

Liver Transplantation: Experience at King Hussein Medical Center, Jordan

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ABSTRACT

Objective: To review the experience and outcome of liver transplantation recipients at King Hussein Medical Center.

Methods: We retrospectively analyzed the results of 67 liver transplantations; 65 living-related donor liver transplantations for 64 recipients and two cadaveric donor liver transplantation at King Hussein Medical Center between June 2004 and December 2011. The grafts were: 60 right liver lobes, four left liver lobes, one hepatic segments II and III and two whole livers (cadaveric). All living donors were closely related to the recipients except for the cadavers. Data were obtained by a specially designed medical record abstract form. Of the 67 liver transplantations, the first 42, were performed under the supervision of the Turkish liver transplantation team. Six recipients had concomitant hepatocellular carcinoma and liver cirrhosis. Retransplantation was performed for one recipient. Simple descriptive statistical methods (frequency, mean and percentage) were used to describe the study variables.

Results: Total mortality rate was 11 (17%). The causes of death were sepsis in four patients, hepatic arterial thromboses in three patients, small-for-size in one patient, and porto-pulmonary hypertension in one patient. Morbidity rate was 49 (73.1 %). The main causes of morbidity were biliary leaks in 13 patients, biliary stricture in nine patients, recurrence of primary disease in nine patients acute rejection in five patients, wound infection in four patients, and bile duct stones in one patient. The follow-up period ranged between one month to 90 months (average 45.5 months). One and three year survival rates were 80% and 70.2% respectively. However, most complications have been treated with interventional techniques. All living donors are alive in a good health and returned to their normal life.

Conclusions: In view of critical shortage of cadaveric donor liver transplantation, living-donor liver transplantation is an opportune option for patients with decompensated liver disease in Jordan. Our patients' outcome is improving with time and this could be attributed to gaining more experience and by-passing the learning curve by the liver transplantation team in our center.

Key words: Complications, Liver transplantation, Outcome

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Introduction

Liver transplantation is the therapeutic option of choice for acute and chronic end-stage liver disease. Transplantation is a relatively new

medical specialty, dating back to only 1954 when Dr Joseph Murray did the first living donor kidney transplantation, then followed by cadaveric donation after eight years.⁽¹⁾ Thomas

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Table I. Patients characteristics of the study group

Recipient characteristics	Number	%
Age		
Adult	58 (17-63year (average 40))	86.6
Pediatric	9 (3-14 year (average 9))	13.4
Sex		
Male	49	73
Female	18	27
Relationship to donors		
Father	6	8.9
Mother	5	7.4
Son	22	32.8
Brother	9	13.4
Sister	9	13.4
Wife	4	5.9
Daughter	1	1.4
Cousin	1	1.4
Nephew	5	7.4
Uncle	1	1.4
Aunt	1	1.4
Emotional	1	1.4
Un-related (cadaver)	2	2.9

Table II. Indications for liver transplantation among the study group

Indication for liver transplantation	Number	%
Cryptogenic hepatitis	14	20.8
AIH	8	11.9
Viral Hepatitis	15	22.3
HBV	8	11.9
HCV	7	10.4
Cholestatic liver disease	6	8.9
Malignancy:	8	11.9
HCC+HBV	5	7.4
HCC+HCV	1	1.4
HCC	1	1.4
Hepatoblastoma	1	1.4
Others	8	11.9

AIH: Autoimmune Hepatitis HBV: Hepatitis B Virus
HCV: Hepatitis C Virus HCC: Hepatocellular Carcinoma

Starzl performed the first three cadaveric human liver transplantations in 1963, all died before reaching 1-year survival, and it was not until 1967 when he did the first successful transplantation.⁽²⁻⁴⁾ The first attempt of Living Donor Liver Transplantation (LDLT) was in children and was performed by Raia *et al.* in 1988, while the first successful LDLT in an adult recipient was done for the first time by the Japanese in 1994 and then Western countries has followed this path.^(5,6) While the shortage of donor organs is a global problem, the situation appears more critical in Asia where cadaveric organ donation remains below five per million populations (pmp).⁽⁷⁾

Although LDLT has several advantages over cadaveric liver donor transplantation (CDLT), the main limitation for successful adult-to adult LDLT is Graft-Recipient weight-Ratio (G-RW-R) mismatch, in which the graft cannot meet the metabolic demands of the recipients.^(8,9) It is obvious that adults need larger graft to meet their metabolic demand. So, left or right hepatectomies were required, which put the donor at the risk of high morbidity from a significantly major operation.^(6,10,11)

The aim of this study is to review our experience and outcome of liver transplantation recipients, at King Hussein Medical Center.

Methods

Between June 2004 and December 2011, a total of 67 liver transplantations were performed for 66 recipients. Sixty five of them were LDLTs including one re-transplantation while the other two were CDLT. Male to female ratio was 49\18 (73%-27%). Fifty eight percent of the patients were adults with the average age of 40 years (range 17-63 years), while the remaining recipients were children (less than 15 years of age) with the average age of nine (range 3-14 years). Recipient characteristics are showed in Table I.

Most of the indications for liver transplantation were chronic liver cirrhosis due to cryptogenic hepatitis (14), viral hepatitis (15), cholestatic liver disease (6), autoimmune hepatitis (AIH) (8), and other factors (Table II).

The pre-transplant condition of the recipients was evaluated by the modified model for end-stage liver disease (MELD) score⁽¹²⁾ which has

Table III. Contraindication for liver transplantation

Contraindication for transplantation
Hepatic malignancy with macrovascular or diffuse tumor invasion
Active and uncontrolled infection outside of the hepatobiliary system
Severe cardiopulmonary or other comorbid conditions
Technical and/or anatomical barriers
Age above 65years
Cholangiocarcinoma
Portal vein thrombosis
Chronic or refractory infection
Active psychiatric illness
Poor social support

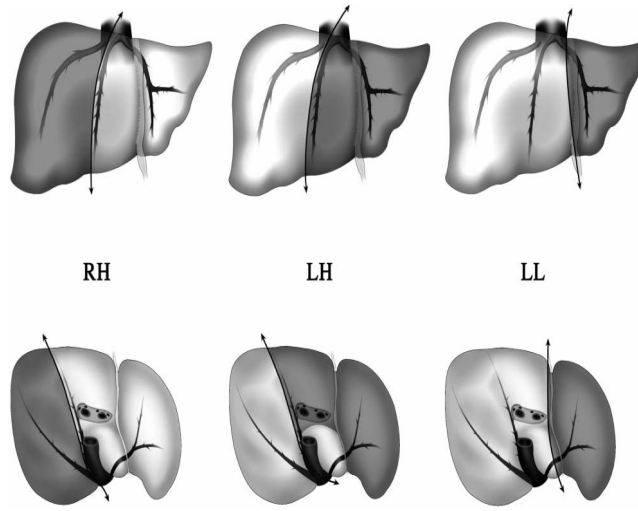


Fig. 1:

RH: Right Hepatectomy
 LH: Left Hepatectomy
 LL: Left Lateral Hepatectomy

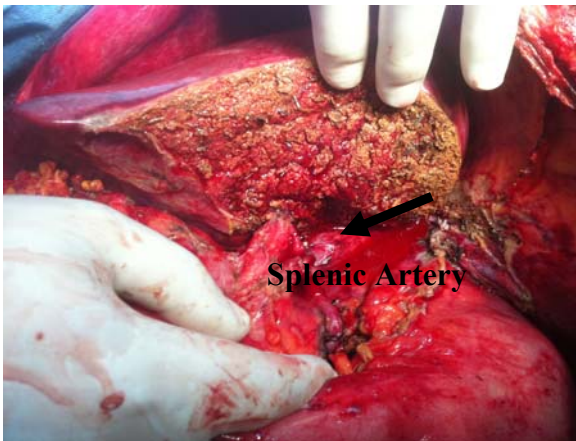


Fig. 2: Splenic artery (arrow) used in the arterial anastomosis



Fig. 3: Right duct: posterior duct (arrow) drainage to Left duct

been documented to be reliable in predicting the prognosis of the patients. The contraindications for transplantation are listed in Table III.

We accepted only donors with graft-to-recipient weight ratios $\geq 0.8\%$ and fatty liver $\leq 20\%$. The remnant of donor's liver (residual liver

volume) always exceeded 35% of the total liver volume as calculated by computed tomography volumetry. The age of the donors ranged from 19 to 55 years (average 37 years). Simple descriptive statistical methods (frequency, mean and percentage) were used to describe the study variables

Donor hepatectomy:

Donor hepatectomy is a standard procedure in all centers.

Three hepatectomies were defined according to the segmental anatomy of Couinaud. Left Lateral Hepatectomy (LL) for resection of segments II and III, left hepatectomy (LH) for segments resection of II, III and IV, and right hepatectomy (RH) for segments V, VI, VII and VIII resection⁽¹³⁾ (see Fig.1).

Recipient operation:

Total hepatectomy performed with the original hepatic veins (with extension to IVC to make triangular shape opening) or vena cava were used for the hepatic vein anastomosis. Biliary, portal and hepatic anastomosis were performed with loop magnification, and the arterial anastomosis performed by a micro-vascular surgeon with microscope. The hepatic veins anastomosed to IVC with continuous suture by Prolene 4\0, also the portal veins (right and left) were anastomosed to the main portal vein by Prolene 5\0. Inferior hepatic veins (larger than 7mm) were anastomosed end to side to the inferior vena cava. After completion of the portal vein anastomosis, removal of the air and stagnant preservative solution from the graft done by washing out with the portal blood. The hepatic artery was anastomosed to the recipient right hepatic artery in the RH LDLTs except for two recipients; we used the splenic artery because of extensive intimal dissection in the hepatic artery which extended to the celiac trunk (Fig. 2), and to the left hepatic artery in the LT, LL LDLTs. In the CDLTs the common hepatic artery of the graft anastomosed to common hepatic artery of the recipient.

Biliary reconstruction was done with a duct-to-duct anastomosis in 60 transplants and with Roux-en-Y hepaticojejunostomy in seven

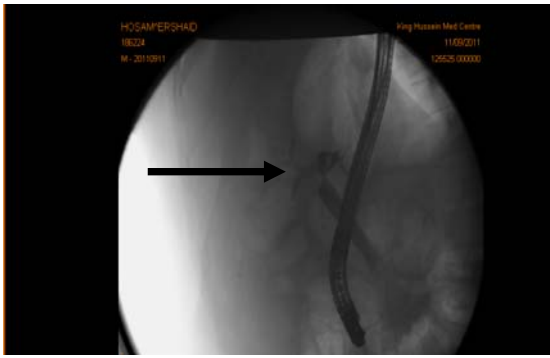
transplants. Twenty eight (41%) of the 67 liver grafts had two bile ducts (Fig. 3). In five of these 28 grafts with two bile ducts, two separate anastomoses were performed. In the remaining 23 grafts, ductoplasty performed by approximating the neighboring bile duct and, sutured together to create a single bile duct opening. One of the 67 liver grafts had three bile ducts. In this situation, two neighboring ducts were sutured together and anastomosed end-to-side to the jejunum, and the third duct anastomosed separately end-to-side to the jejunum (Roux-en-Y hepaticojejunostomy). In this recipient, we placed internal catheters. In three recipients, a straight feeding tube was inserted from the common bile duct to the anastomotic site to enable external bile drainage.

Cell-saver was used during the recipient operation for 13 patients. Standard antibiotic therapy with gram-negative and gram-positive coverage was administered for five postoperative days. Lamivudine, 100 mg daily, was given orally for patients with hepatitis B viral infection before transplantation and continued long life afterward. Hepatitis B immunoglobulin was used in all patient with hepatitis B at the anhepatic phase at a starting dose of 2000iu and then 500iu per day for one week ,then discontinued when HBVAb titer (>100).

Immunosuppression induction therapy was provided with Methyl prednisolone 100mg intraoperatively and on postoperative day one then tapering daily till the day nine to be 20mg prednisolone orally. The postoperative immunosuppression was based on tacrolimus and mycophenolate mofetil and steroids. All recipients also received oral fluconazole 200mg daily after the operation for three months.

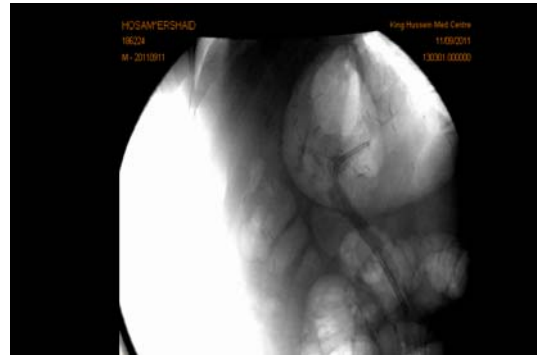
Results

Of the liver transplant recipients in our study, two underwent CDLT and sixty five underwent LDLT (60 underwent right lobe transplantation; four left lobe; and one transplantation of the left lateral segment). In one recipient, retransplantation was performed (8 days after the first transplantation) because of hepatic artery thrombosis. The mean ratio of graft volume to the body mass of the recipients was 1% (range,



Anastomotic stricture

Fig. 4



Stent bypass the stricture



Stones in the CBD

Fig. 5



Stones cleared with insertion a stent

0.8 –1.4) in the adult group and 3% (range, 2.6-3.4) in the pediatric group. The average cold ischemia time of the liver graft was 75 minutes (range, 60-90 minutes). The average operative time was 12 hours (range, 8–16 hours). All except two recipients received blood transfusion (9 U; range 0-18 U). The average postoperative intensive care unit stay was 17.5 days (range, 10-25 days), and the average postoperative hospital stay was 37 days (range, 13-61 days).

Hepatic arterial thrombosis (HAT) has complicated three of our recipients (5.9%) in the early post operative days. This complication was diagnosed during routine liver enzymes test then proved by Doppler ultrasonographic examinations and CT angiogram. One of those three required retransplantation to treat his HAT, but died 24 hours after the operation. Thrombectomy was performed in one recipient, by interventional radiologist, but failed and the patient died. The third one died before any intervention because he developed multi-organ failure.

Two recipients developed bleeding one day after transplantation, which necessitated reopening. One was found to bleed from a branch of the hepatic artery and was successfully

treated by ligation of the bleeding vessel, and the other one from the site of jejunio-jejunostomy and was treated by revision of the anastomosis. Thirteen (19.4%) and nine (13.4%), of the 67 recipients in our study experienced a bile leak and bile duct stenosis respectively, and one of the stenosis group had CBD stones. The bile leak occurred at the anastomotic site in eleven recipients, and from the graft cut surface in two recipients. Anastomotic bile leaks were treated by percutaneous drainage followed by endoscopic placement of a 7-10Fr plastic stent except two, where ductal anastomosis were completely disrupted and converted to roux-en-Y hepatico- jejunostomy. The non-anastomotic bile leaks were treated with percutaneous drainage. Bile duct stenoses occurred at the anastomotic site in seven recipients and at the nonanastomotic site in the remaining two recipients. All bile duct stenoses were treated with internal stent in our hepatology unit by ERCP with excellent results (Fig. 4), except for one that necessitated PTC by interventional radiologist and ERCP with extraction of stones from the CBD and insertion a stent (Fig. 5).

One hepatic vein stenosis, developed during the late postoperative period which were treated by

Table IV: Complications of the recipients and the management

Complication	Number (49)	% (73.1%)	Management
Wound infection	4	5.9	Antibiotics +debridement
Biliary leak	13	19.4	Interventional radiology or H-J
Biliary stenoses	9	13.4	Interventional radiology
Acute rejection	5	7.4	Steroid recycling or pulses
Recurrence of primary Disease	9	13.4	Medical treatment
Incisional hernia	2	2.9	Observation or surgery
Small for size	1	1.4	Somatostatin
CBD stone	1	1.4	Interventional radiology
Lymphoma	1	1.4	Chemotherapy
Drop hand	1	1.4	Physiotherapy
Hepatic vein stenoses	1	1.4	Interventional radiology
Hepatitis B	1	1.4	Antiviral therapy
Bleeding	1	1.4	Re-operation

H-J: hepaticojejunostomy

percutaneous transluminal angioplasty.

Five recipients (7.4%) experienced an episode of acute rejection during the follow-up period. These cases were treated with corticosteroid recycling or pulses therapy.

Two recipients had incisional hernia for which repair was performed; and one of these patients, had hernia repair surgery outside Jordan, which was complicated by bowel perforation and led to his death. One patient with primary sclerosing cholangitis (PSC) had HBV infection post transplant, and he is on treatment. One patient developed lymphoma after one year and he is on chemotherapy.

One recipient developed functional small for size condition (SFS) due to persistent portal hypertension post operatively, and was managed well by somatostatin infusion (250mic g\hour) for five days.

During our study twenty three (34.4%) patients died from the subsequent causes: 11 sepsis with multiorgan failure, three porto-pulmonary hypertension (respiratory distress), three HAT, two recurrence HCC, one after repair of incisional hernia due to bowel perforation, one arrested during removal of central line, one from persistent hyperbilirubinemia. At this time, the remaining 44 recipients (65.6%) are alive with good graft function. Complications experienced in forty two recipients (62.6%) are shown in Table IV.

Discussion

Liver transplantation has become a life saving procedure for fulminant and chronic end-stage liver disease and for selected patients with

hepatic malignancies⁽¹⁴⁻¹⁶⁾ LDLT has been accepted as an alternative choice specially in Eastern societies, who otherwise would have; due to the presence of strong cultural, traditional and religious beliefs, limited or delayed access to a cadaveric organs. As a matter of fact, it is a remarkably effective and real hope of new life for thousands of recipients worldwide.⁽¹⁷⁾ In Jordan we face the same problem according to the availability of cadaveric donations (2 cases within 7 years), so LDLT is considered the cornerstone of the liver transplantation and is now becoming the only life saving with widely accepted treatment modality for chronic liver failure and some selected hepatocellular carcinoma cases.

Livers from living donors offer many potential advantages over livers from cadaveric donors. The most important advantages of living donation are that it optimizing the timing of transplantation and freeing patients from the waiting list, minimizing the preservation time (lower ischemic time), and the operation is done on a hemodynamically stable donors. So, the quality of the living donated liver is much better.⁽¹⁸⁻²⁰⁾

The survival rates after CDLT are expected to be more than 85% and 75% at 1-year and 5-years post-transplantation, respectively, on the other hand, LDLT had much lower survival rate at the time of start of the procedure.⁽⁴⁾ But later, Chuan Li *et al.* reported that LDLT and CDLT have equivalent long-term survival rates, similar severe postoperative complications, similar HBV recurrence rates and required similar numbers of RBC transfusion units.⁽²¹⁾ On the other hand, the

incidence of biliary complication in the patients undergoing LDLT was higher than those who received CDLT. The total biliary complication rate was observed to be significantly different during long-term follow up (25% after a median follow-up of 27 months), which was significantly higher than that after CDLT.⁽¹⁶⁾

Living donor has significant risks, including the risk of donor death (0.2%-2.0%) and substantial morbidity (30%), that must be taken into account before patients, physicians, and transplant programs go on board in LDLT.⁽²²⁻²⁴⁾ However, with improvement in surgical technique, selection of the donor, and postoperative care, it was possible to reduce perioperative morbidity significantly.⁽⁶⁾ So, no effort should be spared in avoiding complications by appropriate patient selection, controlling blood loss, meticulous surgical technique, and post-operative care.⁽²⁵⁾ The initial reports of high recipient successes and low donor morbidity rate led to rapid expansion of adult-to-adult LDLT.⁽¹⁰⁾

All our donors are alive and returned to their normal life soon after surgery.

Due to shortage of deceased donor organ in Jordan, LDLT has acquired a great reputation. From June 2004 to December 2011, 67 cases of LTs were performed in our center.

At the beginning of our program (first 30 cases), the mortality rate among the recipients was eight patient (11.9%) compared to only three recipients death in the following 37 cases (4.4%). This could be attributed to the learning curve and our experience in selecting the patients. Sepsis (bacterial, viral, or fungal), which is the most frequent cause of post transplant mortality, afflicts about 50% of recipients who undergo LDLT. In the last 37 cases, three patients (4.4%) died.

The biliary complication rate in the early part of our program was high where leakage and stenosis occurred in 47% in the first 30 patients. After identification of the possible causes of leakage, the leakage rate was markedly reduced, but late stenosis still occurred. The overall biliary complication rate in the subsequent 37 patients was 27%. There is a decrease in the complication rate over the years as our experience builds up. However, it must be noted that biliary stenosis may occur several years

later. Longer follow-up is required to ascertain a valid comparison. Nonetheless, an improvement of the early result has indeed been observed but it still higher than other centers (14.8%).⁽²⁰⁾

While chronic complications related to immunosuppression and to the transplant itself are quite common and accumulate in the long term, the quality of life of liver transplant recipients is good and remains comparable with that of the general population.^(26, 27) Our results of 1-year and 3-year survival (82% and 70% respectively) are relatively comparable to other centers which is 84% and 79% respectively.⁽²⁰⁾ Most of our recipients returned to their normal life and work. With build-up of experience in surgery and clinical management, timely feedback and proper modification, the outcomes will be better in the future.⁽⁵⁾

Conclusions

With critical shortage of cadaveric donor in our country, LDLT continues to be a life-saving opportunity that may change life expectancy for the majority of patients. Although chronic complications are quite common and accumulate in the long term, the quality of life of liver transplant recipients, even over decades, nonetheless remains comparable with that of the general population.

Our results are comparable with the international figures, although it is still lagging behind some other centers, with accumulation of our experience we started to overcome the learning curve, and to have better outcomes.

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