Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a substantial risk of morbidity and mortality. As of June 18, 2020, more than 8.5 million people have been infected worldwide, and nearly 450,000 have died. This global pandemic has impacted liver transplantation (LT) services in multiple ways: a large number of patients with COVID-19 getting admitted and requiring intensive care are using up some of the resources normally meant for perioperative care of LT recipients; travel restrictions due to lockdown; fear of getting COVID-19 infection from hospital environment; HCWs and surfaces; physicians’ fears and experience of higher morbidity and mortality with COVID-19 among patients with decompensated liver disease and LT recipients/donors; and financial instability due to economic downturn. The financial part becomes more important in countries such as India where the majority of patients pay for transplants out of pocket. The situation is further complicated by nonavailability of effective treatment or a vaccine for COVID; and asymptomatic infection in many, who may transmit infection without coming to attention. Various societies have suggested guidelines to defer hospital visits and LT in stable patients. While there has been a decline of 30–80% in the deceased donor liver transplantation (DDLT) activity in various countries, the impact of the COVID-19 pandemic on LDLT has not been described. We describe our experience of LDLT in time of COVID-19 and compare the transplant activity during a similar non-COVID time period in 2019.

MATERIAL AND METHODS

Ours is a hub-and-spoke liver transplant system where around 240 transplants are performed annually, with around 200 at the main hub (Medanta, Gurugram) and the rest elsewhere, in six other centers.
The effects of the COVID-19 pandemic on LDLT activity were studied at our center in the period March–June, 2020 in the context of COVID protocols and restrictions on transplant activity, and compared with those of the corresponding period in 2019. Outcomes after initial LDLT counseling, evaluation, and after LDLT were compared between the two periods.

Specific hospital-based and LDLT-related COVID protocols were followed during this period:

1. Hospital-based state-guided protocols
   a) Our tertiary-care hospital demarcated its East and West wings separated by a 30-m-wide central building for COVID and non-COVID patients, respectively, each with their own entrance/exit, elevators, and staff. There were separate isolation wards and intensive care unit (ICU) for COVID-19 patients. As per the prevalent government policies, admission was open to all SARS-CoV-2-positive persons in March, whereas only those with moderate and severe disease were admitted later.
   b) COVID-19 real-time polymerase chain reaction (RT-PCR) was mandatory for all patients who needed hospitalization for treatment. Those with unknown COVID-19 status were kept in a holding isolation ward/ICU and triaged once the COVID-19 RT-PCR report was available.
   c) Specific intrahospital SARS-CoV-2-free pathways for common investigations such as ultrasound and CT scan were established. The transplant unit had only single rooms to avoid patient contact, and post-LT visits by relatives were temporarily suspended.
   d) Several strategies were implemented to mitigate in-hospital transmission of SARS-CoV-2. Thermal screening, hand sanitization, and surgical face masks were mandatory for all visitors and staff members upon entering the hospital compound. All staff members were systematically screened for COVID-PCR if they had influenza such as illness or unprotected contact with a COVID-positive patient and were advised quarantine until the PCR results were available. Contact tracing of positive HCWs was done with COVID-PCR.

2. Liver transplantation (LT) protocols guided by the center policy and the guidelines of the Liver Transplantation Society of India (LTSI)
   a) Patient selection: We adopted a strategy of deferring elective transplants among stable patients who could wait for several months and transplanting only sick patients (survival for several months unlikely, acute-on chronic liver failure or acute liver failure). Apart from patients with acute liver failure and acute-on chronic liver failure, stable patients were asked to wait, whereas those in the following categories were considered for LDLT during this period:
      a1 Those expected to have a mortality of up to 40–50% in 3–6 months:
      - Those expected to have a mortality of up to 40–50% in 3–6 months:
      - The current or recent model for end-stage liver disease (MELD) score ≥ 20.
      - Need for repeated large volume paracentesis especially those with a history of spontaneous bacterial peritonitis.
      - Recent recovery from severe acute kidney injury (creatinine > 2 mg/dl).
      - Moderate to severe hepatopulmonary syndrome.
      - Recent and recurrent life-threatening portal hypertensive bleeds.
   b) LT patients and HCW physical distancing: In-person evaluation for new potential wait-list candidates who were outside the criteria listed earlier was kept on hold until the decline of the infection rate curve, or until the patient became sick enough to satisfy the criteria listed in section 2a. All in-patients were nursed in single rooms and post-LT family visits were allowed only by attendants who were COVID-negative. Routine outpatient visits of post-transplant patients were done online via telemedicine, unless they needed physical attention at the hospital. All pre-transplant listing multidisciplinary team (MDT) meetings to discuss individual case details, the weekly MDT meetings to schedule cases, academic meetings, morbidity and mortality meetings, and research meetings were converted to the online format.
   c) Testing: A systematic SARS-CoV-2 screening strategy was implemented for all recipients and donors up to April 05 and also for the attendants after that. It included (1) a questionnaire on prehospitalization symptoms and a clinical examination at hospital admission, (2) nasal and oropharyngeal PCR, (3) a chest CT scan before LT for recipients. Chest CT images were interpreted in accordance with the guidelines from the European Society of Radiology and the European Society of Thoracic Imaging. Initially, one RT-PCR test was done within 48 h before the planned LDLT in both donors and recipients; later from April 10 onwards, this strategy was changed to two RT-PCR tests within 7 days and 2 days, respectively, before LDLT, in both the donor and recipient. While the first PCR test, if positive, serves to reduce exposure to HCWs and other contacts from asymptomatic donors/patients, the second PCR improves the sensitivity for the diagnosis of COVID taking care of some of the false negatives.
   d) Minimally invasive donor heptectomy: We put our Robotic Donor Hepatectomy program on hold during this period because of fears of aerosol generation and spraying during gas leaks from ports.
   e) Surgical consent: In both donor and recipient consent forms, we included the possible impact of COVID-19 on post-transplant outcomes, including false-negative rates.
of the current tests, and the risks of acquiring the infection during their hospital stay/visits.

f) Personal protective equipment (PPE): It was mandatory to wear full PPE during the transplant surgery for all staff in the operating room and post-transplant ICU. All staff on the ward, offices, and outpatients wore N95 masks and followed hand hygiene and physical distancing norms. All staff changed disposable gowns and gloves after every patient contact in all areas.

Study end-points
The profile of patients during March-June 2020 was compared with those in the similar period during non-COVID times in 2019. The data were collected prospectively, and following were noted and analyzed: the number and profile of patients who sought transplant consults, proportion and profile of patients evaluated for LDLT, the number of patients who eventually underwent LDLT or are scheduled for them soon, the LDLT patient population demographics, severity of liver disease (Child’s score and the model for end-stage liver disease scores), indication of transplantation and post-transplant outcomes. In addition, COVID-19 infection rates among recipients, donors, and HCWs were also noted.

Statistical methods
Data are shown as number, percentage, and mean ± standard deviation (parametric data). Two groups [transplant recipients in 15th March to 10th June 2020 (group A) and 15th March to 10th June 2019 (group B)] were compared with the Fisher’s exact test (categorical data) and student’s t test (parametric data). A two tailed P value < 0.05 was considered as significant.

RESULTS
LDLT during non-COVID and COVID times
A total of 39 LDLTs were done from 15th March to 10th June 2019, and 23 LDLTs were done in similar period of 2020. Thus, LDLTs in COVID times decreased to 58.9% of previous year. In addition to cirrhosis with or without hepatocellular carcinoma in adult patients [20 in group A (LT in 2020) and 36 in group B (LT in 2019)], a total of three pediatric patients (two in group A and one in group B), one patient each in group A and B had LDLT for acute liver failure and one patient had combined kidney liver transplantation for primary hyperoxaluria. There was no significant difference in age, gender, and indications of LDLT (decompensated cirrhosis being the most common indication). Comparison of adult patients with cirrhosis with or without HCC is shown in Table 1. The group A had significantly higher MELD scores in patients with decompensated cirrhosis.

Early (30 day) mortality after LDLT: Two patients in group A died because of sepsis (n = 1) and mucormycosis (n = 1), whereas 2 patients died in group B due to sepsis (n = 1) and intracranial bleed (n = 1). None of the donors in the 2019 or 2020 groups had any serious morbidity (Clavien–Dindo class III or IV complications) or mortality.

SARS-CoV-2 infection among patients and HCWs
One of the LDLT recipients was diagnosed with asymptomatic COVID-19 on postoperative day 15. He was tested as one of his attendants was found to have COVID-19. It was decided to maintain the tacrolimus level of 4–6 ng/l along with a standard dose of mycophenolate and tapering

Table 1 Comparison of Adult LT Recipients With Cirrhosis Between Group A (15th March–10th June 2020) and Group B (15th March–10th June 2019)a.

| Parameter | Group A (n = 20) | Group B (n = 36) | P value |
|-----------|----------------|----------------|---------|
| Age (years) of adult patients | 51.9 ± 10.8 | 48.4 ± 10.1 | 0.230 |
| Male: female (patients with cirrhosis) | 18:2 | 33:3 | 1.0 |
| CTP | 9.1 ± 2.0 | 9.0 ± 1.9 | 0.853 |
| CTP (n = 17 and 32, excluding transplants for mainly for HCC) | 9.7 ± 1.5 | 9.6 ± 1.3 | 0.795 |
| MELD | 17.9 ± 7.9 | 15.1 ± 5.9 | 0.138 |
| MELD (n = 17 and 32, excluding transplants for mainly for HCC) | 19.8 ± 7.0 | 16.1 ± 5.6 | 0.034 |
| Indication of liver transplantation | | | |
| Decompensated cirrhosis ± HCC | 17 | 32 | |
| Child’s A cirrhosis with HCC | 3 | 4 | 0.691 |
| Etiology of cirrhosis | | | |
| Alcoholic liver disease: hepatitis C, hepatitis B: NASH/cryptogenic: others | 10:3:2:4:1 | 16:6:4:9:1 | 0.979 |

CTP: Child-Turcotte-Pugh score; HCC: hepatocellular carcinoma; MELD: model for end-stage liver disease score, NASH: non-alcoholic steatohepatitis related.

aAfter exclusion of pediatric patients (n = 3), patients with acute liver failure (n = 2) and combined kidney liver transplantation (n = 1).
doses of steroids. The recipient remained asymptomatic. The COVID-19 RT-PCR was repeated weekly and found to be negative on postoperative day 29. Two prospective LT recipients and one prospective donor tested positive in preoperative COVID-PCR testing. One of these prospective recipients had negative PCR one week before, but turned out to be positive one day before LT, and LT was postponed. All these three (of 71 tested) had been found to be positive on protocol testing during transplant evaluation, and none had symptoms at the time of testing. The two recipients are waiting for transplant once their report (two sets one week apart) become negative for COVID-19, whereas the donor has been rejected for donation for 6 weeks with at least two negative tests one week apart.

Two of the nursing staff taking care of the COVID-positive post-transplant patient also tested positive on contact tracing; one was asymptomatic and one mildly symptomatic. Both recovered without any complications. In addition, six more staff (four nurses, a coordinator, and a resident doctor) also tested positive during March 15 to June 10, 2020. Two of these were asymptomatic, and 4 had mild disease. All recovered uneventfully. Therefore, a total of 8/125 (6%) dedicated LT staff tested positive during this time. We also looked at data after first submission of this manuscript (11th June to August 2020); of 71 prospective LDLTs, seven patients (9.8%) and two donors (2.8%) were positive for SARS-CoV-2 during evaluation. Three of nursing staff and one doctor tested positive during June to August period. All of donors and HCWs had uneventful recovery, while one of recipients died.

**DISCUSSION**

This is the first detailed report of LDLT activity from a single high-volume center during the SARS-CoV-2 pandemic. A careful assessment and reorganization of available resources allowed us to successfully maintain a LDLT program.

Liver transplantation has faced unique challenges due to COVID-19 all over the world. Various governments announced lockdowns to prevent spread of COVID-19, and economies performed poorly. The hospitals were overburdened by patients of COVID-19 in several countries, which affected care of patients with other diseases. Much of the period of the study involved a lockdown with complete cessation of travel between cities and countries. Hospitals have been reluctant to take up nonurgent cases. Equally, stable patients have been fearful of coming to hospitals and getting infected with COVID especially if they are in the high-risk categories such as those over 60 years of age, with chronic liver disease, diabetes mellitus, and presence of comorbidities. The fact that there is no proven cure for COVID-19 has further fueled this fear. Many countries have faced reduction of deceased donor activity. Similarly, DDLT numbers have reduced significantly in India (personal communication). This phenomenon in India and elsewhere may have increased the desperation for LDLT among many sick patients and their treating teams.

We found the LT referral rate fell by over 50% in the COVID era, because of both, travel restrictions and stable patients and their referring doctors, choosing to wait for the pandemic to pass. However, during the pandemic, a much higher proportion of those who consulted underwent LDLT evaluation and, eventually, transplant. The proportion of HCC cases during this period was also higher than usual. These observations were not surprising, considering the potential recipients were sicker and/or would run the risk of dropping out of the wait-list due to HCC progression. The near absence of deceased donor options and our stated LDLT policy during this period were the other contributing factors to this pattern. The fall in the proportion of foreign nationals was also expected because of travel restrictions.

The COVID guidelines by LTIS suggest transplantation only for acute liver failure, acute-on chronic liver failure with organ failure (individual center’s discretion), and a center-based policy for performing relatively urgent cases. Accordingly, during the pandemic period, we transplanted sicker patients with higher MELD scores and patients with HCC who could not wait. Various other societies have also issued guidelines on avoiding elective hospital visits and elective procedures and asking stable patients to wait for liver transplantations. With careful patient preparation and strict COVID protocols, the outcome after LDLT was good at our center despite selecting sicker recipients. Müller et al\(^6\) and Umberto et al\(^10\) also found similar post-transplant outcomes in their patient during this period.

Our single recipient with early post-transplant COVID-19 recovered uneventfully. Umberto et al\(^10\) have reported two cases (of 17 LT) of COVID-19 in the early post-transplant period, of which one died and one recovered. During the 39 days of median post-LT follow-up, no case of SARS-CoV-2 was diagnosed in the 10 LT recipients done during the peak of pandemic in France. There are contrasting reports of outcome among transplant recipients.\(^19,20\)

The ELITA/ELTR COVID-19 registry has reported 16% mortality in liver transplant recipients due to COVID-19.\(^21\)

The results suggest that mortality in liver transplant recipients might be higher in older recipients (>60 year, 22%) than in younger patients (<60 year, 0%) and could be worse in patients with longer time because of transplantation (18% in those transplant done more than 2 year ago versus 5% in those who were transplanted within last 2 years). As of 9 June 2020, COVID-Hep and SECURE-Cirrhosis registries have reported 783 cases of COVID-19 in chronic liver disease: non-cirrhotic (n = 297), cirrhosis (n = 352), liver transplant (n = 134). The reported mortalities among decompensated cirrhosis and after liver transplant are 34% and 19%, respectively. However, the patient population in these registries is largely DDLT patients, with few LDLT...
entries. Hence, the present study gives a unique single-center perspective of the effect of COVID-19 on LDLT activity and outcome.

The incidence and recovery rate of COVID infection among HCWs at our Liver Transplantation institute was 6% and 100%, respectively. It is important to provide protective gear and to keep all precautions for HCWs. Figures from China’s National Health Commission show that more than 3300 healthcare workers have been infected as of early March and, according to local media, by the end of February at least 22 had died. In Italy, 20% of responding healthcare workers were infected, and some have died.23

We also refrained from minimal access donor hepatectomy to avoid inadvertent escape of CO2 aerosols through or around ports during such surgery.24,25

Our in-hospital testing and PPE protocols for LT staff were very strict. There were several reasons for this cautious approach: the risk of fomite and person–person transmission in the hospital setting with huge load of complex ICU patients, the risk of transmission from asymptomatic infected persons,13 a vulnerable patient population who were sick with liver disease or immunosuppressed, the risk of prolonged viral shedding by immunosuppressed patients,26 and the uncertainty about the outcomes if a live liver donor contracts COVID-19 in the immediate postsurgery period. A recent experience from India also did not find any COVID-related issues after surgery in nine patients and donors.27

In view of the accepted false negative rate of 20–30% of conventional RT-PCR tests, our pretransplant informed consent included the small risk of testing positive for COVID-19 any time after surgery with its attendant morbidity and mortality.

The current study includes a small number of patients with short follow-up; therefore, more data with longer follow-up are needed. However, given the unprecedented situation, this preliminary clinical experience should help in the process of moving forward.

The patients with cirrhosis are a high-risk population in whom waiting puts them at a high risk of morbidity, mortality, and/or increased risk of occurrence or progression of HCC. Furthermore, the delay and deterioration in these patients adversely affect post-transplant outcomes. Because waiting is not ideal for these patients and the risk of SARS-CoV-2 infection is unlikely to subside in the near future, the delicate balance of benefits of early transplantation versus risk of infection with COVID-19 needs further deliberation. Preliminary data from the study suggest that with strict COVID protection protocols, and continuous evaluation of both resources and outcomes, it should be possible to extend LDLT activity to more stable patients. It should be noted that at the time of study (15th March–10th June 2020), the total number of cases in India were low, which has increased recently; thus number of SARS-CoV-2 positive patients and donors may increase in presurgery evaluation as seen in the current study. However, the number of HCWs positive for SARS-CoV-2 was less in later period, likely secondary to strict protocols.

In conclusion, we report a preliminary experience of a high-volume LDLT program during the SARS-CoV-2 pandemic. While there was a significant reduction of LT activity in the COVID era, the outcomes remained good. Asymptomatic infection in prospective donors and recipients, and HCW infections were a matter of concern. Efforts in resource planning, strict infection control, optimal recipient selection, and screening of the donor and recipient are keys to maintaining safe LDLT activity and its careful extension to more stable patients. Transplant centers, however, must remain open to readapting their practices as the pandemic evolves.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Arvinder S. Soin: Conceptualization. Narendra S. Choudhary, Sanjay K. Yadav, Arvinder S. Soin: draft writing. Prashant Bhangui, Thiagarajan Srinivasan, Neelam Mohan, Sujee K. Saha, Ankur Gupta, Rohan J. Chaudhary, Kamal Yadav, Swapnil Dhampalwar, Deepak Govil, Nikunj Gupta, Vijay Vohra: data collection, help in draft. Sanjiv Saigal, Neeraj Saraf, Amit Rastogi, Arvinder S. Soin: critical revision.

CONFLICTS OF INTEREST

The authors have none to declare.

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SUPPLEMENTARY DATA
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