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Donor Safety in Adult-Adult Living Donor Liver Transplantation: A Single-Center Experience of 356 Cases

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

CF Haipeng Meng
B Jiayin Yang
ADE Lunan Yan

Department of Liver Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan, P.R. China

Corresponding Author: Lunan Yan, e-mail: yanlunanwestchina@163.com
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Background: As an important means to tackle the worldwide shortage of liver grafts, adult-adult living donor liver transplantation (A-ALDLT) is the most massive operation a healthy person could undergo, so donor safety is of prime importance. However, most previous research focused on recipients, while complications in donors have not been fully described or investigated.

Material/Methods: To investigate donor safety in terms of postoperative complications, the clinical data of 356 A-ALDLT donors in our center from January 2002 to September 2015 were retrospectively analyzed. These patients were divided into a pre-2008 group (before January 2008) and a post-2008 group (after January 2008). Donor safety was evaluated with regard to the type, frequency, and severity of postoperative complications.

Results: There were no donor deaths in our center during this period. The overall complication rate was 23.0% (82/356). The proportion of Clavien I, II, III, and IV complications was 51.2% (42/82), 25.6% (21/82), 22.0% (18/82), and 1.2% (1/82), respectively. In all the donors, the incidence of Clavien I, II, III, and IV complications was 11.8% (42/356), 5.9% (21/356), 5.1% (18/356), and 0.3% (1/356), respectively. The overall complication rate in the post-2008 group was significantly lower than that in the pre-2008 group (18.1% (41/227) *vs.* 32.6% (42/129), $P<0.01$). Biliary complications were the most common, with an incidence of 8.4% (30/356).

Conclusions: The risk to A-ALDLT donors is controllable and acceptable with improvement in preoperative assessment and liver surgery.

MeSH Keywords: Liver Transplantation • Living Donors • Patient Safety • Postoperative Complications

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Background

As the only curative treatment for end-stage liver diseases, liver transplantation has been widely carried out around the world. But in the East Asian countries, due to the influence of traditional values and social customs, people are generally reluctant to donate their organs after death, resulting in an increasing gap between available organs and patients in the waiting list. Especially in China, where brain death has not been enacted, relatively poor quality grafts from cardiac death donors have greatly limited the promotion of donation after cardiac death (DCD) liver transplantation. In this background, living donor liver transplantation (LDLT) has been developing rapidly and achieved satisfactory long-term survival of both graft and recipient, with its unique advantages such as short waiting time, elective surgery, high graft quality and low incidence of immune rejection. However, most previous researches focused on the recipient, while donor safety as the first priority has not been fully described and investigated. Since performed the first adult-adult LDLT (A-ALDLT) in mainland China in 2002 [1], our center has completed 356 cases of A-ALDLT. Recent years, we made some efforts to improve donor safety in LDLT, and this research is aimed to test the effect of these measures by retrospectively analyzing the postoperative complications in all 356 donors.

Material and Methods

The postoperative complications of 356 A-ALDLT donors in our center from January 2002 to September 2015 were retrospectively analyzed. This study was approved by the Regional Ethics Committee of our hospital, and due to its retrospective nature, informed consent was waived. These patients were divided into the pre-2008 group (before January 2008) and the post-2008 group (after January 2008), which marks the first and second half of our 15 years of LDLT experience, respectively. All postoperative complications were graded by the Clavien-Dindo classification [2] and compared between the 2 groups.

Donor selection

All donations are completely voluntary and approved by the ethical review. Potential donors aging from 18 to 60 years old were considered. The donor selection process includes health screening, blood tests, virological examination, imaging examination and psychological assessment. The inclusion and exclusion criteria were reported previously [3].

Preoperative assessment

The donor's total liver volume was calculated by the West China formula we proposed [4]. We also developed our own formula to carry out noninvasive assessment on the degree of hepatic steatosis and avoided pre-donation liver biopsy [4]. Moderate macrovesicular steatosis (30~60% steatosis) was acceptable, but severe macrovesicular steatosis (>60% steatosis) was a contraindication for donation. Three-dimensional spiral enhanced CT was routinely used to check the hepatic artery, hepatic vein and portal vein for variations. MRI was done to define the biliary anatomy. If necessary, intraoperative cholangiogram was performed. Once the operation decision was made, three-dimensional print liver model was made to accurately calculate the total liver volume and the planned remnant liver volume [5]. Whenever possible, the remnant liver volume was maintained at above 40% to ensure donor safety. With the 3D model, the liver surgery was performed based on the intrahepatic duct structures to achieve precise anatomical liver resection.

Living donor hepatectomy

In most cases, we used the right lobe graft without the middle hepatic vein (MHV). Intraoperative ultrasound was used to define the MHV. Without vascular occlusion, the hepatic parenchyma was transected with a Cavitron Ultra-Sonic Aspirator (CUSA) and the MHV was retained to the donor. Laparoscopic-assisted right lobe donor hepatectomy has been a routine practice in our center since 2011 [6], which changed the traditional 20cm right subcostal incision to a 10cm median incision. Postoperatively, donors were sent to ICU for monitoring and treatment until they are stable enough to return to the ordinary ward.

Statistical methods

Continuous variables were expressed as medians with standard deviations (SD), and t test was used for comparison between groups. Categorical data were expressed as ratios and compared using the chi squared test. SPSS version 17.0 was used for all data management and statistical analyses. $P<0.05$ was considered statistically significant.

Results

There were 129 donors in the pre-2008 group (before January 2008) and 227 in the post-2008 group (after January 2008). The demographic characteristics of the 2 groups are presented in Table 1. The average age was 36.0 (19~60) years. The 2 groups were not significantly different in terms of age, sex, height, weight, BMI, or relationship with the recipient ($P>0.05$).

Of all 356 donors, 306 underwent right hemihepatectomy without middle hepatic vein (MHV), 1 underwent right hemihepatectomy with MHV, 42 underwent left hemihepatectomy, and

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Table 1. Demographic characteristics of all donors.

	Pre-2008 group n=129	Post-2008 group n=227	*P* value
Age (years, $\bar{\chi}$±s)	36.2±7.8	35.9±11.0	0.785
Sex (Male/Female, n)	73/56	132/95	0.775
Height (cm, $\bar{\chi}$±s)	166.8±8.2	165.9±7.5	0.294
Weight (kg, $\bar{\chi}$±s)	61.1±8.9	62.6±10.0	0.158
BMI* (kg/m^2, $\bar{\chi}$±s)	22.7±2.6	22.9±2.8	0.570
Relationship with the recipient (n)			
Parent	28	61	0.782
Child	17	28	
Spouse	46	71	
Sibling	18	37	
Other relative	20	30	

* Body mass index.

7 underwent left lateral lobectomy. All donors were alive after a median follow-up of 65 (2~158) months. Postoperative complications occurred in 83 cases (23.3%). According to the Clavien-Dindo classification [2], the incidence of Clavien I, II, III, and IV complications was 11.8% (42/356), 5.9% (21/356), 5.1% (18/356), and 0.3% (1/356), respectively.

As displayed in Table 2, the 2 groups had no statistically significant difference in terms of surgical approach, graft weight, graft/recipient weight (GRWR), or ICU stay ($P>0.05$). Compared with the pre-2008 group, the post-2008 group had significantly shorter operative time and hospital stay ($P<0.05$). We routinely used autologous blood transfusion, and no donors required homologous blood transfusion. The post-2008 group had significantly less blood loss and autologous blood transfusion compared with the pre-2008 group ($P<0.05$). Frequency and severity of complications decreased remarkably in the post-2008 group ($P<0.05$).

Specific complications of the donors are shown in Table 3. Biliary complications, including bile leakage and biliary stricture, were the most common complications, with an incidence of 8.4%. The second most common complication was infection, with an incidence of 7.0%, in which wound infection (3.4%) and abdominal infection (3.1%) accounted for the majority. Postoperative hemorrhage (2.2%) and pleural effusion (3.7%) were rare. Only 1 patient (0.3%) had portal vein thrombosis postoperatively, and was cured by thrombectomy.

It is worth mentioning that in a previous study, in order to investigate the relationship between remnant liver volume (RLV) and complication rate, we collected and analyzed the data of 151 LDLT donors from 2002 to 2009. They were classified according to the RLV as the <35% group, 35~40% group, and >40% group. As shown in Table 4, the incidence of severe complications (Clavien III) of the <35% group, 35~40% group, and >40% group was 21%, 15% and 6%, respectively, with statistically significant differences [3].

Discussion

As an important means to address the worldwide shortage of liver grafts, A-ALDLT is the most serious operation a healthy person could undergo, so donor safety is the absolute priority. The first adult-child LDLT was performed in 1988 [7], but it was not until 2000 that A-ALDLT was widely performed in Europe and the United States due to concerns over donor safety.

Most A-ALDLTs use the right liver lobe as the graft, which accounts for 50~70% of the donor liver volume. Because of the large volume of liver donated and the difficulty of surgery, donor safety in A-ALDLT has raised serious concerns [8,9]. There are currently at least 19 donors who died of postoperative complications worldwide; most are right lobe donors, with a rough estimate of donor mortality at 0.2~0.5% [10]. In addition, 1 donor entered a vegetative state and 3 donors had to receive liver transplantations themselves [10]. Lo et al. [11] investigated 1508 donors from 5 liver transplantation centers in Asia and reported that the complication rate for right lobe donors was 28%. Previous reports ranged from 0% to 67% [12–15]. This diversity in complication rates may be due to the difference

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Table 2. Clinical characteristics of donors.

	Pre-2008 group *n*=129	Post-2008 group *n*=227	*P* value
Surgical approach (n (%))			
Right hemihepatectomy (without MHV*)	105 (81.4)	201 (88.5)	0.184
Right hemihepatectomy (with MHV*)	0 (0)	1 (0.4)	
Left hemihepatectomy	21 (16.3)	21 (9.3)	
Left lateral lobectomy	3 (2.3)	4 (1.8)	
Graft weight (g, $\bar{\chi}$±s)	533.8±166.9	510.5±140.2	0.161
Graft/recipient weight (GRWR) (±s)	0.88±0.43	0.86±0.50	0.703
Operative time (h, $\bar{\chi}$±s)	7.4±1.6	5.6±1.2	<0.001
Blood loss (mL, $\bar{\chi}$±s)	698.1±559.2	510.5±500.2	0.001
Autologous blood transfusion (mL, $\bar{\chi}$±s)	393.9±196.1	320.0±201.5	0.001
ICU stay (d, $\bar{\chi}$±s)	2.11±0.33	2.20±0.51	0.073
Hospital stay (d, $\bar{\chi}$±s)	12.8±4.6	8.0±3.5	<0.001
Complications (n (%))	42 (32.6)	41 (18.1)	0.002
Clavien classification (n (%))			
0	87 (67.4)	186 (81.9)	0.002
I	22 (17.1)	20 (8.8)	0.020
II	9 (7.0)	13 (5.7)	0.638
III	11 (8.5)	7 (3.1)	0.024
IV	0 (0)	1 (0.4)	0.774

* Middle hepatic vein.

in definitions and criteria for postoperative complications in different centers, as well as in graft types and follow-up periods. In view of this, we carried out this investigation of donor complications in our own center to evaluate donor safety and test the effect of the measures we have taken to improve it.

In our study, the overall complication rate of LDLT donors was 23.0% (82/356). More than half of the complications were Clavien I (51.2%), suggesting that most complications were minor and controllable. In all the donors, the incidence of Clavien I, II, III, and IV complications was 11.8% (42/356), 5.9% (21/356), 5.1% (18/356), and 0.3% (1/356), respectively. Patel et al. [16] investigated 433 LDLT donors in 13 liver transplantation centers in the United States and reported the incidence of Clavien I, II, and III complications was 13.4%, 6%, and 2%, respectively, which is comparable to our results. In our study, the most common complication was biliary (8.4%), mostly bile leakage from the hepatic surface. That was different from the study of Ghobrial et al. [17], in which infection was the most common complication, with an incidence of 12%. Kousoulas et al. studied 87 living liver donors and found that donor morbidity did not differ between right- and left-lobe donors [18], but our study of 356 living liver donors revealed that the complication rate of right lobe donors was significantly higher than that of left-lobe donors(25.7% (79/307) *vs.* 8.2% (4/49), $P<0.01$). No complications occurred in any 7 left lateral-lobe donors. In the 42 left-lobe donors, only 4 had postoperative complications: 1 with bile leakage, 2 with wound infection, and 1 with abdominal hemorrhage. Among the 307 right lobe donors, 77 developed various complications (Table 3). We think this difference is due to the increased complexity and trauma of right lobe donation hepatectomy.

It is noteworthy that the overall complication rate in the post-2008 group was significantly lower than that in the pre-2008 group (18.1% (41/227) *vs.* 32.6% (42/129), $P<0.01$). Although it has not been statistically proven, we believe the following 5 measures we took to improve donor safety contributed to the reduced complication rates in the post-2008 group.

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Table 3. Donor complications (n (%)).

	Clavien I			Clavien II			Clavien III			Overall complications (*n*=356)
	Pre-2008 group (*n*=129)	Post-2008 group (*n*=227)	All donors (*n*=356)	Pre-2008 group (*n*=129)	Post-2008 group (*n*=227)	All donors (*n*=356)	Pre-2008 group (*n*=129)	Post-2008 group (*n*=227)	All donors (*n*=356)	
Complications	22 (17.1)	20 (8.8)	42 (11.8)	9 (7.0)	12 (5.3)	21 (5.9)	11 (8.5)	7 (3.1)	18 (5.1)	81 (22.8)
Biliary complications	7 (5.4)	7 (3.1)	14 (3.9)	4 (3.1)	5 (2.2)	9 (2.5)	4 (3.1)	3 (1.3)	7 (2.0)	30 (8.4)
Bile leakage	7 (5.4)	7 (3.1)	14 (3.9)	4 (3.1)	5 (2.2)	9 (2.5)	2 (1.6)	2 (0.9)	4 (1.1)	27 (7.6)
Biliary stricture	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.6)	1 (0.4)	3 (0.8)	3 (0.8)
Infection	6 (4.7)	9 (4.0)	15 (4.2)	2 (1.6)	3 (1.3)	5 (1.4)	3 (2.3)	2 (0.9)	5 (1.4)	25 (7.0)
Wound infection	2 (1.6)	6 (2.6)	8 (2.2)	1 (0.8)	1 (0.4)	2 (0.6)	1 (0.8)	1 (0.4)	2 (0.6)	12 (3.4)
Abdominal infection	4 (3.1)	3 (1.3)	7 (2.0)	0 (0)	1 (0.4)	1 (0.3)	2 (1.6)	1 (0.4)	3 (0.8)	11 (3.1)
Lung infection	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.4)	2 (0.6)	0 (0)	0 (0)	0 (0)	2 (0.6)
Postoperative hemorrhage	0 (0)	0 (0)	0 (0)	2 (1.6)	3 (1.3)	5 (1.4)	1 (0.8)	2 (0.9)	3 (0.8)	8 (2.2)
Abdominal hemorrhage	0 (0)	0 (0)	0 (0)	1 (0.8)	2 (0.9)	3 (0.8)	1 (0.8)	2 (0.9)	3 (0.8)	6 (1.7)
Incision hemorrhage	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.4)	2 (0.6)	0 (0)	0 (0)	0 (0)	2 (0.6)
Effusion	6 (4.7)	4 (1.8)	10 (2.8)	1 (0.8)	1 (0.4)	2 (0.6)	1 (0.8)	0 (0)	1 (0.3)	13 (3.7)
Pleural effusion	2 (1.6)	2 (0.9)	4 (1.1)	1 (0.8)	1 (0.4)	2 (0.6)	1 (0.8)	0 (0)	1 (0.3)	7 (2.0)
Ascites	4 (3.1)	2 (0.9)	6 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (1.7)
Vascular complications	3 (2.3)	0 (0)	3 (0.8)	0 (0)	0 (0)	0 (0)	2 (1.6)	0 (0)	2 (0.6)	5 (1.4)
Portal vein thrombosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	0 (0)	1 (0.3)	1 (0.3)
Others	3 (2.3)	0 (0)	3 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)	0 (0)	1 (0.3)	4 (1.1)

Table 4. Complications with different RLV (n (%)).

RLV	*n*	Complications					*P* value
		0 (*n*=101)	Clavien I (*n*=28)	Clavien II (*n*=9)	Clavien IIIa (*n*=8)	Clavien IIIb (*n*=5)	
<35%	14	3 (21)	5 (36)	3 (21)	2 (14)	1 (7)	0.000
35~40%	20	10 (50)	4 (20)	3 (15)	1 (5)	2 (10)	
>40%	117	88 (75)	19 (16)	3 (3)	5 (4)	2 (2)	

(1) West China formula for standard liver volume

In the donor selection and preoperative assessment process, it is crucial to accurately estimate the donor's standard liver volume (SLV). Generally, a thin-slice CT scan is used for this task, but its error rate was reported to be 5~25% [19]; therefore, we thought it would be of great help to develop a formula for live size calculation.

We carried out a study on 115 LDLT donors in which the weight and volume of their right lobe grafts were measured on the back table intraoperatively. The drainage method was applied to

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determine the liver graft volume, then the data were compared with liver volumes calculated by CT preoperatively. Our statistical analysis led us to develop our West China formula: SLV (mL) =11.5×BW (body weight, kg)+334. Afterwards, we applied this formula to more than 200 LDLTs and achieved satisfactory results [3]. According to our experience, the West China formula has advantages over CT in both accuracy and convenience. It has also been adopted by other liver transplantation centers in China.

(2) RLV >40%

Remnant liver volume is a key factor affecting donor recovery and safety [20]. An appropriate RLV must meet recipient need and ensure donor safety at the same time. There is still controversy as to the optimal RLV. Some scholars suggested that an RLV of 30% is sufficient for donors, but others prefer to keep RLV >35% or even >40% [21]. A recent study by Kentaro et al. [22] found that larger partial resection (≥35% of the original liver volume) may impair postsurgical asialoglycoprotein receptor (ASGPR) function, while smaller resection (<35%) was proved to be under the safety margin of hepatectomy. They suggested that careful attention must be paid to LDLT donors undergoing larger (≥35%) partial resection. In A-ALDLT, we routinely use the right lobe without MHV as the graft so that the donors are safer with a relatively large RLV. To solve the optimal RLV problem, in 2009 we performed a retrospective study on 151 LDLT donors who were classified according to the RLV. As displayed in Table 4, the incidence rates of severe complications (Clavien III) of the 3 groups were significantly different [3]. Based on this result, we try to maintain a minimum RLV of 40% whenever possible.

(3) Noninvasive assessment of hepatic steatosis

Hepatic steatosis is a common risk factor for graft quality and donor safety. Severe macrovesicular steatosis (>60% steatosis) has a strong correlation with primary non-function (PNF), while moderate macrovesicular steatosis (30~60% steatosis) leads to damage in liver function and regeneration [23]. A recent study identified hepatic steatosis as an independent donor-associated risk factor of post-reperfusion severe hyperglycemia (PRSH) in patients undergoing LDLT [24]. Therefore, preoperative evaluation of hepatic steatosis is essential. Liver biopsy is the criterion standard, but is associated with a 1% rate of hemorrhage and 0.01% mortality [25]. Thus, we attempted to build a model to quantitatively predict the extent of hepatic macrovesicular steatosis (HMS) from data obtained noninvasively and thus avoid unnecessary liver biopsies. To evaluate HMS quantitatively, 167 potential living liver donors and 45 subjects suspected of nonalcoholic fatty liver disease (NAFLD) underwent percutaneous liver biopsy. Their hepatic unenhanced CT attenuation, body mass index (BMI), and indices of serum lipids were reviewed. By statistical analyses, the following equation was derived: HMS=47.7–1.47BMI–1.14CT (Hu). This result was published in the journal Liver Transplantation [4]. Subsequently, we have used this equation to evaluate hepatic steatosis preoperatively, avoiding liver biopsy and achieving satisfactory results.

(4) Three-dimensional (3D) print of a liver for preoperative planning

First introduced by the Cleveland Clinic in 2013 [5], 3D print is now routinely used in the preoperative planning of LDLT in our center. The 3D print liver not only enables accurate calculation of SLV and RLV, but also vividly demonstrates the distribution and variation of intrahepatic vessels, thus providing important information for decision-making and detailed planning of surgery. With its use, precise anatomical hepatectomy can be achieved for the donors, avoiding complications such as bile duct injuries.

(5) Laparoscopic-assisted right hepatectomy in donors

Having been shown to not only reduce hospital stay, but also effectively reduce surgical complications, enhanced recovery after surgery (ERAS) protocols have been implemented extensively in gastrointestinal surgery and are now established as standard of care [26]. Recent years have witnessed increasing interest in application of enhanced recovery care programs in liver surgery [27], especially after 2 RCTs demonstrated that overall morbidity was reduced following liver resection managed with fast-track surgery principles compared to conventional practice [28,29].

Minimally-invasive procedures are among the most important contributors to fast-track surgery. First introduced by Koffron et al. [30] in 2006, laparoscopic-assisted right hepatectomy has displayed remarkable advantages over the conventional open procedure by changing the traditional 20-cm right subcostal incision to a 10-cm upper median incision. According to a study by Imamura et al. [31], living donor hepatectomy with an upper median incision is a preferable procedure in terms of physical status and safety. Our center was the first to apply this minimally-invasive procedure to living liver donors in China [6]. We also discovered that donors who received laparoscopic-assisted surgery had significantly less pain and achieved early expectoration, mobilization, and enteral nutrition postoperatively. Based on the theory of ERAS [32], these would result in significant reduction of postoperative complications. Uncomplicated recovery reduced morbidity, hospital stay, and costs. In addition, even willingness to donate was encouraged due to the good cosmetic effects.

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Conclusions

According to our experience, with measures taken to improve preoperative assessment and liver surgery, the risk to A-ALDLT donors is controllable and acceptable.

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Conflicts of interest

The authors declare no conflicts of interest.

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