



Fighting Mortality in the Waiting List: Liver Transplantation in North America, Europe, and Asia

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ABSTRACT

Liver disease is a major cause of mortality worldwide. Liver transplantation (LT) is the most effective treatment for end stage liver disease. Available resources and social circumstances have led to different ways of implementing LT around the world. The experience with pediatric LT corroborates the hypothesis that a combination of surgical strategies can be beneficial. The goal of this manuscript is to describe the strategies used by LT centers in North America, Europe and Asia and how these strategies can be applied to reduce waitlist mortality and increase access to LT.

Key words. Chronic liver disease. Liver transplantation. Living donor liver transplantation. Split liver transplantation. Waitlist mortality.

Liver disease is a major cause of mortality worldwide. The highest rates of mortality from liver cirrhosis (deaths per 100,000 per year) are observed in Egypt (72.7; highest in Africa), Moldova (71.2; highest in Europe), Mongolia (55.1; highest in Asia), and Mexico (38.3, highest in America).¹

Liver transplantation (LT) is the most effective treatment for various diseases of the liver including acute liver failure, cirrhosis, and selected unresectable liver malignancies. Over the years, this procedure has evolved through refinements in organ preservation, surgical technique, perioperative care, and immunosuppression. Available human and technical resources, policies, legislation, awareness of the general public, and even religious beliefs have led to different ways of successfully implementing LT around the world to provide care for patients with liver disease. Innovative region-specific strategies have been used to improve access to LT in North America, Europe, and Asia. This opinion paper outlines how the LT teams in these continents have used strategies unique to their regions to provide LT and how the strategies from each region can be readily adopted by others to increase access to LT.

Liver transplantation milestones in North America and Europe

The history of LT started in 1967 when Thomas Starzl and his team performed the first successful deceased donor LT (DDLT) from a donor after cardiac death (DCD).² In the US, brain death was defined in 1968, which allowed the introduction of donation after brain death (DBD),³ but it wasn't until the introduction of cyclosporine that the true potential for LT was realized. The National Organ Transplantation Act of 1984 brought LT from an experimental procedure to a recognized treatment for both pediatric and adult patients with liver failure.

As more LT programs appeared in North America and Europe, the organ shortage became evident. The discrepancy between the number of patients waiting for a liver allograft and the available number of deceased donors forced transplant teams to explore new options to increase access to LT and decrease waitlist mortality. Pediatric patients had a particularly high mortality on the waitlist. To address this issue, the pioneers Henri Bismuth and Rudolph Pichlmayr introduced split LT (SLT), where a deceased donor liver can be split into two grafts: a left

lateral sector for a pediatric patient and an extended right graft for an adult recipient.^{4,5} The concept of SLT was further expanded in 1989 when a deceased donor liver was split into two hemiliver grafts for 2 adults.⁶

To further address the organ shortage of deceased donors, independently Russell Strong in Australia and Silvano Raia in Brazil performed the first cases of living donor LT (LDLT) with left lateral sector grafts for pediatric recipients.^{7,8} In the USA, Broelsch, *et al.* described the technical refinements that allowed the expansion of these techniques after their experience with SLT and pediatric LDLT.^{9,10} The application of the LDLT procurement technique for left lateral sector allografts led to the development of in situ splitting during DBD procurement in 1996,¹¹ followed by in situ splitting of two hemiliver grafts in 1999.¹² Broering, *et al.* further refined the surgical techniques of SLT in Germany, with the use of the “hanging” maneuver during in situ splitting and the division of the inferior vena cava of the donor in two venous panels, applied today in other areas of hepatobiliary surgery and transplantation.^{13,14}

The introduction of the Model for End-Stage Liver Disease (MELD) in 2002 in the USA and later in Europe improved access to LT for critically ill candidates and patients with hepatocellular carcinoma.^{15,16}

Current status of transplantation in North America and Europe

The need for liver allografts has pushed programs in North America and Europe to expand deceased donor selection criteria constantly. Most of these programs routinely consider extended-criteria grafts for LT in adult recipients, such as selected grafts from older brain-dead donors (> 70 years), as well as donors with steatosis (microsteatosis and/or macrosteatosis < 30%), hepatitis C infection, central nervous system malignancies, increased risk behaviors (i.e., intravenous drug use), or hepatitis B exposure (i.e., hepatitis B core antibody positivity).¹⁷ As a result of this and other strategies to increase donation, according to the Organ Procurement and Transplantation Network, 7,496 DDLT were registered in 2016—a 70% increase over the 4,087 DDLT performed in 1996.

LT programs in Europe that have adopted specific policies for SLT^{18,19} have reported decreased waitlist time and mortality among pediatric recipients, even without LDLT.^{20,21} The programs that have adopted all modalities (DDLT, SLT, and LDLT) have reported a dramatic drop in waitlist mortality (from > 15% to < 5%).²²

The same multimodality strategy has been difficult to implement in the adult population. Despite the fact that paired matched analysis and meta-analysis have shown comparable rates of primary nonfunction,

retransplantation, and biliary and vascular complications for recipients of right extended grafts (segments 1, 4-8) compared to whole liver grafts,²³⁻²⁵ SLT has not seen much growth in the USA, representing only 1.4% of first-time LT performed between 1995 and 2010.²⁶

According to the Organ Procurement and Transplantation Network, in 1996, 65 LDLT were performed in the USA. There was a steady increase, with a peak in 2001 with 524 cases. Up to this year, the Mount Sinai Hospital in New York performed 109 LDLT and became one of the North American centers with the highest volume for both pediatric and adult LDLT.²⁷ Despite its success, a highly publicized donor death led to a national debate on LDLT.²⁸ At the same time, the allocation system in the USA changed, allowing for sicker patients to be transplanted through the MELD score. As an effect of these two events, a decline of > 30% in LDLT cases after 2001 was observed, with 363 cases in 2002 and a progressive decline thereafter. In 2014, only 280 cases were performed in the USA, and LDLT accounts for a small proportion of transplants in the USA.

There appears to be a renewed interest in LDLT nationwide in recent years, particularly for patients who are disadvantaged by the current allocation system (patients with low MELD-Na score, such as patients with primary sclerosing cholangitis, primary biliary cirrhosis, refractory ascites, hepatic hydrothorax, hepatocellular carcinoma outside Milan criteria, etc.), as shown by the moderate increase in the number of LDLT performed in the USA (345 LDLT in 2016).²⁹ Although 45 programs performed at least 1 LDLT in 2016, only 11 programs performed more than 12 LDLT per year (1 per month), and only 2 centers did more than 24 LDLT (2 per month).

A unique success story of LDLT in North America can be seen in Toronto, Canada, where the LDLT volume has stayed around 40 to 50 cases per year. This success can be attributed to many factors, including surgical expertise, regionalized care, and a universal health care system. LDLT has been shown to reduce the risk of mortality on the waiting list at their center,³⁰ and all recipients are offered equal access to LDLT, including patients with acute liver failure.³¹

Liver transplantation milestones in Asia

Although the Asian centers are known for their LDLT efforts, the history of LT started with Nakayama and colleagues' attempts at LT in Japan from DCD in 1964 and 1969.³² The controversial nature of the topic in Japanese society became evident when Juro Wada performed the world's second heart transplant from a DBD in 1968. Initially praised for the scientific breakthrough, he was

later arrested for murder, being acquitted 6 years later.³³ Other Asian countries followed suit, with Chao-Long Chen performing the first successful LT in Taiwan in 1984.

In 1987, Taiwan and Singapore led the approval of brain death legislation in Asia.³⁴ Over 10 years later, Japan followed, with legalization of procurement of organs from DBD, and South Korea legalized use of organs from DBD in 2000.^{35,36} The delayed approval of DBD legislation and the success of LDLT for pediatric patients in the USA contributed to the growth of LDLT programs in Asian countries. Nakamura, *et al.* performed the first LDLT in Japan using a left lateral graft in 1989,³⁷ followed by Makuuchi, *et al.*, who performed the first LDLT using a left hemiliver graft in 1993,³⁸ and Tanaka, *et al.*, who performed the first LDLT using a right hemiliver graft.³⁹ Since then, there has been an explosion of technical innovation in LDLT in Asia. The group in Hong Kong introduced the concept of middle hepatic vein preservation with the right hemiliver graft or “extended right lobe graft” in 1996.⁴⁰ The improved outflow of these allografts improved early function. However, the risk of leaving a small remnant with congestive areas in the donor led to the preservation of the middle hepatic vein in the donor and venous outflow reconstruction of the right anterior sector (segments 5 and 8), now known as “modified” right hemiliver allografts.^{41,42} Technical advances continued as the Tokyo group described the use of right posterior sector allografts, while the Asan group developed the concept of dual allograft LDLT (two living donors for one recipient).⁴³ Teams from Japan and South Korea have developed different ABO-incompatible LDLT protocols (splenectomy, plasmapheresis, rituximab, local infusion therapy, etc.) to prevent antibody-mediated rejection and thrombotic microangiopathy (i.e., nonanastomotic cholangiopathy).^{44,45} ABO-incompatible LDLT represents 25% of the cases in these countries, even after the creation of donor exchange programs in some specialized centers.⁴⁶

Current status of liver transplantation in Asia

Many countries in Asia have actively tried to facilitate deceased donation. For example, the Chinese government realized that sociocultural beliefs and customs should be reconciled with the need to develop a national transplant program. The China Medical Board awarded a grant to the Peking Union Medical College and the University of Chicago in 2006, leading to the publication of procedures for brain death determination in 2009 and the development of a citizen-based voluntary deceased donor organ pilot program in 2011. Measures were initiated to prevent

irregularities and commercialization of living donation, along with legislation to facilitate deceased donation and a humanitarian assistance system for donor families. As a result, 93% of LT cases in mainland China are performed from deceased donors. However, there is a lack of public consensus about the concept of brain death, leading to a high number of DCD (43%) and DBD in whom organ harvesting occurs after circulatory arrest (39%), while DBD are relatively uncommon (11%).⁴⁷ Despite these advances, the DDLT rate in China on 2015 was 1.6 per million population, and these efforts have been obscured by the controversy of organ procurement from executed prisoners.^{48,49}

The government of South Korea approved the Organ Transplant Act in 2000. The policies established, among others, include an organ donation incentive system and the designation of a brain death determination committee and an independent organ procurement organization without financial conflicts. Under the organ donation incentive system, the donor organ is allocated first to a donor's relative who is registered in the organ sharing system, second to a registered candidate who is on a waiting list in the donor's hospital, and last to a patient on the waiting list within the same region. This system was amended in 2006 to provide a monetary incentive (up to US\$5,000) to the bereaved family, meant to be used for hospital charges and funeral expenses. The brain death determination committee consists of 7 to 10 members, including 3 or more medical specialists (with at least one neurologist) and one or more members of the general public (such as a lawyer or a priest). In 2010, the requirements of the committee were modified to reduce the number of required members to 4 to 6, with 2 to 3 medical specialists and one or more nonmedical personnel.⁵⁰

South Korea and Iran had the highest deceased organ donor rate in Asia during 2015, with 9.1 and 8.6 per million population, respectively.⁴⁸ The development of deceased donation in these two countries is particularly interesting, due to the belated legislation of the former and the high percentage of Islamic population in the latter (90%-95%). Religious beliefs have been widely cited as an important cause for the lack of deceased donation in Asia. Organ donation and transplantation are relatively new procedures, and the approach of a religious system to them is a matter of interpretation. For instance, Islam principles of prohibition of harm to the human body and altruism may be in conflict with deceased donation. Some experts have proposed a reconciling principle of 'necessity overrides prohibition', but the donation patterns observed among Muslim populations are different.⁵¹ For example, Muslim populations in the Middle East (Iran) have a higher donation rate than Muslim populations from South Asia.⁵²

The safety of donor hepatectomy (only 1 donor death recorded after 8,000 donor hepatectomies in South Korea),⁵³ now performed laparoscopically in selected cases,^{54,55} along with the excellent outcomes of the recipients has led to widespread application of LDLT in Asia, where there is a tendency to count more heavily on the living donor supply than the deceased donor supply. From 1995 to 2005, the number of LDLT in Asia per year increased 10-fold, representing ~90% of the LT cases, whereas the number of DDLT cases remained static.⁵⁶ Turkey and India have had a significant growth of LDLT, emerging as powerhouses for LT, with some centers performing over 200 LDLT per year.⁵⁷ In 2015, the LDLT rate in South Korea and Turkey was 18.7 and 11.6 per million population, respectively.⁴⁸

Opinion

Transplant programs across the world have fought barriers to LT in order to provide care for patients in need and decrease mortality on the waiting list. North American and European centers have pushed the limits of whole liver grafts by using extended-criteria deceased donors, while Asian centers have pushed the limits of LDLT by using complex and refined surgical techniques.

The maximum utilization of deceased donors may have not been reached in the USA, as shown by the trend towards an increase in the number of liver grafts recovered in recent years. Furthermore, the introduction of hypothermic oxygenated perfusion and normothermic ex vivo preservation may further expand the potential number of grafts recovered.^{58,59} Asian countries will benefit from adopting strategies on deceased donation from the West and from continued policy revamping to adapt to local barriers to donation, to further increase the number of DDLT.

The experience with pediatric LT in Europe corroborates the hypothesis that a combination of the deceased and living donor pools is associated with near-zero waitlist mortality. It is our opinion that a strategy to significantly reduce mortality among adults on the waiting list could be to exploit the experiences that have matured in the West and the East—combining the expertise and protocols for LDLT from Asia, DDLT from North America, and SLT from Europe. Such an approach for adult patients can be seen in centers like Toronto in Canada and Chennai in India, where the surgeons are versatile in DDLT and LDLT.

To implement this strategy as a routine allocation scheme, a significant change in mentality and training is necessary. This would involve offering LDLT and SLT as routine transplant methods for all patients who have a biological MELD score < 30 and reserving whole-organ LT for patients with a biological MELD score ≥ 30.

A major barrier for adoption of LDLT in the USA is the impact to the donor: physical, emotional, and financial. Currently, the risks to the live liver donors are at a historical low. A recent multi-institutional study from 12 centers evaluated 5,202 donors of right or left hemiliver grafts and showed a 2% blood transfusion requirement, 3.8% incidence of major morbidity, and 1 donor death (mortality 0.002%).⁶⁰ The risk of complications was significantly lower among centers that had performed >100 donor hepatectomies.

Unlike most countries in North America and Europe, the USA lacks national health care, which hampers the ability of a candidate to donate. Although the hospital expenses of the donor are covered by the recipient's insurance, lost wages and travel expenses are not. Furthermore, the employment of a potential donor could be threatened by the donation process. Coverage for these losses is necessary and does not represent financial gain for the donor, but rather financial neutrality.

Perceived risks for transplant programs represent another potential barrier. Outcomes after LT are carefully monitored, and insurance reimbursement by Medicare is regulated accordingly. The decision of a transplant center to embark on a technically complex surgical procedure, with well-recognized arterial and, particularly, biliary complications, requires the involvement of multiple departments (imaging, endoscopy, interventional radiology) in the aftercare of the patients. LDLT may introduce potential risks to the transplant center that may affect the program's outcomes. In addition, the possibility of any harm to the donor may negatively impact the program.

Training is essential since a new generation of transplant surgeons versatile in all the above techniques is needed. Currently, the United Network for Organ Sharing requires surgeons performing donor hepatectomies to have documented experience as a board-certified primary surgeon (or first assistant) in 20 major hepatic resectional surgeries (donor operations, splits, reductions, resections, etc.), 7 of which must have been live donor procedures, within the prior 5-year period. Due to its technical demands, LDLT is performed by experienced senior surgeons who have accumulated experience over the course of their careers; although many surgeons could gather these numbers relatively easily, it is unlikely that these numbers can allow a young surgeon to master donor hepatectomy as an independent surgeon.

LDLT experience in the USA is currently "diluted" among many programs due to the competition between the centers and the lack of centralization of liver transplant care. Each center performs only a handful of LDLT procedures per year. For LDLT to grow and flourish in the USA, LDLT should ideally be limited to a few centers

of excellence. These large-volume centers can then act as training centers for young surgeons.

The other significant change is due for SLT. To date, this technique is mainly reserved for left lateral splits. Any other SLT is seldom performed, mainly due to fear of a poorer outcome for the recipients and logistics. As occurred with pediatric LT, refinement in surgical technique for the hepatectomy in living donation could be easily transposed to appropriate deceased donors.

The current liver allocation system in the US, which is based on the "sickest first" principle, creates a complex scenario for SLT. Ideal donor livers for SLT are often allocated to adult recipients with MELD scores ≥ 30 and portal hypertension, who are generally unsuitable for partial allografts. SLT may have a place when a large graft is offered to a small primary recipient with biological MELD < 30 . In this situation, if the transplant program is considering declining the whole graft for size mismatch, a good argument could be made to split the graft for two small recipients. Logistical issues such as unwillingness to "trust" the donor team during *in situ* splitting and use of the split liver graft by a center far away from the recipient hospital in the case of *ex vivo* splitting may be barriers as well. Standardization of SLT techniques and policies across regional centers may provide better communication between teams and aid in increasing the number of SLT procedures.

In summary, in the authors' opinion, a combination of whole and partial LT is the ideal way to fight mortality on the waiting list among adult patients with liver disease. A number of strategies could be explored to further expand the number of partial LT cases in the USA and other countries where partial LT is not routinely performed:

1. Financial neutrality and work stability for living donors must be ensured.
2. LDLT should be limited to high-volume centers of excellence.
3. Such centers should harbor adequate training programs on LDLT.
4. SLT should be a natural evolution among surgeons properly trained in LDLT.
5. SLT techniques and graft sharing policies should be standardized within regions to facilitate the expansion of SLT.
6. LDLT and SLT should be routinely offered to all patients evaluated for LT, particularly patients with MELD < 30 .

The success of DDLT in North America, LDLT in Asia, and SLT in Europe represent each region's response to meet the needs of patients with liver disease. To further meet these needs, partial LT in North America and

Europe and DDLT in Asia will need to grow in a more organized manner than in the past.

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