Original Article

Evolution of Living Donor Liver Transplantation Over 10 Years: Experience of a Single Center

SUSUMU EGUCHI, MITSUHISA TAKATSUKI, MASAAKI HIDAKA, YOSHITSUGU TAJIMA, and TAKASHI KANEMATSU

Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Reprint requests to: S Eguchi

E-mail: sueguchi@nagasaki-u.ac.jp

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Running head: Evolution of Living Donor Liver Transplantation

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Abstract

Purpose. To evaluate the changes in living donor liver transplantations (LDLTs) over the last 10 years, we analyzed our experience of performing LDLT in a single center.

Methods and Results. We performed 73 LDLTs over the 10 years between 1997 and 2007 in Nagasaki University Hospital, Japan. Initially, from 1997 to 2003, LDLT was performed for pediatric patients; then, between 2004 and 2007, adult-to-adult LDLT was introduced, primarily for hepatocellular carcinoma (HCC) in liver cirrhosis. We also began performing LDLTs for adults with ABO-incompatible blood type combination in the latter period. As the number of adult-to-adult LDLTs increased, left-sided grafts became first choice for these patients. Survival rates were 88.3%, 77.2%, 70.2% at 1, 3 and 5 years respectively. There was a relatively low incidence of arterial complications, and although the incidence of biliary complications was high initially, it decreased with experience. Likewise, the operative time, blood loss, and hospital stay after LDLT also improved remarkably.

Conclusion. Over the last 10 years, the indications for, and operative techniques used in LDLT have changed dramatically, even in a single center in Japan.

Introduction

Since the first living donor liver transplantation (LDLT) was reported in 1989, this operation has gained widespread recognition as a life-saving treatment, especially in Japan, where deceased donor liver transplantation (DDLT) is not yet accepted. [1, 2] We started our liver transplant program in August, 1997 and by August 2007, we had performed 73 LDLTs. Although the liver transplant registry in Japan reports the details of LDLTs annually in the Japanese literature, a detailed analysis to define the changes in LDLT over the past 10 years would be difficult based on a nation-wide cohort. Thus, we conducted a retrospective study on LDLT in a single center to evaluate the changes and evolution in this 10-year period.

Patients and Methods

Subjects

The subjects of this retrospective review were 73 patients who underwent LDLT between August, 1997 and August, 2007 at Nagasaki University Hospital, Japan. The median follow-up of the patients after primary LDLT was 30 months (0-123 months). Adult patients are defined as those over 16 years old.

Methods

All partial liver grafts were preserved in University of Wisconsin solution and implanted using a piggy-back technique. Surgeons experienced in microscopic surgery anastomosed all of the hepatic arteries with the aid of an operative microscope. In general, graft selection was based on the results of a volumetric study using computed tomography (CT) to obtain a ratio of graft volume to standard liver volume of more than 35% in the recipients.[3]

A dual or triple immunosuppressive regimen was used, which included Tacrolimus or Cyclosporine A, prednisolone, and micophenolate mofetil. Patients with compromised renal function were given, induction therapy with IL-2 antibodies.[4] Only biopsy-proven rejections were treated if clinical and laboratory signs mandated steroid bolus treatment. Steroid-resistant rejections were treated with OKT3.

The following variables were studied: gender, age, original liver disease, indications for LDLT, Child-Pugh and Model for End-Stage Liver Disease (MELD) score at time of LDLT, ABO compatibility, operative blood loss, operative time, and graft type.

Because the Japanese National Health Insurance policy was changed in January, 2004, to cover most adult recipients, including those with hepatocellular carcinoma (HCC) within the Milan criteria, we analyzed the indications for LDLT before and after January, 2004. Furthermore, as a chief surgeon was appointed for all LDLTs in April, 2005, we compared the operative variables before and after April, 2005.

Overall patient survival was defined as the time in months between LDLT and the death of the patient or the end of the study period, on August 31, 2007. The median follow-up of patients was 29 months (0-120 months) for adults and 35 months (0-123 months) for children.

Statistics

Patient survival was calculated with the Kaplan-Meier method. The Log-rank test was used to compare survival between groups. Operative variables were compared with a non-parametric test. *P*-values less than 0.05 were considered significant.

Results

During the second part of the study period, from 2004 to 2007 (n=45), more adult-to-adult LDLTs were performed than in the first part, from 1997 to 2003 (n=28), because HCC in a cirrhotic liver caused by viral hepatitis became the main indication for LDLT (Table 1, Fig. 1). Accordingly, the donor population changed from “parent to child” to “child to parent”. We also began to perform ABO-incompatible combination LRLTs for adult patients (Table 1). Moreover, as the number of adult-to-adult LRLTs increased, left-sided grafts became the first choice in these cases to ensure the safety of donor surgery.

The changes in operative details and management in adult-to-adult LDLTs are summarized in Table 2. Since pediatric LDLT presents different operative and management challenges than adult LDLT, only cases of adult-to-adult LDLT were compared in this regard. Over the 10 years, blood loss, operative time, and hospital stay improved significantly with better management and advances in operative procedures ($p<0.05$).

The overall patient survival rates 1, 3 and 5 years after LDLT were 88.3%, 77.2%, 70.2%,, respectively. There was no difference in patient survival between the adult and

pediatric recipients (Fig. 3). Portal venous complications occurred in two (2.7 %) patients in the early phase after LDLT, mainly caused by mechanical and immunological events, whereas in late phase, six (8.2 %) patients suffered complications related to stenosis and thrombus in a portal vein, which were primarily treated with anticoagulation and balloon dilation (Table 3).

The results of arterial anastomosis are summarized in Table 4. Anatomical arterial anastomosis of a graft hepatic artery to a recipient hepatic artery was performed in 65 patients (86.6%), whereas a nonanatomical anastomosis of the side of a recipient artery other than a hepatic artery was performed in ten (13.4%) patients. Arterial complications occurred in six (8.2%) patients, including hepatic artery thrombus (HAT) in three (4.1%). Re-anastomosis was performed in five patients, but one these patients died of a second HAT. Hepatic arterial rupture occurred in one patient, as a result of a pseudoaneurysm developing after a fungal infection at the anastomotic site.

The methods of biliary reconstruction and their complications are shown in Table 5. Duct-to-duct anastomosis was performed in 53 (72.6%) patients, most of whom were adults. Biliary complications developed in 14 (19.1%) patients, including anastomotic stricture in 10 (13.7%) patients.

Discussion

Our results show that the indications for LDLT changed dramatically after January 2004 in accordance with the amendments to the National Health Insurance policy in Japan: from being reserved exclusively for pediatric patients and patients with acute disorders to include adult patients with chronic liver failure; most notably, those with HCC secondary to viral hepatitis. Accordingly, the relationship between the living donor and the recipient also changed over this 10-year period. With the extended indications of LDLT for HCC and other chronic liver diseases, the sons and daughters of about half these recipients have become partial liver donors to save their parents.

The 5-year survival rate after LDLT has improved to 70%.[1, 5] Moreover, in April, 2005, our hospital appointed a senior surgeon to head the liver transplant team. This surgeon is responsible for both recipient and donor surgery and a dedicated LDLT team has developed, which includes surgeons, hepatologists, and nurses, as well as case coordinators. As a team, we have succeeded in reducing the operative time, and blood loss, and consequently, the hospital stay after LDLT. Furthermore, the operative technique has been adapted based on updated information from the world literature; for example in relation to the reconstruction of tributaries of the middle hepatic vein,[6-8] or bile duct assessment in the donor [9-11] Interestingly, because of the broader indications

for LDLT, which include HCC rather than end-stage liver cirrhosis in the latter period, the MELD score of the recipients has become lower than in the former period, which might be a contributing factor to the lower blood loss during surgery.

Improved antiviral therapy has also contributed to the favorable outcome of LDLT; including lamivudine, pegylated interferon, and the recent advent of entecavir.[12,13] There were remarkably more patients with viral-related liver disease in latter period of this study than in the former period , at 33 vs. 5, (13 vs 2 with HBV and 25 vs. 3 with HCV), respectively; however, a comparison in survival between the periods was not performed and awaits a longer observation period.

An increase in the number of LDLTs performed successfully in ABO blood type-incompatible patients was achieved with the advent of the anti CD20 antibody (rituximab) to eradicate B cells, which produce the anti-donor blood type antibody, and the development of local infusion therapy in Japan.[14,15] On account of these therapies, the outcomes of LDLT using an ABO-incompatible partial graft have become close to those obtained with an ABO-compatible graft. Naturally, the number of ABO-incompatible LDLTs performed will increase because of the shortage of deceased donor LTs, based on the feasibility of preparing recipients for elective LDLT, by administering Rituximab.

The higher incidence of portal venous complications in LDLT may be attributable to the smaller graft size than in whole-liver LT.[16] Late complications developed in six (8.2%) of our patients, but most were treated with anticoagulants and radiological intervention. Three of the four patients with portal venous stenosis were operated on in the former period and had size mismatch in the portal vein between the recipient and donor livers. The other recipient had predisposing portal venous disease in the form of a portal venous aneurysm. Although portal venous complications in pediatric patients have been studied in detail and the incidence calculated at approximately 8% after LDLT[17], size-mismatched LDLT in adults needs to be analyzed.

Surgery with the aid of an operative microscope has minimized the risks of arterial complications, even though the diameter of each anastomosis is much smaller in LDLT than in DDLT.[18] Moreover, because the arteries are so short, non-anatomical anastomosis is more common in LDLT than in DDLT; however, the short arteries do not increase the incidence of HAT or other problems in arterial anastomosis. HAT requiring reanastomosis developed in three (4.1%) of our patients and this incidence is comparable with those in previous reports on LDLT. [19]

Biliary complications are said to be the “Achilles’ heel” of LDLT; supported by the fact that they occurred in 19% of our patients. However, with advances in operative

procedures, in both donors and recipients, and a better understanding of the anatomy, the incidence of biliary complications has been decreasing. Thus, our policy to perform duct-to-duct anastomosis if possible is justified, although the need for tube splints awaits further clinical trials.

In conclusion, the indications for LDLT and its operative techniques have changed dramatically over the last 10 years, even in a single center in Japan. Nevertheless, further refinement is needed for better postoperative morbidity and mortality.

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Figure Legends

Fig.1 Changes in the indications for living donor liver transplantation over 10 years

LC-B, liver cirrhosis due to hepatitis B; LC-C, liver cirrhosis due to hepatitis C; HCC, hepatocellular carcinoma; BA, biliary atrasia; FHF, fulminant hepatic failure; LC-Alcohol, liver cirrhosis due to alcohol; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SBC, secondary biliary cirrhosis, LC-NBNC, liver cirrhosis without hepatitis B or C

Fig. 2 Changes in the relationship between donors and recipients of living donor liver transplantation

Fig. 3 Patient survival after living donor liver transplantation

Table 1. Summary of living donor liver transplant recipients and procedures

	Total	Aug, 1997 – Dec, 2003	Jan, 2004 – Jul, 2007	p
Number	73	28	45	
Adult	64 (87.6%)	20 (71.5%)	44 (97.8%)	n.s.
Pediatric	9 (12.3%)	8 (28.5%)	1 (2.2%)	
Age	54(0-68)	37.5 (0-63)	56 (11-68)	<0.05
Gender (M/F)	42/31	13/15	22/17	n.s.
ABO blood type combination				
identical	51 (70.0%)	21 (75.0%)	30 (66.6%)	n.s.
compatible	13 (17.8%)	5 (17.9%)	8 (17.7%)	
incompatible	9 (12.3%)	2 (7.1%)	7 (15.5%)	
MELD score	18(7-41)	22.5(11-41)	17(7-36)	n.s.
Graft type				
right sided graft	47 (64.3%)	19 (67.9%)	28 (62.2%)	n.s.
left sided graft	26 (35.6%)	9 (32.1%)	17 (37.7%)	

MELD, Model for End-Stage Liver Disease; n.s., not significant

Table 2. Changes in the surgical techniques and management of adult-to-adult living donor liver transplantation

	Aug, 1997-March, 2005 (n=34)	Apr, 2005 – Jul, 2007 (n=30)	p
Age (years old)	52 (16-65)	57 (16-68)	n.s.
Gender (M/F)	22/12	18/12	n.s.
Child-Pugh score	11(7-14)	10.5 (7-12)	n.s.
Blood loss (g)	12,270 (1,230-121,348)	5,805 (1,100-47,530)	<0.05
Op time (minutes)	1099.5 (666-1,757)	899 (726-1,237)	<0.05
In hospital mortality	4 (11.7%)	2 (6.5%)	n.s.
Admission days	52 (21-388)	37 (18-126)	<0.05

Op time, operation time; n.s., not significant

Table 3. Portal venous complications after living donor liver transplantation

Early complications

Primary disease	GV/SLV	PV flow	Pathogenesis	Treatment	Outcomes
1. 60 F LC-C/HCC	47%	hypoperfusion	compressed (hematoma)	surgery	survived
2. 57 M LC-B/HCC	36.2%	interrupted	kinked (positional)	surgery	survived

Late complications

	Primary disease	PV complication	Treatment	Outcome
1.	16M FHF	stenosis	balloon dilation	survived
2.	61M LC-B	stenosis	anticoaglation	survived
3.	6F Biliary atrasia	stenosis＋thrombus	balloon dilation	died
4.	61F LC-C/HCC Portal vein aneurysm	stenosis＋thrombus	tPA +baloon dilation＋ anticoaglation	survived
5.	61F LC-C/HCC	thrombus（post splenectomy）	anticoaglation	survived
6.	64F LC-C Portal venous thrombus	thrombus	anticoaglation	survived

GV/SLV, graft volume/standard liver volume; PV flow, portal venous flow; FHF, fulminant hepatic failure; LC-B, liver cirrhosis due to hepatitis B; LC-C: LC-C:liver cirrhosis due to hepatitis C;
HCC, hepatocellular carcinoma; tPA, tissue-type plasminogen activator

Table 4. Arterial anastomosis and complications in living donor liver transplantation

Primary anastomosis					
	Anatomical anastomosis	**65 (89.1%)**			
	Non anatomical anastomosis	**8 (10.9%)**			
		direct			
			RGEA	**5**	
			LGA	**1 (HAT)**	
		Interposition			
			SpA-radialA	**1 (HAT)**	
			Saphenous vein	**1 (converted after rupture)**	
Complications	**6 (8%)**		**Re-anastomosis**		
	Rupture	**1**		**Anatomical**	**1 (after intimal dissection)**
	HAT	**3**		**Non anatomical**	**4**
	Intimal dissection	**1**		**RGEA**	**2 (after HAT)**
	Stenosis	**1**		**Saphenous vein**	**1 (after rupture)**
				Ao- SpA-radialA	**1 (after HAT, died)**

RGEA, right gastroepiploic artery; HAT, hepatic arterial thrombus; LGA, left hepatic artery, HA, hepatic artery; SpA, splenic artery; radialA, radial artery; Ao, Aorta

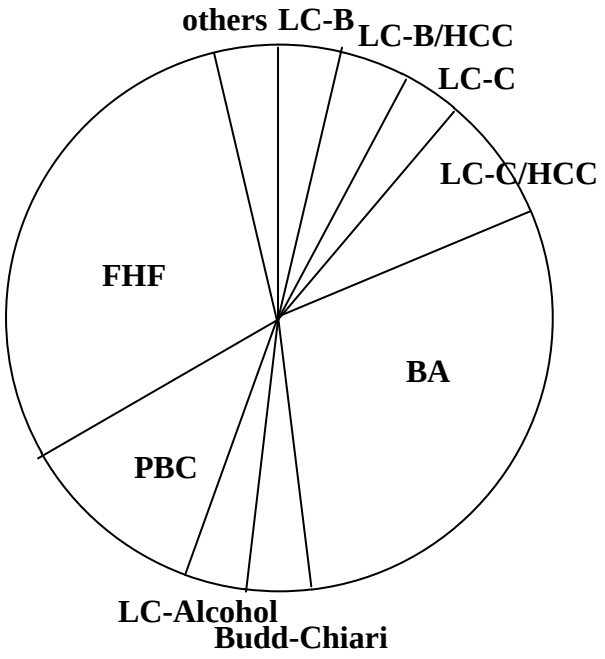
Table 5. Biliary reconstruction and complications after living donor liver transplantation

Reconstruction methods			
Duct-to-Duct	53 (72.6%)	Adult	52
		Pediatric	1
Hepaticojejunostomy	20 (27.4%)	Adult	12
		Pediatric	8
Biliary complications	14 (19.1%)		
Anastomotic stricture	10 (D-D 10, H-J 0)		
Bile leak from cut surface	1 (H-J 1)		
Bile leak at anstomosis	3 (D-D 1, H-J 2)		

D-D, duct to duct anastomosis; H-J, hepaticojejunostomy

Fig. 1. Changes in indications for living donor liver transplantation over 10 years

Aug, 1997 – Dec, 2003 (n=28)



Jan, 2004 – Jul, 2007 (n=45)

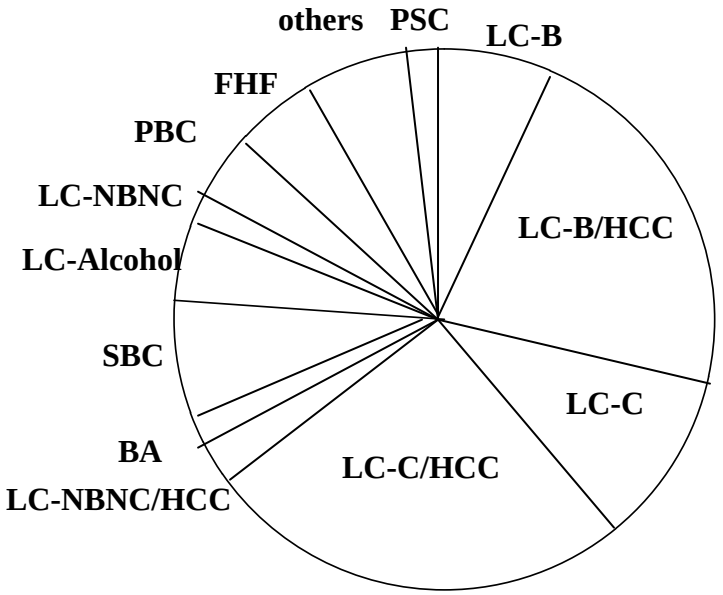


Fig. 2. Changes in relationship between donor and recipient in LDLT

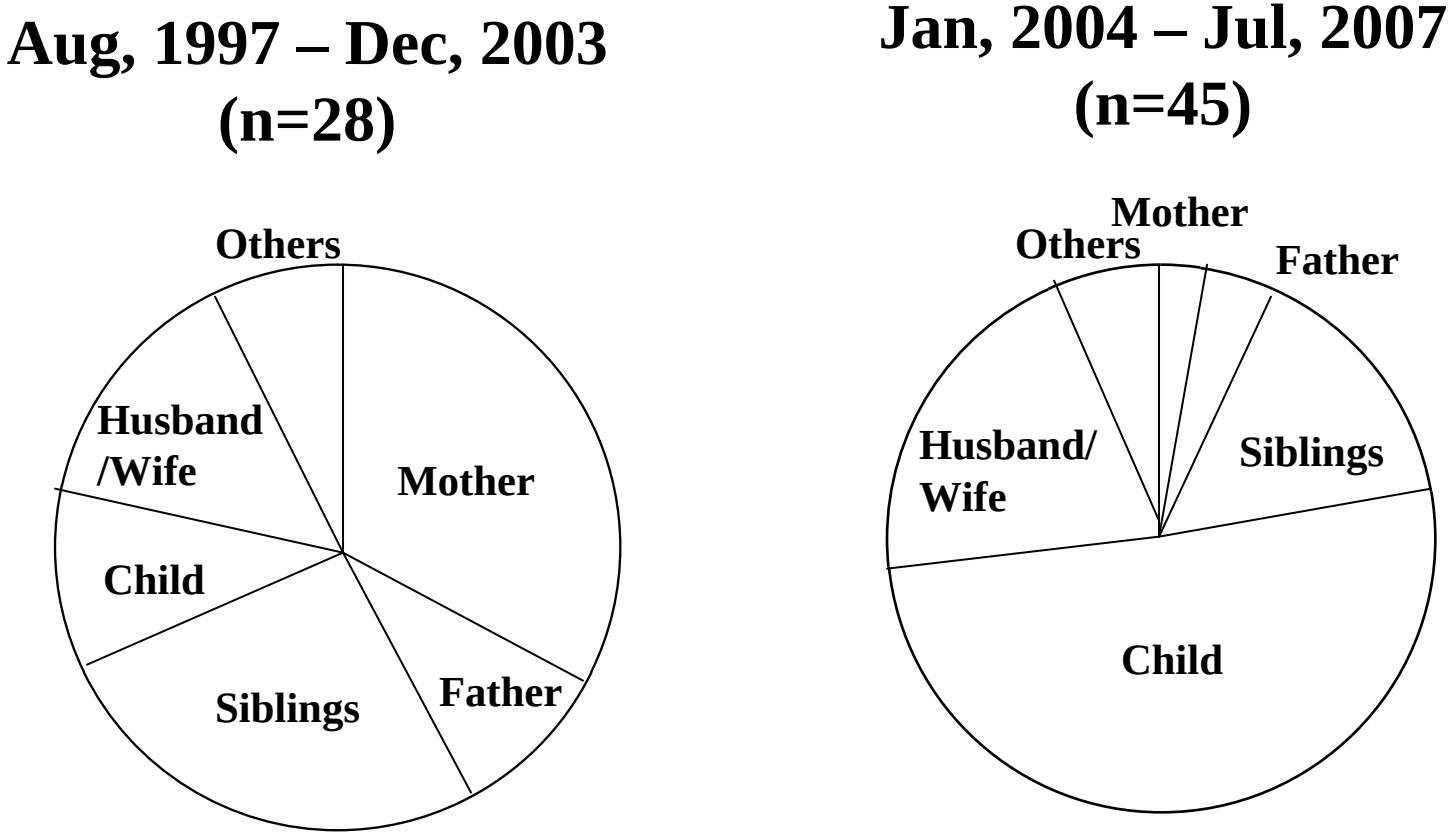
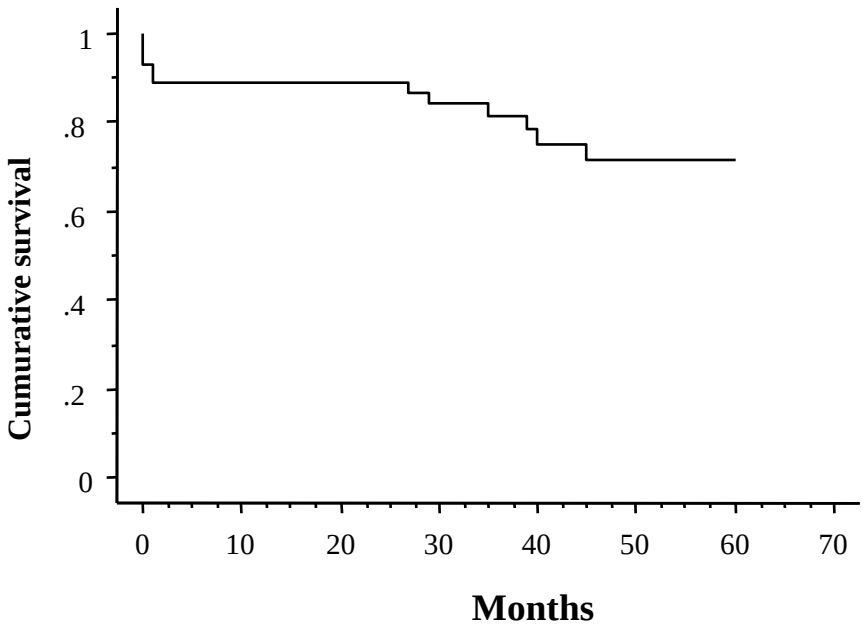
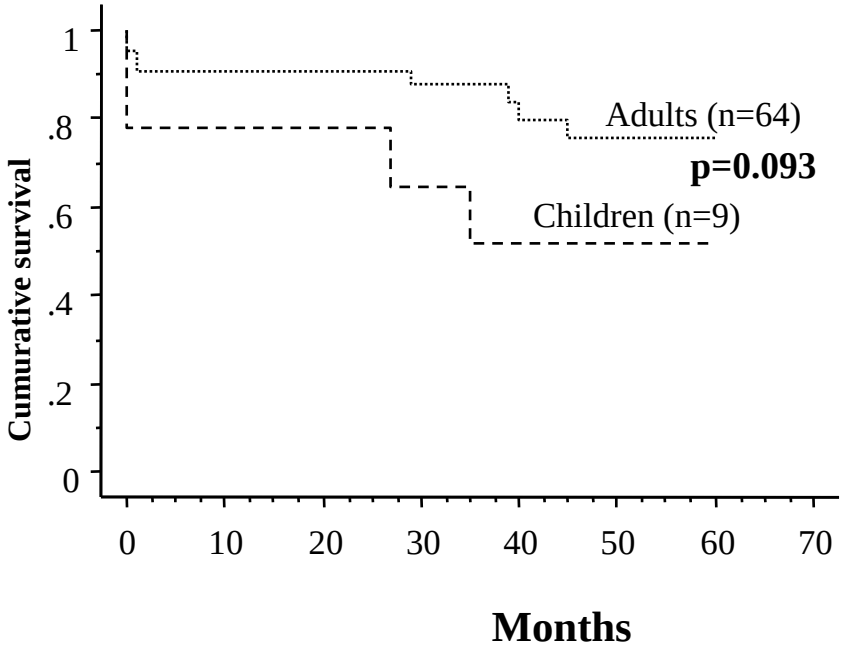


Fig. 3. Patient survival after LDLT



No. at risk

73	*49*	*28*	*16*



No. at risk

Adults			
64	*42*	*24*	*12*
Children			
9	*6*	*4*	*0*