

Liver Transplantation in India: At the Crossroads

Sanjay Nagral^{*}, Aditya Nanavati[†], Aabha Nagral[‡]

^{*}Department of Surgical Gastroenterology, Jaslok Hospital and Research Centre, India, [†]Department of General Surgery, K.B. Bhabha Municipal General Hospital, India and [‡]Department of Gastroenterology, Jaslok Hospital and Research Centre, India

As the liver transplant journey in India reaches substantial numbers and suggests quality technical expertise, it is time to dispassionately look at the big picture, identify problems, and consider corrective measures for the future. Several features characterize the current scenario. Although the proportion of deceased donor liver transplants is increasing, besides major regional imbalances, the activity is heavily loaded in favor of the private sector and live donor transplants. The high costs of the procedure, the poor participation of public hospitals, the lack of a national registry, and outcomes reporting are issues of concern. Organ sharing protocols currently based on chronology or institutional rotation need to move to a more justiciable severity-based system. Several measures can expand the deceased donor pool. The safety of the living donor continues to need close scrutiny and focus. Multiple medical challenges unique to the Indian situation are also being thrown up. Although many of the deficits demand state intervention and policy changes the transplant community needs to take notice and highlight them. The future of liver transplantation in India should move toward a more accountable, equitable, and accessible form. We owe this to our citizens who have shown tremendous faith in us by volunteering to be living donors as well as consenting for deceased donation. (J CLIN EXP HEPATOL 2015;5:329–340)

Liver transplantation (LT) arrived in India many decades after it was successfully performed in the developed world. A few years after the Government of India passed the Human Organs Transplant Act (HOTA) in 1994 recognizing brain death, the first attempt at a deceased donor liver transplant (DDLT) was made in Chennai in 1996 at the Apollo Hospital.¹ Following

this, a few sporadic procedures were performed in Delhi, Mumbai, and Chennai in the late 1990s. It was however only at the turn of the millennium that limited but meaningful LT activity started taking place.

In spite of the law being in place, there had not been much progress on deceased donation for many years. Hence surgeons, many of who had trained in Western centers in deceased donor transplantation and were impatiently waiting in the wings, turned their attention to live donor liver transplantation (LDLT). By that time surgeons in countries like Korea, Hong Kong, and Japan where deceased donation was very limited had perfected the live donor procedure over many years, partly because of their immense experience in hepatobiliary surgery. Surgeons from India traveled to these centers and acquired training.

The first serious attempt at a program of LDLT was at the Sir Gangaram Hospital in Delhi. The early results were not satisfactory.¹ The team persisted and soon started seeing increasing success. With success came numbers as well as replication in other centers. Gradually, the number of transplants as well as centers across the country started increasing. By 2007, it was estimated that 346 procedures had been performed in 22 centers out of which 250 were LDLTs.¹

The last few years have seen an exponential rise in the number of LTs in India. This is mainly a result of a large numbers of LDLTs being performed in a few select centers that have evolved into specialist LDLT departments. They attract patients from all over India as well as neighboring countries. Paralleling this, there has been a significant increase in DDLTs, mainly in Tamil Nadu but also in Maharashtra, Gujarat, Andhra Pradesh, and Kerala.² Though LDLT still remains the dominant form, some centers mainly in the South and West are now beginning to perform a mix of both procedures. Although the lack of

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Address for correspondence: Sanjay Nagral, Department of Surgical Gastroenterology, Jaslok Hospital and Research Centre, Mumbai, 400026, India. Tel.: +91 22 66573338.

E-mail: sanjaynagral@gmail.com

Abbreviations: ALF: acute liver failure; CMV: cytomegalovirus; CT: computerized tomography; DBD: donation after brain death; DCD: donation after cardiac death; DDLT: deceased donor liver transplant; DNA: deoxyribonucleic acid; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HOTA: Human Organs Transplant Act; ICU: intensive care unit; INASL: Indian Association for Study of the Liver; ISOT: Indian Society of Organ Transplantation; KCH: King's College Hospital; LDLT: live donor liver transplantation; LT: liver transplantation; MELD: model for end stage liver disease; NASH: non-alcoholic steatohepatitis; NGO: non-governmental organizations; NOTTO: National Organ and Tissue Transplant Organization; NTORC: non transplant organ retrieval center; OPTN: Organ Procurement Transplant Network; RGJAY: Rajiv Gandhi JeevandayeeArogyaYojana; ROTTO: Regional Organ and Tissue Transplant Organization; SOTTO: State Organ and Tissue Transplant Organization; SRTR: Scientific Registry of Transplant Recipients; TB: tuberculosis; UCSF: University of California San Francisco; UKELD: United Kingdom End stage Liver Disease; UKNHSBT: UK the National Health Services Blood and Transplant Authority; UK: United Kingdom; UNOS: United Network for Organ Sharing; USA: United States of America; ZTCC: Zonal Transplant Coordination Centre

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a centralized registry and database makes it difficult to estimate the precise number, based on personal communication from centers, numbers in publications, and information available on the Internet, we estimate that by now around 7500 liver transplants have been performed across the country.

The availability of LT in India has undoubtedly created the opportunity of a lifesaving procedure for individuals dying from end-stage liver disease. By itself, this is a huge leap forward. A ripple effect on other specialties including the emergence of dedicated hepatologists, anesthetists, and intensivists has also occurred. In a less appreciated phenomenon, in many institutions, clinicians involved with LT have enabled deceased donation from the sidelines. For example, we have been witness to the fact that in Mumbai liver transplant surgeons and physicians played a key role by prodding and fostering deceased donation in the centers they worked. In the first few deceased donations where only kidneys were retrieved, LT surgeons performed the harvesting in fairly challenging and sometimes-hostile surroundings. The role of the liver transplant team at the Army Research and Referral Hospital in promoting a national network of deceased donation among the armed forces medical institutions has been exceptional.³ Thus, LT activity has also spurred the overall growth of deceased donation in India.

Emboldened by success and with increasing confidence with the procedure, the last few years have also seen teams performing split transplantation, dual lobe LDLT, swap LDLT, and a few domino and auxiliary procedures.⁴⁻⁶ This is good evidence of sophisticated technical expertise as well as effective teamwork and coordination. Also, this has led to increased performance of complex hepatobiliary procedures.

However, as the initial sense of euphoria recedes, the number of transplants reaches meaningful numbers and with moves to setup a national network for organ sharing, and this is an opportune time for the LT community to critically analyze what has been achieved over the last decade. For a procedure that demands huge resources as well as public policy interventions, such periodic reflection is necessary not only for grasping the big picture to restore a sense of proportion but also to identify problems and make necessary course correction. The information base for this review consists of publications accessed from standard databases, data from the websites of organ sharing networks, newspaper reports, and personal communications with members of the liver transplant community. Two of the authors have been involved in LT in Mumbai from its inception. The lead author also chairs the liver committee of the Zonal Transplant Coordination Center (ZTCC), Mumbai and has been involved in data collection and organ sharing policy formulation. Some of the observations in the paper draw from this experience.

Early literature on LT in India is marked by reportage of achievements and a certain self-congratulatory note. This is beginning to change and some reflective, analytical writing is beginning to emerge.^{7,8} However, there is still a paucity of substantive discussion on areas like organ sharing protocols, registry, donor problems, recipient outcomes, economic considerations, and inequities in the pattern of activity. One reason for this may be that these are sensitive areas and the solutions may be seen to lie with agencies like the state. However, we feel it is incumbent on the Hepatology and liver transplant community to at least initiate a discourse on some of these issues. Keeping this in mind, in this review we have attempted to flag issues specific to the current trajectory of LT in India, which demand some course correction. Some of the important issues covered include the scale and pattern of LT activity, imbalances, indications, outcomes, challenges in deceased donation and organ allocation, impact of live donor transplant, unique medical problems, accessibility and affordability, and future trends. We also try to offer possible alternatives to overcome some of the challenges.

WHAT IS THE SCALE OF LT? WHAT IS THE PATTERN OF DISTRIBUTION OF CENTERS? WHAT ARE THE IMBALANCES?

Like the rest of the world, chronic liver disease has emerged as a huge burden in India. With increasing incidence of alcoholism, diabetes, and obesity, it is also expected to rise substantially.⁹ As health seeking behavior and the use of diagnostic tests increase, more cases of liver disease and hepatocellular carcinoma (HCC) are being diagnosed. A majority of HCCs in India are seen on the background of liver disease.¹⁰

It has been estimated that approximately 20,000 people require liver transplant in India annually.¹ Even this is likely to be a gross underestimate as it is based on numbers of chronic liver disease patients who seek specialist hospital care. Yet only around 800–1000 LTs are currently performed every year.¹¹ Although across India more than 200 centers are recognized by the government to perform LT, there are only about 25 centers with active programs. In Mumbai city, 20 centers are recognized for LT but currently only 6 perform it regularly.

There are enormous regional imbalances in the availability of LT services in India and are currently largely restricted to metros like Delhi, Hyderabad, Kochi, Chennai, and Mumbai. Large swathes of the country, especially the eastern states and the North-East, have no center offering LT. Large states like Madhya Pradesh, Uttar Pradesh, and Rajasthan have witnessed negligible activity. Though such imbalances are intrinsic to health care in India, the disparity in LT is stark. One reason for this is that LT in India is not an organized national service but a project largely left to the strategic interests of the corporate private sector.

There is a geographical divide in donation patterns in India. The South and the West have a higher proportion of DDLTs.² This is obviously due to the higher numbers of deceased donation in the southern states. In Mumbai, around 40% of the roughly 360 liver transplants performed to date are from donation after brain death (DBD) donors. While there are sociocultural factors responsible for this gap, we believe that this is also due to proactive non-governmental organizations (NGOs) and state support in the South.

This geographical imbalance results in a number of recipients traveling to another city miles away for getting a LT. Even those on deceased donor waiting lists have to stay in another city waiting for an organ. Since listing in multiple centers across states is permissible, there is an unfortunate spectacle of sick patients traveling from city to city for workup, listing, and sometimes false alarms for an organ. All this adds substantially to the already substantial physical, mental, and financial burden of the disease. The Mumbai ZTCC has witnessed debates about whether local residents should be given priority over those from outside the state but currently all patients are treated equally except those from outside the country who are given the lowest priority.

We estimate that overall around 10–15% of patients who undergo live donor liver transplants in India are from foreign countries and in some centers as high as 25%.¹² These patients are typically from the Middle East or from neighboring South Asian countries like Pakistan, Sri Lanka, Bangladesh, and Myanmar. We are not aware of any other country where the proportion of LDLTs for foreign patients is so high. While this acquires revenue and goodwill, it creates its own set of complications. From authenticating the paperwork, reliably establishing relationship with the donor, communication with the donor and recipient in case of a language barrier,¹² and the difficulty in follow-up, such liver transplant tourism can throw up distinctive challenges adding to the stress of the providers. We also need to be cautious that excessive proliferation of LDLT for foreigners can potentially bring memories of the unfortunate period of organ trade that has haunted the history of transplantation in India.

The most conspicuous imbalance in LT in India though is the difference of activity in the public and the private sector. We estimate that currently <2% of LTs take place in public institutions. There are some obvious consequences of such massive dominance by the private sector. Our survey indicates that except three, all other active centers offer packages in the range of 20–30 lakh rupees, which is beyond the reach of the common citizen including the middle class. Often the actual cost is higher as the family has to spend for travel, stay, and sometimes complications where the package amount becomes invalid. In a country where out of pocket expenditure is the commonest mode of health care payment,¹³ even for the few who can put

together this money, it can result in catastrophic expenditure. We consider this as perhaps the biggest challenge facing LT in India today. What is of special concern is that the few public institutions which set up teams, obtained support and funding, and started performing LTs have either slowed down or stopped. Some of these are large, academic centers with good field strength and favored status in terms of funds and state support. To be fair, the domination of the private sector in health care is not peculiar only to LT. However, in other high resource areas like kidney transplantation, cardiac surgery, and oncosurgery, the public sector has been reasonably active and though waiting periods are long, there is an opportunity for the poor to access care.

It may be pertinent here that historically a lot of the advances in health care in India were initiated from public institutions including the first kidney and cardiac transplantation. Academic Departments of Gastroenterology, Hepatology, and Hepatobiliary Surgery are well developed in leading public hospitals in India. There is therefore no lack of trained dedicated manpower and even technology. Of course there are thousands of needy patients. Yet there is some missing link. One explanation is that these institutions are overburdened with the care of a large number of patients with routine illnesses. Also, in the absence of the monetary incentive, there is inability to sustain momentum in an area where failures are common and teamwork is the key. Whatever be the reason the current situation is neither desirable nor sustainable. It will be difficult to get large-scale acceptance of deceased donation if the liver is allotted largely to the affluent in the private sector.

Roughly 85% of the LTs in India are from living donors (LDLT).¹⁴ It seems to have found a fairly quick acceptance amongst family members of recipients. The current rules permit live donation from beyond first-degree relatives (termed unrelated) with special permission after scrutiny from the state transplant authority. The ways the committee functions currently differs from state to state. Precise data regarding the proportion of such donors are difficult to obtain but to our knowledge, a substantial number of donors are family members beyond first-degree relatives or even unrelated donors. In the context of a procedure like LDLT where donor problems are not uncommon, this is a potentially hazardous situation.

WHAT ARE THE COMMON INDICATIONS FOR LT?

The indications for LT in India reflect international trends with some variations. In the absence of national data, extrapolation from series from transplant centers reveals that hepatitis C and alcoholic cirrhosis are the major indications.^{15,16} Hepatitis B still comes third in many reports even though it is on the decline elsewhere in the

world.¹⁶ In the last few years, there is an increasing trend of LT for non-alcoholic steatohepatitis related cirrhosis.⁹ In children, the commonest indication is biliary atresia (75%); however, an increasing number of patients with metabolic diseases are now being treated with LT.⁵ A common indication for LT in India is HCC in a cirrhotic liver. Around 10% of patients transplanted at large centers are for HCC.¹⁷

WHAT IS THE STATUS OF LT FOR ACUTE LIVER FAILURE?

LT has been performed in many centers for patients with acute liver failure (ALF) who are unlikely to respond to medical management. The etiology of ALF in India shows some variation from the West.¹⁸ For example, in some series, ALF has been most commonly due to viral hepatitis followed by drug injury due to anti-tubercular therapy.¹⁸ On the other hand, cases of paracetamol poisoning do not make up a significant number of ALF patients like in the West. Etiologies like zinc phosphate poisoning due to a suicidal attempt are seen in some series including from Kerala.¹⁹ In a series from Western India, typhoid fever, hemophagocytosis, dengue fever, rickettsial infections, amoebic hepatitis, leptospirosis, and falciparum malaria were found to be the other infectious diseases leading to ALF.²⁰ In this series, the mortality from ALF due to viral hepatitis was 50% and from other infectious diseases was 25%. Given the wide variety of etiologies with variable natural histories, some of which are not common in the West, the current trend of following western guidelines on the need for emergency LT in ALF therefore needs to be questioned. Besides, transplantation for liver failure secondary to these systemic infectious causes would theoretically be contra-indicated.

Anti-tubercular drug-related ALF seems to have a worse prognosis compared to acute viral hepatitis especially hepatitis E which is the commonest cause of acute ALF in India. Low albumin, jaundice, ascites, encephalopathy, and high prothrombin time have been described to increase the risk of liver injury from these drugs.²¹ The decision on need for LT for ALF secondary to hepatitis E is based on King's College Hospital (KCH) criteria in most centers in India and is also currently followed by organ sharing networks.²² However, workers from Indian centers have identified other prognostic criteria. For example, cerebral edema is a poor prognostic sign and may need to be considered in the decision making. Dhiman et al. identified 6 early clinical prognostic indicators of adverse outcome on admission in patients with fulminant liver failure due to acute viral hepatitis: age ≥ 50 years, jaundice to encephalopathy interval >7 days, grade 3 or 4 encephalopathy, presence of cerebral edema, prothrombin time ≥ 35 s, and creatinine ≥ 1.5 mg/dL.²³ Patients with 3 or more of these indicators were not likely to survive without a transplant. Further, these clinical prognostic indicators were better

than model for end stage liver disease (MELD) and KCH criteria for predicting adverse outcome. There is therefore a case for separate criteria for acute viral hepatitis related ALF. Rat poison (aluminum or zinc phosphide) is a commonly used suicidal agent in India as it is easily available and cheap. It causes fatal liver failure in a subset of patients. Saraf et al. from Kochi described 30 patients with rat poison consumption of which 9 underwent liver transplant.¹⁹ A MELD score of over 31 on day 6 and the onset of encephalopathy at any time following ingestion were predictors of the need for LT. Thus, the KCH criteria which were based on a cohort of patients from the United Kingdom (UK) with paracetamol overdose being one of the predominant factors therefore may not apply to a substantial number of ALF cases in India. However, since there is a paucity of publications addressing issues in LT for patients of ALF due to diseases peculiar to India, they may continue to be used by default unless there is an attempt to validate alternative criteria.

There are a substantial number of patients who have undergone emergency LDLT for ALF in India with satisfactory outcomes.¹ The ability of centers to perform emergency LDLT in the ALF setting is an indicator of their field strength. The ethical validity of an informed consent process from a live donor in the emergency setting of ALF has been questioned. But in the current situation where the chances of getting a deceased donor organ in a short period of time are very low LDLT will continue to be performed as a life-saving procedure in the setting of ALF. In Mumbai, 120 patients have been listed in the super urgent category for deceased donation over the last 5 years but only 4 got an emergency allocation. In a national sharing network which covers all states, ALF patients would be more likely to get emergency allocation of organs as happens in other countries. Thus, the Hepatology community has a huge stake in promoting the setting up of such a network.

HOW ARE DECEASED DONOR LIVERS CURRENTLY ALLOCATED?

There is variation in the way deceased donor organs are currently shared in the active networks. In Tamil Nadu, the liver is first offered to a patient listed as super urgent. It is then offered to an in-house recipient in the same hospital as the donor and if there is no in-house recipient or the organ comes from a non-liver transplant center, it is offered in rotation to the recognized centers who in turn can choose to use it for any of their wait-listed patients.² Andhra Pradesh follows a model similar to Tamil Nadu. Kerala has been divided into three zones with priority being given to a center in the zone first. However, like in Tamil Nadu, the liver is allotted to centers in rotation and not to a particular patient.

In Mumbai, the ZTCC allocates livers based on urgency, waiting time, and also gives priority to in-house recipients

in the donor hospital. The organ is first offered to a recipient listed as ALF (super urgent) status fulfilling the KCH criteria.²² For a patient to be listed in this category, the center has to send detailed information with original reports which is screened by an expert committee before listing. If there is no super urgent category recipient, then the organ is offered to a routine category patient in the center where the donor is as per the ZTCC waiting list. Thus, unlike Tamil Nadu, the liver is allocated to a patient and not a center. The center may choose to go down the list under certain conditions which include acute on chronic liver failure or presence of tumor within University of California San Francisco (UCSF) criteria. The center has to disclose the reason for allotting out of turn in the list to the ZTCC, which is audited by the liver committee. If there is no recipient in the donor hospital (or the hospital does not perform LT), the organ is distributed to a city-based waiting list and allocated strictly on chronological waiting time.²²

Thus, currently livers from deceased donors in India are allocated either based on in-house priority, waiting period time, or by institutional rotation. This means that except patients with ALF, others are not allotted organs on medical urgency as is the case in other parts of the world. These policies were presumably developed to promote deceased donation (as in-house recipients get priority institutions tend to promote brain death declaration) as well as to keep all centers involved in the program. It is true that DBD programs in India are driven by centers and individuals who are themselves involved in transplantation. Thus, a majority of donations come from centers that are also active transplant centers. However, this scenario is also fraught with a potential conflict of interest. It must be noted that currently there has been a fair level of autonomy given to state organ sharing networks to develop sharing criteria but eventually uniformity at the national level will be the key especially if interstate sharing is to be promoted.

Internationally, organizations like the United Network for Organ Sharing (UNOS) in the United States of America (USA) also started out by allocating livers based on waiting list time. However, this led to patients with compensated liver disease getting livers before those with decompensated liver disease. Also, there was a tendency to list patients very early in the disease.²⁴ UNOS now uses the MELD score and in the UK, the National Health Services Blood and Transplant Authority (UKNHSBT) uses the UK End stage Liver Disease (UKELD) score for prioritization of liver allocation. These score-based allocation policies are based on the premise of justice wherein the organ is distributed to the sickest patient first. The MELD score has been adequately validated for use in liver allocation.²⁵ Realizing the need of developing a score that predicts post-transplant outcomes more precisely, the UK adopted the UKELD score (incorporating serum sodium concentration).²⁶ It is rational that allocation policy should be based

on medical urgency, transplant benefit, and expected post-transplant outcome.²⁶ Further refinements to these scores that incorporate donor risk index and composite prognostic models based on donor age, total ischemic time, and other operative and recipient factors may aid in policy decisions regarding organ allocation and provide the most judicious distribution of organs.^{27,28}

In India, as deceased liver donation expands, we will inevitably need to address the logic of a justice-based system which allocates organs on disease severity and need. This will in turn require a robust and transparent data system in which recipient data are regularly updated and accessible to the network. Since a large amount of the transplant activity is likely to happen in the private sector, the state will have to step in to ensure that the sharing network is given adequate teeth to directly access data from individual centers. Adequate checks and balances may have to be incorporated in reporting of listing criteria and clinical scores if these have to form the basis of allocation. For example, in the USA, transplant centers which are part of the UNOS network, have an agreement that patient details including investigation reports are available for scrutiny. Also, periodic audits and validation of patient data are carried out by UNOS.²⁹

The Government of India has recently constituted the National Organ and Tissue Transplant Organization (NOTTO) which is in the process of setting up a nationwide network for organ sharing through the establishment of regional (ROTO) and state (SOTTO) centers.³⁰ Thus, soon there may be a uniform national protocol for organ allotment as well as sharing of organs across states. This organization can facilitate interstate sharing of organs including livers as per urgency.

WHAT ARE THE CHALLENGES IN DECEASED DONOR LIVER DONATION?

The deceased donation rate in India has increased from 0.05 million in 2006 to 0.34 in 2014.² With increasing numbers, several challenges have emerged in the execution of DDLT. With a growing pool of donor hospitals that are new to the field, obtaining reliable donor information and ensuring appropriate maintenance is one of the first challenges. In Mumbai, the ZTCC has developed a standardized format for donor information as well as a uniform donor management protocol to preserve organ function by holding interactions with intensivists and coordinators.²² Correction of hypernatremia secondary to diabetes insipidus, identification and control of sepsis, and sudden cardiac arrest have been common problems that are faced.

A significant number of deceased donors in India have been reported to be extended criteria donors.³¹ This has also been our experience in Mumbai. Fatty liver is becoming an increasingly common problem and roughly 40% of deceased donors in Mumbai have steatotic livers. Facilities

for reliable liver biopsy for quantification of fat are limited by both the time of the day and the expertise. There is also a relative shortage of surgeons trained in multiorgan harvesting of abdominal organs. Since appropriate retrieval, cold storage, and packing as well as avoidance of a long cold ischemia time are critical factors in the success of DDLT, the donor procedure needs a high level of focus and organization. Currently, since the entire onus of the logistics is on the recipient centers team, this leads to delay in retrieval and restricts sharing beyond certain boundaries. The ZTCC in Mumbai has attempted to facilitate quick retrieval by a series of policy measures which include a limiting the time in which a donor team must retrieve once the liver is accepted to keeping a backup of a second team as well.

The cost of donor maintenance and the retrieval procedure is a difficult issue in the Indian setting, since many donors are in private institutions where the donor is being billed by the clock. In Mumbai, hospitals stop charging the donor once consent is obtained and the ZTCC provides a fixed compensation for the donor hospital for an organ procured. However, often the donor hospital is utilizing the liver or one of the kidneys and hence has an indirect financial stake in absorbing a part of the donor's hospitalization charges.

For the system to move to a severity-based model, as also to bring in more non-transplant centers into the donor pool, the issue of adequate monetary compensation for the donor hospital will need to be solved. Rather the passing on this burden to the recipient, which is how the current system works (since the sharing network charges the recipient hospital which in turn recovers from the recipient), it may be necessary for the state to provide funds for this purpose. That way, the state or its organ like the NOTTO will also increase its credibility to regulate the system.

HOW CAN THE DECEASED DONOR POOL BE EXPANDED?

There is an opportunity to increase the deceased donor pool for livers. One longstanding lacuna of HOTA has recently been resolved by the recent amendment in 2011³² with the recognition of centers, which do not perform transplants but can certify brain death and harvest organs. Although the South has seen donations from such centers, in Mumbai in spite of a large number of non-transplant organ retrieval centers (NTORC) being recognized there has been only one donation from such a center in the last year. This one again highlights the fact that deceased donation is currently driven by hospitals benefitting by performing either kidney or LT. Sharing of organs across cities close to each other is now being done with some regularity but interstate sharing is still difficult mainly because of confusion of whom to share organs with. With the active involvement of the state in the form of an

organization like NOTTO, this should change in the future. With increasing technical expertise and field strength, splitting of suitable livers from appropriate donors to benefit two recipients seems feasible and can contribute to an increase in the numbers.

With the feasibility of retrieving organs after cardiac arrest (donation after cardiac death), an increasing component of cadaveric transplantation in western countries has been raised.³³ However, the practical implementation of this activity is challenging both from the logistics as well as the inferior results.³⁴ However, it is certainly an area worth exploring.

WHAT IS THE IMPACT OF A PREDOMINANT LDLT-BASED MODEL?

LDLT has saved lives and facilitated LT to kick-start in India. Currently, patient selection for LDLT is governed by the individual centers approach to the indication and relative risk factors for the donor and recipient. But it is also dictated by the availability of a suitable donor and affordability. It has been argued that as long as the ethical premise of informed consent from the donor and recipient is honored, LDLT need not be subjected to the restrictions on indication and timing like DDLT since the donation is not depriving another more deserving candidate. While this is somewhat true we need to scrutinize whether the deviations from the time tested guidelines for DDLT are sufficient to justify the risk to the donor. For example, some centers in India have advocated LDLT for patients with HCC irrespective of tumor size and number as long as there is no extra hepatic disease or macro vascular invasion.¹⁷ The argument is that if donors are informed and willing to take the risk, the results of such a policy are vastly superior to other modalities. However, now that there are significant numbers of patients who have crossed few years follow-up, data on at least medium term results are potentially available. This kind of data will be crucial for centers to formulate policy as well for donors to decide on risk taking.

A program with DBD as the dominant form means that a patient spends a considerable amount of time on the waiting list. The natural history of the disease is allowed to play out and by virtue of being under medical supervision to be treated intensively. In some ways, it also allows for the recipient and family to think it through. For example, we have seen at least 15 patients with decompensated alcohol liver disease and were on the deceased donor list who were taken off the list in view of significant improvement due to abstinence.

Perhaps buoyed by success and a push for numbers, we have observed a trend of patients undergoing LDLT with suboptimal attention to etiological workup and treatment of potentially reversible disease. For example, we have known patients with Wilson's disease in a mildly

decompensated state who have been transplanted without an adequate trial of medical therapy. We have successfully treated six patients with Wilson's disease who were advised LDLT and are doing well. Budd Chiari syndrome is a not an uncommon cause of liver disease in India and also tends to be overlooked in the workup. Even patients with poor liver function who will otherwise be candidates for transplant will improve with appropriate radiological interventions or shunting. We have treated patients referred for transplantation with end-stage disease as per the scoring systems with radiological shunting. This is also true for children, especially infants where in any case transplantation is difficult and even less accessible.³⁵ This is especially relevant to the Indian scenario where access to interventional radiology is currently much better than for transplantation. Adequate treatment of conditions like autoimmune hepatitis, hepatitis B, and now hepatitis C may tend to get overlooked in a situation of overwhelming dominance of LDLT programs, especially when patients arrive at an LDLT center with a donor and money already primed that they need an immediate transplant.

IS THE SAFETY OF LIVE LIVER DONORS BEING ASSURED?

An area of major concern in the evolution of LDLT has been donor safety which also includes donor mortality. Firstly, there is no reliable information on the extent of the problem as currently there is no mechanism for mandatory reporting of donor death. To our knowledge, apart from a single published case from Chennai,¹² none of the donor deaths have been formally reported in literature. The print and electronic media have highlighted some of the deaths.³⁶ Although the precise number will never be known, based on a study of media reports as well as personal communications (after assuring anonymity), we estimate the figure to be currently between 18 and 20, thus with roughly 6000 LDLTs being performed that would make a figure of 0.3%. It is difficult to define an 'acceptable' threshold figure for donor deaths but the worldwide figures reported range from 0.2% to 0.5%.¹² Of course, some of these deaths have taken place at very small centers with limited numbers but almost all large centers in India have reported donor deaths. A healthy individual dying in an act of great benevolence is alarming but what is also disconcerting is the lack of transparency and disclosure that surrounds them resulting in media speculation and loss of opportunity for other teams to learn the right lessons.

Donor morbidity similarly has been very scarcely documented except one series.³⁷ The incidence of hepatic steatosis, metabolic syndrome, diabetes, and ischemic heart disease even in young individuals is on the rise in India.⁹ All these are significant risk factors for live liver donation.

A significant proportion of LDLTs in India are performed in ALF settings where the consent process has to be almost immediate. Since almost all of the current LDLT programs are in the private sector, there is pressure on the teams to generate numbers. All these factors predispose to ethical compromise in an area, which demands the highest levels of objectivity and transparency.^{7,38}

At the policy level, transplant centers could be mandated to routinely adopt the time tested and easily implementable step of offering the 'opt out' option to the donor and appoint donor advocates for independent scrutiny to minimize subtle coercion. This will result in a few dropouts but will be a demonstration of our commitment to incontestable informed consent from the donor which is perhaps at the heart of the issue.

WHAT ARE THE MEDICAL CHALLENGES UNIQUE TO THE INDIAN SCENARIO?

There is a growing realization that certain specific challenges arising from the background local scenario impact on LT in India. A large majority of our patients with chronic liver disease are severely malnourished.³⁹ Although the disease by itself is a contributing factor, several traditions and misconceptions related to diet in liver disease exist in Indian culture which compound the problem of malnutrition. Patients are often referred in the advanced stage of the disease with severe sarcopenia.⁴⁰ It is well known that a malnourished patient undergoing transplant will have higher morbidity in terms of transfusion requirements, longer hospital stay, and infections which in turn also increases costs.^{41,42} Short-term pre-transplant nutritional intervention has been shown to translate into better results.⁴³ In our scenario, this primarily involves debriefing the patient and the family from the severe irrational restrictions (including proteins) that they have been placed on by health care providers. Given the poor appetite, supplemental naso-gastric feeding may be an effective strategy before subjecting patients to transplantation especially in the planned LDLT scenario.

India has the highest burden of tuberculosis (TB) in the world⁴⁴ and therefore diagnosis of latent TB is relevant in preventing post-transplant re-activation of TB secondary to immunosuppression. Tuberculin test is not reliable as there is a high incidence of anergy in patients with cirrhosis.⁴⁵ The role of interferon gamma release assays has not been well defined. An X-ray of the chest is of course routinely performed but a more detailed evaluation with a computerized tomography scan may sometimes be necessary. Anti-tubercular prophylaxis has been suggested for those with previous history of or exposure to TB. However, Nagai et al. did not find any benefit of prophylaxis in liver transplant recipients with previous history of TB.⁴⁶ Although the prevalence of post-transplant TB in renal

transplant recipients has been described to be 12.3% in one study,⁴⁷ the prevalence in liver transplant recipients from a study in South India was documented to be lower at 2.3%.⁴⁸ However, the mortality in these patients was high at 40%. This may be due to the fact the very diagnosis of TB in the post-transplant setting is challenging, especially since it is often extra-pulmonary. Besides, the treatment of TB in the post-transplant setting is not straightforward. A rise in transaminases in a patient on anti-tubercular medications post-transplant could be secondary to hepatotoxicity of the drugs, acute rejection or a hepatitis C recurrence (in a hepatitis C virus positive patient). Rifampicin lowers the levels of immunosuppressive drugs in the blood to a large extent. Isoniazid has been found to be safe for prophylaxis.⁴⁹ Another study looked at prophylaxis with levofloxacin pre-transplantation followed by INH post transplantation.⁵⁰ This study had to be suspended mid-way as there was high incidence of tenosynovitis due to levofloxacin. In an era of multi-drug-resistant TB in our country, the role for single drug prophylaxis is questionable. The best prophylaxis and TB treatment regimens are not well defined, need to be studied by pooling data from multiple centers, and some consensus urgently needs to emerge.

Hospitals in India have a high incidence of infections with resistant bacteria and fungi including the extended spectrum beta lactamases, the more recently described carbapenemase and the azole-resistant fungi.⁵¹ This has inevitably reflected in the post-liver transplant scenario also and is also a potential danger for live liver donors.⁵² Although it is true that very often infections are related to graft dysfunction or biliary/vascular complications, the treatment of resistant bugs involves costly and toxic antibiotics, which makes a huge impact on recovery. Some of the large transplant centers have set up independent isolation units to control the problem. However, many of the patients coming to transplant have had multiple admissions to general ICUs across hospital and already harbor resistant bugs. To our knowledge, infections with resistant bugs is a serious problem of large magnitude in most active LT units in India leading to significant morbidity and even contributing to mortality. In our practice, we have a very low threshold of escalating antibiotics to cover resistant bugs at the earliest signs of post-LT sepsis and deescalating them with negative cultures and clinical improvement. In our view, this is one area of liver transplant practice in India which may prove to be its undoing unless the overall scenario of resistant bugs in the community and institutions changes for the better.

WHAT ARE THE OUTCOMES OF LT?

Although a rough guess on the overall numbers of transplants is possible at arrive at from personal communications and websites, published data regarding outcomes

and patient survival are exceedingly sparse. We wrote to all the leading centers in India and requested data on one-year outcomes. Six large centers responded which covers roughly around 70% of liver transplant activity in India. From the information we obtained we calculated the one year survival to be 82%. The ZTCC in Mumbai requested collated data on survival last year. The compliance rate was around 90% and the one-year survival was 76%. In leading centers, graft and patient survival rates have been reported to show improvements over the last two decades from figures of 50–60% in the early 2000s up to 80% and 90% 3- and 5-year survival more recently.^{1,14,15} There are almost no published reports of long-term outcomes and quality of life data from Indian centers. However, good medium-term results for small, selected groups of patients have been reported. For example, a series of 14 LDLTs for hepatopulmonary syndrome reports excellent results with oxygen-free survival in all patients at a mean follow-up of 29 months.⁵³ In a single small series, the estimated success rate of LT for ALF was 70–80%.¹ It has been observed that outcomes in patients with ALF undergoing LDLT have been comparable to those undergoing DDLT.^{54,55}

As already mentioned, information on another critical area, which is donor outcomes in LDLT, is scarce and to our knowledge there is only one publication on the subject.³⁷ This is a serious deficit since quality reporting of live donor outcomes is an internationally established ethical imperative.⁷

Part of the reason for the limited outcome data in LT may be poor follow-up which is a common problem in Indian health care especially when patients come from far flung areas. However, our experience is that transplanted patients have a much better rate of follow-up than other illnesses and in our own small cohort of around 70 patients who have crossed one year we have follow-up on almost all patients. Thus, we are sure that quality follow-up information is available and needs to be brought into the public domain.

The fact that many patients are opting for a hugely demanding procedure like LT indicates that the impression amongst people is that results are good. There are however several compelling reasons why moving toward reliable and verifiable outcome data in the public domain is critical to the field of LT. Conceptually, in any society where deceased donations are promoted and the organs have a status of public goods, there is an implicit right of society to know how these are distributed and the outcomes thereof. While the transplant community in India, NGOs in the field, and specialty organizations repeatedly appeal to the state and society to facilitate organ donation, they have failed to create mechanisms for a registry and reporting results. For that matter, the state which seeks donations from its citizens has as yet not mandated outcomes reporting.

Besides the larger commitment, individual institutions will benefit from outcomes reporting as an audit helps plan and manage what is a very resource intensive and expensive activity. Transparency in reporting outcomes will also help change perceptions regarding the unfortunate association of transplantation and the 'organ trade' in India.

HOW CAN ONE IMPROVE THE QUALITY OF DATA ON LT?

Although collection of reliable data has been a challenge in Indian health care in general, the size of a liver transplant database is currently very limited and within reach. Several experts in meetings and innumerable articles have made a plea for a national registry for transplants. A national level registry for kidney transplant has been set up by the Indian Society of Organ Transplantation (ISOT) but does not feature data from LT as of now.⁵⁶ The NOTTO has set in process a plan for a national registry but to our knowledge this is currently at a conceptual stage. In any case, even now the state appropriate authorities for transplantation in all states have basic data on all transplants performed. These data are not available in the public domain and our understanding is that even basic national data have not been collated. This could be one of the first tasks of the NOTTO.

The medium- or long-term outcomes of transplantation are not available with state authorities and will prove to be bigger challenge. There have been precedents set by various international registries like the Organ Procurement Transplant Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) in the USA and the UK Transplant registry by the UKNHSBT in the UK. While we have copied many of the medical protocols from these countries, both the transplant community and the state have chosen to ignore this aspect of the transplant activity in other countries. Even countries like Iran and Saudi Arabia have a robust centralized reporting system in place.

We believe that repeated calls to voluntary submission of detailed data are unlikely to work. Regulatory bodies like NOTTO should have an understanding with transplant centers about access to hospital records and submission of data. Random audits of each transplant center and data quality control need to be integral in the functioning of such authorities to ensure truthful and high quality data reporting. Penalties involving revoking permissions and heavy fines could be implemented on defaulters. There is a provision under HOTA for state transplant authorities to monitor 'quality' as they are mandated to periodically inspect programs for reaccreditation.⁷ They can immediately choose to insist on detailed outcomes reporting as a part of this procedure. In summary, we need to move from periodic laments and appeals to good sense to serious

regulatory enforcement in an area where there is substantial international precedent.

HOW CAN ACCESSIBILITY AND AFFORDABILITY OF LT BE IMPROVED?

From a basic conceptual perspective, LT is a lifesaving procedure and therefore can be considered a responsibility of the state under the constitutional paradigm of right to life. Increased involvement of the public sector is the most evident step to improve the reach of LT. A few public sector hospitals have been able to set up small LT programs but their numbers are currently very limited and the centers have not been able to sustain the activity. Increased public sector hospital involvement can also lead to a significant contribution to increase the donor pool for DBD. The other way for access to improve is third party insurance cover both in the form of individual and state sponsored mass insurance schemes. Currently, individual insurance policies do not or are not adequate to cover LT. Government funded mass insurance schemes like the Rajiv Gandhi Jeevandayee Arogya Yojana (RGJAY) in Maharashtra which are supposed to provide financial support for high-end procedures and major illnesses including kidney transplantation do not have a provision for LT.⁵⁷

Given the political will and interest, the state can actually mandate public institutions to perform LT. They can create and nurture LT programs in selected large public teaching hospitals. Beyond money, there is also a certain prestige and sense of accomplishment associated with the performance of such a procedure and such an atmosphere needs to be fostered. Finally, the state can also ensure that the private sector performs some procedures at a subsidy. We are aware that due to a retreat of public health, advanced healthcare in India is in any case loaded against the poor but nowhere is the denial so unambiguous as in areas like LT. In LT, the premise for state intervention has a very sound basis in the premise that citizens consent to deceased donation based on the understanding that the organs will be used for the most deserving patients across the social spectrum.

The cost of LT does not end with the procedure. Hence, there is an equally important need to control the post-transplant costs on drugs and investigations. It has been our experience that currently given the pressure, many families somehow gather the money required for the procedure in the short term but are unable to sustain the recurring expenditure that LT involves. In this area, individual centers can make an impact by modifying protocols to reduce expenses.

One development that has helped is the availability of branded generic immunosuppressants, which have been used regularly and found to be efficacious.⁵⁸ It has been observed that Indian patients have a lower requirement of

immunosuppression compared to their Western counterparts.⁵⁸ Also, with the high overall prevalence of infections, it is good strategy to keep the immunosuppression to a minimum.

In our limited experience, we have effectively used other strategies to control costs without compromising safety. These have included less frequent monitoring of tacrolimus levels, use of transaminases, potassium, and creatinine as surrogate markers for toxicity and rejection and use of azathioprine instead of mycophenolate. We believe that selective liver function and ultrasound-Doppler testing post-transplant and serial testing of cytomegalovirus deoxyribonucleic acid load in the susceptible period instead of universal valgancyclovir prophylaxis have also helped us in cost reduction.

LT clinicians in India have creatively modified established protocols to reduce the burden of some of the costs. For example, in the setting of hepatitis B, Wadhawan et al. demonstrated vaccination of donors as one of the strategies in reducing the rate of recurrence of hepatitis B post transplantation without using the expensive immunoglobulin.⁵⁹ Also, hyperimmune plasma derived from donors vaccinated for hepatitis B has been shown to be as effective as hepatitis B immune globulin in preventing post transplantation hepatitis B recurrence, the latter being nearly 14 times the cost of hyperimmune plasma.⁶⁰

WHAT IS THE FUTURE OF LT IN INDIA?

With the large burden of existing and emerging liver diseases and the success of the procedure becoming apparent, the demand for LT is likely to explode in the near future. The first decade of the procedure has witnessed a lot of excitement, hope, and achievements. In a humbling gesture, many large hearted and courageous individuals both living donors and family members of deceased donors have showed tremendous faith and trust in our community.

There is scope for introspection from the liver transplant community which may trigger course corrections. We are aware that the policy changes we have suggested cannot happen in isolation from the evolution of regulation, transparency, and equity in the overall health care scenario in India. In the context of deceased donation however, leaving the distribution of the organs open largely to market mechanisms is a breach of peoples trust.⁶¹ Even in countries where organ transplantation is guided with strong policy oversight and support from the state, professional organizations are proactive as advocates for change. In India under the umbrella of organizations like Indian Association for Study of the Liver (INASL) and ISOT, clinicians could highlight the imbalances and lobby for policy change.

Finally, while the emergence of LT has opened out an incredible opportunity for those suffering from end stage liver disease, we should be mindful not to allow this to

distract us from less exciting but germane areas like preventive hepatology and rational treatment of chronic liver disease which significantly improve the quality of life as well as longevity in patients with decompensated chronic liver disease. And for the large denominator of patients with chronic liver disease who are unlikely to be able to access LT in the future, we should contribute to the creation of better treatment facilities with the same passion and zeal as has been demonstrated in establishing LT in India.

CONFLICTS OF INTEREST

The authors have none to declare.

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