



Predictors of Survival after Adult to Adult Living Donor Liver Transplantation (A-ALDLT)

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Abstract

Objectives: Adult-to-adult living donor liver transplantation (A-A LDLT) is an effective therapeutic modality to treat patients with end-stage liver disease. The aim of this study was to define the pre-, intra- and post- operative factors that may influence patient outcome.

Methods: The data from 161 (A-A LDLT) patients who had operations between 2003 and 2013 were collected and analyzed retrospectively after exclusion of mortality due to intra-operative bleeding. Data were analyzed using uni- and multi-variate analysis according to factors that are known to be associated with outcome in these patients.

Results: Overall, the accurate survival rate of recipients at, 6 months, 1, 3, 5 and 7 years was 67.7%, 63.4 %, 59.0%, 58.4% and 57.1% respectively. On univariate analysis, the following factors were significant predictors of survival, male recipients, Actual GRWR > 0.8, right lobe graft, blood transfusion < 10 units and absence of vascular complications. On multivariate analysis, male recipients, blood transfusion > 10 units and absence of vascular complications were independent predictors.

Conclusions: The reduction of intraoperative RBC, prevention and treatment of vascular complications, selection (GRWR > 0.8, right lobe graft and male recipients) are required to achieve better survivals among patients undergoing A-A LDLT.

Keywords: Living Donor Liver Transplantation, Outcome post LDLT. Vascular complications.

Abbreviations

DDLTL	Deceased donor liver transplantation
IRB	Institutional review board
BMI	Body Mass Index
CUSA	Cavitron ultrasonic surgical aspirator
CNIs	CalciNeurin Inhibitors
CsA	CycloSporine

FK or FK-506	Tacrolimus
GRWR	Graft Recipient Weight Ratio
HBV	Hepatitis B virus
HTK	Hydroxy Tryptophan Ketoglutarate
HCC	HepatoCellular Carcinoma
HCV	Hepatitis C Virus
SFSS	Small for size syndrome
HPB	HepatoPancreatoBiliary
A-ALDLT	Adult to adult living donor liver transplantation
LT	Liver Transplantation
MELD	Model for End stage Liver Disease
MMF	Mycophenolate MoFetil
NLI	National Liver Institute
SRL	SiRoLomus

Introduction

Liver transplantation (LT) is a widely accepted treatment method for patients with end-stage liver diseases [1]. Studies have shown that advances in surgical technology, anesthesia management, and the detection and treatment of complications made over the last decade or so have significantly improved the 1-, 5- and 10-year survival rates by 85%, 70%, and 60%, respectively [2]. In response to the organ donor shortage, A-A LDLT has emerged as an effective alternative to deceased donor liver transplantation (DDLTL). Compared to DDLTL, LDLT offers a reduced waiting time and more optimal timing of surgery, but it is also associated with a high surgical risk and complications for the recipient because of differences in graft quality, size and preservation time [3]. In Egypt, the availability of deceased donors remains extremely limited, because traditional religious and emotional issues continue to present obstacles in regard to performing DDLTL. For this reason, LDLT is the primary type of liver transplantation in Egypt. Different studies have reported some risk factors that affect recipient survival and graft loss after DDLTL [4,5]. On the other hand, in LDLT, graft and recipient survival are

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decided by the combination of donor, intraoperative and recipient factors and the risk factors of survival after LDLT were mentioned in different studies. [6-10]. The aim of this study was to define the pre-, intra- and post- operative factors that may influence patient outcome after A-ALDLT.

Materials and Methods

After approval of institutional review board (IRB) and obtaining written informed consents from both donors and recipients, we retrospectively analyzed the pre-, intra- and post- operative factors that may influence patient outcome in the department of hepatopancreatobiliary (HPB) surgery, national liver institute (NLI), university of Menoufiya, Menoufiya, Egypt, in the period from April 2003 to November 2013 or patient death with median follow up period of 25.6 ± 25.6 m (range, 0-120). The study included 161 (A-A LDLT) patients who had operations between April 2003 and February 2013 after exclusion of mortality due to intra-operative bleeding. All donors were < 19 years old and the donor work-up included liver function tests, liver biopsy, ultrasound examination, psychological assessment and CT angiography, along with hepatic volumetric study and vascular reconstructions. The following data were studied:

A- Preoperative variables

Donor's age, gender, body mass index (BMI), donor to recipient relation, Femal to male donor to recipient matching, blood group matching, liver biopsy of donors, recipients' age, gender, the primary disease, Child Pugh and MELD scores, co morbidity (DM, HTN) and portal hypertension.

B- Intraoperative variables

Type of graft (Right or Left), duration of the operation per hours, actual graft weight, actual graft recipient weight ratio (GRWR > or < 0.8), cold and warm ischemia times per minute, blood transfusion < or > 10 units.

The donor operation was performed through a right subcostal incision extended to the upper midline under general anesthesia. Intraoperative cholangiography was used to define the biliary anatomy of donors, the right or left lobes of the liver were mobilized and the vena cava was dissected. The CUSA device was used to divide the liver parenchyma without inflow occlusion. The falciform ligament was reconstructed, the stumps of the divided hepatic and portal veins were closed by continuous non-absorbable sutures, after graft harvesting, it was perfused in the back table with Hydroxy tryptophan ketoglutarate (HTK) solution and weighted to determine the actual GRWR [8] (Figure 1).

In the recipient surgery, the native liver was explanted while carefully preserving the inferior vena cava. After reconstructing

the hepatic and portal veins, the hepatic artery was anastomosed by the use of a surgical loupe or microscopy. The biliary tract was reconstructed by a duct-to-duct hepatico- choledochostomy or a Roux-en-Y hepatico-jejunostomy [7] (Figure 1).

C- Postoperative variables

a- Hospital stay (per days)

b- Based on our institutional policy: Immunosuppression and postoperative anti-hepatitis B virus (HBV) protocols: the standard is combination of 3 drugs calcineurin inhibitors (CNIs), steroids and mycophenolate mofetil (MMF). The initial methylprednisolone dose is 500 mg intraoperatively with a brief taper of prednisone from 240 to 40 mg/d over 6 days followed by 5–20 mg/d maintenance treatment, with complete withdrawal at the end of 3rd month post LDLT. Cyclosporine (CsA) was used when neurotoxicity or nephrotoxicity developed with Tacrolimus. When CNIs are contraindicated or their side effects halt their use, sirolimus (SRL) was given at an initial dose of 3 mg/m² and adjusted over time to achieve blood trough levels of approximately 5–8 ng/mL. Biopsy-proven acute rejection episodes were treated with steroid pulses (IV methylprednisolone 200 to 500 mg/d for 3 days), which were tapered over several days to the baseline dose. The postoperative anti-HBV protocols consisted of lamivudine combined with therapy with a low-dose intramuscular hepatitis B immune globulin. Hepatitis B immune globulin was administered to all recipients with HBV infection during and after the transplantation [8].

c- Complications (Biliary, vascular and small for size syndrome).

Statistical Analysis

All data were tabulated and processed with SPSS software (Statistical Product and Service Solutions, version 21, SSPS Inc, Chicago, IL, USA) and Windows XP (Microsoft Corporation, Redmond, Washington, USA). Qualitative data were expressed in frequency and percentage and analyzed with the chi-square test. Quantitative data were expressed as the mean and standard deviation and were compared with the t test. The previous (preoperative, intraoperative and postoperative) variables were descriptively studied. Univariate analysis and then multivariate analysis for significant predictors in univariate analysis were done to detect the relationship between the previous data and overall survival of patients in the follow up period after A-ALDLT. The Kaplan–Meier method was applied for survival analysis and compared using log-rank tests. In all tests, a P value of <0.05 was considered significant.

Results

Characters of patients and their donors

They were classified as 141 (87.6%) males, and 20(12.4%) females. Their mean age was 46.27 ± 8.3 . Their donors were classified as 109 (67.7%) males and 52(32.3%) females, their mean age was 27.07 ± 6.6 and donor to recipient female to male match was 97(60.2%). The liver biopsy was abnormal (steatosis, minimal or mild PPF) in 32 (19.9%) of donor. The patients were classified according to Child-Pugh score into 9 (5.6%) class A, 47 (29.2%) class B, and 105 (65.2%) class C, and MELD score < 18 was found in 56 (34.8%). 61(37.9%) of them had co morbidity, in the form of Hypertension, DM, cardiac diseases and morbid obesity, Portal HTN affected 154 (95.7%) of them. The donor to recipient Bl. Group matching was classified into identical in 117 (72.7%) and Compatible in 44 (27.3%) of them. The right lobe graft was given to 153 (95%) and the left lobe was given to 8 (5%) of them. The mean actual graft weight was 820.16 ± 172.9 and actual GRWR > 0.8 was found in 145 (90.1%) of patients. The mean cold and warm ischemia times were 73.8 ± 51.4 and 51.8 ± 16.09 respectively. More than 10 units of intra-operative blood transfusion were given to 34 (21.1%). The incidence of post operative biliary, vascular and small for size syndrome (SFSS) complications were 72 (44.7%), 34 (21.1%) and 19 (11.8%) respectively (Table 1).

Indications of LT

The most frequent indications were HCV followed by HCC (Table 2).

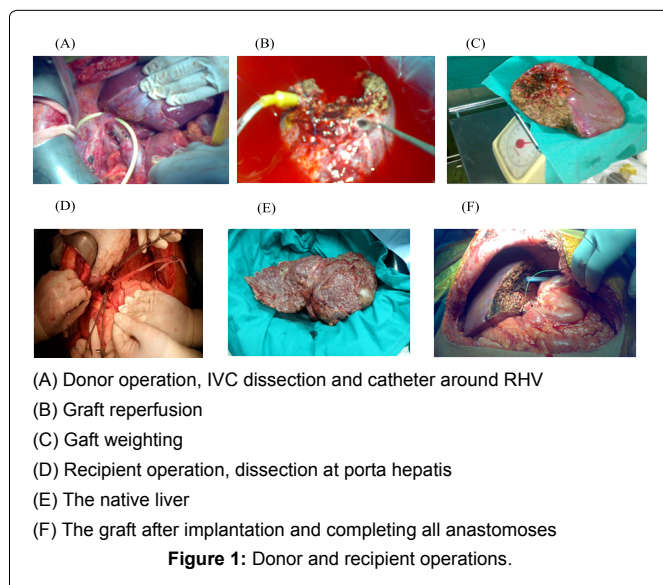


Table 1: Characters of patients and their donors.

Donor age(years) (Mean±SD)	27.07±6.6
Recipient age(years) (Mean±SD)	46.27±8.3
Donor gender	
males	109 (67.7%)
females	52(32.3%)
Recipient gender	
males	141(87.6%)
females	20(12.4%)
Donor to recipient Female to male match	97(60.2%)
Child class	
A	9(5.6%)
B	47(29.2%)
C	105(65.2%)
MELD score < 18	56(34.8%)
Co morbidity	61(37.9%)
Portal HTN	154(95.7%)
Bl. Group	
Compatible	44(27.3%)
Identical	117(72.7%)
Liver biopsy	
Normal	129(80.1%)
Abnormal	32(19.9%)
Graft type	
Right lobe	153(95%)
Left lobe	8(5%)
Actual graft weight (Mean±SD)	820.16±172.9
Actual GRWR > 0.8	145(90.1%)
Cold ischemia time (min) (Mean±SD)	73.8±51.4
Warm ischemia time (min) (Mean±SD)	51.8± 16.09
Intraoperative blood transfusion>10 units	34(21.1%)
Duration of operation (hours) (Mean±SD)	13.1± 3.3
Hospital stay (postoperative)(days) (Mean±SD)	23.3± 15.9
Immunosuppression regimen	
Regimen including FK	139(86.3%)
Regimen including Cyclosporine	48(29.8%)
Regimen including sirolomus	10(6.2%)
Biliary complications	72(44.7%)
Vascular complications	34(21.1%)
Small for size syndrome	19(11.8%)

MELD: Model for End stage Liver Disease, **GRWR:** Graft Recipient Weight Ratio.

Table 2: Indications of LT.

HCV	87(54%)
HCC	55(34.2%)
Cryptogenic cirrhosis	7(4.3%)
HBV	4(2.5%)
BCS	2(1.2%)
PSC	2(1.2%)
PBC	1(0.6%)
Wilson’s disease	1(0.6%)
Autoimmune hepatitis	1(0.6%)
Alcoholic cirrhosis	1(0.6%)

BCS: Budd chiary syndrome, PSC: Primary sclerosing cholangitis, PBC: Primary biliary cirrhosis.

Table 3: Outcome of patients.

Total number	161 (100%)
Mortality	69 (42.9%)
Over all	
6 months survival	109(67.7%)
1-year survival	102 (63.4%)
3-year survival	95 (59%)
5-year survival	94 (58.4%)
7-year survival	92(57.1%)
Survival per months((Mean±SD)(Range)	25.6± 25.6(0-120)

Outcome of patients

The overall mortality was 69 (42.9%). While overall 6-months, 1-, 3- and 5- year survival of our patients were 109(67.7%), 102 (63.4%), 95 (59%), 94 (58.4%) and 92(57.1%) respectively, (Table 3).

Recipients and donors risk factors as predictors of outcome

A- On univariate analysis, the following variables were found to be

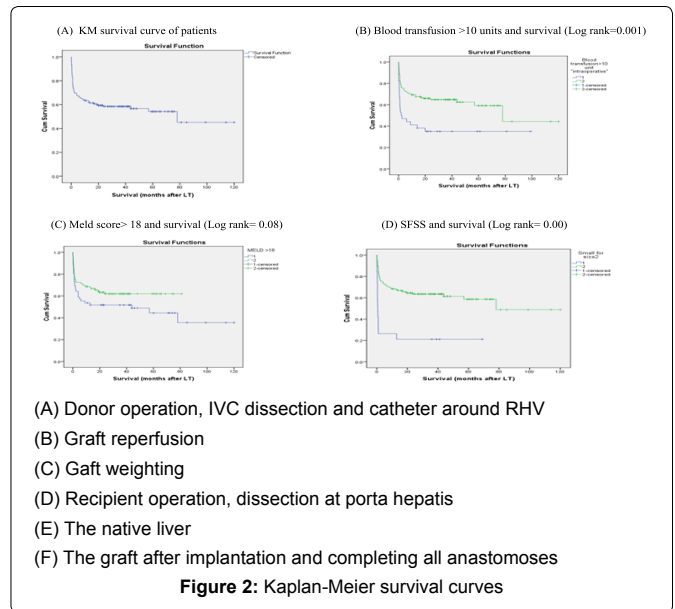


Table 4: Recipients and donors risk factors as predictors of outcome.

Category	Survival No (%)	p-value
Number of patients	92/ 161 (57.1%)	
Donor gender		
- Male	62/109(56.9%)	> 0.05
- Female	30/52(57.7%)	
Recipient gender		.002
- Male	87/141(61.7%)	
- Female	5/20(25%)	
Donor to recipient Female to male match		> 0.05
Yes	57/97(58.8%)	
No	35/64(54.7%)	
Child class		> 0.05
A	7/9(77.8%)	
B	25/47(53.2%)	
C	60/105(57.1%)	
MELD score < 18		.033
Yes	26/56(46.4%)	
No	66/105(62.9%)	
Co morbidity		> 0.05
- Yes	34/61(55.7%)	
- No	58/100(58%)	
Portal HTN		> 0.05
Yes	90/154(58.4%)	
No	2/7(28.6%)	
Bl. Group		> 0.05
Compatible	25/44(56.8%)	
Identical	67/117(57.3%)	
Liver biopsy		> 0.05
Normal	75/129(58.1%)	
Abnormal	17/32(53.1%)	

statistically significant predictors of outcome: Male recipients, Actual GRWR > 0.8, MELD score > 18, right lobe graft, blood transfusion >10 units and absence of vascular and SFSS complications. On the other hand, there was trends towards survival with the following variables: Less mean recipient age (45.7±8.2 years), more mean actual graft wt (838±166.8 gm), Less mean cold ischemia time (69.7±47.3minutes) and shorter mean operative time (12.7±3.1h) (Table 4, Table 5, Table 6, Figure 2).

B- On multivariate analysis, male recipients, blood transfusion >10 units and absence of vascular complications were independent predictors (Table 7).

Discussion

From the first report of A-A LDLT in 1993 by Yamaoka et al, 1993 [11], the cases of A-A LDLT have grown rapidly to address the shortage of livers. Living donor liver transplantation especially A-A LDLT has advantages over deceased donor grafts. Nevertheless, the complicated techniques in the recipient procedure and the potential risks for the donor require careful preoperative evaluation [9].

Table 5: Recipients and donors risk factors as predictors of outcome.

Category	Survival No (%)	p-value
Number of patients	92/ 161 (57.1%)	
Graft type		.011
Right lobe	91/153(59.5%)	
Left lobe	1/8(12.5%)	
Actual GRWR > 0.8		.027
Yes	87/145(60%)	
No	5/16(31.3%)	
Intraoperative blood transfusion>10 units		.004
Yes	12/34(35.3%)	
No	80/127(63%)	
Immunosuppression and steroid regimen		> 0.05
FK, MMF, steroids	83/139(59.7%)	> 0.05
Cyclosporine, MMF, steroids	32/48(66.7%)	.002
Sirrolimus, MMF, steroids	9/10(90%)	
Biliary complications		> 0.05
Yes	39/72(54.2%)	
No	53/89(59.6%)	
Vascular complications		.011
Yes	13/34(38.2%)	
No	79/127(62.2%)	
Small for size syndrome		.001
Yes	4/19(21.1%)	
No	88/142(62%)	

FK: Tacrolimus, MMF: Mycophenolate mofetil.

Table 6: Recipients and donors risk factors as predictors of outcome.

Category	Survived (Mean± Std. deviation)	Died (Mean± Std. deviation)	p-value
Recipient age	45.7±8.2	46.9±8.4	0.2
Donor Age	27.1±6.9	26.9±6.2	> 0.05
BMI of Donor	25.3±3.4	25.08±3.5	> 0.05
Actual graft wt	838±166.8	796.3±179.3	0.1
Cold ischemia time/ minutes	69.7±47.3	79.3±56.4	0.1
Warm ischemia time/ minutes	51.8±17.1	51.9±14.7	> 0.05
Operative time/ h	12.7±3.1	13.7±3.5	.2
Postoperative hospital stay (days)	24.7±16.7	21.6±14.6	> 0.05

Table 7: Multinomial logistic regression test.

Model	P value	95.0% Confidence Interval	
		Lower Bound	Upper Bound
Recipient gender	0.012	0.490	14.188
Actual GRWR < 0.8	0.357	0.008-	7.238
Graft type	0.328	0.298	37.223
Blood transfusion <10 unit intraoperative	0.025	0.163	0.885
Vascular complications	.018	0.158	0.842

Researchers have identified several risk factors for graft loss after LDLT, such as donor age [12], MELD score [4,5,13-15], intraoperative blood loss [13,16] and small-for-size syndrome [17-20].

The inverse correlation between recipient age and LT outcome has been reported repeatedly [21-23]. Similarly, it showed statistical significance with survival in The univariate analysis in the (Jin et al, 2012) [24] study and trends towards poor survival in the recent study.

In our study, there was no significant difference between younger and older donors regarding survival. Similarly Kuramitsu et al, 2007 [25] reported no significant difference between selected right lobe donors from aged 60 years or older and younger donors regarding survival. In contrast Yoshizumi et al. 2008 [26], Morioka et al. 2007 [27] and Toshima et al. 2014) [28] have reported donor age to have a negative impact on the outcomes of recipients in LDLT. Similarly Yoshida et al, 2008 [29] found that aged grafts (<50 years) were observed to have significantly poor outcomes.

Ninety five percent of our patients were given RT lobe graft with significant effect on good survival in univariate analysis; inversely the Tokyo University Group demonstrated that the survival outcomes of AALDLT recipients of non-right-liver grafts were significantly superior to those of recipients of right lobe or extended right lobe

grafts [30]. On the other hand in Morioka et al, 2007[27] and Yoshida et al, 2008 [29] studies graft type was not associated with graft failure.

The MELD score, which has been used for allocating liver grafts in DDLT in the United States [31] has been reported to predict death before implementation of LT in patients with end stage liver disease [32]. On the other hand, The studies by Du et al. 2013 [10], Yoshizumi et al. [26], Morioka, et al. [27], Toshima et al. 2014 [28] and Saab et al. 2003 [33] demonstrated that high MELD score could predict post-transplant survival outcomes. Similarly the present study revealed that MELD score < 18 was significant predictor of poor outcome in univariate analysis and in [Yoshida et al. 2008 [29] study, recipients with a high MELD score (<21) were found to have significantly poor outcomes compared with recipients with a low MELD score (>21). In contrast Hayashi et al. 2003 [34] and Kenneth et al. 2013 [35] reported that the MELD score did not predict the recipient survival in LDLT.

Most studies have shown that a GRWR (considered to be a direct reflection of small for- size syndrome) less than 0.8% increases the opportunity for early graft failure [6,9,36]. Similarly, in our study, GRWR> 0.8 was significant predictor of poor outcome in univariate analysis. The clinical significance of this result urges us to emphasize graft-to-recipient matching. On the other hand, Ben-Haim et al. 2001[37] showed that mortality rates among Child's class B or C patients whose GRWR less than 0.85%, three-fold greater than among those with GRWR greater than 0.85% in Child's class A.

Our data showed that intra-operative transfusion of more than 10 exogenous packed RBC units was independent predictor of poor outcome. Similarly, Chuan et al. 2011 [8], Xu et al. 2011 [9], [Du et al. 2013 [10] and Chung et al. 2013 [38] Found that intra-operative blood loss was significant predictor of poor outcome. However Lee et al. 2004 [6] demonstrated that intraoperative transfusion of more than six exogenous packed RBC units was an independent factor influencing graft survival. They explained this by increase of perioperative cytokine responses (i.e. IL6); that affect graft survival with the increased amount of intra-operative transfusion.

Vascular problems after liver transplantation are among the most serious complications that frequently result in graft failure and patient death [39]. In the studies by Sevemis et al. 2011 [40], Steinbrück et al. 2011 [41] and Orlandina et al. 2014 [42] vascular complications had significant effect on survival. Similarly, in our study, there was significant correlation between vascular complications and survival.

Conclusions

The reduction of intraoperative RBC, prevention and treatment of vascular complications, selection (GRWR > 0.8, MELD Score >18, right lobe graft and male recipients) are required to achieve better survival among patients undergoing A-A LDLT.

Declaration

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