Liver Transplant Society of India Guidelines for Liver Transplant During COVID-19 times

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Coronavirus disease-2019 (COVID-19) pandemic has affected liver transplantation in many ways. There is risk of infection to the transplant recipients; and COVID-19 is associated with significant risk of mortality in patients on wait list. The Liver Transplant Society of India (LTSI) has prepared guidelines regarding selection of adult and pediatric patients for liver transplantation, transplant for acute liver failure, use of deceased donor organs, transplant techniques and minimally invasive donor hepatectomy, pre- and postsurgery testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related coronavirus disease 2019 in donors and recipients, role of COVID-19 antibody testing, shifting of recipients from COVID-19 to non-COVID-19 areas after recovery, isolation policy of team members exposed to COVID-19 patients, drug therapy of proven or suspected COVID-19 infection early posttransplant, care of SARS-CoV-2 positive donors and recipients and a separate COVID-19 consent for surgery. (J Clin Exp Hepatol 2022;12:180–185)

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related coronavirus disease-2019 (COVID-19) pandemic has had profound effects on the health system, and every country in the world has struggled to overcome its ill consequences. At many hospitals, routine activity has declined markedly so that the care of COVID-19 patients can be undertaken on priority. In the year 2020, there was so much panic that even cadaveric donations were proscribed by National Organ and Tissue Transplant Organization (NOTTO). The Liver Transplant Society of India (LTSI) formulated guidelines for transplants during the first wave of COVID-19 in India which led to gradual resumption of liver transplant services.

Subsequently, as the second surge happened rather unexpectedly consequent on early easing of restrictions, development of mutants and COVID-19 fatigue causing risky behavior, healthcare resources have been severely constricted leading to shortage of oxygen, intensive care beds and ventilators. This second wave has driven home the point that this pandemic will not end overnight. The Society feels that liver transplant activity by virtue of it being lifesaving must continue during this period. At the same time, attempt must be made to reduce the risk of infection in donors, not to compromise outcomes in recipients and to protect the team who provide care to these recipients. These guidelines are meant for management of liver diseases during the entire COVID-19 period (and not just for COVID-19 peaks).

METHODOLOGY

The Executive met on several occasions to formulate these guidelines for Liver Transplant Activity in the COVID-19 Era. A questionnaire was framed which was circulated in the Executive and to the high-volume liver transplant centers; opinion was taken from experts treating COVID-19 patients; a review of published guidelines from around the world was carried out; and agreement was reached on most of the clinical issues. Where there was no consensus, it was decided that Institutional level guidelines should be followed. The current guidelines are based on expert opinion in the absence of controlled trials, meta-analyses, or cohort/case-controlled studies.

The following questions were addressed:

1. Liver transplant (LT) indications for adult and pediatric recipients;
2. Transplant in Acute Liver failure (ALF);
3. Transplant in Chronic Liver failure (CLF);
4. Transplant in Acute on Chronic Liver failure (AOLF);
5. Pre-surgery preparation of recipient;
6. Selection of donors.

Keywords: COVID-19, vaccination, mortality, liver transplantation, donors

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Abbreviations: ACLF: acute-on-chronic liver failure; COVID-19: Coronavirus disease 2019; LTSI: Liver Transplantation Society of India; NOTTO: National Organ and Tissue Transplant Organization; PPE: Personal protective equipment; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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Liver Transplant Indications for Adult and Pediatric Patients

Liver Transplant Society of India (LTSI) acknowledges that liver transplantation (LT) in COVID-19 times may be a difficult endeavor and centers must ensure recipients’ and donors’ safety. At times of local surges, transplant activity may be reduced so as not to overwhelm hospital resources. However, as there is no alternative to LT, activity must continue keeping in mind the anticipated mortality based on the Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD) scores. A rough guide to urgency can be decided based on Child–Turcotte–Pugh and MELD scores.

Apart from the use of these scores, patients who have recovered from an episode of spontaneous bacterial peritonitis (SBP) or have recurrent hepatic encephalopathy (HE) or hepatorenal syndrome (HRS) should be prioritized for transplant. Similarly, patients with acute-on-chronic liver failure (ACLF) with organ failure should be taken up for transplant when the team anticipates a favorable outcome as shown in Table 1.5

Patients with hepatocellular carcinoma (HCC) (e.g., within Milan/University of California San Francisco [UCSF]/Local Institutional criteria) should be transplanted as survival benefits are favorable. Those beyond criteria could be considered for downstaging or nonsurgical therapy.

Pediatric transplants should proceed as per usual indications based on individual center’s guidelines. Children with high bilirubin and recurrent cholangitis should be given preference. Transplants in metabolic conditions such as Primary Hyperoxaluria (PH) and Crigler Najjar Syndrome could be deferred till there is control of the pandemic unless there are urgent indications such as loss of dialysis access or recurrent metabolic crises. Children with malignancies such as hepatoblastoma should not have their transplant delayed.

At this moment, it is not clear whether children with Multisystem inflammatory syndrome (MIS-C) from COVID-19 infection with Acute Liver Failure (ALF) should be transplanted or not.

Liver Transplant for Acute Liver Failure

If the recipient tests negative for COVID-19 infection, transplant should be considered based on Center’s selection criteria.

If the recipient tests COVID-19 positive and if the selection criteria suggest poor prognosis without transplant, LTSI recommends that transplant should be considered as has been determined and reported by Cleveland Clinic recently.6 A detailed assessment of the COVID-19 positive recipient must be carried out such as computerized tomography (CT) chest score, inflammatory markers, and input from Infectious Diseases team so that the recipient does not develop posttransplant COVID-19 pneumonia.

On the other hand, if the potential donor tests positive, donation should not proceed. One must also keep in mind that the donor may have been similarly exposed and the team must satisfy themselves that the negative polymerase chain reaction (PCR) test is not a consequence of testing too early after exposure.

The operation should be carried out with full personal protective equipment (PPE) cover, particularly at the time of induction. The team should don standard full PPE, apart from the lead surgeon and his first assistant as it may not be possible for them to wear magnifying loupes with PPE. However, waterproof gown, plastic apron, caps, masks, shoe covers, and glasses will suffice.

The Hospital should designate an operation theater (OT)/OTs for COVID-19 cases as this may be necessary even for nontransplant cases which require urgent surgery.

Use of deceased donor organs

The use of organs from deceased donors without COVID-19 infection should proceed as usual. Prior to donation, a negative PCR test such as cartridge-based nucleic acid amplification test (CBNAAT) would be mandatory. No recommendation can be made regarding use of livers from donors with adverse event following vaccination in absence of large-size data.

If the potential donor has had COVID-19 infection in the past, and a 3-week gap from the time of testing is there, liver donation can proceed as there is evidence that a positive test at this stage does not imply risk of transmission.7 However, if the positive PCR test is more than 3 months old, a new test should be done.8
The group acknowledged that there has been no reported case of donor-to-patient transmission of COVID-19 infection either from blood transfusion or from liver donation, but it still felt strongly that cadaveric organs from a recently tested positive donor should be rejected to protect the huge numbers of personnel involved in organ retrieval.

The group also recommended that Non-Heart Beating donors or machine perfusion of marginal donors should be suspended till the Hospital’s positivity rate is less than 5%.10

Minimally Invasive Donor Procedures and Other Transplant Protocols
At the start of the pandemic, fear about aerosol generation and spread of COVID-19 infection led to the initial recommendation that they should not be done. However, there has been sufficient evidence to suggest that this is not the case.11 We suggest that use of minimally invasive procedures can be done as usual.

Use of blood and blood products should be minimized as Blood Banks have reported difficulty in donors willing to come to the hospital for purposes of donation.12

Vaccination for Recipient and Donor
It is recommended that patients with chronic liver disease be vaccinated, as they may be more prone to COVID-19 infection and deterioration of their liver disease as a result.

The group recommended that while pretransplant vaccination would be desirable, it would not be practical to insist on vaccination prior to transplant keeping in mind the urgency of transplant. Based on available evidence that a single dose of COVID-19 vaccine may confer protection from severe disease after 3 weeks, the LTSI recommends that potential recipients should receive at least the first dose of COVID-19 vaccine if an interval of 3 weeks prior to transplantation is available.13

The donors should also be considered for vaccination 3 weeks prior to planned donation.

Following recovery from the transplant operation, vaccination should be carried out after 3–6 months.14

COVID-19 Antibody Testing in Donors and Recipients
The LTSI expressed the opinion that antibody testing in donors and recipients was of no clinical value as antibodies may wane after infection or vaccination.

Timing of RT-PCR for Donors and Recipients Before Surgery
All recipients and donors should be tested for active COVID-19 infection using a reverse transcriptase polymerase chain reaction (RT-PCR)-based testing methodology not less than 72 h before the procedure to facilitate the arrangement of blood and blood products and reduce the pressure on laboratories performing the analysis. After negative COVID-19 testing, recipient and donor must follow strict isolation protocols.

Some hospitals may have local protocols such as 2 negative tests before transplant and they may be adhered to in keeping with Institutional practice.

If the recipient has tested positive and remained asymptomatic for 3 weeks, repeat testing would not be needed as RT-PCR tests may remain positive for extended periods even in patients with no viable viral particles.7

Screening/Selection/Postponement of Donors Who Test Positive
The second surge has seen many young individuals developing life-threatening pneumonia, and the LTSI recommends that donors who have developed moderate or severe disease should be rejected even if they recover from their illness as long-term risks of lung fibrosis and risk of thromboembolism is not known.

Donors who have had an asymptomatic or mild illness should ideally wait for 7 weeks prior to donation. This is based on evidence from nontransplant studies which have reported that the peri-operative risk for patients...
undergoing surgery after a COVID-19 infection returns to baseline after 7 weeks. However, recent guidelines by the American Society of Anesthesiologists (ASA) regarding elective surgery after COVID-19 and early data from some Indian centers suggest that liver donation surgery 4 weeks after RT-PCR-proven asymptomatic or mild COVID-19 infection may be equally safe. In keeping with the current practice in all living donor liver transplantation units in the country, the LTSI recommends that a 4-week gap may be sufficient to proceed with donation. Donor vaccination can be done after 1 month of surgery.

Policy for Donor and Recipient Testing Following Surgery

The LTSI recommends that donors and recipients be tested for 7 days following a suspected exposure if they remain asymptomatic. The degree and duration of exposure should be assessed as exposures with full mask on and at distances >2 m and duration of <15 min are unlikely to result in transmission of infection. However, if the person is symptomatic, testing should be done on that day. It seems that post donation COVID-19 infection generally runs a mild course as most of these donors are healthy, young, and fit individuals and therefore it may be important not to unduly alarm them in their recovery process. Pain relief, fluid balance and breathing exercises should be given due importance for steady recovery.

If the hospital policy dictates, COVID-19 positive donors should be moved to the designated COVID-19 area. Busy transplant units could arrange for segregating the Transplant Area into COVID-19 and non-COVID-19 areas. No matter where the patient is housed, management decisions must be taken jointly by the transplant and the hospital ID team. Further, they must be seen and spoken with by the transplant team daily.

When Can the COVID-19 Positive Recipient be Shifted to Non-COVID-19 Area?

The current guidelines from the Indian Council of Medical Research (ICMR) are that if the person is asymptomatic and recovered from transplant, they can be discharged without further testing. Although, limited data shows that transplant recipients may have prolonged viral shedding, LTSI suggests following ICMR guidelines in the absence of high-quality data.

In case where they still need transplant-related care, but have recovered from COVID-19 infection, they can be shifted to the Transplant area once the RT PCR is negative.

If according to local protocols, such as in the State of Kerala, rapid antigen testing is being used for decision making, it should be done at 10 days and repeated after another 7 days before the recipient can be shifted to a Non COVID-19 area.

Isolation Policy of Team Members Exposed to COVID-19 Patients

LTSI encourages that all team members of a liver transplant program should be fully vaccinated on priority. The team members who have completed their vaccination schedule and are asymptomatic need not undergo testing following low risk exposure.

Care must be taken by nonvaccinated team members that they are not exposed without protection. All patients in the pandemic should be regarded as potentially infected and due precautions taken.

Drug therapy of Proven or Suspected COVID-19 Infection Early Posttransplant

The drug therapy of a suspected COVID-19 patient should continue as per hospital guidelines.

Drugs such as azithromycin may cause changes in drug levels of calcineurin inhibitors should be used with caution and the dose adjusted to maintain the desired drug levels.

Some of the therapies such as intravenous immunoglobulin therapy (IVIG) and plasma therapy may have an impact of graft function and its use must be evidence based.

The use of monoclonal antibody combination of casirivimab and imdevimab may be considered in patients within 7 days of detection of COVID-19 infection and prior to hospitalization or requirement of oxygen therapy.

Once recovery is happening, one must be alert to the possibility of rejection with Immune Reconstitution Syndrome.

Units which run on low tacrolimus levels combined with antimetabolites such as mycophenolate mofetil should continue to do so with the intention of keeping the level of immunosuppression low. Limited data showed that use of mycophenolate at baseline may be associated with severe disease.

Prone Position/Early Tracheostomy Posttransplant

There are no contraindications for keeping the recipient in prone position if it were to improve the oxygenation. Worries about graft twisting and causing outflow obstruction are probably unfounded.

Similarly, early tracheostomy may be done. Although there were initial concerns, it appears it has a role in COVID-19 pneumonia and acute respiratory distress syndrome (ARDS).

Care of Donors Who May Turn COVID-19 Positive Posttransplant

Once they have been discharged, donors must be encouraged for vaccination if they have not been vaccinated.

Following discharge, if they develop fever, surgical issues such as wound infection, infected pleural effusion or infected
abdominal collection must be ruled out even if they test positive for COVID-19 infection. Treatment in the unfortunate event of moderate to severe COVID-19 disease should be administered by a multi-disciplinary team of ID specialists, intensivists, hepatologists and transplant surgeon.

Treatment of Recipients Who Develop COVID-19 Infection After Discharge

Most patients continue to remain in the care of their original transplant team who have taken them through often a stormy postoperative period.

1. Vaccination must be encouraged to all transplant recipients.
2. If they need care, a member of ID team should be contacted and ensure that they are looked after.
3. Immunosuppressive medication may be adjusted if they have not been adjusted for a long time. If they are a year out after transplant, antimetabolites can be stopped.
4. The use of monoclonal antibody should be considered and administered if eligible.22
5. Treatment of blood pressure and diabetes should be advised.

COVID-19 Consent

Patients and family should be made aware about the risks of carrying out a major surgical procedure during the pandemic. There exists a definite risk of contracting COVID-19 from the health personnel during hospital admission.

The risk if any, of performing major surgery on those who have recovered from mild COVID-19 disease or were asymptomatic, but COVID-19 test positive in the past is currently not known. Nevertheless, a small but finite risk of major complications and even mortality cannot be ruled out. It is particularly important for donors to be cognizant of this possibility.

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The following are author contributions:
- NS, SS: concept and help in draft.
- SG: first draft.
- AV, SS, CP, NNM, JV, SS, MSR, MSV, PB, RM, SA, SR: help in draft and critical revision.

CONFLICTS OF INTEREST

The authors have none to declare.

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