INTRODUCTION

Liver transplantation is the only effective and available therapy for patients with end-stage liver disease. Many advances in the field, such as refined surgical techniques, improved intensive care, more targeted immunosuppressive agents, improved organ procurement techniques and better preservation solutions, have led to excellent short-term and long-term clinical outcomes, yielding patient survival rates of approximately 85% and 75% 1 year and 5 years after transplantation, respectively ***(Verdonk et al., 2007)***.

Growing experience with the liver splitting technique and favorable results equivalent to those of whole liver transplant have led to wider application of split liver transplantation (SLT) for adult and pediatric recipients in the last decade ***(Lauterio et al., 2015)***.

In Egypt, the introduction of the living donor liver transplantation (LDLT) as in elsewhere, has raised important psychological conflicts and ethical questions ***(Abdeldayem et al., 2014)*** but the law considers the sale of organs as an illegal act. A proof of a relationship between potential donor and patient must be provided before the procedure ***(Abdeldayem, 2012).***

Risks to the donor are the most important concerns in LDLT. Autonomy indicates that individuals should decide what

sort and amount of risk they are willing to face ***(Shapiro & Adams, 2007)***. For potential donors, LDLT represents the only means to save the lives of their loved ones. However, the very short time and the lack of alternative treatment, the impact of moral guides, the social circumstances, and the possibility of complications constitute high pressure and considerable amount of coercion on the donor's will. This assumption would add to the ethical considerations regarding the motives of the donor ***(Abdullah et al., 2007).***

Live donor liver transplantation, specifically, performance of a major hepatectomy on a healthy individual who has no medical indication other than offering an allograft liver for the recipient, has long been viewed with caution. Therefore, substantial efforts are expended to ensure the safety and long-term well-being of the donor. The best outcomes for both donors and recipients have been maximized via technical refinements, innovative pre- and postoperative management strategies, and careful follow-up ***(Jeon and Lee, 2010).***

Following living donor liver transplantation, the donor's liver regenerates to full size within a few weeks without long-term impairment of liver function. Most donors are hospitalized briefly (about 1 week after the donation) and recover completely. However, the estimated risk of mortality is 0.5 to 1%. Overall donor morbidity is high, estimated to be roughly 35%. This is usually related to the surgical incision and the possibility of blood clots. Others reported problems include

bleeding, infection, bile leaks, and damage to the bile tree, or risks from anesthesia. Donors also have reported chronic problems, including bile strictures, reoperations and chronic pain ***(Patel et al., 2007)***.

The most common postoperative complications among donors for living donor liver transplant involve the biliary tract were the incidence of biliary complications in donors is approximately 5%. Most of the biliary complications can be treated by nonsurgical methods or interventional procedure ***(Yuan and Gotoh, 2010)***.

AIM OF THE WORK

- Primary aim: to evaluate the postoperative outcomes among donors after live donor liver transplantation.
- Secondary aims: to identify possible risk factors for the complications & to determine long term sequelae of these donors (within one year) if possible & data were available.

Chapter 1
REVIEW OF LIVER TRANSPLANTATION

The liver is a wedge-shaped organ with four lobes of unequal size and shape. A human liver normally weighs 1.44–1.66 kg representing 2.5% of the total body weight ***(Si-Tayeb et al., 2010)***. It is both the heaviest internal organ and the largest gland in the human body. Located in the right upper quadrant of the abdominal cavity, it rests just below the diaphragm, to the right of the stomach and overlies the gallbladder ***(Gerard and Bryan, 2008).***

Surgical anatomy of the liver:

Understanding the anatomy of the liver has been subjected to many changes through centuries. In 1897, Sir James Cantlie noted a line ran from the fundus of the gall bladder to the I.V.C which represented the true anatomical division between the right and left lobes. This line was called Cantlie line ***(Cantlie, 1897; Chen & Chen, 1999).***

Couinaud fundamental system was adopted by the surgical community which was based on the rule of individual segments of the liver must have independent vascular inflow, outflow &biliary drainage. This classification allowed segmental surgery without injuring adjacent structures as shown in figure (I) ***(Couinaud, 1999).***

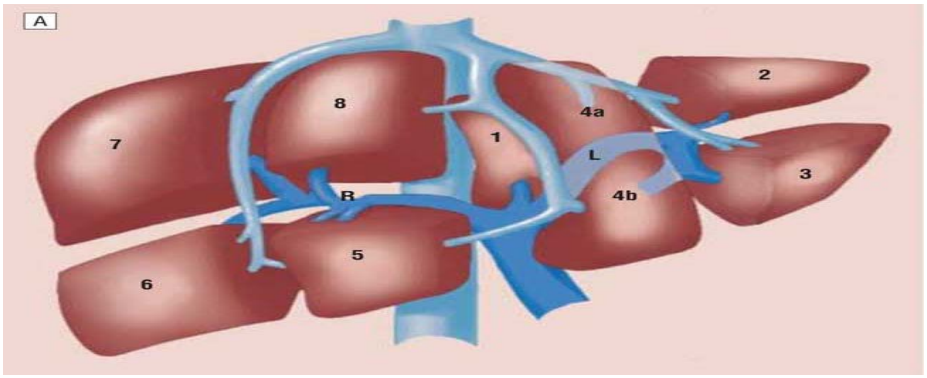

Fig. (I): Couinaud liver segments. (A) Segments divided by hepatic vasculature. R indicates right portal Vein; L, left portal vein; unlabeled branches demonstrate hepatic vein anatomy ***(Pauli et al., 2012).***

Lastly, Brisbane committee ***(Strasberg, 2005 & Bismuth, 2013)*** added some valuable changes to Couinaud system, whereas in this taxonomy the liver is divided into right and left hemi-livers at Cantlie's line than subdivided by right and middle hepatic veins into right posterior and left posterior& the left lobe is divided into left lateral and left medial segments as showed in figure (II). This segmentation was preferred by surgeons during hepatectomy ***(Juza & Pauli, 2014)***

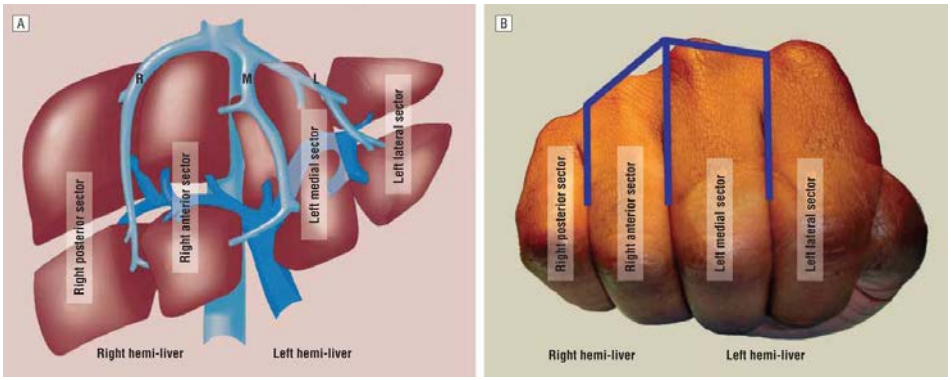

Fig. (II): (A) Hepatic veins, (R): Right, (M) Middle, and (L): Left, creating four hepatic divisions. Right and left hemi-livers separated by Cantlie's line. (B) Veins overlaid on our hand model of the liver ***(Pauli et al., 2012).***

Liver disease is the twelfth commonest cause of mortality in adults in the United States, resulting in 34, 000 deaths annually from cirrhosis ***(Hoyert & Xu, 2012)***. In addition, the rising incidence of hepatocellular carcinoma (HCC) in the United States is reflected in an increasing number of deaths from HCC. Access to liver transplantation (LT), however, has profoundly altered the management of advanced liver disease. Management of decompensated cirrhosis and acute liver failure before the advent of LT was limited to attempts to ameliorate complications. In contrast, successful LT extends life expectancy and enhances quality of life ***(Duffy et al., 2010)***.

Starzl and his colleagues at the University of Colorado Health Sciences Center in Denver performed the first human whole-liver transplantation for the treatment of end stage liver disease in 1963. With the introduction of new immunosuppressive therapy and the constantly improving organ preservation and surgical techniques, liver transplantation is considered an accepted and successful treatment of end stage liver disease ***(Starzl et al., 1963)***.

The Organ Procurement and Transplantation Network recorded a total of 6318 liver transplantations in the United States in 2008. In June 2008, 16597 patients were waiting for liver transplants ***(OPTN, 2009)***.

The MELD (Model of End stage Liver Disease) score is used to assess prognosis in cirrhosis in a variety of settings, including organ allocation for LT, and can be calculated for individual patients. It is a mathematical model that incorporates serum creatinine and bilirubin levels with the international normalized ratio (INR) of prothrombin time. The MELD score is on a continuous scale from 6 to 40 that corresponded to a 3-month survival of 90% to 7%, respectively ***(Fede et al., 2012)***.

MELD incorporates 3 widely available laboratory variables including the international normalized ratio (INR), serum creatinine, and serum bilirubin. The original mathematical formula for MELD is: MELD = 9.57 × $\log_e$ (creatinine) + 3.78 × Log_e (total bilirubin) + 11.2 × Log_e (INR) + 6.43 ***(Wiesner et al., 2003).***

Evaluation for LT should be considered once a patient with cirrhosis has experienced an index complication such as ascites, hepatic encephalopathy, or variceal hemorrhage or hepatocellular dysfunction results in a MELD Score ≥15 ***(Martin et al., 2014)***.

Serum sodium (MELD-Na), serum sodium and age (integrated MELD) scores have been proposed to improve the predictive value of MELD. Delta MELD (DMELD), meaning the change of MELD over time, might also be a better predictor of mortality ***(EASL, 2015).***

As the MELD has several limitations, patients with liver diseases requiring LT, whose severity is not described by the MELD, should be recognized. A different priority needs to be given to these patients by experts.

HCC is a particular MELD exception that requires extra points to get access to the transplant. These points have to be standardized in each country and have to take into account size, number of nodules, AFP levels, recurrence after down staging therapy ***(EASL, 2015).***

Indications for Liver Transplant (LT) is indicated for severe acute or advanced chronic liver disease when the limits of medical therapy have been reached (see Table I).

Table (I): Common Indications for Liver Transplantation ***(Martin et al., 2014):***

1-Acute Liver Failure
2-Complications of cirrhosis: • Ascites • Chronic gastrointestinal blood loss due to portal hypertensive gastropathy • Encephalopathy • Liver cancer (HCC) • Refractory variceal hemorrhage • Synthetic dysfunction
3- **Liver-based metabolic conditions with systemic manifestations:** • a1-Antitrypsin deficiency • Familial amyloidosis • Glycogen storage disease • Hemochromatosis • Primary oxaluria • Wilson disease

4-Systemic complications of chronic liver disease:

- Hepato-pulmonary syndrome
- Porto-pulmonary hypertension

Table (II): Contraindications for Liver Transplantation ***(Martin et al., 2014):***

- MELD Score < 15
- Severe cardiac or pulmonary disease
- AIDS (Acquired Immune Deficiency Syndrome)
- Ongoing alcohol or illicit substance abuse
- Hepatocellular carcinoma with metastatic spread
- Uncontrolled sepsis
- Anatomic abnormality that precludes liver transplantation
- Intrahepatic Cholangio-carcinoma
- Extra-hepatic malignancy
- Fulminant hepatic failure with sustained ICP >50 mm Hg or CPP <40 mm Hg*
- Hemangio-sarcoma
- Persistent noncompliance
- Lack of adequate social support system

ICP, intracranial pressure; CPP, cerebral perfusion pressure.

Although potentially lifesaving and despite of good outcomes for recipients, living donor liver transplantation (LDLT) is a very complicated surgical procedure, and donor safety remains an issue of concern ***(Lee et al., 2017)***

Clearly, living-related liver transplantation (LRLT) represents the natural evolution of other surgical procedures, namely reduced-size liver transplantation and split-liver

transplantation ***(Heffron et al., 1998)***, and is based on the segmental anatomy of the liver and on its peculiar capacity to regenerate. This procedure represents a major challenge for the centers involved, though it has been widely reported that it is a valuable option for decreasing mortality rates and drop out from waiting lists ***(Gruttadauria et al., 2007)***.

Different types of liver transplantation:

1. *Conventional or "Standard" liver transplantation – Whole liver grafts:*

The liver graft is implanted in the right upper quadrant, in the place formerly occupied by the diseased liver. The surgical technique differs according to whether or not the recipient's inferior vena cava (IVC) is preserved ***(Gonzalez et al., 1998).***

2. *Domino liver transplantation:*

The most common indication for this type of procedure is FAP (familial amyloid poly-neuropathy) or Corino de Andrade's Disease. FAP). FAP is a progressive degenerative disorder of autosomal dominant inheritance. It is caused by the mutation of the transthyretin (TTR), one of the prealbumins, which is most commonly due to a single amino acid substitution of valine to methionine at position 30 (Val30Met). Plasma TTR is predominantly synthesized by the liver and mutated forms of TTR are the precursor protein of amyloid

fiber and amorphous aggregates in patients' tissues. It is characterized by extracellular amyloid tissue accumulation ***(EASLD, 2015).***

Since the disease involves extra-hepatic organs and the liver function is otherwise absolutely normal, the FAP patient liver is given to another patient while he receives a deceased organ ***(Yamamoto et al., 2007).***

3. Partial graft transplantation:

Partial liver grafts are used at times. It may be necessary to provide partial support for metabolic needs due to a specific or complete metabolic deficiency ***(Moon et al., 2010).***

4. Auxiliary liver transplantation.

Auxiliary transplantation essentially provides an alternative in two situations. **The first** is in the cases of patients with acute liver failure in whom a partial graft is used to provide support to the patient's diseased liver while it recovers. Once the native liver returns to normal function, the graft is removed and immunosuppression is withdrawn. **The second case** is for patients with functional congenital or metabolic disorders affecting a normal liver. Implanting a partial graft while preserving the native liver allows correction of the metabolic disorder while avoiding a full liver transplant ***(Lodge et al., 2008).***

5. Split liver:

This alternative procedure is used to provide two recipient liver grafts from one liver donor, the size of the grafts depends on the recipients (weather a child and an adult recipient or two adult recipients). **In the first case** left lateral segment for the child and a right lobe graft for the adult recipient ***(Lee et al., 2013).***

6. Living donor LT.

The impossibility of transplanting a child with a donor organ of the appropriate size led to the development of a number of alternatives, one of which is the use of segments II and III of an adult donor for transplantation into a child. The use of LDLT gradually expanded, culminating with the procedure of adult patients receiving right lobe grafts from living donors ***(Yamaoka et al., 1994)***.

Pre-operative evaluation process:

A- The preoperative evaluation for the recipient:

The formal evaluation process includes a series of tests and consultations, to confirm the irreversible nature of the patient's liver disease and lack of effective medical therapy. In addition, the evaluation addresses any potential psychosocial issues as well as medical comorbidities (***Martin et al., 2014)***.

Table (III): Transplantation evaluation for the recipient ***(O'Leary et al., 2008):***

Financial screening	Secure approval for evaluation
Hepatology evaluation	Assess disease severity and prognosis, confirm diagnosis and optimize management
Surgical evaluation	Confirm need for transplant, identify technical challenges (e.g. prior abdominal surgery, portal vein thrombosis etc.), discuss donor options (deceased, living, extended)
Laboratory testing	Assess hepatic synthetic function, serum electrolytes, renal function, viral serology, markers of other causes of liver disease, tumor markers, ABO Rh blood typing, creatinine clearance, urine analysis and urine drug screen.
Cardiac evaluation	Initial non-invasive evaluation with echocardiography. Noninvasive stress testing and cardiology evaluation if cardiac risk factors are present (hyperlipidemia, hypertension, diabetes, cigarette consumption, age >60 years)
Hepatic imaging	Ultrasonography with Doppler to document portal vein patency, triple-phase computed tomography or gadolinium magnetic resonance imaging for tumor diagnosis and staging
General health assessment	Chest film, Pap smear and mammogram (women), colonoscopy if patient is age 50 years or older or has primary sclerosing cholangitis
Dental assessment	Identify dental caries, buried roots and dental abscesses. Coordinate dental extractions if necessary
Anesthesia evaluation	Required if unusually high operative risk, i.e., patient has port pulmonary hypertension, hypertrophic obstructive cardiomyopathy, previous anesthesia complications
Psychiatry, psychology or mental health professional consultation	Determine if history of substance abuse, psychiatric illness, or adjustment difficulties (e.g. behavioral or adherence problems)
Social work evaluation	Address potential psychosocial issues, adequacy of support, and possible effect of transplantation on patient's personal and social system
Financial and insurance Counseling	Itemize costs of transplantation and post transplantation care, review insurance coverage, help develop financial management plans
Nutritional evaluation	Assess nutritional status and patient education
Infectious disease	Identify infectious processes that require intervention prior to transplant (e.g. latent TB or post-transplant e.g. CMV naive recipient)

B- Preoperative evaluation for living liver donor:

First of all the evaluation of possible complication risks that may face donors during LDLT that's why ***Feng et al. (2006)***developed, a **Donor Risk Index (DRI)** with the aim to quantify the effect of specific donor characteristics on the risk of post-transplant graft failure. The value of such information is heightened by the life-saving and life-threatening potential of every decision to either accept or reject a particular opportunity for transplantation ***(EASL, 2015).***

Donor Evaluation is a complicated process to ensure donor safety and to decrease the donor's mortality and morbidity after hepatectomy. Detailed pre transplant evaluation is shown in **(figure III*) (Esmat et al., 2005)***.