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Adult-to-Adult Living Donor Liver Transplantation at the Asan Medical Center

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Between February 1997 and December 2003, 580 adult-to-adult living donor liver transplants (A-A LDLTs) were performed at the Asan Medical Center for patients above 20 years of age. Indications for A-A LDLT were: chronic hepatitis B (309), chronic hepatitis C (18), hepatocellular carcinoma (144), alcoholic cirrhosis (20), Wilson's disease (4), autoimmune hepatitis (4), hepatic tuberculosis (1), cholangiocarcinoma (2), cryptogenic cirrhosis (5), secondary biliary cirrhosis (7), primary biliary cirrhosis (2), fulminant hepatic failure (18), primary sclerosing cholangitis (2), vanishing bile duct syndrome (1) and re-transplantation (4). Of 580 A-A LDLTs, 119 were of high medical urgency, 96 were for acute on chronic liver failure, 18 were for acute and subacute hepatic failure, 1 was for Wilson's disease, and 4 were for re-transplantation. Recipient age ranged from 20 to 69 years. The age of the donors ranged from 16 to 63 years. There was no donor mortality. Implanted liver grafts were categorized into seven types: 307 modified right lobes (MRL), 85 left lobes, 44 left lobe plus caudate lobes, 41 right lobes, 93 dual grafts, 5 extended right lobes, 4 posterior segments, and 1 extended left lateral segment. In the MRL, the tributaries of the middle hepatic vein were reconstructed by interpositioning a vein graft. Indication for dual graft implantation was the same as single graft A-A LDLT, and seventeen of 93 were emergency cases. As a right-sided graft, 47 received left lobes; 31 received a extended left lateral segment or a lateral segment; 13 received a right lobe with or without the reconstruction of middle hepatic vein tributaries; and 2 received a posterior segment. Graft volume ranged from 26.5% to 83% of the standard liver volume of the recipients. There were 46 (8.0%) one year mortalities among the 576 patients after 580 A-A LDLTs. Of the 119 patients who received emergency transplants, 108 (90.8%) survived. These encouraging results justify the expansion of A-A LDLT to adjust to increasing demands, even in urgent situations. We have aimed establish the efficacy of A-A LDLT in various end-stage chronic and acute liver diseases, as well as new technical advances to overcome the small-for-size graft syndrome by using dual-graft implantation and MRL, both of which were first developed in our department.

Key Words: Adult living donor liver transplantation, modified right lobe, dual grafts

INTRODUCTION

After the introduction of the living donor liver transplantation (LDLT) as a life-saving treatment modality for children with end-stage liver disease,[1] attempts have been made to extend this innovative procedure to adult patients,[2] especially in East Asia where the brain-dead donor organ procurement is severely restricted. Although LDLT has several advantages over cadaveric donor liver transplantation (CDLT), such as good graft quality, better histocompatibility, a shorter cold ischemia time, and a timely operation within a shorter waiting period, the main limitation for successful adult-to adult(A-A) LDLT is caused by graft-size insufficiency,[3] in which the graft cannot meet the metabolic demands of the recipients. Furthermore, it is still not clear whether A-A LDLT is safely applicable in the same situation as CDLT, particularly for urgent or emergency cases. Our purpose was to establish the efficacy of A-A LDLT in various end-stage liver diseases and to introduce the new advances that were developed at our center to overcome the problem of small-for-size graft syndrome.

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MATERIALS AND METHODS

At the Asan Medical Center, Ulsan University Medical School, from the first clinical cadaveric liver transplantation on August 1992 until December 2003, 807 liver transplants (134 CDLTs and 673 LDLTs) were performed. Since February 1997, 580 adult-to adult (> 20 years) LDLTs have been performed at our instutution, while 93 paediatric LDLTs have been performed since December 1994 (Fig. 1).

Indications for A-A LDLTs are listed in Fig. 2. Of the 580 A-A LDLTs, 119 were in United Network of Organ Sharing (UNOS) status I and IIa (18 were acute and subacute hepatic failure, 96 were for acute on chronic liver failure, 1 was for Wilson's disease, and 4 were for re-transplantation) and required urgent surgery. 1 year graft survival was 92.0%. ABO-blood groups were identical or compatible in all cases. Recipient age ranged from 20 to 69 years, and donor age ranged from 16 to 63 years. All donations were approved by the ethics committee of our local authority and the Korean Network of Organ Sharing (KONOS), which is affiliated with the Korean Ministry of Health. The legal age of consent for donation in Korea is 16 years if the recipient is their parent, but in other circumstances, the legal age for consent is 20 years.

The factors that are considered during the pre-transplantation evaluation of donors include liver function chemistry, viral markers for both hepatitis B and C, survey for cytomegalovirus, ultrasound, volumetric computed tomography (CT) of the liver, and hepatic angiography. Endoscopic retrograde cholangiopancreatography was not preoperatively performed, and liver biopsy had been performed only when steatosis was suspected on a clinical or imaging basis. However, despite normal imaging, severe steatosis (> 75%) was often found on the frozen biopsy in the operating room. Thus, we now routinely perform preoperative liver biopsies of every donor. Recently, invasive conventional angiography has been replaced by 3-dimensional CT angiography. At the beginning of our A-A LDLT program, the minimum required graft volume was greater than 30% of the standard liver volume (SLV) of the

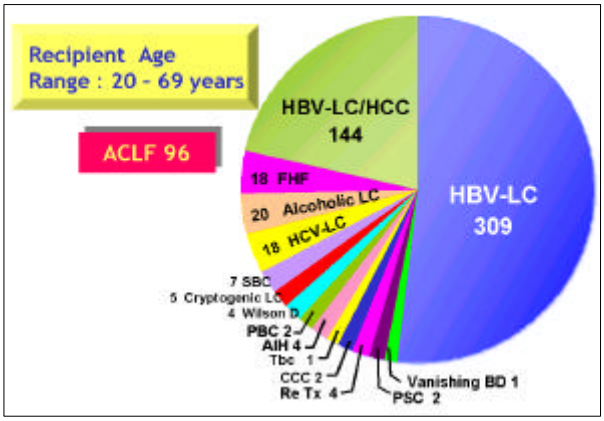
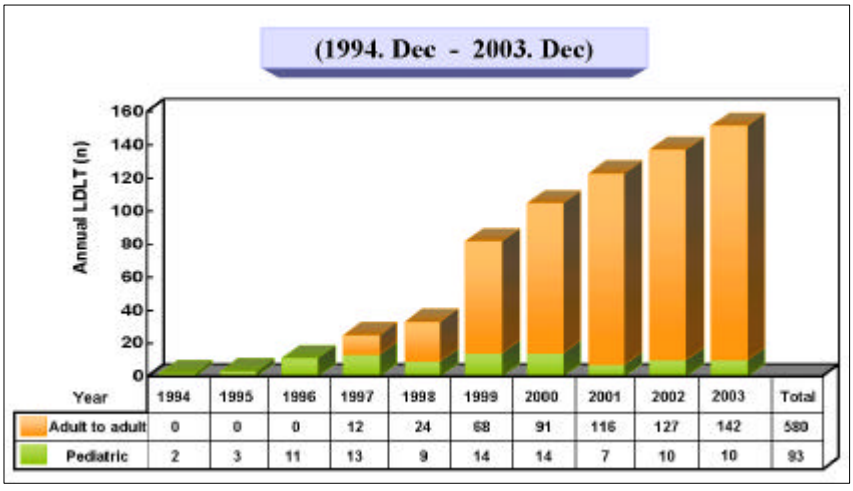


Fig. 2. Indications for adult-to-adult living donor liver transplantation. HBV-LC, hepatitis B virus-liver cirrhosis; HCC, hepatocellular carcinoma; FHF, fulminant hepatic failure;, HCV, hepatitis C virus; SBC, secondary biliary cirrhosis; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; CCC, cholangiocellular carcinoma; Re-tx, re-transplantation; BD, bile duct; ACLF, acute on chronic liver failure.



Year	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	Total
Adult to adult	0	0	0	12	24	68	91	116	127	142	580
Pediatric	2	3	11	13	9	14	14	7	10	10	93

Fig. 1. Annual number of living donor liver transplants (LDLTs) at the Asan Medical Center, Ulsan University Medical School.

recipient, and later, this required volume changed to greater than 40% of the SLV of the recipient. The percentage of the graft volume was calculated using the following formula developed in our department:

$$\text{BSA } (m^2) = \text{BW (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 0.007184$$

$$\text{SLV (ml)} = 691 \times \text{BSA } (m^2) + 95$$

The percentage of graft volume (%) equals graft volume(g)/ SLV of recipient(ml) × 100, where BSA (m^2) is body surface area, and BW (kg) is body weight.

The primary reason for using a right lobe graft was the estimated volume of a left lobe graft of the potential donor was less than 40% of SLV of the recipient. The implanted liver graft were categorized into eight types from 673 donors in 580 A-A LDLTs: modified right lobe (317), right lobe (44), left lobe (211), left lobe plus caudate lobe (44), left lateral segment (39: all were used for dual-graft implantation), extended left lateral segment (7: six was used for dual graft implantation), extended right lobe(5), and posterior segment (6: two was used for dual graft implantation) (Fig. 3). In the modified right lobe graft, the tributaries of the middle hepatic vein originated from the anterior segment of the right liver graft (V5,V8) was reconstructed by way of vein graft interposition (autogenous or cadaveric homologous) in order to prevent possible congestion of the anterior segment (Fig. 4).[4]

Noticeably, dual-graft implantation into a single recipient was performed in 93 patients from March 2000 to December 2003. The indication for this procedure was the same as that of the single graft A-A LDLT, and seventeen of 93 were emergencies (three fulminant hepatic failure, fourteen acute on chronic liver failure). As a right-sided graft, 47 received left lobes, 31 received an extended left lateral segment or a lateral segment, 13 received a right lobe with or without reconstruction of the middle hepatic vein tributaries, and 2 received a posterior segment (Fig. 5).

In order to minimize the cold ischemia time of the graft, donor and recipient operations were started simultaneously, and the hepatic artery, portal and hepatic veins of the graft were not divided until the recipient was ready to receive the graft. The procured graft was flushed with 1 L of cold (4℃) HTK solution through the portal vein at the back table.

At the back table, reconstruction of the tributaries of the middle hepatic veins of the right lobe graft (V5, V8) were performed by connecting V5 and/or V8 with the interposition vein graft, which was obtained from the recipient's saphenous vein, or with the cryopreserved cadaveric iliac vein, when V5 and/or V8 had a caliber larger than 5 mm. In the recipient, passive veno-venous bypass (Anthron tube, Toray Industries, Tokyo) was used to divert portal inflow into the femoral vein during the anhepatic phase, which aided in avoiding the splanchnic venous congestion in the absence of large coronary vein collaterals or spontaneous spleno-renal shunt. All sizeable accessory right hepatic veins (> 5 mm) were reconstructed to provide sufficient venous outflow. Microscope-assisted hepatic arterial anastomosis was performed in all cases. Billary reconstruction has been performed preferentially through duct-to-duct anastomosis rather than by hepaticojejunostomy since the beginning of 2000.

The immunosuppression was induced with methylprednisolone, tacrolimus, or cyclosporine. If renal function was not optimal, mycophenolate mofetil was used as the primary immunosuppressive agent until renal function returned to normal. In order to stabilize graft function, gabexate mesilate (Foy, Ono Pharmaceutical Co., Japan) and alprostadil (Eglandin, WelFide Co, Korea) were administered after graft reperfusion. Anticoagulation therapy, which included the administration of low-molecular weight heparin, anti-thrombin III and the maintenance of hematocrit within the range of 25% to 30%, was maintained for 2 weeks after surgery to prevent hepatic artery thrombosis, especially when the caliber of the hepatic artery was smaller than 2 mm.

RESULTS

Of 673 living donors (356 donated more than just the right lobe) for 580 A-A LDLTs, there was not a single mortality. The minimal remaining

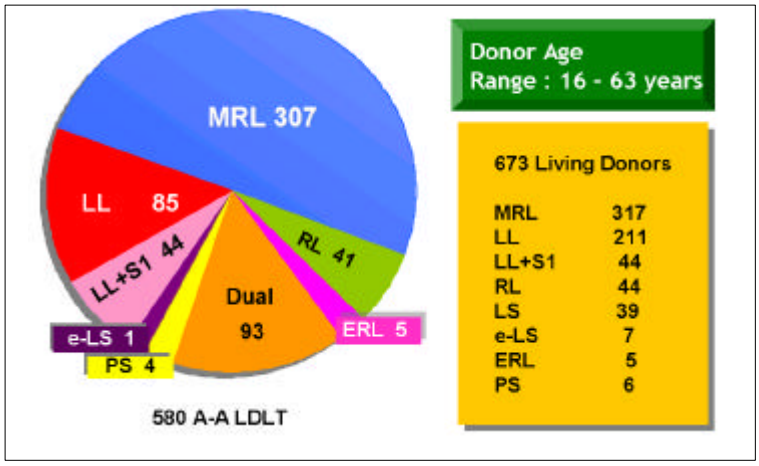


Fig. 3. Types of liver grafts in 580 adult-to-adult living donor liver transplants. MRL, modified right lobe; LL, left lobe; RL, right lobe; LL+S1, left lobe plus segment 1; LS, left lateral segment; e-LS, extended left lateral segment; ERL, extended right lobe; PS, posterior segment.

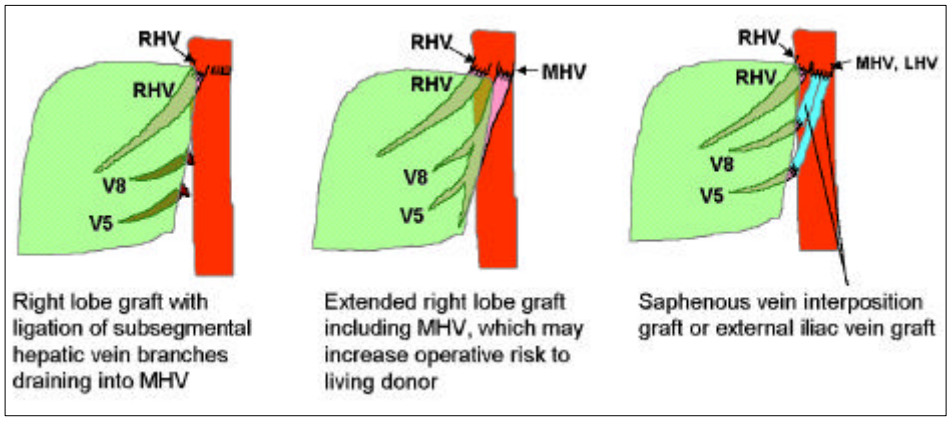


Fig. 4. Scheme for modified right lobe (MRL) liver grafting. RHV, right hepatic vein; MHV, middle hepatic vein; LHV, left hepatic vein; V5, hepatic venous tributaries from segment 5; V8, hepatic venous tributaries from segment 8.

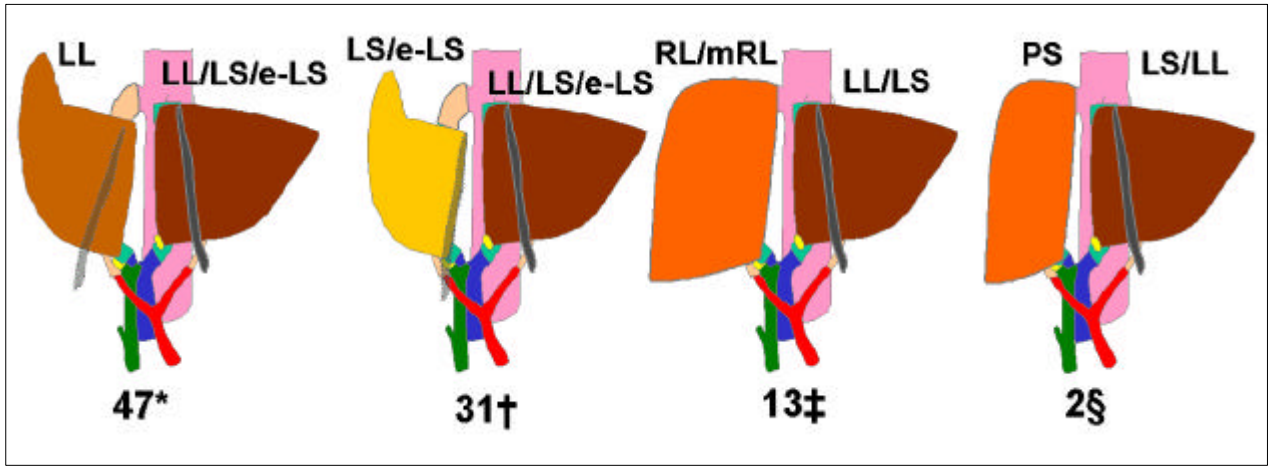


Fig. 5. Adult-to-adult living donor liver transplantation using dual-grafts. *A left lobe (as a right-sided graft) and a left lobe or left lateral segment or an extended lateral segment (as a left-sided graft) were used. †A left lateral segment or an extended left lateral segment (as a right-sided graft) and a left lobe or a left lateral segment or extended lateral segment including one cadaveric donor's lateral segment (as a left-sided graft) were used. ‡A right lobe with or without reconstruction of the middle hepatic vein tributaries (as a right-sided graft) and a left lobe or a left lateral segment (as a left-sided graft) were used. §A posterior segment (as a right-sided graft) and a left lobe or a left lateral segment (as a left-sided graft) were used. LL, left lobe; LS, left lateral segment; e-LS, extended left lateral segment; RL, right lobe; mRL, modified right lobe; PS, posterior segment.

liver volume of a donor after right lobectomy was calculated to be 27% of the total liver volume of the donor, in whom postoperative serum bilirubin was elevated to 9.0 mg/dL. By December 2001, major donor complications included two donors with cases of postoperative hemorrhage that required re-exploration, three with biliary strictures that needed balloon dilatation and internal stenting, one with portal vein stenosis that required percutaneous metallic stenting, one with portal vein thrombosis treated by thrombectomy and intraoperative metallic stent insertion via the inferior mesenteric vein, and another developed renal failure due to contrast allergy following hepatic angiography. All of these major complications developed after the right lobe harvest. However, only two donor complications, which needed re-exploration, occurred between January 2002 and December 2003. One complication was a case of intestinal obstruction caused by the intussusception of the small bowel, and the other one was a case of persistent bile leak from the remnant medial segment after left lateral segmentectomy. Then, completion medial segmentectomy was performed. The two complications mentioned above did not occurred after right hepatectomy but after left sided hepatectomy (Table 1).

After right lobectomy, if the remaining liver volume of the donor was less than 30% of the total liver volume, intrapotal glucose and insulin infusion were given until the 7th postoperative day to accelerate the regeneration of the donor's liver. The mean blood loss during donor hepatectomy was 590 ± 480 ml for right lobectomy and

Table 1. Donor Morbidity and Mortality in 580 A-A LDLT at the Asan Medical Center, Ulsan University from February 1997 to December 2003

In 311 LDLTs from February 1997 to December 2001		
	Type of Grafts	
	Left lobe(n=97)	Right lobe (n=213)
Complication		
Bile leakage requiring drainage	1	
Bile duct stricture		3
Hyperbilirubinemia (TB ≥ 10 mg/dL)		3
PVT		2
CRF		1
Intra-abdominal bleeding		3
Intestinal obstruction	2	
Reoperation		
Intra-abdominal bleeding		3
Intestinal obstruction	1	
PVT		1
Mortality	0	0
In 269 LDLTs from January 2002 to December 2003		
	Type of Grafts	
	Left lobe (n=183)	Right lobe (n=158)
Complication		
Intestinal obstruction	1	
Bile leakage requiring medial segmentectomy	1	
Reoperation	2	0
Mortality	0	0

LDLT, living donor liver transplantation; TB, total bilirubin; PVT, portal vein thrombosis; CRF, chronic renal failure.

475 ± 42 ml for left lobectomy. Five donors required non-autologous blood transfusion. The mean hospital stay was 12 days (range, 10 to 28 days).

In recipients, the ratio of graft volume to SLV of the recipient ranged from 28% to 83%. All right lobe grafts met the minimal required graft volume of > 40% of the SLV of the recipients.

Acute rejection developed in fewer than 30% of recipients, most of who responded to pulsed steroid therapy. Interestingly, there were four cases of massive haemorrhagic necrosis of right lobe grafts (3) and posterior segment graft (1), which illustrated rapid elevation of the transaminase level, deteriorating graft function and normal angiography, and Doppler flow between the 5th and 7th day posttransplant. There were 46 (8.0%) short term mortalities (< 6 months posttransplant) among the 576 recipients after 580 A-A LDLTs. Prior to the middle hepatic vein reconstruction in right lobe graft, and the more liberal use of large volume graft in more ill patients (from 1997 to 1998), grafts and patients survival were approximately 70%. After the adoption of these policies, both grafts and patients survival have recently increased to around 95% (Table 2).

DISCUSSION

In Korea, liver transplantation is now becoming a widely accepted treatment modality for both acute and chronic liver failure, with the number of liver transplants increasing year by year. Because cadaveric donor resources are severely restricted in Korea, LDLT was first introduced in 1994 by our department as a possible solution for the persistent shortage of cadaveric organs for pediatric patients. Since Hashikura et al reported the first successful A-A LDLT,[2] the use of this innovative treatment procedure has steadily increased in Japan, Hong Kong, Taiwan, and also in Korea. Nonetheless, the expansion of LDLT to adult patients has been met with limited success largely due to the small-for-size graft syndrome, when only the left lobe is used for grafting. Lo et al. published the first report on their cumulative experience with right lobe A-A LDLT,[5] which could overcome the small for size graft syndrome. The first successful A-A LDLT using a right lobe in our country was performed at our department in July 1997 for a 43-year-old HBV-cirrhotic, the donor being his wife.

With our first experience of five right lobe grafts (not including a middle hepatic vein), two grafts developed severe congestion of the anterior segment (AS), which were complicated by prolonged massive ascites and severe graft dysfunction, and it lead to death in one recipient.[6] Nakamura and Tsuzuki reported that the right hepatic vein drains the posterior segment, and the middle hepatic vein predominantly drains the AS.[7] In these incidences, the preparation of a right liver graft without middle hepatic venous outflow drainage resulted in the isolation of venous tributaries from the anterior segment, which evoked

Table 2. Short-Term Outcomes of Adult Living-Donor Liver Transplant at the Asan Medical Center, Ulsan University Medical School

Year	1997-1998*	1999	2000	2001	2002	2003
	MHV reconstruction in right lobe graft More liberal use of large volume graft in more ill patients ↓					
6 month-graft survival	25/36 (69%)	61/68 (90%)	84/91 (92%)	106/116 (91%)	120/127 (94%)	134/142 (94%)
6 month-patient survival	25/35 (71%)	63/68 (93%)	84/91 (92%)	106/116 (91%)	122/127 (96%)	134/142 (94%)

*In 1997 February, first adult living donor transplantation (LDLT) was performed; MHV, middle hepatic vein.

congestion and ultimately infarction of the AS. This led to the development of the modified right lobe graft to avoid AS congestion in the late 1998.[4] Besides the extended right lobe graft, the preservation of middle hepatic vein drainage of a right lobe graft is possible because of the modified right lobe graft in which the hepatic venous tributaries of the AS (> 5 mm caliber) are reconstructed via autogenous interposition vein graft (recipient's great saphenous vein, external iliac vein, umbilical collateral vein, or cryopreserved cadaveric cavoiliac vein) into the recipient's middle and/or left hepatic veins or inferior vena cava.

Once congestion injury of the AS develops, future graft function depends on the volume of the posterior segment. If the estimated liver volume of the posterior segment of the right lobe graft is under 35% of the SLV of the recipient, reconstruction of the middle hepatic vein tributaries is indicated.

Sugawara and Makuuchi suggested a donor graft volume of 30% of the SLV as an adequate liver volume for recipients with metabolic liver disease and 40% for recipients with cholestatic liver disease.[3] Lo et al. reported cases of survival with grafts that were only 25% of the SLV of the recipients who had fulminant hepatic failure.[8] In our study, two deaths were related to graft failure, which were caused by small-for-size graft syndrome (30% and 31% each, both suffering from chronic parenchymal liver disease). Thus, we increased the acceptable minimal graft volume to greater than 40% of the SLV of the recipient.

Insufficient graft size has been an obstacle to the expansion of A-A LDLT, especially if the donor graft is taken only from the left lobe. In order to expand the application of A-A LDLT, right lobe grafts have been widely used, but the risk to the donor is high. The safety of donor right lobectomy varies, which mainly depends on the remaining volume of the left lobe. Although a donor may have a large right lobe that is suitable as a graft for a larger-size recipient, the remaining left lobe may be too small to assure donor safety in many cases, and if this is the case, the potential donor cannot be accepted. As an alternative, dual-graft transplantation, which is a process of transplanting from two donors into one recipient, was developed to solve not only the graft size insufficiency but also to minimize donor risk.[9] Our patient survival rate A-A LDLT is comparable to the results of cadaveric full-size liver transplantation, even in urgent cases.

A-A LDLT provides a new donor pool in East Asia, where cadaveric organ donation is severely restricted. Furthermore, A-A LDLT using a right lobe graft has further extended the limitation created by the size of the recipient. Nonetheless, the donor risk involved in right lobe harvesting is still high, particularly when the remaining liver volume of the donor is less than 35% of his or her total liver volume. Careful assessment of potential donor complications should be continued perioperatively in view of donor safety.

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