

Living donor liver transplantation in Egypt

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Abstract: In Egypt there is no doubt that chronic liver diseases are a major health concern. Hepatitis C virus (HCV) prevalence among the 15–59 years age group is estimated to be 14.7%. The high prevalence of chronic liver diseases has led to increasing numbers of Egyptian patients suffering from end stage liver disease (ESLD), necessitating liver transplantation (LT). We reviewed the evolution of LT in Egypt and the current status. A single center was chosen as an example to review the survival and mortality rates. To date, deceased donor liver transplantation (DDLT) has not been implemented in any program though Egyptian Parliament approved the law in 2010. Living donor liver transplantation (LDLT) seemed to be the only logical choice to save many patients who are in desperate need for LT. By that time, there was increase in number of centers doing LDLT (13 centers) and increase in number of LDLT cases [2,400] with improvement of the results. Donor mortality rate is 1.66 per 1,000 donors; this comprised four donors in the Egyptian series. The exact recipient survival is not accurately known however, and the one-year, three-year and five-year survival were 73.17%, 70.83% and 64.16% respectively in the International Medical Center (IMC) in a series of 145 adult to adult living donor liver transplantation (AALDLT) cases. There was no donor mortality in this series. LDLT are now routinely and successfully performed in Egypt with reasonable donor and recipient outcomes. Organ shortage remains the biggest hurdle facing the increasing need for LT. Although LDLT had reasonable outcomes, it carries considerable risks to healthy donors. For example, it lacks cadaveric back up, and is not feasible for all patients. The initial success in LDLT should drive efforts to increase the people awareness about deceased organ donation in Egypt.

Keywords: Liver; transplantation; living donor liver transplantation (LDLT); Egypt

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Introduction

In Egypt, there is no doubt that chronic liver diseases are a major health concern. hepatitis C virus (HCV) prevalence among the 15–59 years age group is estimated to be 14.7%. Accordingly, Egypt has the highest HCV prevalence in the world. This unparalleled level of exposure to this infection appears to reflect a national level epidemic. It has been postulated that the epidemic has been caused by extensive

iatrogenic transmission during the era of parenteral-antischistosomal-therapy mass-treatment campaigns. Today, HCV infection and its complications are among the leading public health challenges in Egypt (1). Living donor liver transplantation (LDLT) has become an option for patients with end stage liver disease (ESLD) when cadaver transplantation is not available. In Egypt, cadaver transplant is not yet implemented, and LDLT is the only option for patients with ESLD.

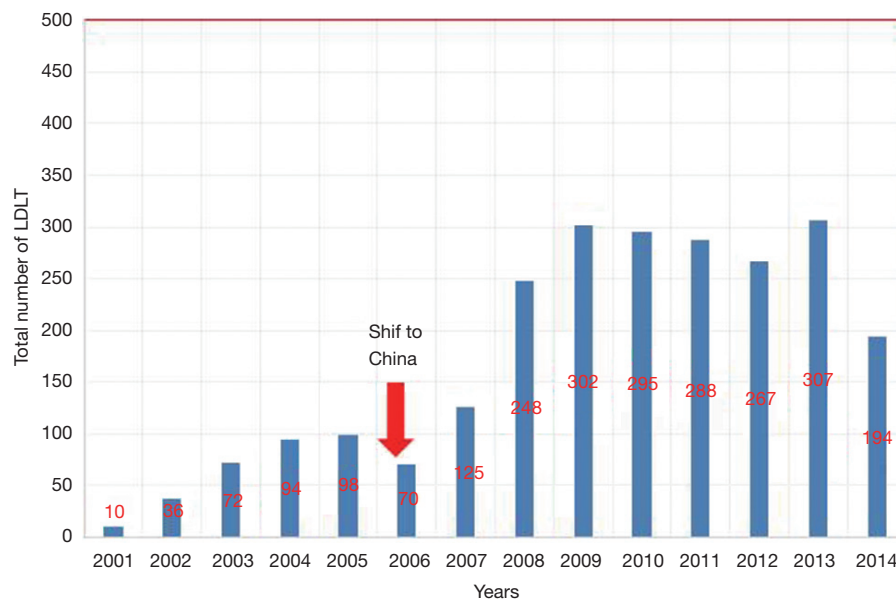


Figure 1 The exact number of LDLT done in Egypt annually. LDLT, living donor liver transplantation.

Historical background

In July 1989, Strong *et al.* performed the first successful transplantation of a liver graft from a living related donor; the donor was a 29-year-old woman and the recipient was her 17-month-old son (2).

LDLT using left-lobe grafts was introduced to adult recipients in 1993 (3) but this procedure did not become widespread owing to the inability of these relatively small-sized grafts to meet the metabolic demands of all adult recipients. To overcome the problem of inadequate graft volume encountered by left-lobe grafts, transplantation with right-lobe liver grafts was introduced to adult recipients in 1996 (4,5).

Living donor liver transplant (LDLT) was first performed in Egypt in 1991 by the surgical team at the National Liver Institute (NLI), Menoufeya University, with the help of Prof. Habib. The longest recipient survival was 11 months. This pioneer work led to efforts to pass a law legalizing cadaveric organ donation, culminating in the 1992 decree permitting cadaveric organ harvested from prisoners who were sentenced to death. The surgical team at the National Cancer Institute (NCI), Cairo University in 1992 performed two cadaveric liver transplantation (LT) procedures but, unfortunately, both recipients died in the early postoperative period (unpublished data).

The regulations were made by the Egyptian medical syndicate. Programs started with the assistance and under

supervision of oversea teams. The breakthrough was made in Dar Al-Fouad Hospital by starting the program of LDLT (August 2001), with Prof. Tanaka, Kyoto University, Japan. This was followed by Wady El-Neel Hospital (October 2001), NLI, Menoufeya University (April 2003) and Maadi Armed Forces Hospital (September 2003). By that time, there was increase in number of centers doing LDLT (13 centers) and increase in number of LDLT cases [2,500] with improvement of the results of LDLT.

Current status

There are thirteen LDLT centers in Egypt, including six university centers, two military centers, three private centers and two centers in the ministry of health hospitals.

By the end of June 2014, the total number of cases reached 2,406. *Figure 1* shows details about the exact number of LDLT done in Egypt annually.

This number comprised 2,246 adult cases (93%) and 160 pediatric cases (7%) (*Figure 2*). The vast majority of indications were HCV hepatitis (*Figure 3*).

LDLT in Egypt in relation to the Arab Region

Between 1990 and August 2013, 3,804 liver transplants [3,052 (80%) LDLT and 752 (20%) deceased donor liver transplantation (DDLTL)] were performed in 11 Arab

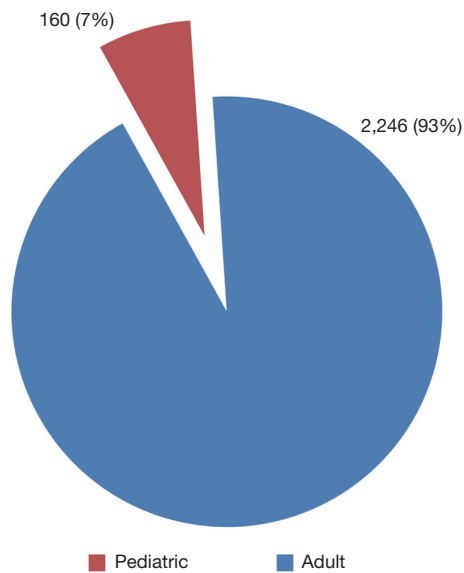


Figure 2 The number of adult and pediatric patients underwent LDLT. LDLT, living donor liver transplantation.

countries.

The largest percentage of LT has been performed by 13 transplant centers in Egypt (56%) followed by four transplant centers in Saudi Arabia (35%) and two transplant centers in Jordan (5%). In the remaining eight Arab countries, liver transplant activity has been limited to one program in each country (6) (Tables 1,2).

Deceased donor program

Law

After the regulation was made by the Egyptian Medical Syndicate, LDLT programs were established without backup by doing LT from deceased (cadaveric) donors. This agreement was based on the concept of equalization between blood transfusion and liver donation. Because of the power of regeneration of the bone marrow, the liver in LDLT has the same power of regeneration. In this way, blood transfusion is equal to liver donation regarding the concept. By the time LDLT develops and the number of cases increase, we start to face the problem of donor complications and donor mortality which leads to discussion whether the law accept the concept of brain death as step to develop liver transplant from deceased donors. The law was raised in the Egyptian Parliament which was trying to pass the law, but it was very difficult at this time because there was an impact of many factors related to the concept.

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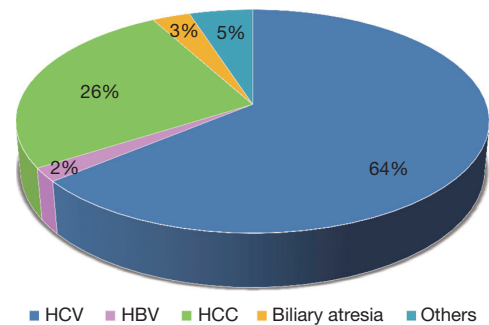


Figure 3 Indications of LDLT. LDLT, living donor liver transplantation.

Table 1 Liver transplant activity in the Arab world until August 2013 arranged according to date of the first liver transplant

Country	First LT	LDLT	DDLT	Total	%
Saudi	1990	648	690	1,338	35
Egypt	1991	2,138	2	2,140	56
Tunisia	1998	8	31	39	1
Lebanon	1998	4	19	23	0.6
Algeria	2003	36	–	36	1
Jordan	2004	174	4	178	5
Libya	2005	21	–	21	0.5
UAE	2007	2	–	2	0.1
Kuwait	2010	–	2	2	0.1
Iraq	2011	21	–	21	0.5
Qatar	2011	–	4	4	0.1
Total		3,052	752	3,804	

LT, liver transplantation; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation.

After the Declaration of Istanbul was created in 2008, the Egyptian Parliament approved the law in 2010 (7).

Religious factors

The main problem, from the religious point of view, is the acceptance of the brain death concept. Many of Egyptian population believe that death occurred when the heart stop beating. So in case of clinical death with the heart still beating, they considered this victim still alive.

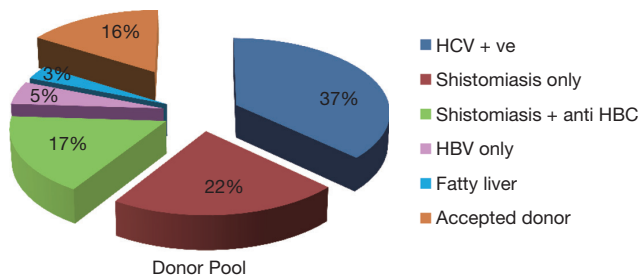
Cultural factors

If we look for the impact of culture on the field of LT, we

Table 2 Liver transplant activity in Egypt until August 2013 arranged according to date of the first liver transplant

Center	First LT	LDLT	DDLT	Total	%
National Liver Institute	1991	205	–	205	9.6
National Cancer Institute	1992	–	2	2	0.1
Wadi El-Nile	2001	400	–	400	18.7
Dar El-Foad	2001	350	–	350	16.4
Maadi Hospital	2003	131	–	131	6.1
Cairo University	2004	129	–	129	6
Al-Mansoura University	2004	267	–	267	12.5
International Medical Center	2005	170	–	170	7.9
El-Sahel Hospital	2007	115	–	115	5.4
Egypt Air	2007	160	–	160	7.5
Al-Azhar University	2008	25	–	25	1.2
Ain Shams University	2008	155	–	155	7.2
Other	–	31	–	31	1.4
Total		2,138	2	2,140	

LT, liver transplantation; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation.

**Figure 4** Potential donors for LDLT. LDLT, living donor liver transplantation.

find that the majority of population lack medical awareness. Besides, the religious impact has a stronger effect in decision of donation especially in case of LT. It is believed that the liver is a bloody organ that cannot be touched by knife. In addition, it is believed that the humans are the product of God so, how can you donate a part of your liver, which you do not own by yourself?

Regarding LT from deceased donors (cadaveric), it is believed that death means that the heart stops beating. So,

in case of clinical death with a beating heart, the potential donor is still considered alive. This concept has major impact on the implementation of LT from deceased donors.

Before the start of LDLT, we raised the medical awareness of population and the concept of donating a part of liver. This was accepted because the liver has a power of regeneration so it is equal to blood donation. The bone marrow also has a power to give new blood cells and blood transfusion is accepted from the religious point.

Living donor liver transplantation (LDLT) program

Donor motivation

Several factors seemed to contribute to motivation for donation: the seriousness of the potential recipient condition, the relationship and personal history between the donor and the potential recipient, the religious beliefs, the trust in the health care system, and family dynamics and obligations.

Absolute coercion on the living-liver donor's motives may not be realistic because of the serious condition of the potential recipient. It is mandatory that the donor is truly willing to donate (8).

Pool of donors

The potential number of donors for LDLT in Egypt is small, and this is mainly due to the high prevalence of HCV and schistosomiasis infection in apparently healthy family members who are the potential donors for patients with ESLD (Figure 4).

Whether patients with schistosomiasis can be donors for LDLT is not known. We currently exclude these donors, and this has to be studied further if the potential donor pool is to increase.

Relation to recipient

The law permits that the relationship with the recipient can be up to third degree relatives. Non-related living donation was accepted only when an independent ethical and legal committee approve that none of the patient's relatives is suitable as a right liver lobe donor. The legal age of consent for donation in Egypt is 18 years when the recipient is a parent, otherwise it is 21 years.

All cases must have a final approval from the Supreme Committee of Organ Donation, Ministry of Health and

Population. The members review all the medical reports and scans and meet both patient and donor.

Graft quality

HCV infection

The problem in Egypt regarding liver diseases is the high prevalence of HCV infection, especially in the rural areas. According to WHO reports, Egypt is considered to be one of the countries with highest prevalence of HCV infection. This is one of the factors mostly affecting the donor pool especially in cases of related donors, because they are in the same community and have the same incidence of exposure to HCV infection. Also, this high prevalence may be due to lack of awareness and some bad habits like toothbrush or shaving equipment sharing among family members of diseased patient. Particularly in rural areas, the barbers may use their instruments without sterilizing the instruments between usages.

Steatosis

Steatosis due to the type of food adds another problem in the donor pool. A large percentage of the population is overweight due to the food high fat content and poor eating habits.

Donor and recipient evaluation

Donor evaluation

The law has defined the liver donor age to be between 18 and 55 years (18 years only for donating sons and daughters, otherwise the minimum age is 21 years). However, most centers are limiting the maximum age to 45 years.

According to the 2008 Census held by the Central Agency for Mobilization and Statistics (CAPMAS), only 6.08% of Egyptians are aged above 60 years (9). This implies that most chronic diseases occur at a younger age in Egyptians in comparison with other populations. This justifies our choice of an upper age limit of 45 years, although many centers in other countries accept higher age limits, even greater than 60 years.

Body mass index (BMI) more than 30 is usually rejected. However some centers accept donors with a BMI >35 if they are re-evaluated after they are committed to a successful weight loss program (10).

Absolute exclusion criterion is ABO incompatibility.

No history of major abdominal surgery; negative

serological findings for HBV, HCV, and human immunodeficiency virus; a normal psychiatric evaluation; a normal oncological and hematological evaluation; normal liver and kidney function; normal cardiopulmonary function; and negative findings on a pregnancy test for female candidates.

As Egypt has the highest prevalence of HCV in the world, which is estimated nationally to be 14.7%, liver biopsy is routinely done for all donors. Liver biopsy is performed prior to imaging studies for graft assessment [computed tomography (CT) angiography, volumetry and magnetic resonance cholangio-pancreatography (MRCP)] mainly for economic reasons and in view of the fact that it is almost risk free. Candidate who had >10% macrovesicular steatosis or pathological findings is rejected to be a living donor.

Liver volumetry and vascular anatomy are determined by dynamic CT while biliary anatomy is determined by MRCP.

Adequate donor's remnant liver volume (RLV) is determined to be $\geq 35\%$ of total liver volume (TLV). The estimated graft volume is determined to be $\geq 1\%$ of recipient's body weight. In almost all centers, grafts with more than two biliary ducts are rejected.

Recipient evaluation

Recipients are considered for LDLT if they are deemed to be "medically eligible", "surgically suitable" for the procedure and there is an indication for LT with no contraindication for the procedure.

There is debate regarding the age limit for LDLT. Though most centers do not accept recipients older than 60 years, two centers rely on the biological age rather than the chronological age. They perform more cardiopulmonary assessment including cardiac catheterization for recipients older than 60 years.

The older ages recorded were 68 years in International Medical Center (IMC) and 70 years in Wady El Neel Hospital.

Advancement in surgical technique

To expand the pool of donors in the absence of cadaveric program, some centers are accepting complicate vascular variants in donors, using left lobe graft (LLG) in adults and cutting down the expected graft volume to 0.8% of the recipient's weight.

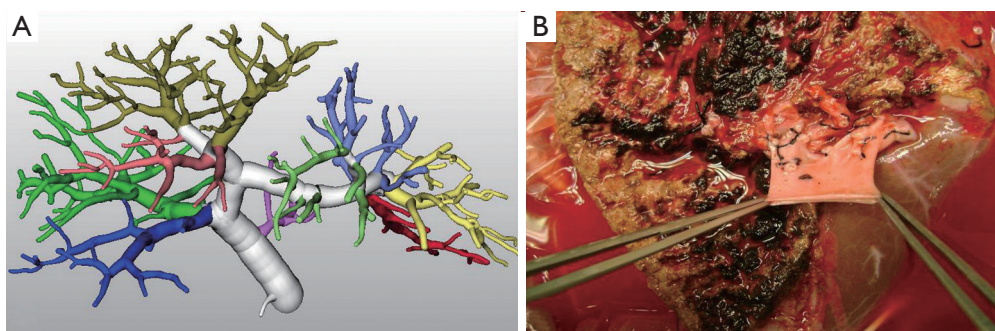


Figure 5 (A) 3D portal analysis of a donor with trifurcated PV; (B) the Y natural venous graft taken from the explanted liver.

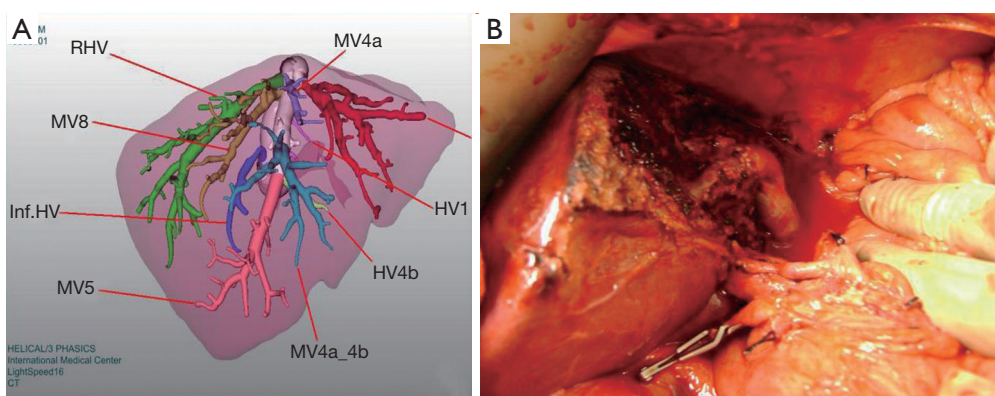


Figure 6 (A) 3D venous analysis of a donor with a big V5; (B) the use of the umbilical vein as a natural vascular graft.

Portal vein variations

Most centers rejected donors with trifurcated portal vein in their initial experience, but lately this type of portal vein variation is accepted by some centers and the native portal vein of the explanted liver is used as a Y natural venous graft (11) (*Figure 5*).

Hepatic venous variations

In middle hepatic vein dominant livers, the middle hepatic vein mainly drains the anterior segment of the right lobe of the liver (segments five and eight). In these donors when right lobe grafts are procured without the middle hepatic vein, the graft may harbor large segment five and/or eight veins that need to be reconstructed to avoid graft congestion and subsequent graft dysfunction.

Reconstruction using natural vascular grafts (*Figure 6*) or synthetic grafts as ringed expanded polytetrafluorethylene (ePTFE) (*Figure 7*) has become an additional technique to

overcome anterior segment congestion in the graft and to expand the donor pool.

Kamel *et al.* (12) concluded that synthetic vascular expanded polytetrafluoroethylene grafts could be used effectively and safely in middle hepatic vein tributary reconstruction to overcome the unavailability of autologous or cryopreserved vessel grafts or just to avoid the additional burden of recovering autologous grafts (*Figure 7*). Neither graft occlusion nor infection is reported in this series.

Left lobe graft (LLG) for adults

Right lobe graft without middle hepatic vein is the standard graft selection for adult to adult living donor liver transplantation (AALDLT) in Egypt.

However, few centers use the LLG for adults for donor safety. All donor mortality in Egypt was in right lobe graft donor. An algorithm has been developed for the use of LLG (13) (*Figure 8*).

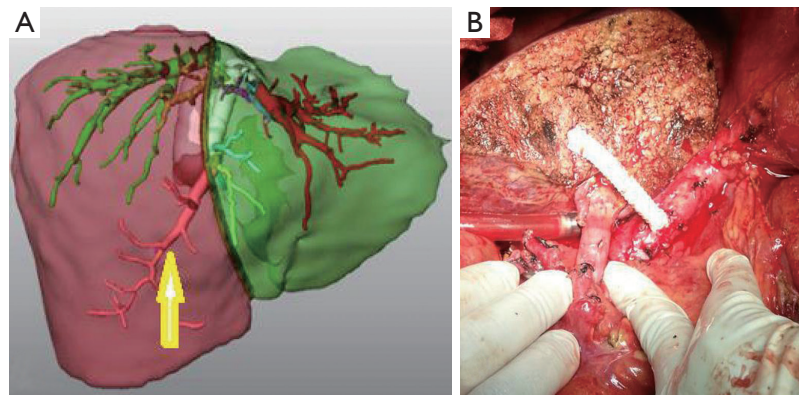


Figure 7 (A) 3D venous analysis of a donor with a big V5; (B) a ringed expanded polytetrafluorethylene (ePTFE) synthetic vascular graft.

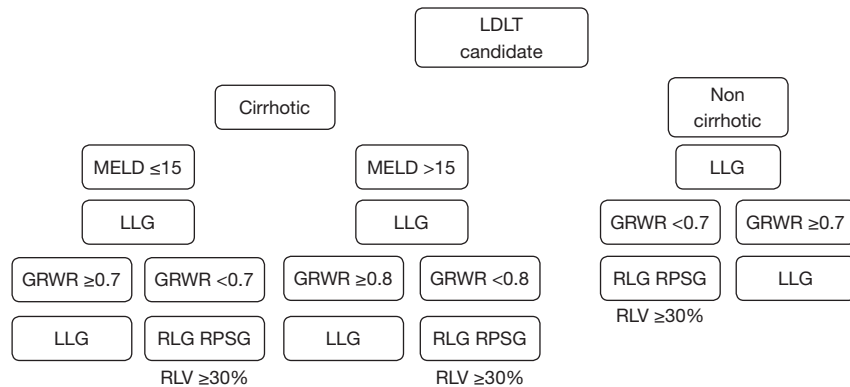


Figure 8 Innovated graft selection algorithm. LDLT, living donor liver transplantation; LLG, left lobe graft; GRWR, graft volume/recipient body weight ratio; RLG, right lobe graft; RPSG, right posterior segment graft; RLV, remnant liver volume.

Postoperative evaluations

The remnant livers of all donors are evaluated daily after transplantation through liver function tests and prothrombin time until the parameters normalize. All complications after donor hepatectomy are graded as proposed by modified Clavien classification system. The liver grafts of all recipients are evaluated daily through serum liver function tests until the parameters normalize. To check the patency of the graft vessels Doppler ultrasonography is performed daily in the first 7 days after the operation and then twice per week.

Immunosuppressive drugs

The immunosuppressive regimen consists of a combination of calcineurin inhibitor (tacrolimus prograf or cyclosporine: neoral) and steroids with or without mycophenolate mofetil

(MMF) (CellCept). Currently, the triple regimen including calcineurin inhibitor, steroids and MMF is the standard protocol for HCV patients. Steroids are basically tapered off by 6 months after LDLT. MMF 1,000–2,000 mg/day is administered from postoperative day 1 lasting for 3–6 months. The immunosuppressive dose is adjusted on daily bases guided by trough level.

Donor mortality

In a national study of all live liver donors in the United States over a 17-year period, Muzzale *et al.* showed that the risk of death after liver donation was 1.7 per 1,000 donors and the risk of catastrophic outcomes including early death and acute liver failure was 2.9 per 1,000 donors (14). A previous US survey had indicated that the risk of death quoted by transplantation teams to potential donors varied by more than a factor of 10, from less than 1 per 1,000

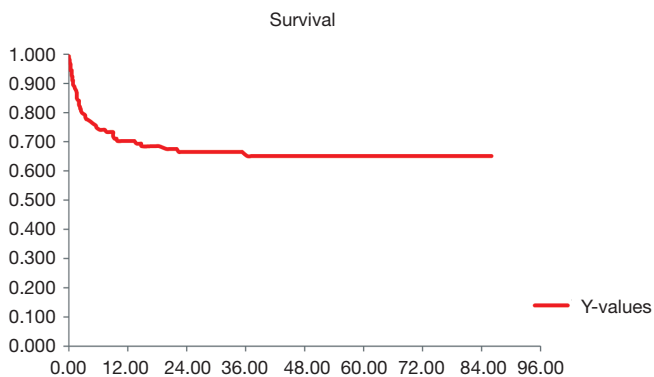


Figure 9 Survival after LDLT in International Medical Center (IMC). LDLT, living donor liver transplantation.

to more than 10 per 1,000. This survey estimated that the actual risk of catastrophic outcomes would be 4 per 1,000 (15).

Donor mortality rate is 1.66 per 1,000 donors. This comprised four donors. The first one died three months after hepatectomy due to biliary leak followed by infection, septicemia and multi organ failure (16). The second one died twelve days after donation due to portal vein thrombosis. The third one was due to Rt. subclavian artery injury during CL (central line) insertion, leading to massive right hemothorax. The fourth one died one month after donation due to hepatic insufficiency and hepatic failure.

A major morbidity was also recorded due to hepatic insufficiency and the donor needed LDLT that was performed 4 weeks after donation.

Recipient survival after LDLT

Data of overall survival is difficult to be obtained. However, here we can present the results from the IMC as a single center experience.

Between October 2005 and June 2012, 145 ALDLT were undertaken. These included 126 men and 19 women with a mean age of 49.76 ± 5.2 years. A total of 74% graft used was right lobe without middle hepatic vein (RLG-MHV), 21% LLG, 4% right lobe graft with middle hepatic vein (RLG + MHV) and 1% right posterior segment graft (RPSG).

The mean graft volume/recipient body weight ratio (GRWR) was 1.02% (0.75–1.41%) in RLG and 0.77% (0.59–1.2%) in LLG.

The 1-, 3-, and 5-year survival were 73.17%, 70.83% and 64.16% respectively. There was no donor mortality in this series (17) (Figure 9).

Conclusions

Although LDLT had reasonable outcomes, it carries considerable risks to healthy donors because it lacks cadaveric back up, and is not feasible for all patients.

We hope that the initial success in LDLT will not deter the efforts to increase people's awareness about deceased organ donation in Egypt.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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