Donor Safety in Living Donor Liver Transplantation: The Korean Organ Transplantation Registry Study

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Major concerns about donor safety cause controversy and limit the use of living donor liver transplantation to overcome organ shortages. The Korean Organ Transplantation Registry established a nationwide organ transplantation registration system in 2014. We reviewed the prospectively collected data of all 832 living liver donors who underwent procedures between April 2014 and December 2015. We allocated the donors to a left lobe group (n = 59) and a right lobe group (n = 773) and analyzed the relations between graft types and remaining liver volumes and complications (graded using the Clavien 5-tier grading system). The median follow-up was 19 months (range, 10-31 months). During the study period, 553 men and 279 women donated livers, and there were no deaths after living liver donation. The overall, biliary, and major complication (grade ≥ III) rates were 9.3%, 1.7%, and 1.9%, respectively. The graft types and remaining liver volume were associated with significantly different overall, biliary, and major complication rates. Of the 16 patients with major complications, 9 (56.3%) involved biliary complications (2 biliary strictures [12.5%] and 7 bile leakages [43.8%]). Among the 832 donors, the mean aspartate transaminase, alanine aminotransferase, and total bilirubin levels were 23.9 ± 8.1 IU/L, 20.9 ± 11.3 IU/L, and 0.8 ± 0.4 mg/dL, respectively, 6 months after liver donation. In conclusion, biliary complications were the most common types of major morbidity in living liver donors. Donor hepatectomy can be performed successfully with minimal and easily controlled complications. Our study shows that prospective, nationwide cohort data provide an important means of investigating the safety in living liver donation.

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Liver transplantation (LT) is the treatment of choice for end-stage liver disease, but the continued shortage of deceased donors remains problematic. Since the first living donor liver transplantations (LDLTs) were performed with pediatric recipients[1] in 1988 and with adult recipients[2] in 1993, LDLT has been widely used worldwide and has become an effective, lifesaving alternative to deceased donor liver transplantation (DDLT). LDLT has distinct advantages over DDLT, such as direct availability of the organ, elective surgery with low recipient morbidity, and reduced incidence of primary dysfunction.[3] Despite good outcomes for recipients, LDLT is a very complicated surgical procedure, and donor safety remains an issue of concern. Studies have reported mortality[4-6] and morbidity rates ranging from 0% to 67%[5,7] for healthy liver donors.

Abbreviations: ALT, alanine aminotransferase; ANOVA, analysis of variance; AST, aspartate transaminase; BMI, body mass index; DDLT, deceased donor liver transplantation; ENBD, endoscopic nasobiliary drainage; ERBD, endoscopic retrograde biliary drainage;

A large-scale prospective cohort study was needed to better understand the risk factors and accurately determine the complication rates for LDLT. In the Republic of Korea, 18.73 per million population (actual number, 942) living liver donations were performed in 2015.[8] We undertook to accurately assess the risks of morbidity and complications among Korean liver donors using prospectively collected data from a nationally representative cohort of Korean patients.

Patients and Methods

THE KOREAN ORGAN TRANSPLANTATION REGISTRY

The Korean Organ Transplantation Registry (KOTRY) initiated a national organ transplantation registration system in April 2014. The registry is composed of 5 cohorts representing 5 types of solid organ transplantation: kidney, liver, heart, lung, and pancreas. The liver cohort consists of a central coordination unit, a medical research coordinating center, and 15 participating transplantation centers, which performed 81.5% of Korean LTs (1139/1398) in 2015. The KOTRY liver cohort contains data from donors and recipients and performs at least 50% (732 out of 1398 patients in 2015) of all Korean LTs. Each of the independent institutional review boards at the 15 transplantation centers approved the study protocol. All patients provided written informed consent prior to enrollment in the study.

KOTRY, Korean Organ Transplantation Registry; LDLT, living donor liver transplantation; LG, left lobe group; LT, liver transplantation; MHV, middle hepatic vein; PCD, percutaneous catheter drainage; PTBD, percutaneous transhepatic biliary drainage; PV, portal vein; RG, right lobe group; RLV, remnant liver volume.

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PATIENTS AND STUDY DESIGN

All of the 832 living donors registered in the KOTRY between April 2014 and December 2015 were enrolled in the study. Only potential donors who met the generally accepted selection criteria for living donors were evaluated according to each local protocol with minor differences between institutions.[9] Donation should be absolutely voluntary. Detailed surgical techniques and donor selection criteria as applied in donor operations were described in previous reports by the centers involved in Korea.[10-13]

We prospectively collected the medical records of all of the donors, which included age, sex, medical history, height, weight, hospital stay after hepatectomy, liver volume estimated by computed tomography or magnetic resonance imaging, graft-to-recipient weight ratio, and remnant liver volume (RLV), using the Internet-based Clinical Research and Trial management system maintained by the Korean National Institute of Health.[14] All types of donor complications were recorded, including infections and vascular, biliary, cardiovascular, pulmonary, and surgical complications. Laboratory data including bilirubin, aspartate transaminase (AST), and alanine aminotransferase (ALT) levels were collected before surgery and 6 months, 1 year, and 2 years after surgery.

We divided the 832 living liver donors into a left lobe group (LG; n = 59) and a right lobe group (RG; n = 773). The LG was composed of patients who donated a left lateral segment (or monosegment), left lobe, or extended left lobe graft. The RG was composed of patients who donated a right posterior section, right lobe, or extended right lobe. We analyzed the relations between complications and graft types and between complications and RLV. The median follow-up was 19 months (range, 10-31 months).

COMPLICATIONS

We graded surgical complications using the 5-tier Clavien-Dindo grading system[15] (Table 4). Grade I complications were defined as any deviations from the normal postoperative course that did not require pharmacological treatment or surgical, endoscopic, and radiologic intervention. Grade I complications included the cases in which the donor did not recover normal liver enzyme (AST and ALT > 60 IU/L) or total bilirubin (>2.0 mg/dL) status by the time of the 6-month routine follow-up visit. In addition, grade I complications included cases in which the donor

required a prolonged postoperative hospital stay of >14 days, regardless of cause.

Grade II complications were defined as those requiring pharmacological treatment with drugs other than those allowed for grade I complications, including cases that required antibiotic administration and delayed drain removal for bile leakage or intra-abdominal fluid collection. Biliary leakage was defined as any fluid collection or ascites containing a higher bilirubin level than that of the serum.[16]

Grade III complications were defined as those requiring surgical, endoscopic, or radiological intervention. Grade IV complications were defined as life-threatening conditions requiring intensive care. Grade V complications were defined as those resulting in death. We defined grade III, grade IV, and grade V complications as major complications. We performed our analysis to identify the risk factors for overall, major, and biliary complications.

STATISTICAL ANALYSIS

We expressed our results as means (± standard deviations) for continuous variables and as numbers (proportions) for categorical variables. We performed the analysis using SPSS, version 22 (SPSS Inc., Chicago, IL). We used Fisher's exact test or the chi-square test to determine the significance of intergroup differences in categorical variables. We used the independent Student *t* test or analysis of variance (ANOVA) to determine the significance of differences in continuous variables. We estimated the association between RLV and donor age by univariate linear regression. We assessed the risk factors for overall, major, and biliary complications by logistic regression. Statistical significance was accepted for *P* values < 0.05.

Results

PATIENTS

During the study period, 553 men and 279 women donated their liver. The proportion of adult-to-adult donation was higher in the RG than in the LG (99.6% versus 35.6%; $P < 0.001$), as was the proportion of male donors (67.7% versus 50.8%; $P < 0.001$). The mean donor age was lower in the RG than in the LG (36.8 ± 10.8 years versus 31.0 ± 10.7 years; $P < 0.001$). The most common donor-to-recipient relationship in the LG was parent-to-offspring (40.7%), whereas that in the RG was offspring-to-parent (72.2%; $P < 0.001$). The mean donor body mass index (BMI) was lower in the RG than in the LG (23.1 ± 3.0 kg/m^2 versus 24.6 ± 3.6 kg/m^2; $P < 0.001$), as were the mean graft-to-recipient weight ratios (1.19 ± 0.28 versus 1.31 ± 0.72; $P = 0.03$) and the mean RLVs (36.2% ± 5.4% versus 60.1% ± 17.4%; $P < 0.001$). In contrast, the mean graft volume was higher in the RG than in the LG (729.4 ± 142.6 g versus 404.4 ± 174.9 g; $P < 0.001$). There were no significant intergroup differences in the proportions of donors with hypertension, diabetes, or history of smoking or alcohol consumption, or in the mean duration of postoperative hospital stay ($P = 0.37$). Table 1 provides the detailed baseline characteristics and demographics.

COMPLICATIONS AND LABORATORY FINDINGS ACCORDING TO GRAFT TYPE AND RLV

The overall, biliary, and major complication rates were 9.3%, 1.7%, and 1.9%, respectively, and were similar in the 2 study groups ($P = 0.64$, $P = 0.62$, and $P = 0.62$, respectively). Furthermore, the graft type did not affect the rates of overall, biliary, or major complications ($P = 0.75$, $P > 0.99$, and $P > 0.99$, respectively). None of the donors died following hepatectomy. Table 2 provides a detailed description of the complication grades by graft type.

Among the 832 donors, the median RLV was 36% (range, 24%-91%). The RLV was not related to overall, biliary, or major complications; postoperative hospital stay; or laboratory findings. In the RG, the median RLV was 35% (range, 24%-69%). The RLV had no significant effect on overall, biliary, or major complications. Among the 24 donors with RLV < 30%, the overall complication rate was 8.3%, and the major complication rate was 4.2%. Among those donors, the mean ALT level 6 months after donation (35.0 ± 36.7 IU/L) was significantly higher than that among donors with RLV ≥ 30% ($P = 0.04$). In contrast, the AST and total bilirubin levels 6 months after donation were not significantly different among donors with different RLVs. The complication rates for different RLV ranges in the RG are summarized in Table 3. Figure 1 shows the distribution of RLV according to donor age among the 733 donors in the RG.

Age, sex, previous laparotomy, diabetes, hypertension, BMI, macrosteatosis, graft type, and RLV were not significant risk factors for overall, biliary, or major

TABLE 1. Baseline Characteristics and Demographics of the 832 Living Donors

	LG (n = 59)	RG (n = 773)	*P* Value
Transplantation type			<0.001
Adult-to-adult	21 (35.6)	770 (99.6)	
Adult-to-child	38 (64.4)	3 (0.4)	
Sex of donor, male:female (male %)	30:29 (50.8)	523:250 (67.7)	<0.001
Age of donor, years	36.8 ± 10.8	31.0 ± 10.7	<0.001
BMI of donor, kg/m^2	24.6 ± 3.6	23.1 ± 3.0	<0.001
Relationship			0.84
Living related donor	52 (88.1)	668 (86.4)	
Living unrelated donor	7 (11.9)	105 (13.6)	
Hypertension	4 (6.8)	25 (3.2)	0.14
Diabetes	1 (1.7)	9 (1.2)	0.52
Smoking			0.67
Never	42 (71.2)	503 (65.1)	
Former	4 (6.8)	52 (6.7)	
Current	13 (22.0)	218 (28.2)	
Alcohol consumption			0.08
None	35 (59.3)	382 (49.4)	
Social drinking	21 (35.6)	372 (48.1)	
Habitual drinking	3 (5.1)	19 (2.5)	
Previous laparotomy	1 (1.7)	31 (4.0)	0.72
Graft volume, g	404.4 ± 174.9	729.4 ± 142.6	<0.001
Graft-to-recipient weight ratio	1.31 ± 0.72	1.19 ± 0.28	0.03
Remnant liver volume, %	60.1 ± 19.4	36.2 ± 5.4	<0.001
Macrovesicular steatosis, %*	6.4 ± 10.4	3.6 ± 4.9	0.05
Hospital stay after LT, days	10.0 ± 2.6	10.7 ± 4.5	0.37

NOTE: Continuous variables are expressed as means ± standard deviations with *P* values calculated using the *t* test. Categorical variables are expressed as n (%) with *P* values calculated using the chi-square or Fisher's exact test. The LG was composed of patients who donated a left lateral segment (or monosegment), left lobe, or extended left lobe graft. The RG was composed of patients who donated a right posterior section, right lobe, or extended right lobe.
*33 of 832 donors did not undergo liver biopsy.

TABLE 2. Donor Complications According to Graft Types Among 832 Living Donors

	LG				RG					
	Left Lateral Segment (n = 18)	Left Lobe (n = 27)	Extended Left Lobe (n = 14)	LG Total (n = 59)	Right Lobe (n = 734)	Extended Right lobe (n = 32)	Right Posterior Section (n = 7)	RG Total (n = 773)	*P* Value*	*P* Value†
Grade										
Grade 0	17 (94.4)	26 (96.3)	12 (85.7)	55 (93.2)	664 (90.5)	30 (93.8)	6 (85.7)	700 (90.6)	>0.99	0.97
Grade I	1 (5.6)	1 (3.7)	1 (7.1)	3 (5.1)	42 (5.7)	2 (6.3)	1 (14.3)	45 (5.8)		
Grade II	0 (0.0)	0 (0.0)	1 (7.1)	1 (1.7)	12 (1.6)	0 (0.0)	0 (0.0)	12 (1.6)		
Grade IIIa	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (1.8)	0 (0.0)	0 (0.0)	13 (1.7)		
Grade IIIb	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.3)		
Grade IVa	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)		
Grade IVb	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Grade V	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Overall complications	1 (5.7)	1 (3.6)	2 (14.3)	4 (6.8)	70 (9.5)	2 (6.3)	1 (14.3)	73 (9.4)	0.75	0.64
Biliary complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (1.9)	0 (0.0)	0 (0.0)	14 (1.8)	>0.99	0.62
Major complications‡	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (2.2)	0 (0.0)	0 (0.0)	16 (2.1)	>0.99	0.62

NOTE: Data are given as n (%). The LG was composed of patients who donated a left lateral segment (or monosegment), left lobe, or extended left lobe graft. The RG was composed of patients who donated a right posterior section, right lobe, or extended right lobe.
**P* values were calculated according to all graft types using Fisher's exact test.
†*P* values of LG versus RG comparisons were calculated using Fisher's exact test.
‡Major complications were defined as those of Clavien grade III or more.

TABLE 3. Complications and Laboratory Findings According to the Remnant Liver Volumes in 773 Right Lobe Donors

	RLV < 30% (n = 24)	RLV = 30%-< 35% (n = 293)	RLV = 35%-< 40% (n = 293)	RLV ≥ 40% (n = 163)	*P* Value
Overall complications	2 (8.3)	36 (12.3)	22 (7.5)	13 (8.0)	0.22
Biliary complications	0 (0.0)	6 (2.0)	4 (1.4)	4 (2.5)	0.75
Major complications*	1 (4.2)	7 (2.4)	4 (1.4)	4 (2.5)	0.48
Hospital stay after LT, days	10.6 ± 3.3	11.1 ± 3.8	10.7 ± 5.1	10.4 ± 4.5	0.63
AST 6 months after donation, IU/L	30.6 ± 17.7	24.5 ± 7.0	24.0 ± 9.3	23.0 ± 7.1	0.13
ALT 6 months after donation, IU/L	35.0 ± 36.7	20.5 ± 10.7	20.3 ± 11.1	21.4 ± 10.1	0.04
Total bilirubin 6 months after donation, mg/dL	0.6 ± 0.2	0.8 ± 0.4	0.8 ± 0.3	0.8 ± 0.4	0.69

NOTE: Continuous variables are expressed as mean ± standard deviations with *P* values calculated by ANOVA. Categorical variables are expressed as n (%) with *P* values calculated by the chi-square or Fisher's exact test.
*Major complications were defined as those of Clavien grade III or more.

complications. Table 4 summarizes the specific donor complications and management procedures for the different Clavien-Dindo grades. Of the 16 major complications, 9 (56.3%) were biliary complications (2 biliary strictures [16.5%] and 7 bile leakages [43.8%]).

Six months after liver donation, the mean AST, ALT, and total bilirubin levels were 22.6 ± 5.6 IU/L, 20.7 ± 9.2 IU/L, and 0.7 ± 0.3 mg/dL, respectively, in the LG and 24.0 ± 8.3 IU/L, 20.9 ± 11.5 IU/L, and 0.8 ± 0.4 mg/dL, respectively, in the RG ($P = 0.44$, $P = 0.94$, and $P = 0.11$, respectively). Figure 2 depicts the laboratory findings 6 months after donor hepatectomy.

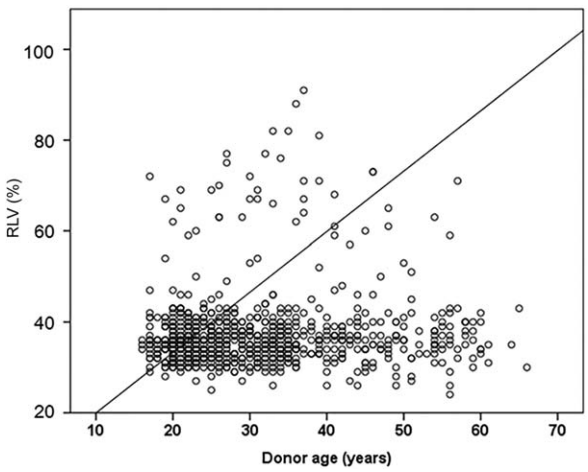

FIG. 1. Association of remnant liver volume with donor age by univariate linear regression (ß ± standard errors = 0.00059 ± 0.00028, $P = 0.04$).

Discussion

Our prospective study indicates the safety of donor hepatectomy in a representative sample of the South Korean population. The rate of major complications requiring intervention or surgery among the donors was 1.9%. There was no mortality among the 832 living liver donors. There was 1 grade IVa complication. In that case, the donor was intubated and placed under ventilator care in an intensive care unit for pulmonary edema 4 days after surgery and was discharged to a general ward 4 days later. All of the donors returned to normal activity and recovered normal or nearly normal liver functions within 6 months of hepatectomy.

LDLT has become an alternative lifesaving method that reduces patient waiting time and mortality.[17] Although recipient outcomes after LDLT are similar or superior to those after DDLT, concerns about donor safety appear to be on the rise. In 2002, Beavers at al. performed a systematic review of 211 published reports and found that donor morbidity varied widely (from 0% to 67%) after right lobe hepatectomy,[5] although at the time, there was no standardized definition of morbidity. In an analysis of 214 published studies of adult liver donors, Middleton et al. reported a donor mortality rate of 0.2%, a median donor morbidity rate of 16.1%, and a biliary complication rate of 6.2%.[4] Adcock et al. reported an overall complication rate of 41% among right lobe donors in a Canadian cohort.[18] Similarly, Lauterio et al. reported a morbidity rate of 33.3% and a major complication rate of 12.6% in an Italian cohort including 220 right lobe donors, 10 left lobe donors, and 15 left lateral segment donors.[19] The donor complication rate is lower in Asia, however, where LDLT is more widely performed

TABLE 4. Specific Complications and Their Management According to Modified Clavien Grades of Overall Complications After Hepatectomy in 832 Living Donors

Grade	Definition	Specific Donor Complications and Management	Number of Cases	Percent of Patients (Percent of All Complications)
I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic, or radiologic intervention. This grade also includes wound infections opened at the bedside.	Bedside wound management for seroma	8	1.0% (10.4%)
		Observation for mild liver enzyme*	4	0.5% (5.2%)
		Observation for mild bilirubin elevation†	1	0.1% (1.3%)
		Observation of mild PV stenosis	2	0.2% (2.6%)
		Observation of mild bile duct dilation	1	0.1% (1.3%)
		Delayed discharge regardless of reason‡	32	3.9% (41.6%)
II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are included.	Delayed drain removal for ascites	1	0.1% (1.3%)
		Delayed drain removal for bile leakage	2	0.2% (2.6%)
		Antibiotics for bile leakage	3	0.4% (3.9%)
		Antibiotics for intra-abdominal fluid collection	7	0.8% (9.1%)
IIIa	Requiring surgical, endoscopic, or radiologic intervention without general anesthesia.	ERBD for bile leakage	3	0.4% (3.9%)
		ENBD for bile leakage	1	0.1% (1.3%)
		ERBD for biliary stricture	1	0.1% (1.3%)
		PTBD for biliary stricture	1	0.1% (1.3%)
		PCD for bile leak leakage	2	0.2% (2.6%)
		PCD for intra-abdominal fluid collection	2	0.2% (2.6%)
		Thoracentesis for pulmonary effusion	1	0.1% (1.3%)
		PV stent placement for PV stenosis	1	0.1% (1.3%)
		Incision and drainage for wound abscess	1	0.1% (1.3%)
IIIb	Requiring surgical, endoscopic, or radiologic intervention with general anesthesia	Surgical wound repair for wound dehiscence	1	0.1% (1.3%)
		Segmental resection of PV for PV stenosis	1	0.1% (1.3%)
IVa	Single-organ dysfunction	Intubation for pulmonary edema and ventilator care in the intensive care unit	1	0.1% (1.3%)
IVb	Multiorgan dysfunction	None	0	0.0% (0.0%)
V	Death	None	0	0.0% (0.0%)

*Patients with elevated AST or ALT > 60 IU/L at 6 months after donation.
†Patients with elevated total bilirubin > 2.0 mg/dL at 6 months after donation.
‡Patients with prolonged postoperative hospital stay >14 days regardless of reason.

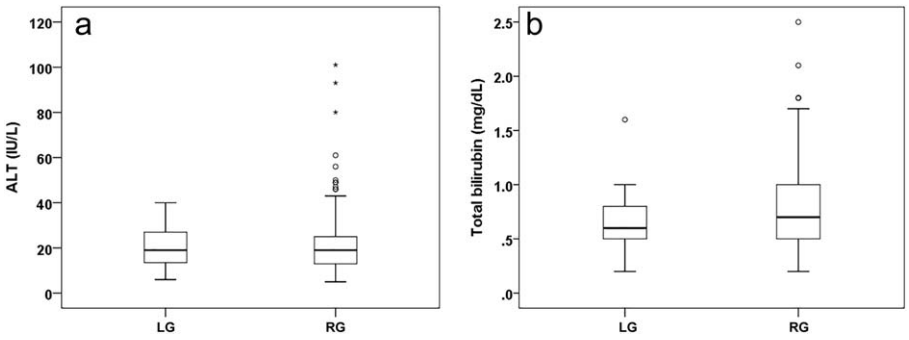

FIG. 2. Laboratory findings 6 months after hepatectomy in 832 living donors. (A) ALT; (B) Total bilirubin.

because of a shortage of deceased donors. In a study of 5 Asian centers, Lo reported an overall complication rate of 15.8% and a reoperation rate among donors of 1.1%.[20] Hwang et al.,[12] Shin et al.,[11] and Suh et al.[10] reported major complication rates of 3.2%, 3.0%, and 1.6%, respectively, in South Korea.

We failed to identify any significant risk factors for overall, biliary, or major complications, because the number of complications in our sample was very small. There were no biliary or major complications in the LG, and the biliary and major complication rates in the RG were 1.8% and 2.1%, respectively. A right lobe graft was previously suggested as a risk factor for donor complications, but a recent large-scale study reported comparable outcomes for right lobe and left lobe donations.[21-23] The volume of the liver graft should be determined to ensure the absolute safety of the donor but also to meet the need of the recipient. Insufficient RLV has been reported to be a major risk factor for donor mortality and morbidity.[24-26] The RLV should be no less than 30%-35% of the initial whole liver volume according to the International Liver Transplantation Society Guidelines.[9] However, Kim et al. reported that there was no significant difference in overall complication between RLV $< 30\%$ and RLV $\geq 30\%$ in liver donor with a preserved middle hepatic vein (MHV), age < 50 years, and no or mild fatty changes.[27] In our study, the median and mean RLV were 36.0% (range, 24.0%-91.0%) and 37.4% $\pm$ 0.8%, respectively, among the 832 donors. There were no statistical differences in laboratory results or complications even between the donors with RLV $< 30\%$ and those with RLV $\geq 30\%$, except for a difference in ALT levels 6 months after donation (Table 3). We propose several possibilities to explain why donors with RLV $< 30\%$ were comparable to donors with RLV $\geq 30\%$ in mortality and morbidity. First, right lobectomy without MHV was the standard procedure (95.0%) in right lobe donation. This technique enabled an improvement in donor safety with the lowest possible loss of hepatic parenchyma and retention of the MHV in the remnant.[9] Second, young donors could tolerate relatively small RLVs (Fig. 1). More study is needed to determine the nature of the relation between RLV and complication rates. Unfortunately, because our study was not a randomized controlled study, it included only a small number of donors with RLV $< 30\%$ (n = 28, 3.4% of donors).

Our study has several limitations that warrant consideration. First, the prospective cohort data did not contain information on specific intraoperative factors, such as intraoperative bleeding or operation times. Second, we were unable to compare minimally invasive hepatectomy with open donor hepatectomy. Third, because of the short follow-up period, we were unable to access longitudinal changes. Nonetheless, our study is one of the largest prospective registry studies to be conducted for LDLT-associated donor complications.

In conclusion, biliary complications were the most common type of major donor complication among living liver donors. Donor hepatectomy can be performed successfully with minimal and easily controlled complications. Our study shows that prospective, nationwide cohort data provide an important means of investigating the safety in living liver donation.

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