INTRODUCTION

Living donor liver transplantation (LDLT) is now an accepted treatment modality for end-stage liver disease, it has become an alternative in the era of organ shortage, this procedure is possible because of the segmental structure of the liver and the regeneration potential of the remnant parts ***(Taner et al., 2008).***

After years of extensive experience in adult-to-child left-lobe liver transplantation, right donor hepatectomy has become a common practice in centers performing adult-to-adult LDLT ***(Taner et al., 2008).***

Despite impressive results, right-lobe LDLT involves one of the most complicated and technically demanding surgical procedures and has created considerable controversy with respect to donor safety ***(Taner et al., 2008).***

The issue of donor safety has been taken up by governmental agencies and professional societies, and LDLT for adults is currently performed in the United States under intense scrutiny. Nevertheless, the underlying driving force which is the lack of cadaveric donor livers and the resultant deaths of patients awaiting transplants has led patients, their families and friends, and transplant programs to carry on ***(Koffron and Stein, 2015)***.

Yaprak and associates said that Residual Liver Volume (RLV) to total liver volume ratio is predictive of postoperative adverse effects on donor ***(Yaprak et al., 2012).***

It has become an alternative in the era of organ shortage. This procedure is possible because of the segmental structure of the liver and the regeneration potential of the transplanted and remnant parts ***(Trotter et al., 2006).***

After years of extensive experience in adult-to-child left-lobe liver transplantation, right donor hepatectomy has become a common practice in centers performing adult-to-adult LDLT. Despite impressive results, right-lobe LDLT involves one of the most complicated and technically demanding surgical procedures and has created considerable controversy with respect to donor safety ***(Trotter et al., 2006).***

With a extreme shortages of deceased donor organs in Asia (due to problems with acceptance of brain-death criteria), and variable shortages in most other parts of the world, the concept of donating a piece of one's liver to help save the life of a family member has considerable appeal, but reliable information about risks must be provided to prospective donors ***(Neuberger et al., 2003)***.

An estimate for donor mortality for LDLT (involving adult or child recipients and any graft type) is about 0.2%, but this may be an underestimate ***(Neuberger et al., 2003).***

A significant correlation between the residual liver volume and liver dysfunction, serious adverse postoperative events, and longer hospital stays. Donor safety should be the first priority of all living liver donor programs ***(Reichman et al., 2011).***

Reichman et al that the surgical procedure removing the smallest amount of the liver required to provide adequate recipient graft function should become the standard of care for living liver donation ***(Reichman et al., 2011).***

Generally reported lower complication rates with left lobe donation. Salamé et al. reported that right liver donation was associated with longer anesthesia times, greater blood loss, and greater postoperative biochemical liver abnormalities ***(Reichman et al., 2011).***

Salvalaggio et al. compared donors who underwent RH and donors who underwent LH or LLS, and they reported a higher rate of complications and more severe complications with right lobe donation ***(Reichman et al., 2011).***

So in the past, several surgeons documented the accepted lower safety margin of donor remnant liver volume might be 30% of the total liver volume in LDLT. Transplant surgeons have to set strict limitation for the safety margin of remnant liver volumes. Otherwise, a tragedy caused by an extremely small remnant liver would occur ***(Uchiyama et al., 2014).***

Even though the settled limit of remnant liver volume was at 35%. There have been devastating consequences after living liver donation around the world, most of which occurred after right hepatic donation ***(Uchiyama et al., 2014).***

AIM OF THE WORK

To evaluate postoperative donor outcome as regard liver function and complications in donors for LDLT with different residual liver volumes.

Primary end point: restoring liver function post LDLT.

Secondary end point: rate of complications post LDLT.

Chapter 1
LIVER TRANSPLANTATION IN LITERATURE

History & evolution

The history of liver transplantation began with experimental transplants performed in dogs in the late 1950s. The first deceased donor liver transplant (DDLT), also known as orthotopic liver transplant (OLT), was attempted in humans was in 1963 by Thomas Starzl. The recipient was a 3-year-old boy with biliary atresia who unfortunately died of haemorrhage (Table 1). The first successful liver transplant was in 1967, again by Starzl at the University of Colorado Health Sciences Center, Denver. Yet, for the next 10 years, liver transplants remained essentially experimental, with survival rates well below 50%. Still, advances in the surgical procedure and in anesthetic management continued to be made during that time ***(Arvelakis et al., 2013)***.

The major breakthrough for the field came in the early 1980s, with the introduction and clinical use of the immunosuppressive agent cyclosporine. Patient survival dramatically improved, and liver transplantation was soon being recognized as a viable therapeutic option. Results continued to improve through the 1980s, due to ongoing improvements in immunosuppression, critical care management, surgical

technique, and preservation solutions. The late 1980s and 1990s a dramatic increase in the number of liver transplants, and an even greater increase in the number of patients waiting for a transplant. This in turn increased waiting times as well as mortality rates for those waiting their turn for transplant ***(Melancon and Fishbein, 2013)***.

Table (1): History of liver transplantation ***(Busuttil and Klintmalm, 2005).***

Year	Description
1955	First article in the literature of auxiliary liver transplantation
1958-1960	Formal research programs of total hepatectomy and liver replacement in dogs
1963	Azathioprine prednisone cocktail introduced and recognition of organ induced tolerance
1963	First human liver transplantation (university of Colorado)
1965	First clear evidence of hepatic tolerogenicity
1966	First liver xenotransplantation on July 15, 1966 (chimpanzee donor)
1966	Clinical introduction of anti lymphocyte globulin (ALG)
1966-1970	Proof that human leukocyte antigen matching would not be a major factor in liver transplantation
1967	First successful human liver replacements under Azathioprine, prednisone and ALG
1967-1968	Acceptance of brain death concept
1976	Improved liver preservation permits long distance procurement
1979	Cyclosporine introduced for organ transplantation including two liver recipients
1980	Cyclosporine steroid cocktail introduced clinically
1981	80% 1 year survival reported using cyclosporine prednisone
1983	Introduction of pump driven venovenous bypass without anticoagulation
1983-1984	US consensus development conference conclusion that liver transplantation is a service is followed by rapid proliferation of transplant centers worldwide
1987	University of Wisconsin solution improves liver and other organ preservation
1989	Clinical introduction of FK506 based immunosuppression
1990	First successful use of live liver donors (left side fragments)
1994	Live donor transplantation of right side liver fragments

The longer waiting time and higher mortality rates for patients on the deceased-donor liver transplant waiting list led to the development of innovative surgical techniques such as split-liver transplants and living donor liver transplants (LDLT). Initially these new techniques were mainly applied to pediatric patients because of the difficulty associated with finding appropriate size-matched organs for them. However, as the number of adults on the waiting list grew, these techniques began to be applied for adult recipients as well ***(Fan et al., 2014)***.

Waiting list mortality for adults continued to increase strongly, and the use of left lobes for adult recipients began in Japan in 1993; the first successful transplant using the right lobe from a living donor was reported in 1994 ***(Morioka Et al., 2007).***

In 1998, the first report of right lobe LDLT in the United States appeared and was followed by others ***(steel et al., 2013).***

Although right lobe LDLT has been controversial from the outset because of concern about the magnitude and risk of the donor operation, the popularity of the procedure increased to the point where in 2001, 408 adult LDLT procedures, 9% of all adult liver transplants performed in the United States, were with living donors ***(United Network For Organ Sharing, 2004)***.

Although many deaths of living liver donors had been acknowledged previously, the widely publicized death of a right lobe donor in New York in early 2002 sent a shock wave through the transplant community worldwide. In 2002, the number of adult LDLT procedures decreased by 29% to 288 in United States ***(Kim and Testa, 2016)***.

Types of Liver Transplantation

- Deceased Donor Liver Transplant.
- Living Donor Liver Transplant.

Living Donor Liver Transplantation (LDLT) Versus Deceased Donor Liver Transplantation (DDLT):

Several retrospective reviews have demonstrated that LDLT for HCC has a similar survival to that of deceased donor transplantation. The results from LDLT appear to show good long term survival rates with retrospective studies showing comparable rates to OLT ***(Thuluvath and Yoo, 2004)***.

There are some published retrospective studies which show a higher rate of tumor recurrence than with conventional OLT ***(Fisher et al., 2007)***.

The reason for this is unknown, but perhaps it is due to the 20% to 50% dropout rate seen in patients on the wait list for deceased donor transplantation, which may serve to screen out

biologically more aggressive tumors that would have had a propensity to metastasize or recur. LDLT is called "fast-track" transplantation because of the short waiting time. So, due to a short waiting time which does not permit adequate time to access the biological behavior of the tumor, more patients with aggressive tumors may be included in the LDLT group ***(Fisher et al., 2007)***.

Some authors suggested that hepatectomy in LDLT is not radical. LDLT needs to preserve the native vena cava as well as the greater length of the hepatic artery and bile duct. All of these may result in tumor remnants which become the root of recurrence. Another potential explanation is that more manipulation during LDLT may lead to dissemination of HCC via the hepatic vein. All of these surgical procedures and the short waiting time for LDLT may promote the recurrence of HCC ***(Fisher et al., 2007)***.

About 50% of HCC patients who are initially candidates for liver transplantation will become ineligible, if the median waiting period exceeds 1 year ***(Yao et al., 2002)***.

The crucial element limiting the general applicability of LDLT is the risk of harming a healthy living donor. In the literature, the overall mortality attributed to living donor procedures is lower than 1%, but the risk of morbidity is significant, being around 38% as a whole, and <10% when severe complications are considered alone ***(Ghobrial et al., 2008)***.

So the transplant community takes an extremely protective approach to the living donor, however, and consequently assigns greater ethical weight to the donor's risk of death than to the recipient's risk of death ***(Ghobrial et al., 2008).***

Advantages of LDLT (over DDLT):

There are more than 2000 cases per year of acute liver failure (ALF) in the United States. As the rapid evolution of ALF and the shortage of deceased donor livers, many patients with ALF die waiting for a DDLT. LDLT has the potential to reduce waiting time and provide more optimal timing of surgery compared with DDLT ***(Quintini et al., 2012).***

LDLT Guarantees that a transplant will be performed ***(Chan et al., 2008)***.

LDLT avoids the often lengthy waiting period of DDLT as the average waiting time for DDLT was about 169 days if compared to that for LDLT which was about 68 days ***(Chan et al., 2008)***.

One potential advantage of LDLT is that allows the transplant team to choose the proper timing, a factor that can allow an attempt at pretransplant viral eradication. Liver transplant in a recipient negative for serum HCV RNA on therapy has a low chance of post-transplant recurrence (~10%)

and could represent a cure for HCV infection ***(Quintini et al.,2012).***

Furthermore, LDLT has the ability to occur at lower MELD scores, when the chance of tolerating antiviral therapy is higher ***(Quintini et al., 2012).***

The damage to liver during prolonged CIT has been hypothesized as being the cause of PNF. This in turn has been hypothesized to result from injury to the hepatic sinusoidal epithelial cells, which in turn results in a cascade of injuries involving the microcirculation and the release of various cytotoxic products ***(Stahl et al., 2008).***

Minimal cold-ischemia time appears to be a good predictor of not only PNF but also of patient and graft survival ***(Stahl et al., 2008).***

Grat et al. reported that the negative effects of prolonged CIT seem to be limited to patients with moderate MELD receiving organs procured from older donors and to high-MELD recipients, irrespective of donor age. Varying effects of donor age and CIT according to recipient MELD score should be considered during the allocation process in order to avoid high-risk matches ***(Grat et al., 2016).***

Russo et al. reported that Total LDLT costs (evaluations of rejected donors + evaluations of accepted donors + donor hepatectomy + donor follow-up care for 1 year + pretransplant recipient care [90 days pretransplant] + recipient transplantation + recipient 1-year posttransplant care) = 162.7 Cost Unit. Total mean cadaveric transplant costs (pretransplant recipient care [90 days pretransplant] + recipient transplantation [including organ acquisition cost] + recipient 1-year posttransplant care)=134.5 CU ***(Northup et al., 2009).***

By contrast, a later cohort study found that the costs were similar to deceased donor transplantation when LDLT was performed in highly experienced transplant centers ***(Northup et al., 2009).***

Chapter 2

DONOR COMPLICATIONS OF LDLT

Systematic Grading of Surgical Complications

In 2002, ***Beavers et al.*** conducted an extensive review of the literature and identified 12 reports covering more than 400 right-lobe donors. Morbidity rates in these reports ranged from 0% to 67%. The variation among different centers highlighted the need for a large registry to collect accurate and consistent data so that potential donors can base their decision on accurate information. It was soon recognized, however, that although the definition of surgical mortality is straightforward, the definition of morbidity is not. How morbidity is defined influences how centers report their complications and calculate the incidence of morbidities ***(Sugawara et al., 2007).***

In this issue of the journal, ***Yi et al.*** address this important issue and present the outcome of live liver donors from their LDLT series and classified the surgical morbidity. They report that 65 (78%) of 83 donors experienced postoperative complications. Of these 65, 64 experienced grade I, 11 experienced grade II, and 1 experienced grade III complications. None had grade IV or V complications. Grades I through V were defined as follows: I, minor complications; II, potentially life threatening complications requiring pharmacologic treatment; III, complications requiring invasive intervention; IV, complications causing organ dysfunction

requiring management in the intensive care unit; and V, complications resulting in the death of the patient ***(sugawara et al., 2007).***

They originally devised this system with reference to the classification system of ***Broering et al.*** which classify complications into 4 grades which was defined as follows : I, any complication that isn't life threatening, doesn't lead to disability, doesn't need any intervention or drugs except (analgesics, antipyretics, antiemetics and anti-inflammatory); grade II, any complication that is potentially life threatening requiring therapeutic management or > 1 foreign unit of blood, doesn't need invasive intervention and doesn't lead to disability; grade III, any complication that is potentially life threatening requiring therapeutic management or > 1 foreign unit of blood, needs invasive intervention, leads to ICU readmission and doesn't lead to disability; grade IV, any complication that is potentially life threatening leads to disability or leading to death ***(Sugawara et al., 2007).***

The classification system of surgical complications introduced by ***Clavien et al.*** in ***(1992)*** was originally intended for procedures with relatively low morbidity, it differentiates complications into 4 severity grades. Grade 1 included minor risk events not requiring therapy (with exceptions of analgesic, antipyretic, antiemetic, and antidiarrheal drugs or drugs required for lower urinary tract infection). Grade 2 complications were defined as potentially life-threatening