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Summary

Acceptance of liver transplantation (LT) as an established treatment modality for end stage liver disease led an exponential increase in the demand for organs. This had a domino effect on the ever-increasing gap between availability of organs and the sick waiting for it. Interestingly, the west and the east influenced by cultural, socio-economic and other constraints attempted to address this problem of shortage in different ways. Living donor LT (LDLT) became polarised to the east with over 90% of LT in this region being LDLT. On the other hand, the west chose to concentrate their efforts on optimising the use of cadaveric livers by techniques such as split LT, and use extended criteria donors including donation after cardiac death, machine perfusion devices etc. Consequently, LDLT did not find the widespread acceptance it did in the east and hence over 90% of all LT are DDLT in this region. We attempt to provide a view from each of the two regions' perspective and provide a globally viable roadmap to bridge this widening gap between the demand and availability of livers for LT.

Keywords: Living Donor Liver Transplantation; Deceased Donor Liver Transplantation; Organ Shortage; East Vs West

Lay Summary

The west and the east influenced by various cultural and socio-economic constraints attempted to address the problem of organ shortage in different ways. We provide a view from each of the two regions' perspective and provide a globally viable roadmap to bridge this widening gap between the demand and availability of livers for LT.

Why Are There So Many Liver Transplants from Living Donors In Asia And So Few In Europe And The US?

Introduction

The last two decades of the 20th century witnessed the evolution of liver transplantation (LT) into a standardised treatment modality for patients with end stage liver disease. As a result, the availability of organs could not cope with the exponential increase in demand, resulting in an ever-increasing gap between number of organs and the sick waiting for them. There was hence an urgent need to address this problem of organ shortage. Interestingly, the west and the east, each influenced by various idiosyncrasies chose different paths in addressing this conundrum.

Transplant teams in the western world chose to concentrate their efforts in optimising the use of deceased donor livers by techniques such as split LT, and the use of extended criteria donors including donation after cardiac death, machine perfusion devices etc. On the other hand, driven by cultural and socio-economic factors, LT centres in Asia became polarised towards living donor LT (LDLT). (Figure 1) We attempt to provide a view from each of the two regions' perspective and provide a globally viable roadmap to bridge this widening gap between the demand and availability of livers for LT.

Eastern Perspective

LT in Asia started almost two decades after the west^[1]. Although the first LT in Asia was a deceased donor LT (DDLT), confusions relating to various legalities involving brain death led to mistrust amongst clinicians and the general public, leading to a near moratorium on organ donation^[1,2]. With viral hepatitis being endemic in various parts of Asia, the burden of liver disease is immense. To put things into perspective, countries like Mongolia and Myanmar have one of the highest age adjusted mortality rates due to liver cirrhosis in the world (55.1 & 42.6 per 100000 population) and India accounts for the one fifth the global cirrhosis deaths; given this burden of disease (20 per million population (PMP)), India would need to perform 25,000 LT/year^[3]. Hence, LDLT developed in Asia out of necessity. It is

interesting to observe the reasons behind the variable growth of LDLT programs across various time points in different regions of the continent. Asia is a potpourri of different cultures, ethnicities, religions and economies. The spectrum of this variation is highlighted by the presence of diverse governmental and social hierarchies. It is a continent where democracies and autocracies, along with most backward and advanced economies share common borders. These incongruities apply to the healthcare sectors of these countries as well, sometimes even within the same country.

Religious beliefs and leaders play a crucial role in the daily life of an average Asian. Traditionally, Hinduism and Christianity especially in South Asia have been strongly supportive of organ donation, and Asian religions like Buddhism and other belief systems have been equivocal in their stance^[1,4,5]. Various regional interpretations of Islam have also led to ambiguity with regards to donation of organs^[6,7]. Despite these established beliefs, most religious leaders across the continent have unequivocally supported the noble cause of saving a life by donating organs^[1,4-6]. The common cultural belief especially among south-east Asians on the need to preserve the intactness of the human body after death has led to a reluctance in deceased organ donation^[2,8]. On the other hand, given the liver's regeneration in a living donor, the same tenet has led to a wider acceptance of LDLT in the region. (Figure 2) The sense of family remains strong among Asians, with most people strictly obeying familial hierarchies and bonds. These emotional attachments make living donation to family members an instinctively natural process. Then again, deceased donations suffer because it is often difficult for multiple decision-makers in these extended families to agree in unison to part with their deceased beloved's organs^[6,9].

LDLT programs especially in the Indian subcontinent are run by private stakeholders who thrive on medical tourism. Patients from countries where LT is unavailable preferentially come to these eastern countries, which in turn increases the throughput of LDLT. Overseas patients benefit from the quality, excellent results and cost effective aspects of treatment in these countries^[7,10]. Other important aspect are the infrastructural mandates of LDLT and DDLT units. While a LDLT program can successfully function in an isolated resource-rich hospital with its well trained and experienced transplant professionals, DDLT program need a wide-spread change in healthcare practices^[1,2,9]. These include co-operation between public and private sectors, agencies to oversee organ donation and distribution, the transparent legalities, education of the general public along with nurturing the emergency and intensive care units to foster trust in the system. Apart from this milieu of mistrust, a lack of coordination and implementation of policies at the various administrative levels make

widespread application of deceased donation a difficult task in most Asian countries^[2,7,9]. Most LT programs across Asia are privately funded and there remains a gripe that the economically underprivileged who have access only to the poorly funded public sector hospitals become donors for the recipients in the private hospitals^[1,2,7,9,11]. A grievance which often breeds sensationalism within the media leading to mistrust in the process of deceased donation^[2,9]. It is hence not surprising that Asia has lowest DDLT rates in the world from 0.1-7.5 PMP in 2019 as compared to countries in the west like Spain and the USA which have donation rates of 26.1 and 25.6 PMP respectively^[12]. (Figure 1)

China is the only country in Asia where the majority of LT are performed from deceased donor organs. (Figure 1) China's practices of organ procurement and transplantation have been a matter of international medical and ethical attention for several decades resulting in intense debates on human-rights violation and organ trafficking^[1,2,13-15]. This was due to the presence of close ties between the judicial system and organ procurement agencies, resulting in the use of non-voluntary organ donation mainly from executed political prisoners. With intense international scrutiny and ostracisation of their medical professionals, China revised statutes and in 2005, set up the Chinese transplant registry allowing for a transparent process of organ donation. In 2007, the Human Organ Transplantation Regulation of China banned transplant tourism and defined the source and rights of the organ donor. In 2010, in response to continued international criticism, medical administrators began a series of pilot programs to transition from the use of prisoners as an organ source to voluntary donors. The China Human Organ Donation and Transplantation Committee officially announced that from 2015 the use of organs from executed prisoners will be completely discontinued, and voluntary organ donation by citizens would be the only legal source of deceased donor organs^[13-15]. As a consequence, following decades of scorn for violating medical ethics, Chinese transplant surgeons were welcomed back into the international transplant fraternity and are now able to attend conferences and publish in respected journals. It however disheartening to note that there still remains a grey area. There are reports from independent agencies which suggest that some of the data may be falsified, and apparently non-voluntary donors are misclassified as voluntary; spawning a belief in some quarters that the trust may have been violated and that the reputations of these Chinese professionals dedicated to the highest standard of transplant medicine may be impugned^[10,13-15].

An all-inclusive state-run healthcare system with modernised public sector hospitals would solve the problem of economic inequity and provide universal access to health^[16]. While practical in the developed western world, it may sound rather idealistic in a "third-

world” country. However, this model has successfully been applied in various regions of Asia, including parts of India, leading to increased organ donation rates several fold higher than the rest of the region [9,17]. Although these efforts have borne results with improving donation rates over the past two decades (from no DDLTs in 2000 to 0.47 PMP in 2019), these efforts are sporadic [12]. There remains the need for a concerted effort along with strong and unwavering support from the state administration and all concerned parties to make this a nation- and furthermore a continent-wide reality. This paradigm shift is time consuming and requires patience and perseverance to achieve a durable permanence. It is also crucial to appreciate that even a single untoward incident may derail the whole deceased donor program, and even set it back by many years.

Western Perspective

At the end of 2019, over 12,000 patients in the United States were active on the national liver transplant waiting list [12,18]. However, only 8,372 DDLT were performed that year, which meant that a third of the patients had to wait for over a year to receive a liver. A similar picture presents itself across the Atlantic as well. According to the European Liver Transplant Registry, there are sections of Europe where over 40% of those on the waitlist have needed to wait for over two years for LT [19]. Moreover, notwithstanding the increasing numbers in the last decade, LDLT numbers have remained relatively static in the west and this operation accounts for a paltry 1-5 % of all European and American LT volume [18–20]. Due to the relatively larger number of DDLT, the drive to promote LDLT has not been as vigorous in the west as is in Asia.

There are other reasons for this reluctance in the acceptance of LDLT. Early series on LDLT in America showed significantly higher rates of biliary and vascular complications, attributed to the smaller calibre of graft arteries and bile ducts [21,22]. A higher recurrence rates with hepatocellular carcinoma was also noted in these cohorts [18,21]. Reasons cited included shorter wait-listing periods resulting in non-assessment of tumour biology, and liver regeneration driven tumour recurrence. Initial cost analyses also found higher hospitalization rates and increased inpatient costs with LDLT than DDLT [18,23]. However, the telling blows for LDLT in the west were the published donor deaths, leading to a perceived heightened risk to the donor and a loss of double equipoise in LDLT [24,25]. Since the first LDLT in 1989, there have been a total of 36 living donor deaths worldwide (Table 1) [9,19,25–29]. It must be acknowledged that this figure suffers from a severe under-reporting bias, and the actual number of donor deaths may never be truly identified. Unlike in Asia, the intolerance to non-

zero donor mortality and donor morbidity, along with a well-established DDLT system across the west severely hampered the growth of LDLT in the region^[18,23,30].

More recently however, there have been numerous series from large volume centres in north America demonstrating indisputably superior survival outcomes with LDLT^[22,23,25,30-32]. Moreover, these centres showed that both recipient and donor outcomes improved markedly when centre volumes were large and appropriate expertise available to help flatten the learning curve of LDLT. The dramatic reduction in the waitlist numbers and mortality in LDLT, along with a plateauing of deceased donor numbers has led to a realistic demand for resurgence of LDLT in the western hemisphere^[23,25,30,31].

Nonetheless, success and growth of LDLT in the west requires a conceptual change at restructuring policies from a dogmatic attitude to an evidence based approach^[18,23,25,30,31]. A more receptive approach to offer LDLT as a first option to patients low on the DDLT waitlist has been suggested as a good starting point. Apart from reducing the waiting list, this will help transplant team hone their LDLT skills, thereby further improving outcomes. Systematic approach to setting up a structured process of perioperative and postoperative assessment and management of the donor and recipient by incorporating an effective multi-disciplinary team will also help standardise procedures across the region. This change in mindset is no easy undertaking. It requires extensive and realistic campaigns on the safety and benefits of living donation, an approach which needs to target not only the public but also the healthcare providers and management personnel. Centralisation of DDLT services is an approach which has been a successful model in countries like the UK. This model could be extrapolated to the practice of LDLT as well. High volume centres which are rich in resources and experienced personnel will have a domino effect of cumulative experience and consequently, safer and superior LDLT outcomes. Training is another aspect which cannot be ignored, especially in cutting-edge technology like robotic and minimal access techniques for the current and future generation of transplant professionals.

The Turkish Model

While discussing about Asia and the west, it is fascinating to deliberate regarding Turkey which lies at the cusp of Europe, Asia and the Middle East. A melting pot of cultures originating within various Asian and European empires, it straddles two continents. Despite its religious beliefs and culture being similar to Asia, due to geo-political reasons the Turks have considered themselves more European than Asian^[33,34]. With over 90% of the population being Islamic, Turkey traditionally held conflicting views with regards to organ

donation. It was not until 1979, that the Religious Affairs Supreme Council in Turkey provided their concordance with regards to organ transplantation, which they ruled was in accordance with Islamic rules and the Quran^[33–35]. Further amendments and approval from the parliament and the Department of Religious Affairs paved the way for a formal development of deceased donation program. Nonetheless, like other Asian countries, DDLT has remained a poor second to LDLT. Most Turkish centres thrive on international medical tourism especially from the neighbouring middle east countries, providing further impetus to living donor programs. It was not until the turn of the century that a governmental umbrella organisation was created to promote deceased donations and overcome the hurdle of lack of knowledge among healthcare professionals and public in general^[33–36]. Efforts were made to increase awareness through the media, schools, and many public and private institutions. This system increased deceased organ procurements from 0.9 PMP in 2001 to 7 PMP in 2019. Improvements in legislation, education and coordination have been the key to increasing the quality and the quantity of transplantation activities in Turkey and remain a model for many Asian countries. Till 2019, 14185 LT (4187 deceased, 9998 living) were performed in 82 centres nationwide^[36]. It is indeed satisfying to see Turkey following the European models of promoting deceased donor donation, while maintaining the Asian touch of LDLT; truly straddling the two continents in the transplant world as well.

The Equipoise

The patterns of liver disease and indications of LT are evolving. Though there are decreasing number of patients undergoing LT for Hepatitis B and C, the epidemic of NAFLD continues to exponentially increase the numbers of patients requiring a LT^[7,19,22,23]. With a better understanding of disease processes, the list of pathologies conventionally considered as contraindications for LT is shrinking and newer indications are continuously added onto this ever-growing list. Consequently, the chasm between patients needing a LT and the availability of organs keeps increasing.

DDLT and LDLT have each developed as standardised procedures and have its proponents, but a practical way forward would be to amalgamate the two programs with aim to encourage organ donation both living and deceased on the whole. To this end, it is important to acknowledge that the two practices are not mutually exclusive, but complementary treatment modalities aimed at saving the lives of those with liver disease.

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Figure Legends

Figure 1: Worldwide data on liver transplantation activity (numbers) in 2019 comparing living donor and deceased donor liver transplant volumes by country^[12]

Figure 2: Worldwide data on liver Transplantation activity (persons per million population) in 2019 comparing living donor and deceased donor liver transplant volumes by country^[12]

Table 1: Living Liver Donor Deaths – 1989 to 2019

Country/Continent	Donor Death/Vegetative State Related to the Operation	Unpublished Donor Deaths Related to the Operation*	Donor Death Unrelated to the Operation	Total
Asia				
Hong Kong	1			
India	8	3		
Singapore				
Pakistan	1	2		
Japan	1			
South Korea	1		52	
Others	2		6	
North America				
USA	6		13	6
South America				
Brazil	2		2	2
Africa				
Egypt	1			1
Europe	8		1	8

* Media Reports

Figure 1: Worldwide data on liver transplantation activity (numbers) in 2019 comparing living donor and deceased donor liver transplant volumes by country [12]

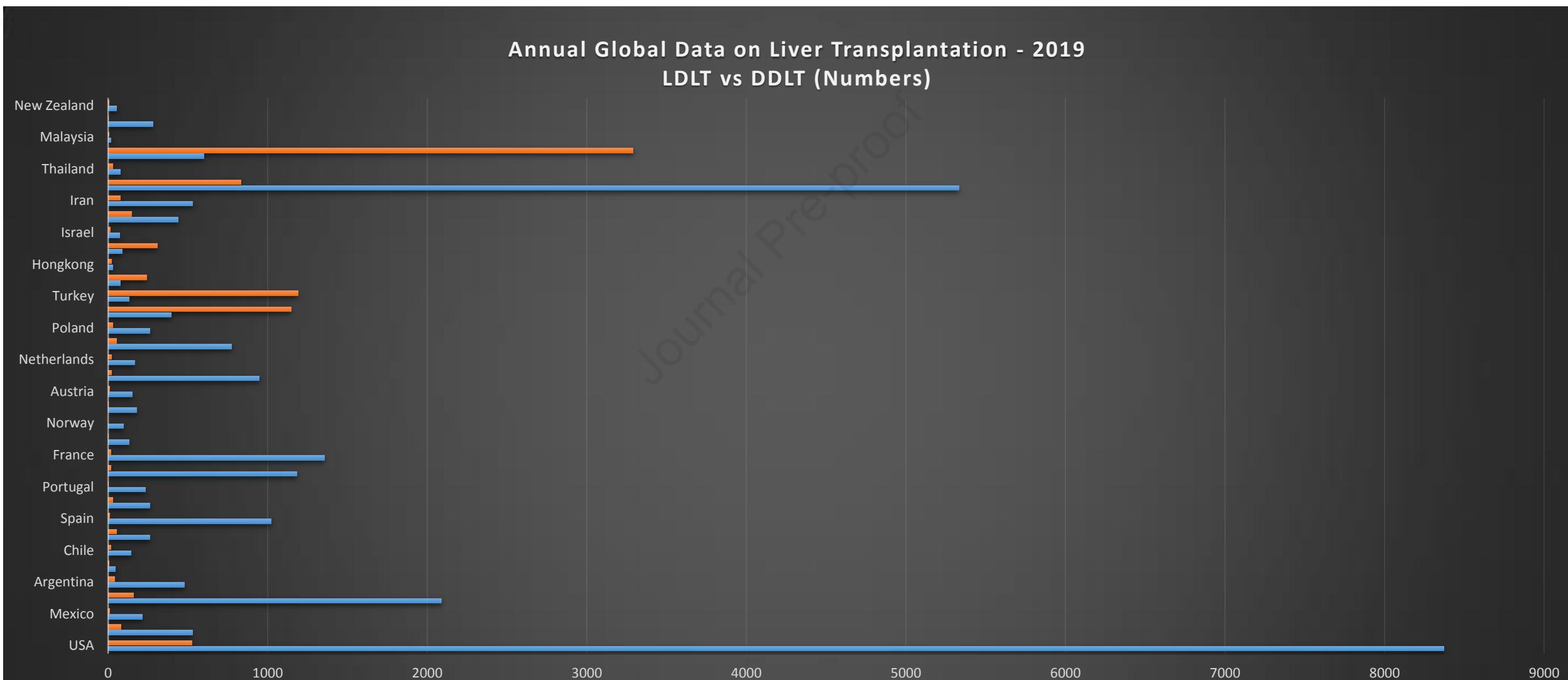


Figure 2: Worldwide data on liver Transplantation activity (persons per million population) in 2019 comparing living donor and deceased donor liver transplant volumes by country [12]

