplant patients are at higher risk of viral replication and can be a source of viral transmission. Therefore, routine clinic visits should be modified to alternative modalities such as virtual clinics or telemedicine. In addition, we recommend to provide patients with general guidance, listed in Table 3, to minimize their risk of acquiring COVID-19. The treatment of confirmed cases is supportive care. However, multiple antiviral agents and vaccines are currently being evaluated. To date, there is no single antiviral agent considered to be the standard of care.

Most transplant centers use a combination of calcineurin inhibitors and mycophenolate mofetil (MMF) during the first 6-12 months, and oral prednisone for the first 3 months following transplantation. Withdrawing MMF especially in severe illness should be attempted. Reducing the dosage of calcineurin inhibitors could also be considered, with close monitoring of liver enzymes and graft function. Decisions on immunosuppressive manipulation varies on an individual basis depending on many factors including severity of illness, renal function and time since transplantation, and should be left to the discretion of the treating physician. Further information regarding testing and management of LT transplant recipients can be found on the SCOT website.^[19]

Recommendations

- Immunosuppression does not require to be reduced or discontinued in LT patients without COVID-19, although due consideration can be given to reducing, but not stopping, immunosuppressive therapy in LT patients with COVID-19
- 2. Transplanted patients must be provided with preventive measures from COVID-19, listed in Table 3
- 3. Limitation to the number of patients coming to the post-LT clinic should be considered, with virtual clinics, tele-medicine or electronic consultations serving as alternative options for non-emergent cases.

CONCLUSION

The ongoing COVID-19 outbreak is vastly unpredictable, with the situation rapidly evolving and in a state of constant flux. This crisis has created unprecedented challenges for the nation's healthcare system and necessitates urgent and definitive action so that candidates awaiting lifesaving organ transplants are not adversely affected. Experience with previous coronavirus outbreaks suggests that immunosuppressed patients are not at increased risk of severe pulmonary disease compared to the general population, both in children and adults. Efforts should be made to persevere with normal transplant activity. Intensive measures must be adopted to identify and urgently create pathways for managing these patients within individual transplant programs. Going forward, SASLT intends to continue providing LT centers with guidance regarding the implications of COVID-19 on transplant activity within the country.

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Conflicts of interest

There are no conflicts of interest.

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