Post-operative outcome among donors of liver transplantation, retrospective study

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Background
Living donor liver transplant (LDLT) is an accepted and widely practiced modality for treatment of end-stage liver disease. Donor safety has always been of paramount importance.
Aim
To evaluate donor complications in LDLT.
Patients and methods
This retrospective study was conducted at Ain Shams Specialized University Hospital (ASUSH) and Wadi El Nile Hospital on 1000 donors (all donors underwent LDLT from January 2001 till March 2020). They underwent clinical assessment and radiological and pathological investigations.
Results
Only 36 (3.6%) cases of 997 donors had advanced Clavien gradient scores (grade III, grade IV, and grade V) with only two deaths, one following sepsis after bile leakage and the other due to massive pulmonary embolism in LDLT, from January 2001 to March 2020 at Ain Shams University Hospital and Wadi El Nile Hospital.
Conclusion
LDLT is an accepted and widely practiced modality for treatment of end-stage liver disease. Donor safety has always been of paramount importance. Our center had very good outcomes following donor hepatectomies, and most donors returned to their predonation work within a reasonable period. Their willingness to donate again also further reinforced our results. Meticulous workup and strict adherence to protocols were the major reason we attribute to this. The Clavien grading system is useful to evaluate and compare surgical outcomes among various surgeons and centers.

Keywords:
donors, liver transplantation, postoperative complications

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Introduction

Liver transplantation is probably the only treatment strategy in patients with terminal liver diseases. However, despite the tremendously growing demand for available organs and mortality of the waiting list, the amount of grafts available is low. This disparity facilitates a more open acceptance of livers procured from other channels, including living-donor liver transplantation (LDLT). As an alternative of cadaveric liver transplantation, LDLT was first attempted in 1988 [1] and was successfully performed in 1990. Several advantages, such as shorter waiting time, no warm ischemia time, and diminished cold ischemia time [2], make LDLT an ideal solution, especially when no other grafts are available and the surgery is urgent.

In spite of all the benefits, the safety of living donor remains controversial. Since the adoption of the right lobe liver for LDLT [3], concerns about a perfectly healthy donor receiving a major hepatectomy have emerged, though the risk is low but almost definite. According to a recent survey, the average prevalence rates of mortality and morbidity are 0.2 and 24%, respectively [4]. The current consensus is that the donor age, degree of steatosis, and remnant liver volume (RLV) are the most important predictive factors for donor safety, and the right lobe of liver is the most ideal graft to avoid poor recipient outcomes [5].

Postoperative complications in LDLT are evaluated with the modified Clavien classification system. Clavien and Dindo introduced a classification system of surgical complications in 1992, which was modified to assess living donor scenarios by Broering in 2004. In

light of the apparent risks to the donors, several large centers have documented LDLT outcomes. However, the incidence rates of complications differ widely [3].

Aim

In this study, we aimed to evaluate donor complications in LDLT.

Patients and methods

Approval was taken from the ethical committee, and written informed consents were obtained from each donor and each recipient. Moreover, approval was obtained from the ethics and indication committees at our institution for each LDLT procedure as well as the supreme committee of organ transplant, MOH, Egypt. This retrospective study was carried out on 1000 donors. All donors underwent LDLT from January 2001 till March 2020 at Ain Shams Specialized University Hospital (ASUSH) and Wadi El Nile Hospital.

The study included all donors who had a blood group that matched with the recipient, had ages varying between 18 and 50 years, were medically free with no history of malignancy, had BMI less than 28, and had steatosis less than 10% in liver biopsy.

However, patients with ABO incompatibility, ages less than 18 or more than 50 years old, medical comorbidities, history of upper abdominal operations, steatosis more than 10% in liver biopsy, and RLV less than 35% in computed tomography (CT) volumetry were excluded from the study.

Ethical considerations

All patients included in the study were meticulously assessed and were informed about the operation and its risks, the technique, and postoperative course.

Study procedures

All patients were subjected to the following:

Preoperative assessment

Clinical assessment, including careful history taking, general condition assessment, local examination, full assessment (psychological, chest, and cardiological consultations), and BMI calculation

Investigations (radiological and pathological): routine preoperative investigations (blood grouping, complete blood count, biochemistry, liver function test, coagulation profile, renal function test, iron studies, and viral serology screening), thrombophilia gene assessment, imaging studies (i.e. abdominal ultrasound, CT scan, angiography with volumetry, and magnetic resonance cholangiopancreatography), liver biopsy and pathology, and cardiological assessment with ECG and Echo.

Operative procedure

A hockey stick skin incision was done. Liver mobilization was done, and then size of the graft, residual liver volume for donor, and quality of the graft were roughly assessed. Fatty appearance of the liver indicates frozen section.

Full mobilization of the right lobe of the liver was initiated, and after dissection of the ligaments around the liver, dissection of the liver from infereior vena cava was done (piggyback maneuver).

Cholecystectomy was then done with primary cholangiography through cystic duct stump. This indicates number and type of biliary anatomy, right or left hepatic pedicle, with preparation of hepatic artery and portal vein.

Intraoperative ultrasound was done to identify the intraparenchymal hepatic veins for segment 5 or 8. The middle hepatic vein was localized and marked, and hepatic transaction imaginary line was drawn. Interlobar plain could be known also by right or left pedicle clamping. Discoloration of the clamped pedicle lobe occurs in seconds. Dissection of the required lobe is done with preservation of the anatomy of each lobe. The following parameters were assessed: right or left lobe, weight of the graft, intraoperative duplex, operative time, and back table.

Postoperative care

The donor is transferred postoperatively to the ICU and then to the ward when clinically and hemodynamically stable.

Follow-up

The patients were followed up for 3 months, early (during the first month) and late (during second and third months).

Clinical assessment included the following:

(1) Vital data, including pulse, temperature, blood pressure, and respiratory rate to detect any hemodynamic instability and respiratory complications.
(2) Bowel habits: drain amount and color of the drain.

Laboratory assessments

Complete blood picture, serum chemistry, and coagulation profile were done every daily during the

first week, then day after day for 2 weeks, and then once weekly for 2 months.

Radiological assessments

Abdominal duplex ultrasonography was done daily during the first week, then day after day for 2 weeks, and then once weekly for 2 months.

Detection of postoperative complications was done as bile-stained discharge from the drain and confirmed by measuring the amount of total bilirubin in the drain as compared with that of the serum of the donor. Bloody discharge from the drain was confirmed by measuring the amount of hemoglobin in the drain compared with that of the hemoglobin level of the donor. Drain was removed when it stops to drain or after being completely sure that there is no bile leak.

Postoperative complications were recorded. An initial classification of grading of severity of postoperative complications was advocated by the modified Clavien classification, and it was used by some studies to evaluate donor's complications.

Informed consent

Informed consent was obtained from patients in the research. All of the patient data are confidential, and the patient was not mentioned by name in any published paper.

Statistical analysis

The data were collected tabulated and statistically analyzed. Description of quantitative variable was done as mean and SD and qualitative data as frequency. χ^2 test was used to compare the groups regarding qualitative variables. Student *t* test was used to compare groups regarding quantitative variables in parametric data. The results were considered significant (S) with *P* value less than 0.05 and highly significant (HS) with *P* value less than 0.01. *P* value more than or equal to 0.05 was considered nonsignificant (NS). Analysis of data was done using IBM SPSS software (Statistical Package for the Social Sciences, version 23.0, Armonk, NY: IBM Corp).

Results

The results present the demographic data of the donor, type and characteristics of the graft, and intraoperative and postoperative complications, which will be compared with the results of LDLT in other centers.

Table 1 shows that this study was conducted on a wide age group, ranging from 18 to 50 years (mean age, 27.73 ± 5.99 years). There was a male predominance, with a male-to-female ratio of about 3.2 : 1. Their weight ranged from 21 to 98 kg, with mean±SD of 71.48 ± 9.60 kg. As for the BMI [wt/(ht)^2], it ranged from 20 to 28 kg/m^2, with a mean of 24.36 ± 2.86 kg/m^2. Regarding relationships, 60.4% were related and 39.6% were unrelated. The majority of patients had a blood group of O+ve (51.4%). Overall, 16.9% of donors had previous surgery.

Table 1 Baseline characteristics distribution among the study group

Baseline characteristics	Total (*N*=997) [*n* (%)]
Age (years)	
Range	18–50
Mean±SD	27.73 ± 5.99
Sex	
Female	237 (23.8)
Male	760 (76.2)
Weight (kg)	
Range	21–98
Mean±SD	71.48 ± 9.60
BMI [wt/(ht)^2]	
Range	20–28
Mean±SD	24.36 ± 2.86
Previous surgery	
Surgery	169 (16.90)
No surgery	828 (83.049)
BL group	
A–ve	21 (2.1)
A+ve	266 (26.7)
AB–ve	2 (0.2)
AB+ve	52 (5.2)
B–ve	11 (1.1)
B+ve	113 (11.3)
O–ve	20 (2.0)
O+ve	512 (51.4)
Relations	
Related	602 (60.4)
Unrelated	395 (39.6)

Table 2 Factor V mutation distribution among the study group)

Factor V mutation	Total (*N*=997) [*n* (%)]
Not available	510 (51.2)
Normal	481 (48.2)
Heterozygous	6 (0.6)

Table 2 shows that factor V data are not available in 510 (51.2%) donors, 481 (48.2%) donors were normal, and six (0.6%) donors were heterozygous according to factor V mutation.

Table 3 shows that 973 (97.3%) donors had less than 10% steatosis, 21 (2.1%) donors had 10% steatosis, and three (0.3%) donors had 15% steatosis according to liver biopsy.

Table 4 shows that 953 (95.5%) donors had right lobe graft without Middle hepatic vein (MHV), two (0.2%)

Table 3 Liver biopsy distribution among the study group (*N*=997)

Liver biopsy	*n* (%)
<10% steatosis	973 (97.5)
10%	21 (2.1)
15%	3 (0.3)

Table 4 Type of the graft among the study group (*N*=997)

Type of the graft	*n* (%)
Right lobe without MHV	953 (95.5)
Right lobe with MHV	2 (0.2)
Left lobe graft	8 (0.8)
Left lateral graft	34 (3.4)
V5	165 (16.5)
V8	254 (25.5)
Mackotchi	160 (16.0)

Table 5 Types of portal vain distribution among the study group (*N*=997)

Types of portal vain	*n* (%)
Type 1	944 (94.7)
Type 2	43 (4.31)
Type 3	9 (0.9)
Type 4	1 (0.1)
Total	997 (100.0)

Table 6 Hepatic artery origin among the study group (*N*=997)

Hepatic artery	*n* (%)
Right	
Celiac trunk	931
SMA	42 (96)
Single origin	917 (3.97)
Double origin	38
Left	
Celiac trunk	42
Left gastric artery	6
Single origin	39 (92.8)
Double origin	3 (7.1)

donors had right lobe with MHV, eight (0.8%) donors had left lobe graft to adult recipients, and 34 donors had left lateral graft to pediatric recipients. A total of 165 (16.5%) donors had V5 and 254 (25.5%) donors had V8. Moreover, 160 (16%) donors had MACKOTCHI according to accessory hepatic veins intraoperatively.

Table 5 shows that 944 (94.7%) donors had type 1, 43 (4.3%) donors had type 2, nine (0.9%) donors had type 3, and only one (0.1%) donor had type 4.

Table 6 shows single right hepatic artery origin in 917 (96%) donors and double origin in 38 (3.97%) donors among those with right hepatectomy, whereas left hepatic artery had single origin in 39 (92.8%) donors and double origin in three (7.1%) donors % among those with left hepatectomies.

Table 7 Bile duct distribution among the study group (*N*=997)

Bile duct	*n* (%)
Single duct	360 (36.1)
Two ducts	513 (51.4)
Three ducts	122 (12.2)
Four ducts	2 (0.2)

Table 8 Remnant liver volume % distribution among the study group (*N*=997)

RLV%	Statistics
30–35%	235 (23.6)
>35%	762 (76.4)
Range	30–74.30
Mean±SD	41.27 ± 10.62

RLV, remnant liver volume.

Table 9 Graft weight (g) distribution among the study group (*N*=997)

Graft weight (g)	Total (*N*=997) [*n* (%)]
Graft weight	
Range	280–1500
Mean±SD	892.53 ± 157.43
Actual WT	
Range	280–1330
Mean±SD	771.46 ± 227.16
Difference	
Range	–392 to 362
Mean±SD	–53.80 ± 116.37
Level change weight	
The same	5 (0.5)
Negative value	683 (68.5)
Range	–392 to –1
Mean±SD	–109.02 ± 87.22
Positive value	309 (31.0)
Range	2–362
Mean±SD	67.38 ± 53.51

Table 7 shows that most donors had two ducts [513 (51.4%) donors], followed by single duct [360 (36.1%) donors], then three ducts [122 (12.2%) donors], and the least had four ducts [two (0.2%) donors], according to bile duct distribution within the graft of the donors.

Table 8 shows that 235 (23.6%) donors had RLV% from 30 to 35% and 762 (76.4%) donors had RLV% of more than 35%. The RLV% ranged from 30 to 74.3%, with a mean of 41.27 ± 10.62.

Table 9 shows that five (0.5%) donors had the same change, 683 (68.5%) donors had negative value, and 309 (31%) donors had positive value according to graft weight (g).

Table 10 shows that the mean±SD bilirubin highest level was 3.76 ± 2.00, mean±SD highest international normalized ratio level was 2.17 ± 0.43, mean±SD highest aspartate aminotransferase level was 333.47 ± 177.09,

Table 10 Laboratory data distribution among the study group (*N*=997)

Laboratory data	Total
Bilirubin highest level	
Range	0.85–15.8
Mean±SD	3.76±2.00
Day of highest level	
Range	1–19
Median (IQR)	1 (1–2)
Day return to normal bilirubin level	
Range	1–45
Median (IQR)	6 (5–7)
Highest INR	
Range	1.2–5.2
Mean±SD	2.17±0.43
Day of INR to normal	
Range	1–17
Median (IQR)	5 (4–6)
Highest AST	
Range	117–1980
Mean±SD	333.47±177.09
Day of normal AST	
Range	3–24
Median (IQR)	7 (6–8)
Highest ALT	
Range	58–1820
Mean±SD	385.15±180.23
Day of normal ALT	
Range	3–23
Median (IQR)	8 (7–10)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; IQR, interquartile range.

Table 11 Operation distribution among the study group (*N*=997)

Operation	Total
Operation time (h)	
Range	3–9.5
Mean±SD	6.30±1.01
Intraoperation blood loss (ml)	
Range	100–2440
Mean±SD	233.19±197.37
Cell saver (*N*=207)	
Range	100–2400
Mean±SD	499.88±312.82

mean±SD highest alanine aminotransferase level was 385.15±180.23, day of highest bilirubin level was 1 (1–2), day return to normal bilirubin level was 6 (5–7); day of international normalized ratio to normal was 5 (4–6); day of normal aspartate aminotransferase was 7 (6–8), and day of normal alanine aminotransferase was 8 (7–10).

Table 11 shows that the operation time ranged from 3 to 9.5 h, with mean±SD of 6.30±1.01 h. The intraoperative blood loss ranged from 100 to 2440 ml, with mean±SD of 233.19±197.37 ml, and cell saver range was 100–2400, with a mean±SD of 499.88±312.82.

Table 12 Postoperative complications distribution among the study group (*N*=997)

Postoperative complications	*n* (%)
Bleeding	
Management:	13 (1.3)
Conservative	5 (38.4)
Exploration	8 (61.5)
Bile leak transfusion	6 (0.6)
Bile leak	
Management:	40 (4.01)
Conservative	25 (62.5)
Conservative with pig-tail drainage	14 (35)
Exploration and drainage of collection	1 (2.5)
Biliary stricture	
Management	2 (0.2)
ERCP and stent	2 (100.0)
Ascties	
Management	17 (1.7)
Conservative	15 (88.2)
Conservative with pig tail	2 (12)
Pancreatitis	
Management	4 (0.4)
Conservative	4 (100.0)
Reoperation	
Cause	13 (1.3)
Bile leakage	1 (7.69)
Bleeding	8 (61.5)
Elevated liver enzymes due to weak flow of left portal vein	1 (7.69)
Intestinal obstruction	2 (15.38)
Portal vein thrombus	1 (7.69)
Wound infection	
Management	20 (2)
Antibiotic and dressing	20 (100.0)
Incisional H	4 (0.4)
PL effusion	
Management	73 (7.3)
Conservative	73 (100.0)
Acute DVT	4 (0.4)
Intestinal obstruction	4 (0.4)
Pulmonary embolism	3 (0.3)
Liver decompensation	1 (0.1)
Suicidal attempt	1 (0.1)
Death	2 (0.2)

ERCP, endoscopic retrograde cholangiopancreatography.

Table 12 shows postoperative complications. There were 13 (1.3%) donors who had postoperative bleeding; five (38.4%) donors were treated with conservative management, eight (61.5%) donors needed exploration to stop bleeding. Moreover, six (0.6%) donors needed blood transfusion. Regarding biliary leakage, 40 (4.01%) donors experienced bile leak, with 25 (62.5%) donors treated with conservative management, 14

(35%) donors treated conservatively with pig-tail drainage, and exploration and drainage of collection in one (2.5%) donor. Furthermore, biliary stricture was found in two (0.2%) donors and were treated with endoscopic retrograde cholangiopancreatography and stent (100.0%). Ascites was present in 17 (1.7%) donors with 15 (88.2%) donors being treated conservatively and with pig-tail insertion in two (12%) donors. Moreover, four (0.4%) donors experienced pancreatitis and were treated with conservative management (100%). Reoperation occurred in 13 (1.3%) donors, where eight (61.5%) donors were reoperated owing to bleeding, two (15.38%) donors owing to intestinal obstruction, one (7.69%) donor owing to bile leakage, one (7.69%) donor owing to elevated liver enzymes due to weak flow of left portal vein with resection of the left stump and anastomosis with the main portal vein, and one (7.69%) donor with PVT was reoperated with removal of thrombus with packs under the liver to keep the flow and then reoperated again for removal of packs. It is clear that wound infection was seen in 20 (2%) donors and were treated with antibiotic and dressing (100.0%). In addition, incisional H was present in four (0.4%) donors. Pleural effusion was present in 73 (7.3%) donors, who were treated with conservative management (100.0%). Moreover, four (0.4%) donors experienced acute Deep venous thrombosis (DVT) and were treated conservatively; four (0.4%) donors experienced intestinal obstruction, where two (50%) were managed conservatively and two (50%) needed exploration; three (0.3%) donors had pulmonary embolism, where two (66.7%) were managed conservatively and one (33.3%) died; there was just one (0.1%) suicidal attempt; and lastly, two (0.2%) donors died, one due to pulmonary embolism and the other owing to sepsis after bile leak and exploration.

Table 13 shows that 188 (18.8%) donors had 'complications' and 809 (81.14%) donors had 'no complications' according to overall complications after operation.

Table 14 shows a highly statistically significant higher mean value in the complication group compared with the no-complication group according to ICU stay (days), with *P* value less than 0.001.

Table 15 shows a highly statistically significant higher mean value in the complication group compared with the noncomplication group according to hospital stay (days), with *P* value less than 0.001.

Table 16 shows that 90 (47.87%) donors of 188 donors had grade I complication according to the modified Clavien grading of surgical complications, 61 (32.4%) donors had grade II, 34 (18%) donors had grade III, one (0.5%) had grade IV (liver transplantation) due to liver decompensation, and two (1%) had grade V death, one of them owing to bile leakage and exploration followed by sepsis and death, and the other owing to massive pulmonary embolism and death.

Table 13 Overall complications after operation distribution among the study group (*N*=997)

Overall complications after operation	*n* (%)
No complications	809 (81.14)
Complications	188 (18.8)
Total	997 (100.0)

Table 14 Comparison between no complications and complications according to ICU stay 'days'

ICU stay (days)	No complications (*N*=792)	Complications (*N*=205)	*U* test	*P* value
Mean±SD	2.71±0.69	2.97±0.97	18.968	<0.001**
Range	1–4	1–5		

**Highly significant.

Table 15 Comparison between no complications and complications according to hospital stay 'days'

Hospital stay (days)	No complications (*N*=792)	Complications (*N*=205)	*U* test	*P* value
Mean±SD	11.13±2.69	16.91±8.10	283.077	<0.001**
Range	5–28	8–41		

**Highly significant.

Table 16 The number and percent of complications according to modified Clavien grading of surgical complications

Grades	*n* (%)
Grade I	90 (47.87)
Grade II	61 (32.4)
Grade III	34 (18)
Grade IV	1 (0.5)
Grade V	2 (1)

Discussion

Liver transplantation was previously accepted as the only effective treatment for patients with end-stage liver disease. However, this management was limited by the widening gap between organ availability and need, which is the result of the worldwide graft shortage [6].

Since the introduction of LDLT in 1989, nearly 4000 adult to child LDLTs and over 2000 adult-to adult LDLTs have been performed worldwide [7].

The Ethics Committee of the Transplantation Society recently recommended that transplantation of nonrenal organs from living donors should be done only when

the aggregate benefits to the donor–recipient pair (survival, quality of life, psychological, and social well-being) outweigh the risks to the donor–recipient pair (death, medical, psychological, and social morbidities) [8].

In LDLT, the availability of a living donor is a serious problem, because such candidates are limited to family members, especially in Japan [9].

In our study, the mean donor age was 27.73 ± 5.99 years, with a range of 18–50 years, with the maximum age for donation being 50 years, as restricted by the Egyptian Ethical Committee, and also the higher the age, the higher risk of other comorbidities and less power of regeneration. This was nearly similar to the study by Fernandes *et al.* [10], in which the overall mean age was 31 years (range, 18–46 years).

Moreover, in a study by Sevmis *et al.* [11], the donors were younger than 50 years old in 117 (92.1%) cases of volunteers, and in a study by Rafik *et al.* [12], all donors were adults younger than 60 years. Moreover, in a study by Umeshita *et al.* [13], the mean donor age was 37 years (median, 35 years; range, 17–69 years).

In our study, donors comprised 760 (76.2%) males and 237 (23.8%) females, with a male : female ratio of 3.2 : 1. This is in contrast to what was reported in a study by Marsh *et al.* [14], which was done on 121 donors, where 55% were females and 45% were males. Moreover, in a study by Umeshita *et al.* [13], which was done on 1841 donors, 943 were men and 898 were females, and a male : female ratio of 1 : 1, with the mean age being 27.73 ± 5.99 years and range of 18–50 years.

In our study, donors are most frequently related to the recipient; 602 (60.4%) donors were either offspring of their parents or siblings among each other, which could reflect the strong family relationship encountered in the Egyptian society. Moreover, to a lesser extent, unrelated donors represented 395 (39.6%) individuals who were approved by the ethical committee as there were no compatible relatives as donors in the recipient's family and the only curable strategy was transplantation.

Moreover, in the study by Sevmis *et al.* [11], the most frequent relationship between the donor and recipient was the first degree (76%).

In a study by Rafik *et al.* [12], two-thirds of donors were biologically related to the recipient as adult sons and daughters. In another study by Umeshita *et al.* [13], parents were the most common donors, but in a study by Fernandes *et al.* [10], the majority of donors (83%) were related up to the fourth degree (cousin or uncle).

In our study, BMI was done for all potential donors as a part of the evaluation process to identify the obesity and hepatic steatosis. It was found that the mean BMI of the donors was 24.36 ± 2.86 kg/m^2, with a range of 20–28 kg/m^2, with 648 (65.0%) donors with BMI 20–25 kg/m^2 and 349 (35.0%) donors with 25–28 kg/m^2. The maximum accepted BMI was 28 kg/m^2 as they had a low degree of steatosis and low risk of postoperative complications. It was noted that there were 973 (97.5%) donors with less than 10% steatosis, 21 (2.1%) had 10% steatosis, and three (0.3%) donors had 15% steatosis. The maximum accepted percentage of steatosis in liver biopsy was less than 10% in right lobe donations and 15% in left lobe donations to decrease the incidence of postoperative complications such as prolonged cholestasis, ascites, and decrease in the power of regeneration.

A study by Rinella *et al.* [15] showed that 78% of potential donors with a BMI greater than 28 kg/m^2 had hepatic steatosis (>10% steatosis) on liver biopsy.

Ryan *et al.* [16] reported that 73% of overweight (BMI >25 kg/m^2) donors had little or no hepatic fat and 9% of candidates with a BMI of 25 kg/m^2 or less had 10% or greater steatosis.

Regarding vascular and thromboembolic manifestations, the factor V Leiden (FVL) mutation is the most common genetic defect that predisposes to venous thrombosis [17].

FVL heterozygosity increases the lifetime risk of venous thrombosis by 5–10-fold and 50–80-fold in homozygous individuals [18].

The FVL mutation causes factor Va to be resistant to cleavage by activated protein C, resulting in more factor Va being available, thereby increasing the generation of thrombin. Thus, the FVL mutation and the resultant activated protein C resistance cause a hypercoagulable state [19].

Previously, as stated, it is a matter of debate whether potential donors with a mildly increased risk for thrombotic events as in heterozygote carriers of a FVL gene mutation should be excluded from donation [20].

In our study, we have 481 (48.2%) donors with normal FVL, six (0.6%) donors with heterozygous mutation, and 510 (51.2%) donors with no available laboratory

data about this gene mutation, as it was not routinely done in the early years of transplantation.

In our study, the majority of the grafts [953 (95.5%) cases of transplantation] were right lobe without MHV, two (0.2%) cases had right lobe with MHV, eight (0.8%) cases had left lobe graft to adult recipient, and 34 (3.4%) cases had left lateral graft to pediatric recipient.

Based on studies of hepatic resection in animals and humans, it appears that the minimum amount of liver necessary to sustain normal hepatic function is ~30% of total liver volume, which corresponds to 0.8 g/kg of body weight [21].

In our study, the mean remaining liver volume was 41.27 ± 10.62%, with a range of 30–74.3%.

This is similar to the study by Fernandes *et al.* [10], in which according to the Brisbane nomenclature system, they performed 49 right hepatectomies, two left hepatectomies, and 49 left lateral segmentectomies. However, in a study by Umeshita *et al.* [13], the left lateral segment graft was the graft most used, followed by left lobe graft and right lobe graft. This is due to high number of pediatric transplantation cases in this study.

In this study type 1, type 2, and type 3 portal veins are accepted as LDLT, whereas type 4 is rejected with intraparenchymal partition of anterior portal vein branch, orifices are far away from each other, not allowing for direct back-wall plasty, and the only case done in our center was accidentally discovered intraoperatively.

In our study, abdominal ultrasound, triphasic CT of the abdomen and pelvis, CT angiography, and magnetic resonance cholangiopancreatography were done for all donors for the assessment of the donor livers and to detect their anatomical variations.

Guo-Qiang *et al.* [22] reported that with advances in radiologic evaluation of the liver, donors could be safely evaluated and liver resection approaches could be planned with new imaging techniques.

A number of studies by Bogetti *et al.* [23] and Fulcher *et al.* [24] have shown excellent correlation between MRI or CT angiography and conventional angiography in the delineation of hepatic vascular anatomy. Other studies by Kopka *et al.* [25] and Kanematsu *et al.* [26] have concluded that CT and MR angiography are inadequate for the detection of portal and hepatic arterial anatomy.

The role of liver biopsy in the donor evaluation process varies greatly from center to center. Some centers perform liver biopsy on all potential donors, whereas others perform liver biopsy on potential donors based only on clinical findings, which suggest some degree of concern regarding histological status of the liver, for example, significant history of alcohol intake, BMI greater than 28 kg/m^2 (selected patients), elevated serum ferritin level, presence of steatosis on imaging studies, and so on. Protocol liver biopsies in an otherwise suitable donor with normal liver function test results may discover minimal abnormalities (minimal portal inflammation or <10% steatosis) [27].

Brandhagen *et al.* [21] reported that it is best to perform a liver biopsy in most, if not all, donor candidates. The group in which a liver biopsy reasonably may be avoided is patients with a BMI less than 25 who do not have diabetes, hypertension, or a history of excess alcohol consumption. In addition, they also should have normal liver test results and lipid levels and undergo tests to exclude chronic liver disease and hepatic imaging studies.

A survey by Brown *et al.* [28] of transplant centers reported that liver biopsy was performed routinely in all donors by only 14% of centers and never performed at 26% of centers.

In our study, 976 (97.9%) donors had histologically normal liver with steatosis less than 10%; whereas 14 (1.4%) donors showed steatosis more than 10% and seven (0.7%) donors showed minimal to mild periportal fibrosis.

Marsh *et al.* [14] reported in a study done on 121 donors that macrovesicular steatosis was 5.46 ± 7.18%. In addition, in a study by Brandhagen *et al.* [21], steatosis has been reported in one-third to one-half of living donor candidates undergoing liver biopsy as a standard part of the donor evaluation. A study by Ryan *et al.* [16] found that microvesicular steatosis in only 5% of donor livers.

Ryan *et al.* [16], Rinella *et al.* [15], and Marcos *et al.* [29] reported that the maximal acceptable amount of steatosis in the donor liver varies among LDLT programs and ranges from 10 to 30%. In our center, the same range of steatosis in liver biopsies is accepted.

A study by Marcos *et al.* [29] also found no difference in donor or recipient liver function or regeneration if donor hepatic steatosis was less than 30%.

In our study, the graft weight ranges from 280 to 1500 g, with a mean weight of 892.53 ± 157.43 g by CT volumetry, and the actual weight ranges from 280 to 1330, with a mean weight of 771.46 ± 227.16 g, so the difference ranges −392 to −362, with a mean difference of −53.80 ± 116.37.

Similar to our study, Leelaudomlipi *et al.* [30], in a study of 155 living donors, showed a good linear correlation between right hepatic liver volume determined by volumetric CT and actual weight at the time of surgery. Moreover, a study by Kamel *et al.* [31] reported good interobserver agreement in volumetric measurement of the right liver by CT.

In contrast to this, a study by Fan *et al.* [3] reported variation between 3.9 and 12.5% for liver volumes determined by MRI compared with actual weight at surgery in 17 donors undergoing right or left hepatectomies.

In our study, the mean operative time was 6.30 ± 1.01 h (range, 3–9.5 h). In a study by Fernandes *et al.* [10], the operative time averaged 7.15 h, with a range of 4–10.5 h.

Bleeding is a major risk in liver resection, and excessive bleeding necessitates transfusion, which carries additional risks. Therefore, the ultimate goal of a donor hepatectomy is a bloodless operation.

In our study, the mean operative blood loss was 233.19 ± 197.37 ml, with range from 100 to 2440 ml blood, with cell saver transfusion of 499.88 ± 312.82 ml. However, in a study by Sevmis *et al.* [11], the operative blood loss was 500 ml or less in 115 (90.5%) donors, 501–1000 ml in four (3.1%), 1001–2000 ml in six (4.7%) donors, and blood loss 2000 ml in two (1.55%) donors.

A study done in five Asian medical centers showed that blood loss less than 1000 ml can be achieved in nearly 95% of the donor operations, and only 0.5%, or approximately one in 200 donors, may require banked blood transfusion. The incidence of complications, however, remains high at 15.8% and complications tend to be more common and more serious in right lobe donors. Although there was no hospital mortality in the present survey of 1508 living liver donors in the five Asian centers, some of the more serious complications such as portal vein thrombosis could potentially have been fatal if the diagnosis and treatment had been delayed [32].

In our study, the mean ICU stay was 2.77 ± 0.76 days, whereas in a study by Liu *et al.* [33], the mean ICU stay was less than 48 h.

In our study, the mean hospital stay was 12.32 ± 4.96 days, with a range of 5–41 days. On comparison between without complications and with complications, the duration of ICU stay was 2.71 ± 0.69 and 2.97 ± 0.97, respectively, and hospital stay was 11.13 ± 2.69 (range, 5–28) and 16.91 ± 8.10 (range, 8–41) days, respectively, which revealed increase in the duration with parallel increase in the cost of stay. In a study by Umeshita *et al.* [13], the mean postoperative hospital stay was 15.6 days, with a range of 4–124 days, whereas in a study by Fernandes *et al.* [10], the mean length of hospital stay was 6.5 days, with a range of 4–14 days.

In our study, 13 (1.3%) donors needed reoperation related to donor hepatectomy. Of them, eight underwent relaparotomy on the same day or the next day of surgery to explore bleeding, mostly owing to bleeding in the cut surface; all were successfully controlled. One needed reoperation owing to significant bile leak. One needed reoperation owing to elevated liver enzymes due to weak flow of left portal vein with resection of the stump and reanastamosis with the main portal vein. Two cases were reoperated due to intestinal obstruction, one due to extensive adhesions between the bowel and cut surface and the other due to diaphragmatic hernia. Another case was reoperated due to postoperative compromised main portal vein flow after closure of right portal vein stump that needed relaparotomy and removal of main portal vein thrombus with packing and then reoperation again for removal of packs, and the donor was fully recovered.

In a study by Umeshita *et al.* [13], 23 (1%) donors of 1841 donors needed reoperation related to hepatectomy. Surgery for biliary complications was done in 10 donors. Six were operated for intestinal obstruction, two of whom needed resection of part of the small intestine. In two, who developed gastric stasis, adhesions between the stomach and the cut surface of the liver were divided. Incisional hernia was repaired in two. Other reasons for reoperation were intra-abdominal bleeding, abdominal sepsis, and portal thrombus formation.

In our study, the right lobe donors [51 (79.7%) donors] had more complications than those [13 (20.3%) donors] who had procedures involving the lateral segment or left lobe. This was also revealed by a study by Umeshita *et al.* [13].

In our study of 997 donors who underwent liver resection for living-donor liver donation between January 2001 and March 2020, postoperative morbidity was 18.7% (187 donors), with 48.12% (90) of donors having grade I complications, 61 (32.6%) donors had grade II complications, 33 (17.6%) donors had grade III, one (0.5%) donor had grade IV complications, and two (1%) donors had grade V complication according to Clavien system for classification of negative outcomes in General Surgery and Solid Organ Transplantation.

The most frequent complication was pleural effusion [73 (7.3%) donors], which was managed conservatively (100%), followed by biliary complications [42 (4.2%) cases]. There were 40 (4%) donors with postoperative biliary leak and only two (0.2%) donors had biliary stricture. These cases were managed as follows: 25 cases with biliary leak improved and the leak has stopped with only conservative treatment (operative drain), 14 cases needed pig-tail application, and one case needed re-exploration but sepsis and death occurred. Two donors had biliary stricture managed by endoscopic retrograde cholangiopancreatography and stent insertion in common bile duct.

The third most frequent complication was found to be wound infection, which was managed conservatively. A total of four (0.4%) donors experienced pancreatitis and treated with conservative management (100%). Reoperation occurred in 13 (1.3%) donors, where eight (61.5%) donors were reoperated due to bleeding, two (15.38%) donors due to intestinal obstruction, one (7.69%) donor due to bile leakage, one (7.69%) donor due to elevated liver enzymes due to weak flow of left portal vein, and one (7.69%) donor with PVT reoperation and removal of packs. Incisional hernia was present in four (0.4%) donors. Moreover, four (0.4%) donors experienced acute DVT and treated conservatively, whereas four (0.4%) donors experienced intestinal obstruction, where two (50%) were managed conservatively and two (50%) needed exploration. In addition, three (0.3%) donors experienced pulmonary embolism, where two (66.7%) were managed conservatively and one (33.3%) died. Suicidal attempt was seen in one (0.1%) case, which was managed conservatively without any residual disturbance in function or disability. Lastly, two (0.2%) donors died, one due to massive pulmonary embolism and the other due to sepsis after bile leak and exploration.

In a study by Fernandes *et al.* [10], the most common postoperative complication among living liver donors in their center was a biliary tract injury. They experienced 6% biliary complications (n=6), namely, four bilomas and two leaks, both of which were treated by percutaneous drainage or by the postoperative peritoneal drain. They injected saline with methylene blue intraoperatively via the cholangiography catheter to test for leakage in all donors; if it was detected, additional sutures were then placed.

Biliary complication has been reported from centers in Japan, United States, and Europe, with incidences of 4, 7, and 8%, respectively [11].

On the contrary, in a study by Rafik *et al.* [12], the most common postoperative complication was infections (12.5%).

Biliary complications also account for the most frequent complication, ranging from 5 to 10% in an American survey by Renz and Busuttil [34] to 14.6% in a European survey by Broelsch *et al.* [35] to 18.6% in a retrospective analysis [27].

In another study by Rafik *et al.* [12], biliary leak was seen in 9.2%. Improvement in surgical technique is required to avoid such a complication, especially for the bare surface area of the remaining liver.

In our study, vascular (PV) complications were found to be 0.2%, involving two cases: one case had postoperative portal vein thrombosis and needed re-exploration and removal of thrombus with packing and then exploration again for removal of packs, whereas the second case was due to postoperative deep venous thrombosis with massive pulmonary embolism, which resulted in death.

In the study by Pomfret [36], portal vein thrombosis was seen in one (0.18%) of 561 donors.

Moreover, in the study by Jiang *et al.* [37], a case (3.8%) with portal vein thrombosis was diagnosed on the third postoperative day with routine daily Doppler ultrasound examination and then treated successfully by relaparotomy and intraoperative tissue plasminogen activator infusion, leading to an excellent result.

In a study by Sevmis *et al.* [11], portal vein thrombosis developed in a donor (2.08%), but the portal vein was recanalized without interference, and the patient recovered without treatment.

In a study by Rafik *et al.* [12], portal vein thrombosis occurred in two donors: one required operative thrombectomy with subsequent ICU stay and 14 days of hospitalization, and the other was managed by radiologic intervention and medical treatment. Both events resolved within 3 months. Another donor

had inferior vena cava thrombosis that resolved with medical management.

In our study, 20 (2%) of 997 donors had wound infection.

In a study by Umeshita *et al.* [13], it has been reported that 27 (1.5%) of 1841 donors had wound infections. In our study, three (0.3%) patients had pulmonary embolism, but only one (0.01%) donor unfortunately was subjected to massive pulmonary embolism postoperatively, despite adequate anticoagulation. This is the second mortality case to be reported by our team after the patient who had sepsis after bile leakage.

The results on mortality studies from Europe, Asia, and the United States point to a higher risk of mortality after donation of the right liver lobe [31].

An important cause of death is pulmonary thromboembolism [34]. A history of smoking and the presence of obesity are important factors for the development of a pulmonary thromboembolism [38].

Moreover, in our study, there was no intraoperative mortality for donors, and this is similar to what a study by Umeshita *et al.* [13] had reported.

Ghobrial *et al.* [39] reported that four of 393 donors had died: one owing to infection and multiple organ failure during primary hospitalization, and the other three died more than a year later from a drug overdose, a suicide, and a pedestrian-train accident. The psychiatric risks of right lobar donation have been shown in a study by Marsh *et al.* [14].

Umeshita *et al.* [13] also reported that another possible factor to account for these results is the low frequency of perioperative pulmonary embolism in Japan. On comparison, at least two deaths due to pulmonary embolism have been reported in living liver donors in the west.

Trotter *et al.* [27] reviewed all published articles for donor deaths from 1989 to February 2006. They classified each death as 'definitely,' 'possibly,' or 'unlikely' related to donor surgery. They identified 19 donor deaths (and one additional donor in a chronic vegetative state). A total of 13 deaths and the vegetative donor were 'definitely,' two were 'possibly,' and four were 'unlikely' related to donor surgery. The estimated rate of donor death 'definitely' related to donor surgery is 0.15%. The rate of donor death that is 'definitely' or 'possibly' related to the donor surgery is 0.20%.

Regarding liver enzymes, the peak postoperative aspartate aminotransferase and alanine aminotransferase were 333.47 ± 177.09 and 385.15 ± 180.23 U/l, respectively. Most values peaked on postoperative day 1 and continued to decline during the first week to reach normal level at day 7 (6–8) and 8 (7–10), respectively, with a range of 3–24 days. The serum total bilirubin peaked on day 1 (1–2), with the highest mean level of 3.76 ± 2.00 mg/dl and returned to normal at day 6 (5–7) postoperatively. The peak prothrombin time-international normalized ratio occurred on postoperative day 1, and the highest level was 2.17 ± 0.43 and returns to normal level at day 5 (4–6). Deterioration of liver function after donation was resolved in all donors.

In comparison with a study in Korea, the peak postoperative aspartate aminotransferase and alanine aminotransferase were 204 ± 146.5 and 201 ± 114.2 U/l, respectively. Most values peaked on postoperative day 1 and continued to decline during the first week to reach normal level at day 7 (6–8) and 8 (7–10), respectively. The serum total bilirubin peaked on day 1, with the highest mean level of 2.9 ± 1.6 mg/dl. The peak prothrombin time-international normalized ratio occurred on postoperative day 1, and the highest level was 1.65 ± 0.3, but prolongation was slight.

Regarding the overall donor complication in the Korean publication, no complications were observed in 744 (90%) donors, whereas 83 (10%) donors experienced some morbidity. The most common complication was surgical wound problems, with an incidence of 57.9%. Biliary complications occurred in 16 (19.3%) donors. Hepatic artery or portal vein thrombosis and unplanned surgical re-exploration, except for bleeding or liver failure requiring listing for liver transplantation, did not occur. Progression to death or any morbidity resulting in permanent illness did not occur. The mean hospital stay of donors with morbidities was 15.8 (range, 19.3–31.5) days. The surgical complications observed after live donor hepatectomy were graded according to the classification system proposed by Clavien *et al.* [40]. The system consists of five major grades with subdivisions; all complications were classified as grades I, II, or III. There were no cases of life-threatening organ dysfunction or irreversible. All donors were alive at the time of writing this paper [41].

In a study done by Benzing *et al.* [42], 104 patients underwent liver resection for living-donor liver donation between December 1999 and March 2013. Postoperative morbidity was 35.9%, with 56.8% of patients having minor complications. No postoperative, 30-day, or 90-day mortality was evident. At year 1

after transplant, 30 (28.8%) patients had (ongoing) complications, of which 80% were considered minor according to Clavien-Dindo classification. Regarding health-related quality of life, liver donors were characterized as having significantly higher scores in donor outcome. In this study, 37 (35.9%) donors had complications, with 21 (56.8%) having minor complications (grade I per modified Clavien-Dindo system). Grade II complications were observed in 16 (43.2%) patients, and no patient having a grade III complication. Postoperative mortality was nil. In four (3.9%) donors, CT-guided drainage of an intra-abdominal liquid collection was necessary; in six patients, an endoscopic retrograde cholangiopancreatography had to be performed. Redo-surgery of any kind was needed in seven (6.8%) patients.

Conclusion

LDLT involves risks for both the recipient and the donor. The safety of the donor operation is the main concern in these cases. Accurate assessment of the donor liver is an important component of the living-donor liver evaluation and critical to ensure a successful outcome for both donor and recipient. Major complications of the donor such as biliary complications are expected to decrease with improved techniques and increasing experience but not minor complications.

The Clavien grading system is useful to evaluate and compare surgical outcomes among various surgeons and centers.

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Conflicts of interest

There are no conflicts of interest.

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