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Deceased Donor Liver Transplantation in India in the COVID-19 Era: Current Scenario and Future Perspectives

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has been recently declared a global pandemic. As of June 5, 2020, over 75,000 cases have been reported with nearly 2500 deaths in India alone. COVID-19 has severely impacted deceased donor liver transplant (DDLT) programs throughout the world. Acceptance of deceased liver donors has decreased worldwide because of the unknown risks associated with COVID-19 transmission or postoperative infection in the immediate post-transplant period, along with the risks to the health care workers in a multidisciplinary setting. In India, DDLT has come to a standstill in the setting of a national lockdown. Many national guidelines have emerged on how to safely perform transplant as well on immunosuppressive regimens and care of patients posttransplant. Here, we take a look at the current situation and summarize the different guidelines and future perspectives of DDLT in India in the COVID-19 era.

IN December 2019, the first case of coronavirus disease 2019 (COVID-19) infection was reported in Wuhan, China, caused by severe acute respiratory syndrome coronavirus [1]. As of June 4, 2020, about 6.6 million cases have been diagnosed worldwide with over 380,000 deaths [2,3]. In India alone, nearly 75,000 cases have been reported with over 2400 deaths [2,4]. On March 11, 2020, the World Health Organization declared COVID-19 a global pandemic [3]. The health care sector around the world has been at the forefront of fighting against this epidemic, which has led to strain on the economy and availability of resources [5].

COVID-19 has severely impacted solid organ transplant programs throughout the world. The risk and outcomes of COVID-19 infection in liver transplant recipients are being studied all around the world [6–8]. There is still a paucity of information regarding the overall safety of liver transplant recipients in the COVID-19 era. There is also the risk of transmission of COVID-19 from donor to recipient, surgical teams, and other health care professionals involved in a multidisciplinary program such as liver transplantation. Elective operations, such as living donor liver transplant (LDLT), have been temporarily suspended in many countries according to their national guidelines. However, many countries continue to perform deceased donor liver transplant (DDLT) based on modified donor and recipient criteria [9–11].

COVID-19 AND DDLT

Acceptance of deceased liver donors in the past few months have decreased worldwide because of the unknown risks associated with COVID-19 transmission or postoperative infection in the immediate post-transplant period [10,12,13]. The risk of viremia in a liver donor (up to 15% of cases) potentially places all recipients at risk of acquiring it through organ transplant [14,15]. Donor screening before acceptance has become mandatory around the world, using a combination of clinical, radiologic, and laboratory criteria. This varies in different countries between universal nucleic acid testing or reverse transcriptase polymerase chain reaction (RT-PCR) using nasopharyngeal swabs or bronchoalveolar lavage [12]. Recipient screening is also being done in a few countries using nucleic acid testing or RT-PCR [12]. The American Society of Transplant Surgeons COVID-19 strike force has recommended testing in all donors [15]. The International Liver Transplant Society has issued a general guideline that suggests avoiding transplant and immunosuppression for someone with developing

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or active disease [16]. Most countries have deferred transplant for nonurgent indications, including LDLT, while DDLT has been continued for urgent indications, such as acute liver failure or acute-on-chronic liver failure with appropriate consent [7,10–12,17–21]. So far, no donor derived infection has been reported.

THE INDIAN SCENARIO

India responded relatively early to the COVID-19 pandemic, and because of early restriction and quarantine practices, spread has been limited. However, community transmission is now prevalent with a surge predicted in the upcoming periods. The use of RT-PCR in Indian Council of Medical Research–approved laboratories has been prevalent here, with 2 negative tests considered confirmatory. Despite LDLT being the predominant type, DDLT has been progressively on the rise over the years between 2007 and 2018 [22]. After the advent of COVID-19, many national and international guidelines have been put in place for appropriate selection of donor and recipient for DDLT. Prominent among them are the Indian Council of Medical Research, Indian Society of Organ Transplantation, and the Liver Transplant Society of India [23–25]. The National Organ and Tissue Transplant Organization of India has also come up with a set of rules for DDLT and LDLT [26]. The common and important features of these recommendations are the following:

1. The living donor transplant program may be temporarily suspended in line with the Ministry of Family and Health Welfare's Advisory for Hospitals and Medical Institutions dated March 3, 2020 [27]. However, urgent lifesaving transplant may be done only after appropriate counseling and consent.
2. DDLT can be performed for acute liver failure or acute-on-chronic liver failure in highly selected cases after appropriate counseling and consent.
3. Deceased donors should be appropriately screened with 2 negative RT-PCR tests from nasopharyngeal swabs or bronchoalveolar lavage specimens, with or without chest computed tomography. The potential recipient must be COVID-19-negative by RT-PCR with or without negative chest computed tomography.
4. The possible impact of COVID-19 on a transplant recipient and false negative rates of the current tests along with risks must be mentioned clearly in the consent.
5. Transplant should be performed in an experienced center, with adequate protection (personal protective equipment) of the entire transplant team (COVID-free safe transplant pathway). The transplant team should be dedicated and, if possible, divided into 2 teams to facilitate care.
6. Post-transplant care should include COVID-19 testing as per clinical judgment, and follow-up in clinic can be done via telemedicine in the absence of clinical issues.

With the advent of lockdown in India on March 29, 2020, the National Organ and Tissue Transplant Organization officially declared for DDLT to stop throughout the country

until further notice. As a result of this, only 1 DDLT was performed throughout the country in the month of April 2020. In May 2020, the policy of phased relaxation of curfew measures, with gradual reopening of business activity, was resumed. Eventually, in the second week of May 2020, 2 cases of DDLT were performed. At present, transplant centers should attempt to minimize exposure of recipients to the health care setting by reducing the frequency of clinic visits and laboratory testing in a stable patient. All elective procedures, such as stent removal or protocol biopsies, can be deferred. We feel that transplant centers should develop their own guidelines to determine which symptomatic patients need evaluation, testing, and management by the transplant center and which patients can be followed up closely by telephone or telemedicine.

IMMUNOSUPPRESSION IN LIVER TRANSPLANT RECIPIENTS

At the time of writing this article, no universal agreements exist on the modification of immunosuppression in the immediate post-transplant period. There is a potential concern for higher risk of COVID-19 infection in solid organ transplant recipients. However, as of now, there is no clinical evidence of the risks of immunosuppression, and standard immunosuppressive protocol should be used in the post-transplant period [21,22,28,29]. However, during an active infection of COVID-19 in a post-transplant recipient, reduction of immunosuppressant may be considered, although withdrawal may result in acute rejection [30]. A study from New York has described their general approach to hold antimetabolites while reducing the dosage of other immunosuppressive agents as per clinical judgment [7].

COVID-19 INFECTION IN POST-TRANSPLANT RECIPIENTS

The risk of COVID-19 infection in post solid organ transplant recipients and their outcomes are being evaluated worldwide. In their initial report of 90 patients, Pereira et al reported the most common presenting features as fever, cough, and dyspnea. Just over 50% of them required intensive care unit care with a mortality rate of 18% (16 patients) [7]. Zhang et al reported 2 cases of solid organ transplant recipients who both recovered [30]. Bhoori et al reported 3 deaths of 6 patients with COVID-19 infection among liver transplant recipients [8]. Webb et al analyzed 39 liver transplant recipients and reported a mortality rate of 23% (9 patients) [6].

Several registries have been collecting patients' data on transplant recipients with COVID-19 infection, especially the University of Washington and the CAREDX' International COVID-19 Solid Organ Transplant Registry [31,32]. Despite these reports, more data will be required to determine the risk factors for mortality in COVID-19 infection in this population, and the optimal management strategies for both the treatment of COVID-19 and the immunosuppressive regimens.

FUTURE PERSPECTIVES

As India continues its journey in the community transmission phase, the relaxation of the curfew and the growing burden on the economy will ultimately result in a phased return to normalcy. This will be followed by a resumption of the DDLT programs around the country and eventually LDLT programs. The anticipation of a peak in the country will make transplant surgeons wary of performing avoidable cases in the near future. The promise of a vaccine or a cure, although probable, is still a distant reality. Eventually, we may also have to succumb to the age-old strategy of herd immunity while we wait for a research breakthrough. Until then, with proper donor and recipient selection strategies, DDLT will try to strike a fine balance between life and death on the liver transplant waiting list.

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REFERENCES

- [1] World Health Organization. Disease outbreak news: update. Novel coronavirus—China. <https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/>; 2020 [accessed 20.05.10].
- [2] Worldometer. COVID-19 coronavirus pandemic. <https://www.worldometers.info/coronavirus/>; 2020 [accessed 20.06.04].
- [3] World Health Organization. Coronavirus disease (COVID-19) pandemic. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/>; 2020 [accessed 20.06.04].
- [4] Ministry of Health and Family Welfare, India. COVID-19 India. <https://www.mohfw.gov.in/>; 2020 [accessed 20.06.04].
- [5] Das AP, Nundy S. Rationing medical resources fairly during the COVID-19 crisis: is this possible in India (or America)? *Curr Med Res Pract* 2020;10:127–9. <https://doi.org/10.1016/j.cmrp.2020.05.002>.
- [6] Webb GJ, Moon AM, Barnes E, et al. Determining risk factors for mortality in liver transplant patients with COVID-19. *Lancet Gastroenterol Hepatol* 2020;5:643–4. [https://doi.org/10.1016/S2468-1253\(20\)30125-4](https://doi.org/10.1016/S2468-1253(20)30125-4).
- [7] Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter [e-pub ahead of print]. *Am J Transplant* <https://doi.org/10.1111/ajt.15941>, accessed June 4, 2020.
- [8] Bhoori S, Rossi RE, Citterio D, et al. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol* 2020;5:532–3. [https://doi.org/10.1016/S2468-1253\(20\)30116-3](https://doi.org/10.1016/S2468-1253(20)30116-3).
- [9] Fernández-Ruiz M, Andrés A, Loínaz C, et al. COVID-19 in solid organ transplant recipients: a single-center case series from Spain [e-pub ahead of print]. *Am J Transplant*. <https://doi.org/10.1111/ajt.15929>, accessed June 4, 2020.
- [10] Ahn C, Amer H, Anglicheau D, et al. Global Transplantation COVID Report March 2020 [e-pub ahead of print]. *Transplantation*. <https://doi.org/10.1097/TP.0000000000003258>, accessed June 4, 2020.
- [11] Zhang BH, Yan LN, Yang JY. Organ transplantation management in the midst of the COVID-19 outbreak: a synopsis. *Hepatobiliary Surg Nutr* 2020;9. <https://doi.org/10.21037/hbsn.2020.03.16>. 250–2.
- [12] Kumar D, Manuel O, Natori Y, et al. COVID-19: a global transplant perspective on successfully navigating a pandemic [e-pub ahead of print]. *Am J Transplant*. <https://doi.org/10.1111/ajt.15876>, accessed June 4, 2020.
- [13] De Vries APJ, Alwayn IPJ, Hoek RAS, et al. Immediate impact of COVID-19 on transplant activity in the Netherlands. *Transpl Immunol* 2020;61:101304. <https://doi.org/10.1016/j.trim.2020.101304>.
- [14] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5).
- [15] American Society of Transplant Surgeons. COVID-19 strike force. <https://asts.org/advocacy/covid-19-resources/asts-covid-19-strike-force/>; 2020 [accessed 20.06.04].
- [16] International Liver Transplantation Society. ILTS COVID-19 statement: general consensus and recommendations from the ILTS Infectious Diseases and Liver Transplantation. <https://ilts.org/education/discussions/covid-19-statement-from-the-infectious-diseases-and-liver-transplantation-sig/>; 2020 [accessed 20.06.04].
- [17] Center for Medicare and Medicaid Services. Non-emergent, elective medical services, and treatment recommendations. <https://www.cms.gov/files/document/cms-non-emergent-elective-medical-recommendations.pdf>; 2020 [accessed 20.06.04].
- [18] Fix OK, Hameed B, Fontana RJ, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement [e-pub ahead of print]. *Hepatology*. <https://doi.org/10.1002/hep.31281>, accessed June 4, 2020.
- [19] Boettler T, Newsome PN, Mondelli MU, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep* 2020;2:100113. <https://doi.org/10.1016/j.jhepr.2020.100113>.
- [20] Boyarsky BJ, Po-Yu Chiang T, Werbel WA, et al. Early impact of COVID-19 on transplant center practices and policies in the United States [e-pub ahead of print]. *Am J Transplant*. <https://doi.org/10.1111/ajt.15915>, accessed June 4, 2020.
- [21] Gori A, Dondossola D, Antonelli B, et al. Coronavirus disease 2019 and transplantation: a view from the inside [e-pub ahead of print]. *Am J Transplant*. <https://doi.org/10.1111/ajt.15853>, accessed June 4, 2020.
- [22] National Organ and Tissue Transplant Organization. Organ report. <https://notto.gov.in/organreport.htm>; 2020 [accessed 20.06.04].
- [23] Indian Council of Medical Research. Guidelines for liver transplantation and COVID-19 infection. https://www.icmr.gov.in/pdf/covid/techdoc/Guidelines_for_Liver_Transplantation_and_COVID_13042020.pdf; 2020 [accessed 20.06.04].
- [24] Indian Society of Organ Transplantation. ISOT position statement for transplantation in era of COVID-19. https://isot.co.in/file/ISOT_V2_28_April_2020.pdf [accessed 20.06.04].
- [25] Saigal S, Gupta S, Sudhindran S, et al. Liver transplantation and COVID-19 (coronavirus) infection: guidelines of the liver transplant Society of India (LTSI) [e-pub ahead of print]. *Hepatol Int*. <https://doi.org/10.1007/s12072-020-10041-1>, accessed June 4, 2020.
- [26] National Organ and Tissue Transplant Organization. National transplant specific guidance for COVID-19. https://notto.gov.in/WriteReadData/Portal/News/711_1_FINAL_GUIDANCE_COVID-19_31.03.2020.pdf; 2020 [accessed 20.06.04].
- [27] Ministry of Health and Family Welfare, India. Advisory for hospitals and medical education institutions. <https://www.mohfw.gov.in/pdf/AdvisoryforHospitalsandMedicalInstitutions.pdf>; 2020 [accessed 20.06.04].
- [28] American Association for the Study of Liver Diseases. Clinical insights for hepatology and liver transplant providers during the COVID-19 pandemic. <https://www.aasld.org/sites/default/files/2020-04/AASLD-COVID19-ClinicalInsights-4.07.2020-Final.pdf>; 2020 [accessed 20.06.04].
- [29] The Transplantation Society. Guidance on coronavirus disease 2019 (COVID-19) for transplant clinicians. <https://tts.org/23-tid/>

tid-news/657-tid-update-and-guidance-on-2019-novel-coronavirus-2019-ncov-for-transplant-id-%20%20; 2020 [accessed 20.06.04].

[30] Zhong Z, Zhang Q, Xia H, et al. Clinical characteristics and immunosuppressant management of coronavirus disease 2019 in solid organ transplant recipients [e-pub ahead of print]. *Am J Transplant*. <https://doi.org/10.1111/ajt.15928>, accessed June 4, 2020.

[31] The Transplantation Society. COVID-19 coronavirus. https://tts.org/index.php?option=com_content&view=article&id=692&Itemid=115; 2020 [accessed 20.06.04].

[32] CAREDx. International. COVID-19 Solid Organ Transplant (C19TxR) Registry. <https://www.c19txr.org/>; 2020 [accessed 20.06.04].