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Review Article

Liver Transplant – An Indian Perspective

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Abstract

Liver transplantation has gained acceptance in India for end-stage liver disease in the past decade. Living donor transplants contribute to 80% and deceased donor transplants to 20% of liver transplants in India. The majority of these procedures occur in private sector hospitals, with public sector hospitals lagging behind. This article provides an overview of the evolution of liver transplantation in India and future challenges.

Abbreviations

ALF -Acute Liver Failure

DBD -Donation after brain death

DDLT -Deceased donor liver transplantation

LDLT -Living donor liver transplantation

LT -Liver transplantation

NA -Not available

NOTTO -National Organ and Tissue Transplant Organization

PMP -Per Million Population

THOA -Transplantation of Human Organs Act

TRANSTAN -Transplant Authority of Tamilnadu

UCSF -University of California, San Francisco

WHO -World Health Organization

History and Evolution of Liver Transplantation in India

Since 1971, renal transplants, primarily from living donors, have been conducted in India. However, liver transplantation had a later start with the first successful deceased donor liver transplantation (DDLT) and living donor liver transplantation (LDLT) performed in 1998.(1)

The growth of liver transplantation in India was slow in the first half of the following decade, with limited success. By 2004, only 131 liver transplants had been performed, increasing to 3713 by 2022. The deceased donation program had not made significant progress, despite the Transplantation of Human Organs Act authorizing deceased donation in 1994. In the past decade, there has been distinct growth in liver transplantation in specific regions of India. Delhi, particularly in northern India, became a hub for LDLT(2), while Chennai and Hyderabad in southern India played a pivotal role in establishing DDLT. The total number of liver transplants in India is approximately 7500, with around 80% being LDLT and the rest DDLT. Currently, there are seven high-volume transplant centers conducting over 75 transplants per year, with a total of around 30 liver transplant centers in India.

Exemplary performance of Living Donor Liver Transplantation in India

There was a significant time gap between the implementation of THOA in 1994 and the development of successful and thriving DDLT in India. This delay forced many patients requiring liver transplantation to seek treatment abroad, which was feasible for only a privileged few who could afford the expenses. As a result of this delay in DDLT growth, LDLT programs emerged as an alternative solution. Despite the need for specialized medical, surgical, and intensive care resources, the successful implementation of LDLT was made possible by concentrating resources and expertise in specific hospitals. Two LDLT programs established in Delhi experienced rapid growth over the past decade, with each center having performed over 1500 liver transplants.(3,4) Their achievements have instilled confidence and paved the way for the expansion of LDLT techniques throughout the country.(Fig 1).

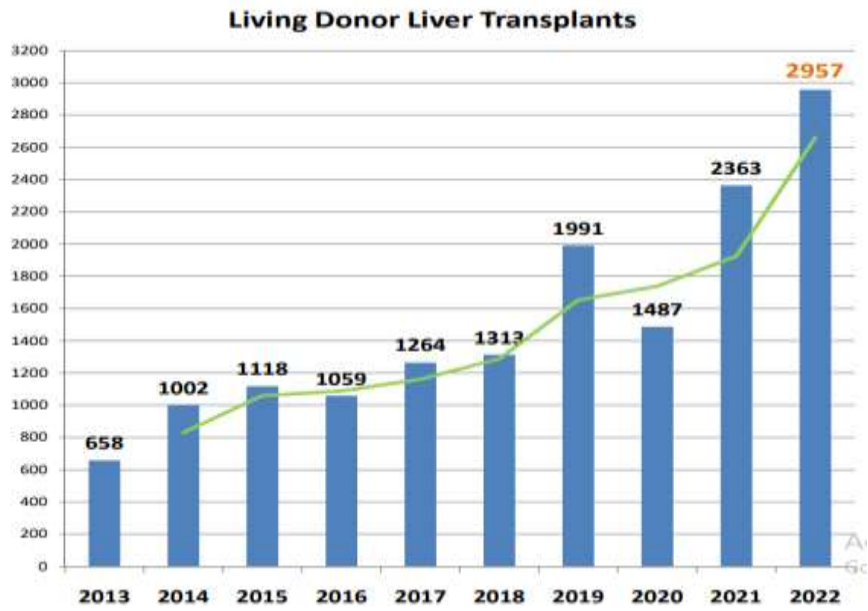

Fig 1 : Number of living donor liver transplant from 2013 – 2022

Strides in Deceased Donor Programs

The aspiration of any transplant community in a country would be to establish a deceased donor program of sufficient scale to cater to all patients on the waiting list. However, the challenges involved in setting up a deceased donor liver transplantation (DDLT) program differ significantly from those of living donor liver transplantation (LDLT). DDLT, which has been successfully implemented in many Western countries, necessitates a comprehensive system that involves collaboration with various disciplines not directly related to transplantation (such as neurosciences, forensic medicine, legal system, government and non-government bodies, and the public). It also requires coordination with multiple healthcare providers who may have different priorities. DDLT carries an additional social responsibility in terms of ensuring transparency in the system, optimal utilization of organs, and equitable distribution.

The complexities of establishing a DDLT program in a developing country like India, with its vast socioeconomic disparities, were further compounded by the growing popularity of LDLT as a viable alternative. This reduced the motivation to develop a DDLT program. However, there was an urgent need for the government to address India's previous reputation regarding commercialization of transplantation.

The Transplantation of Human Organs Act (THOA) was passed in 1994, authorizing deceased donation and transplantation in the country, but it required amendments to make it applicable in the present context.(Fig 2).

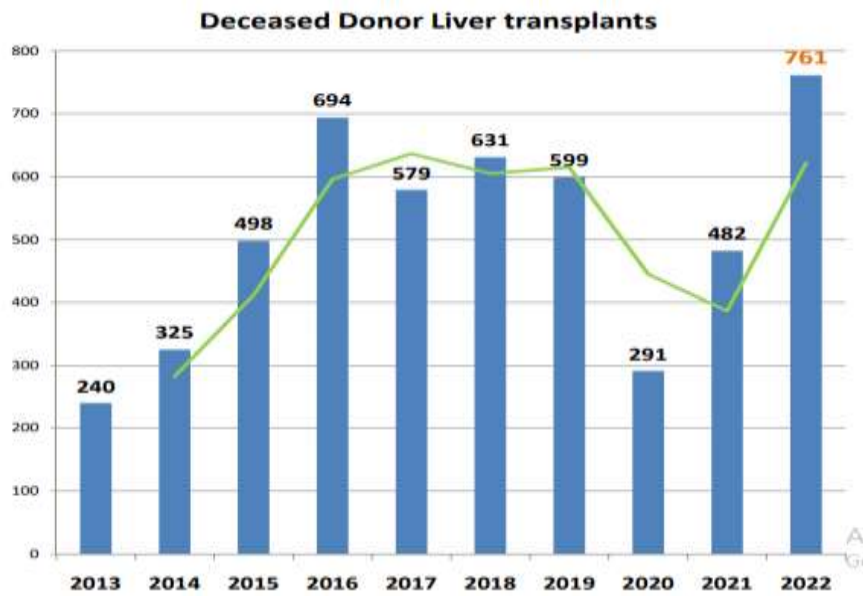

Fig 2 : Number of diseased Donor Liver Transplant from 2013-2022

Role of Transplant organ Regulatory Body in India

The Indian Liver Transplant Registry (ILTR, www.iltr.org) is now established and accruing prospective data from August 2019. While there is currently no legislation or official requirement mandating all centers to submit data to the Indian Liver Transplant Registry (ILTR), the Liver Transplant Society of India (LTSI) is making efforts to encourage every active center to contribute their data. The National Organ and Tissue Transplant Organization (NOTTO) serves as a regulatory body and is designated to act as a central hub for coordinating and networking activities related to organ and tissue procurement and distribution across India.

Tamilnadu, a state in southern India, pioneered the establishment of a deceased donor transplantation system. The Transplant Authority of Tamilnadu (TRANSTAN), created in 2015, oversees all living donor and deceased donor transplant activities in the state. Since 2008, Tamilnadu has recorded 740 deceased donors and performed 692 deceased donor liver transplants.(5) The successful Tamilnadu model has been replicated in 10 other states in India.

Over the past two years, there has been a significant increase in the deceased organ donation rate in the country. In 2012, there were 196 donors (0.2 per million population), which more than doubled to 411 donors (0.3 pmp) in 2014, and further increased to 570 donors (0.5 pmp) in 2015 .(6) As a step towards centralizing transplant activities, the National Organ and Tissue Transplant Organization (NOTTO) was established as the apex regulatory body under the Ministry of Health and Family Welfare, along with state and regional units. Currently, each state with a deceased donor program has its own coordinating body (e.g., TRANSTAN for Tamilnadu) for deceased donor liver transplantation (DDLT), while the state ethics committee oversees the approval process for living donor liver transplantation (LDLT). The transition from the current system to a proposed centralized regulatory body is expected to take place in the coming months.

Allocation of Organs

The number and distribution of transplant centers are not regulated. While some state capitals and a few cities have more than five centers, most state capitals do not have any transplant centers. (Fig 3) However, any new program seeking to perform transplants must obtain a license from the regional health authority. This license is granted based on the minimum requirements of infrastructure and expertise.

The allocation of organs from deceased donors is managed by the state coordinating body. Currently, in most states, organs are allocated to approved centers within the state on a rotational basis, regardless of the number of patients registered at each center. The allocation process does not consider factors such as disease severity (e.g., Model for End-Stage Liver Disease or Child-Pugh scores) or other patient-related factors.

In the state of Maharashtra, organs are allocated to patients based on the chronological order of their registration, with the patient who has been waiting the longest receiving the organ first. This system encourages the establishment of new centers because they have the advantage of receiving organs even with shorter waiting lists. However, patients waiting at larger centers have a higher risk of mortality due to the longer waiting times. As a result, these centers with long wait lists often resort to living donor liver transplantation (LDLT). However, there are provisions in place to prioritize patients with acute liver failure (ALF) on a statewide basis. Unfortunately, the limited frequency of available organs makes it less likely for these patients to receive an organ in time for a successful outcome.

If an organ becomes available in a state where liver transplantation is not performed, it is shared with an adjacent state.

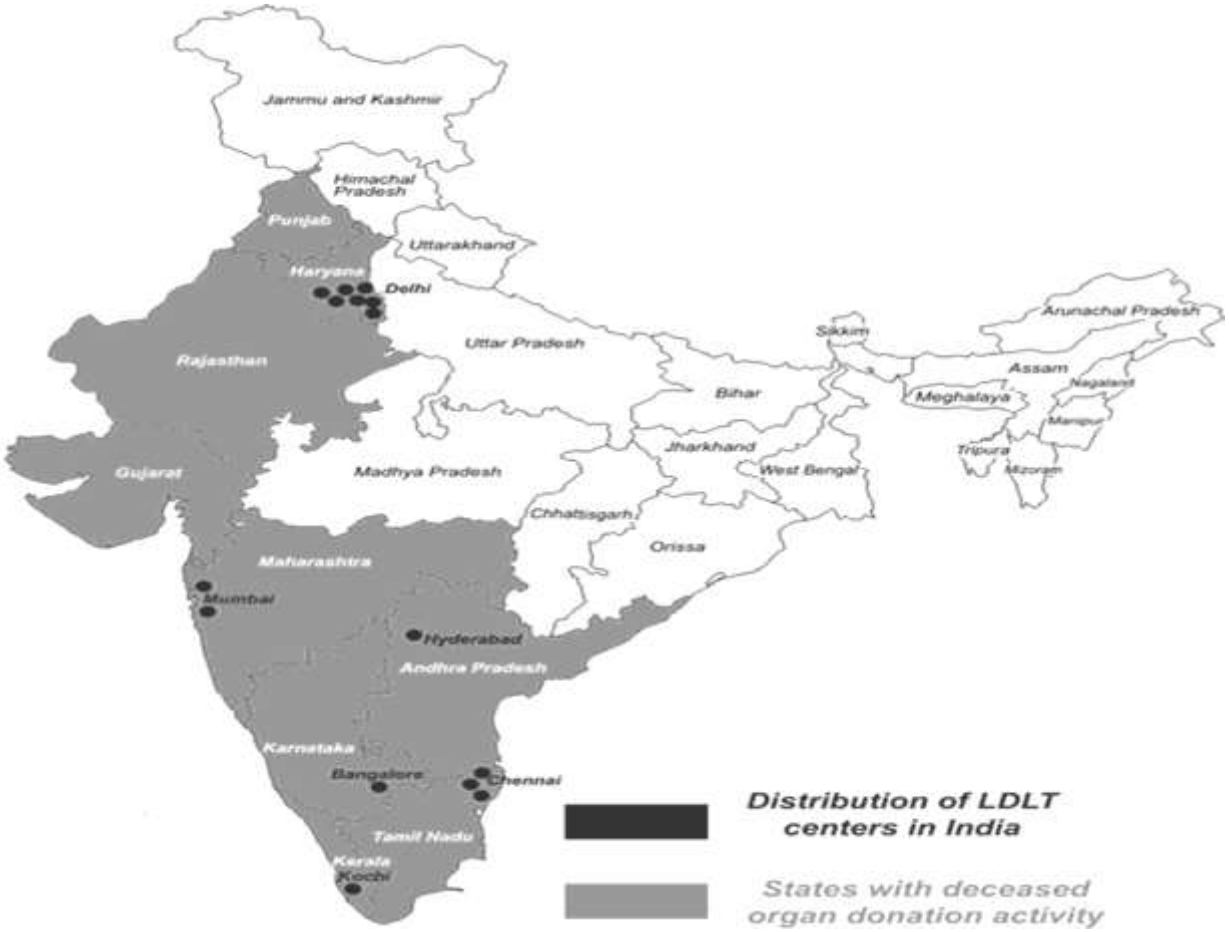

Fig 3 : Map of Liver Transplant centers in India

Disease Pattern and Referral

In India, there is a significant burden of liver disease, as indicated by the Global Health Observatory data from the World Health Organization (WHO), which reports 22.2 deaths per 100,000 population attributed to cirrhosis. (7)The causes of chronic liver disease among adults in India are similar to those in other countries, including alcoholic liver disease and viral hepatitis. However, nonalcoholic steatohepatitis is also becoming an important cause of liver disease in India, likely due to the growing diabetic population resulting from insulin resistance.

The etiology of acute liver failure (ALF) in India differs from that in Western populations. Hepatitis E is the most common cause of ALF,(8) and drug-induced ALF, particularly induced by antituberculosis therapy, is also frequent(9). Among children requiring liver transplantation, biliary atresia is the most common cause, followed by metabolic liver disease, especially Wilson's disease.(10)

The timely referral for liver transplantation (LT) remains a significant challenge. Unfortunately, the lack of a systematic approach results in late referrals or, in some cases, no referral at all for transplantation. The delay in referral is further exacerbated by the emergence of multidrug-resistant infections due to frequent hospitalizations for decompensation.

There is also a demographic divide between patients seeking treatment in public and private sector hospitals, which adds to the complexity. Public sector hospitals follow a system of primary/secondary/tertiary care, offer free medical services, and primarily serve a large proportion of the lower socioeconomic class. On the other hand, private sector hospitals cater to self-funded patients and operate on a physician-based practice model. Most LT programs are located in private hospitals, while only a few transplants have been performed in public sector hospitals, with exceptions such as the Military Hospital and Institute of Liver and Biliary Sciences in Delhi, where a significant number of transplants have taken place.

In India, there is no nationally agreed-upon set of minimum criteria for listing patients for transplantation. Similarly, the criteria for liver transplantation in cases of hepatocellular carcinoma (HCC) vary widely. Some larger centers offer living donor liver transplantation (LDLT) for HCC beyond the criteria set by the University of California, San Francisco (UCSF). However, most deceased donor liver transplantation (DDLT) programs follow the UCSF criteria.

There are significant regional disparities, but in general, the majority of liver transplant recipients in India are males (80%) and most of them are adults (85%). Unlike the Western world where deceased donor liver transplantation (DDLT) is more common, living donor liver transplantation (LDLT) is the prevailing approach in India, accounting for approximately 85% of cases (as per personal communication from the Indian Liver Transplant Registry).(11,12)

Asia, in contrast to the Americas and Europe, exhibits notable diversity in social, economic, and cultural aspects. Factors such as religious and cultural beliefs, limited access to universal healthcare, and insufficient legislative support have hindered the promotion of deceased donor liver transplantation (DDLT) in some regions. Therefore, LDLT remains the predominant form of liver transplantation in India.

Research, Innovation, and Improvement in Overall Health Care

Due to limited resources such as organs and finances, there has been a drive for innovation in liver transplantation (LT) in India. The increasing popularity of living donor liver transplantation (LDLT) has addressed the needs of many patients; however, there is still a subset of patients in northern India who do not have a suitable ABO-matched living donor within their family. In these cases, some centers have successfully performed ABO-incompatible transplants using the cost-effective cascade plasmapheresis technique, especially in regions where deceased donor liver transplantation (DDLT) options are also limited.

The use of immune globulin in transplantation for hepatitis B liver disease significantly increases the cost of the transplant by more than 30%. To overcome this cost factor, innovative trials were conducted early on using oral antiviral medications alone, which proved to be successful in achieving positive outcomes.

Split liver transplantation (spilt LT) has been introduced early on in the DDLT program in India. This is partly due to the expertise gained from LDLT procedures and the influence of surgeons who have received training in the Western world and have established transplantation programs in India. Additionally, with a large pool of patients, especially those with metabolic disorders, techniques for transplantation without the need for a traditional donor organ have been developed.

One such innovative approach is the auxiliary domino transplant, which has been performed in a child with Crigler-Najjar syndrome.

Regional Transplantation Hub and Guidelines for International Patients

India has emerged as a leading regional center for liver transplantation (LT) in Southeast Asia. A considerable portion (around 35%) of living donor liver transplants (LDLTs) in India are performed on foreign nationals from neighboring countries like Pakistan, Nepal, Burma, Sri Lanka, Maldives, as well as from the Middle East and Africa (including Oman, United Arab Emirates, Iraq, Bahrain, Yemen, Sudan, and Kenya). These countries bear a significant burden of liver disease but lack the necessary infrastructure and expertise to establish their own LT programs. Additionally, countries with smaller populations may not have enough demand to justify establishing such programs.

The favorable outcomes achieved by transplant programs in India, along with the significantly lower cost (approximately one-fourth of what would be incurred at Western centers, around US $50,000), provide an additional reason for referral. Most LT centers in India have established strong working relationships with physicians in neighboring countries, ensuring a robust referral system and providing post-transplant care when patients return to their home countries.

According to the Transplantation of Human Organs Act (THOA) in India, a foreign national can only receive a deceased donor organ if there is no suitable Indian recipient available, which is a rare situation given the long waiting lists of Indian patients. Therefore, in practical terms, LDLT from a living donor is the only viable option for foreign nationals seeking transplantation in India. The THOA also mandates that all foreigners undergoing LDLT in India must obtain approval from a state-authorized ethics committee, which is based on documentation provided by the patient's country of origin through the external affairs ministry.

Challenges

Increasing Deceased Donor Organs

The Transplantation of Human Organs Act (THOA) was implemented in 1994, marking India's first legal framework to address brain death. Initially, the legislation focused on brain death in relation to organ transplantation. However, expanding the recognition of brain death as an independent diagnosis and cause of death would greatly facilitate organ donation. This would necessitate the establishment of a framework akin to the Uniform Declaration of Death Act in the United States.

Currently, in India, the only form of deceased donation practiced is donation after brain death (DBD). However, there are concerns about incorporating donation after cardiac death (DCD) due to unresolved issues regarding the scope and implementation of DBD. Despite these concerns, the inclusion of DCD is a topic that deserves further exploration and consideration.

Improving Referral Patterns

Early referral of patients plays a vital role in optimizing outcomes in liver transplantation. Strategies to facilitate early referral include orientation programs for healthcare professionals, incorporating transplantation training in medical education, and streamlining insurance claims to expedite referral to specialized centers. The development of successful transplant programs in public sector hospitals also aids in promoting early referral by exposing trainees to the benefits of transplantation. Positive patient feedback and successful transplant outcomes serve as significant motivators for encouraging early referral.

Documentation of Outcomes

Despite a significant number of liver transplants (LTs) being performed in India, there is a lack of comprehensive outcome data. It is crucial to address this challenge by establishing a registry that records data and outcomes of LTs in India. The establishment of such a registry is not optional but mandatory according to the WHO guiding principle 11 on Human Cell, Tissue, and Organ Transplantation issued in 2010. Having a transparent system to register transplantation outcomes is essential to enhance India's credibility within the international transplant community. Efforts toward transparency have been made, including broader representation and data sharing in international conferences, as well as the publication of outcome series.

The National Organ and Tissue Transplant Organization (NOTTO) has recognized the importance of a national registry as one of its objectives, and steps are being taken to make this a reality in the near future.

In conclusion, India has made significant advancements in the field of LT, particularly in the area of living donor liver transplantation (LDLT) over the past decade. However, there is ample room for improvement, such as increasing deceased organ donation, developing effective organ allocation policies, and reporting transplant outcomes. Additionally, for the next decade, it would be desirable to focus on clinical and basic research in liver disease and transplantation, along with addressing the aforementioned aspects.

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