Low residual volume in donors for living donor liver transplantation, donor safety

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Background
Liver transplantation is the treatment of choice for cirrhotic patients, decompensated disease, fulminant hepatitis, and hepatocellular carcinomas within Milan criteria. In the past decades, liver transplantation has progressed from an experimental approach with a very high mortality to an almost ordinary procedure with good short-term and long-term survival rates.
Aim
The aim of the present study was to investigate the relationship between donor recovery, postoperative complications, and the volume of remnant liver.
Patients and methods
This is a retrospective observational cohort study that included 63 liver donors operated upon in Ain Shams Specialized Hospital and in Egypt Air Hospital from January 2016 to January 2018, who were divided into in two groups: group A with residual volume with Middle Hepatic Vein (MHV) ranging from 33 to 35% with 19 donors in it, and group B with residual volume with MHV ranging from 35 to 38% with 44 donors in it.
Results
There was no significant difference between the two groups regarding age, sex, steatosis, and operation center. Comparing the two groups according to postoperative bilirubin resulted in no significant difference between the two groups. Moreover, comparing complications [grade according to modified Clavien scale of post-operative complications (P=0.966), as well as type 'respiratory, cardiac, vascular, wound infection, intraperitoneal hematoma, biliary complications, pancreatitis, hernia, and multiple complications' (P=0.499)] did not result in any statistical difference between the two groups in spite of the mild complications.
Conclusion
Low residual volume up to 33% in donors of living-donor liver transplantation does not affect their safety, as there is no difference in the increase in the recovery period. Moreover, there is no significant difference in postoperative complications rate regarding donors with residual volume more than 35%, and at the same time, increase the availability of liver graft for patients in need for transplantation.

Keywords:
Clavien scale and postoperative complication, living-donor liver transplantation, residual volume

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Introduction

Liver transplantation is the best curative treatment for cirrhotic patients, decompensated disease, fulminant hepatitis, and hepatocellular carcinomas within Milan criteria [1]. In the past decades, a marked progress has occurred in liver transplantation from an experimental operation with a very high rate of mortality to an almost ordinary procedure with good short-term and long-term survival rates [2].

Although more than 1100 transplants from cadavers are performed every year, more than 300 patients lose their life each year on the liver transplant waiting list (Eurotransplant). Living-donor liver transplantation (LDLT) makes organ more available. In the past decade, a lot of centers of liver transplant have started to perform adult-to-adult right lobe LDLT [3]. The cornerstone in the success of LDLT is donor safety. So, it is essential that transplant physicians have a complete awareness of possible complications in living donors, so that the potential risk of the procedure may be described in detail to donor candidates, and steps are taken to minimize the potential risks [4].

LDLT is now an approved management for end-stage liver disease. The deep understanding of liver anatomy especially the segmental structure of the liver and regenerative ability of both the remnant and

transplanted parts make live transplant a possible procedure. After years of cumulative experience in adult-to-child left-lobe liver transplantation, now right donor hepatectomy is considered a common procedure in expert centers performing adult-to-adult LDLT [5].

Despite impressive results, right-lobe LDLT is one of the most sophisticated and technically demanding operation, and considerable debate has been created regarding donor safety. Till now, 17 donor deaths have been reported, and the morbidity is 20–30% in most available studies. A right donor hepatectomy is performed in most cases of adult-to-adult LDLT to meet the metabolic demands of the recipient. It is well known that the ratio between graft-to-recipient body weight must be at least 0.8% to avoid small-for-size syndrome in the recipient. Moreover, a large enough left lobe should be kept in the donors to meet metabolic demand until regeneration of the remnant part to a sufficient size. Initial, past experience suggested leaving a remnant of not less than 30%. In centers where living donors are the main source for livers, with increase of experience, transplant teams now can perform the donor hepatectomy even if the remnant liver volume is not more than the suggested 30% [6]. Considering the debate regarding safety and the extent of remnant liver volume in right-lobe LDLT, we decided to analyze our own data. We retrospectively collected the data of the remnant liver volume in our donors and compared donors with less than 35% remnant liver volume with donors having a remnant liver volume equal or more than 35%. This study aimed at the exploration of this last point: whether or not minimizing the residual volume in donors after LDLT affects donors' morbidity, with special reference to postoperative donors' bilirubin level, liver transaminases pattern, and complications according to Clavien scale.

Patients and methods

This is a retrospective observational cohort study that included 63 liver donors operated upon in Ain Shams Specialized Hospital Liver Transplantation Unit and in Egypt Air Liver Transplantation Unit from January 2016 to January 2018.

Regarding donors' selection, potential donors were selected from Ain Shams Liver Transplantation Unit Registry and from Egypt Air Hospital Liver Transplantation Unit Registry hospitals by the same recruiter, so their evaluation was the same. The age of these donors was from 18 to 45 years. They were evaluated in four steps: step 1 included clinical evaluation: history, physical examination, and laboratory tests (after exclusion of any comorbidities). Step I was divided into three phases:

Evaluation phase: this included assessment of blood group and Rh, urine for drug abuse (cocaine, cannabis, barbiturates, benzodiazepines, opiates, amphetamines, and tramadol), aspartate aminotransferase (AST), alanine aminotransferase (ALT), hepatitis C virus antibody, hepatitis B surface antigen, and HIV.

Phase 1: liver profile included total and direct bilirubin, total protein, albumin, alkaline phosphatase, γ-glutamyltransferase, and amylase. Renal profile included blood urea nitrogen, creatinine, and uric acid. Serum electrolytes included Na^{+}, K^{+}, Ca^{+2}, Mg^{+2}, P^{+3}, and Cl. Lipid profile included cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein. Tumor markers included α-FP, CEA, CA19-9, PSA, and CA125. Viral markers included HAV Ab IgM, HAV Ab IgG, HBs Ab titer, HBeAg, HBeAb, and HBcAb IgM. Diabetes profile included fasting blood sugar and 2 h postprandial glucose. Complete urine analysis, complete stool analysis, bilharzial antibody titer, and β-human chorionic gonadotropin (quantitative) were done for females. C-reactive protein quantitative assessment was done.

Phase 2 included coagulation profile such as protein C, protein S, antithrombin III, lupus anticoagulant, anticardiolipid IgM, anticardiolipid IgG, and thrombophilia gene screening; viral markers such as hepatitis C virus PCR qualitative, HBV PCR qualitative, CMV IgM, CMV IgG, EBV IgM, and EBV IgG; and circulating bilharzial antigen (If needed).

Step 2 included imaging studies: first, abdomen and pelvic ultrasound; second, computed tomography (CT) scan; third, CT volumetry of liver with calculation of potential graft volume and donor's residual volume assuming the graft is the right lobe, and also calculation of the GRWR was done, to be more than 0.8–1; fourth, CT angiography with separate 3D reconstructions of portal vein origin, branches and anomalies, hepatic veins with anomalies (Makuuchi vein or posterior inferior veins), and origin of hepatic artery with anomalies; and fifth, MRCP was done to asses extrahepatic biliary passages and their variants and finally psychological assessment.

Step 3 included special studies, such as ECG, chest radiography, pulmonary function test, echocardiography, and stress test; laboratory investigations such as thyroid function test (thyroid stimulating hormone, T3, and T4), serum Fe+3, transferrin, a-1-antitrypsin, ceruloplasmin, factors VII and VIII, and activated protein C resistance; and selected consultations, such as chest, cardiological, psychological, and gynecological for women.

Step 4 included liver biopsy to exclude steatosis (exclude donor with steatosis more than 10% and no to mild fibrosis (≤20%) of portal tract), hepatologist consultation, anesthesiological consultation, Ethics Board evaluation, and final informed consent.

All imaging studies are reviewed before the operation by the surgeon. Once all the investigations are done, each donor–recipient pair is reviewed at our weekly liver transplant conference. We specifically cared about the metabolic demand of the recipient and the volume and biliary and vascular anatomy of the donor liver.

Operative procedure

The donors and recipients are admitted to the hospital two nights before the time of operation. A right hockey-stick incision (part of upper midline incision and right Kocher's incision) was used. After an intraoperative ultrasound evaluation of the vascular structures and cholecystectomy, cholangiography through the cystic duct stump for evaluation of the biliary tree is performed. Mobilization of the liver (dissection of falciform ligaments, triangular ligaments, and coronary ligaments) is done, followed by Piggy backing (dissection of posterior hepatic veins draining directly into inferior vena cava). Dissection of hepatic plate and right side of pedicle was done to expose right portal vein, right hepatic artery, and right hepatic duct. Resection was done using CAUSA and harmonic for hemostasis along with ligation of bleeding vessels and identification of middle hepatic vein and preservation of any large vein to avoid graft congestion (Macchuchi, V5, V8). The liver graft is first weighed and then washed with HTK solution at the back-table. Closure of vessel stumps was done with continuous, nonabsorbable sutures (Prolene) after removal of graft, whereas the stump of the right biliary duct is closed with continuous, monofilament absorbable sutures (Polydioxanone PDS). Then cholangiogram is done through the cystic duct stump to ensure that there is no biliary leakage. A silastic drain is inserted in the right upper part before the closure of abdomen. On the recipient side, total hepatectomy with cava sparing is performed. Then inferior vena cava is clamped, and once the graft is ready, it is followed by closure of left/middle hepatic vein opening, and the right hepatic vein stump is fashioned to a larger triangular opening. Then graft right/middle hepatic vein is sutured to this opening using prolene 4–0. If the graft contains any inferior hepatic veins, they are sutured to a separate opening in the inferior vena cava. Anastomosis of the donor right portal vein to the recipient main portal vein is performed using prolene 6–0, and the graft is subsequently re-perfused. Hepatic artery reconstruction is performed under loupe magnification using prolene 8–0. Moreover, biliary anastomosis is then performed using PDS 6–0.

Postoperative care

Donors are extubated in the operating theater and then transferred to the ICU overnight. Donors are started on ambulation and oral clear liquid diet on second day postoperatively. The diet is advanced slowly on postoperative day 3.

Early assessments (in the first 2 weeks)

Clinical examination and laboratory investigations (ALT, AST, total bilirubin, direct bilirubin, total protein, alkaline phosphatase, γ-glutamyltransferase, albumin, prothrombin time, international normalized ratio, serum creatinine, Na, K, hemoglobin, total leucocyte count, and platelet) are done every day for the first 10 days and then every other day. Ultrasound is done every day during the first week and then every 3 days in the second week.

Data gathering

Data were gathered from serial transplantations and donors' follow-up. Then two groups of donors were formed according to preoperative CT liver volumetry: group A, with residual volume with Middle Hepatic Vein (MHV) ranging from 33 to 35%, comprising 19 donors, and group B, with residual volume with MHV ranging from 35 to 38%, comprising 44 donors.

They are selected with special consideration regarding age, fibrosis, steatosis, graft lobe, and HBcIgG. Then comparing between these two groups postoperatively was done according to the following: first, total maximum bilirubin level; second, hospital stay; third, complications; and fourth, pattern of liver enzymes.

Their data were collected from the hospitals' registry departments in two steps: (step A) collection of donors' data preoperartively and postoperatively from January 2016 to January 2018 from Ain Shams Liver

Transplantation Unit Registry and from Egypt Air Hospital Liver Transplantation Unit Registry, and (step B) filtration of data according to preoperative CT volumetry and only donors with suspected residual liver volume including MHV from 33 to 38%.

Statistical analysis

Collected data were tabulated and analyzed using the Statistics Open for ALL (SOFA) version 1.5.3 (Paton-Simpson & Associates Ltd, Auckland, New Zealand). The quantitative data were presented as medians and ranges and means with SD, whereas qualitative variables were presented as number and percentages. The χ^2-test was used to compare categorical data, whereas the Mann–Whitney *U*-test or the *t*-test was used for comparison of quantitative data. A *P* value less than 0.05 is considered to be significant.

Results

There were 19 patients in group A and 44 patients in group B. The mean follow-up was 15 months. Donor demographic characteristics such as age and sex were the same between the two groups. Donors with steatotic liver more than 10% were excluded from this study. The preoperative estimations of total liver volume, the ratio of estimated right lobe volume to the intraoperative, and immediate post-right lobectomy actual weight were similar between the two groups. The range of remnant liver ratios ranged from 33 to 35% for group A and ranged from 35 to 38% for group B.

In group A, age ranged from 21 to 37 years. The mean±S.D ages for group A was 27.43±6.95 years. In group B, it ranged from 18 to 40 years of age, and their mean±SD age was 27.6±4.35 years. Age differs insignificantly between the two groups (*P*=0.61).

Regarding residual volume with MHV (Fig. 1), in group A, it ranged from 33.4 to 35%, and the mean ±SD volume was 34.3±0.39%. However, in group B, it ranged from 35.8 to 38%, and the mean±SD volume was 37.14±0.87. (*P*<0.001) (Table 1).

In group A, 16 (84.2%) donors were operated in Ain Shams Specialized Hospital and four (15.8%) donors were operated in Egypt Air Hospital. Moreover, in group B, 35 (79.5%) donors were operated in Ain Shams Specialized Hospital and nine (20.5%) donors were operated in Egypt Air Hospital.

In group A, bilirubin level ranged from 0.7 to 5.79 mg/dl, and mean±SD level was 3.42±1.62 mg/dl. In group B, it ranged from 1.45 to 6.9 mg/dl, and the mean ±SD level was 2.75±1.14. There was no difference between the two groups in maximum bilirubin level, its mean levels postoperatively (Figs 2 and 3) or the duration after, when it returned to normal (*P*=0.204) (Table 2). There is no difference in liver enzymes ALT and AST postoperatively between the two groups (Figs 4 and 5).

Figure 1

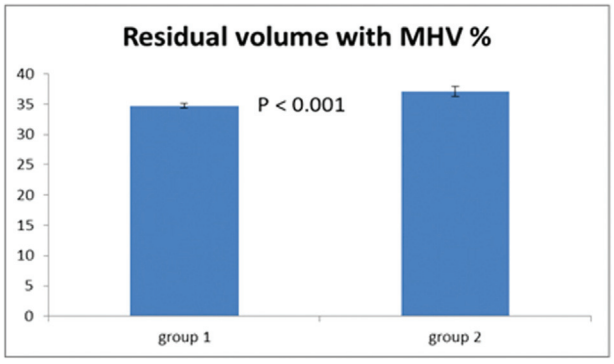


Chart showing the difference between the two groups according to postoperative complications (*P*=0.499).

Figure 2

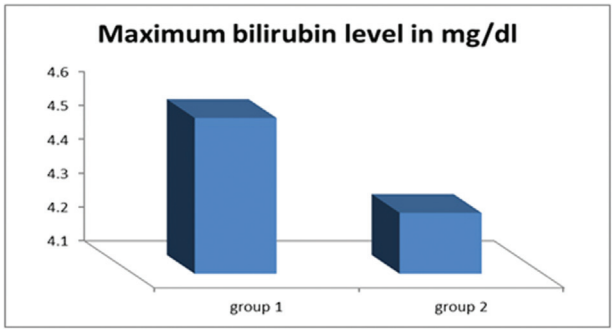


Chart showing significant difference between two groups in residual volume (*P*<0.001).

Table 1 Comparison of age and residual volume

	Groups										*P* value
	Group 1					Group 2					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Age	27.60	4.35	27.50	21.00	37.00	27.43	6.95	26.00	17.00	40.00	0.610
Residual volume with MHV %	34.20	0.39	34.1	33.4	35.00	37.14	0.86	37.00	35.80	38.00	<0.001

MHV, middle hepatic vein.

Table 2 Comparison of post-operative bilirubin data (its maximum level, its mean in 7 days and when it returned to normal), grade of complications, and hospital stay

	Groups										*P* value
	group 1					group 2					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
After how many days postoperatively bilirubin returned to normal?	12.20	7.90	11.00	1.00	25.00	10.09	5.89	8.00	5.00	32.00	0.470
Maximum bilirubin level in mg/dl	4.56	2.18	4.80	1.20	8.50	4.28	1.68	4.00	1.90	8.60	0.640
Mean bilirubin level in 7 days postoperatively in mg/dl	3.42	1.62	3.68	0.80	5.79	2.75	1.15	2.50	1.46	6.90	.204
Grade of complications according to Clavien's scale	1.00	0.67	1.00	.00	2.00	1.03	0.77	1.00	0.00	3.00	0.966
Hospital stay	15.90	6.33	13.50	9.00	27.00	15.21	8.28	13.00	8.00	41.00	0.620

Figure 3

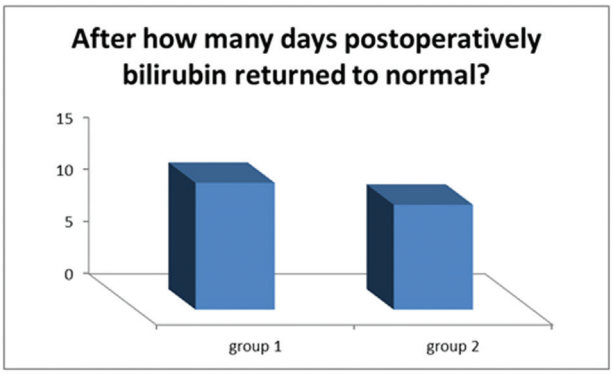


Chart showing the difference between the two groups regarding maximum bilirubin level postoperatively (*P*=0.64).

In group A, complication rate ranged from 0 to 2 according to Clavien's scale (Table 3). The mean±SD score for group A was 1±0.67, and the median was 1. However, in group B, it ranged from 0 to 3, and the mean±S.D. score was 1.03±0.77 and the median was 1 (*P*=0.966).

In group A or 1, four (21%) had no complications, two donors only (10.5%) had wound infection, and 13 (68.8%) had multiple complications ranging from respiratory complications, hematoma, and pancreatitis (elevation of amylase and lipase). No complication passed grade 2 of Clavien's scale of postoperative complications. However, in group B or 2, 14 (31.8%) had no complications, five (11.36%) donors had respiratory complication, four (9.0%) had wound infection, three (6.8%) with intraperitoneal hematoma, three (6.8%) had pancreatitis, and 15 (34%) had multiple complications ranging from respiratory complications to hematoma. One donor was in grade 3 of Clavien's scale of postoperative complications with moderate right-sided pleural effusion (*P*=0.499). There were no deaths in either group (Fig. 6 and Table 4).

Regarding hospital stay, in group A, it ranged from 9 to 27 days postoperatively, and the mean±SD stay was 15.9±6.33 days. In group B, it ranged from 8 to 41 days postoperatively, and the mean ±SD stay was 15.21 ±8.28 days (*P*=0.62) (Table 2).

Discussion

LDLT is the only transplantation technique in Egypt, as the law prohibits diseased liver transplantation (only two DDLT since 1991), as stated by Khaled and Marwan [3] In Egypt, adult LDLT is a complicated technique, needs public orientation about the importance of this operation, as it is the only hope for patients with hepatic cell failure, and needs more training and research.

The residual volume (RLV) of donors preoperatively was agreed to be more than 35%, but in the past decade, some studies were done to discuss reducing the residual volume without affecting the safety of donor [1,7,8].

The careful choice of suitable donors is essential for both donor and recipient safety. The volume of the graft liver should ensure not only the absolute safety of the donor but also sufficient for metabolic demand of the recipient [9].

In our study, 19 donors in group A with RLV 33–35% were compared with 44 donors in group B with RLV 35–38%. We found that there was no significant difference between two groups regarding age, sex, steatosis, and operation center. Comparing the two groups according to postoperative bilirubin (after how many days did it returned to normal) (*P*=0.47), peak of bilirubin level (*P*=0.64), and mean level postoperatively (*P*=0.204), the results showed no significant difference between the two groups.

Figure 4

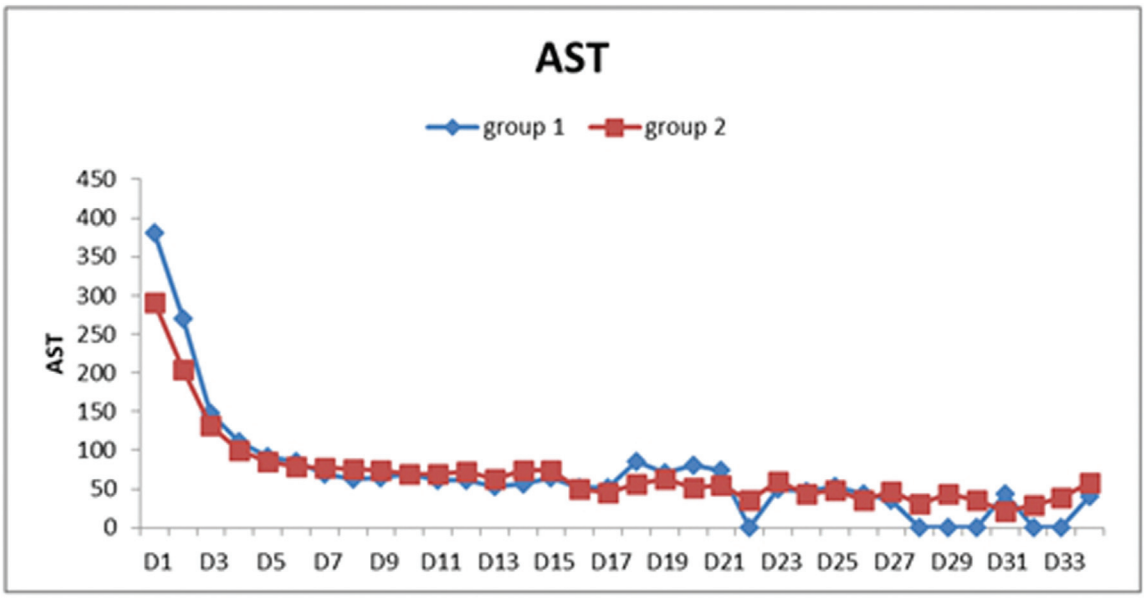
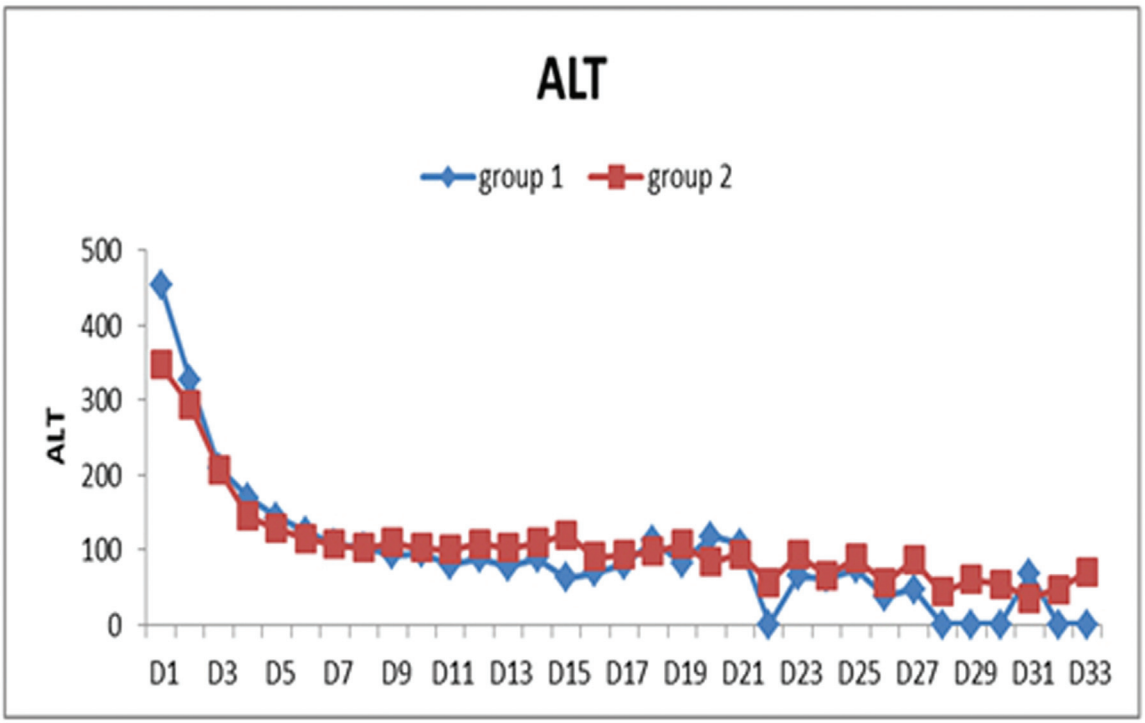


Chart showing the difference between the two groups regarding after how many days postoperatively bilirubin returned to normal (P=0.47).

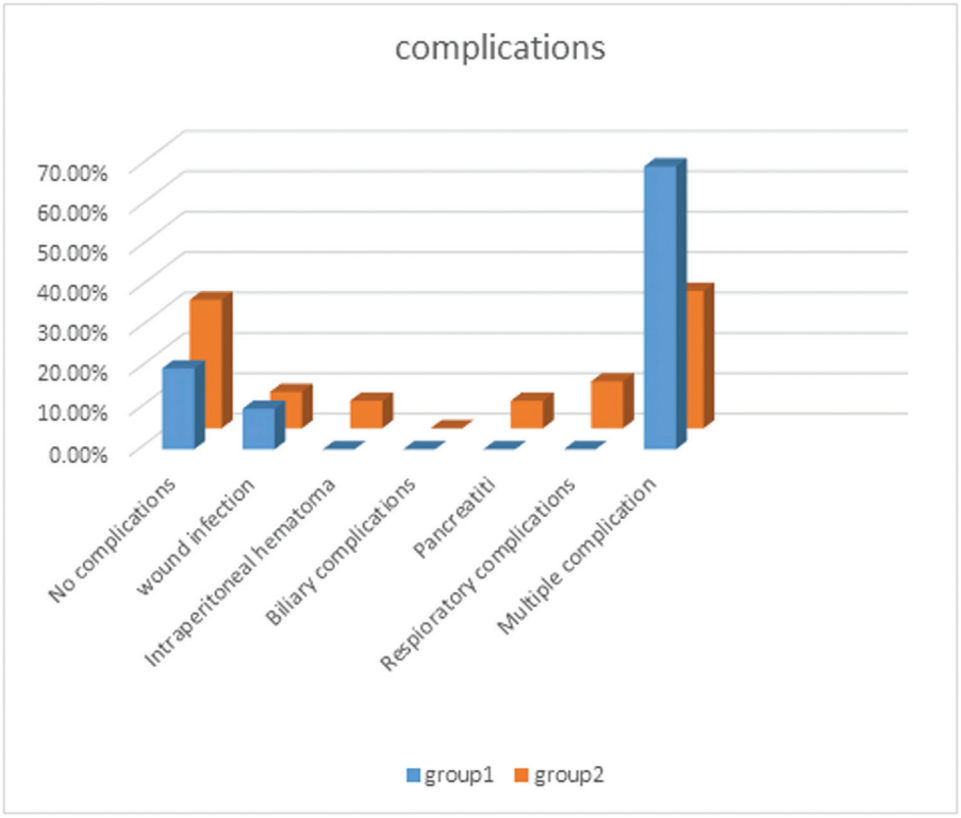
Figure 5



Graph showing aspartate aminotransferase pattern postoperatively.

Moreover, comparing complications (grade according to Modified Clavien's scale of postoperative complications 'P=0.966, as well as type 'respiratory, cardiac, vascular, wound infection, intraperitoneal hematoma, biliary complications, pancreatitis and multiple complications'; 'P=0.499'), the results showed no statistical difference between the two groups. Regarding hospital stay between the two groups (P=0.62), it was statistically insignificant, and also comparing the pattern of liver enzymes postoperatively between the two groups resulted in no significant difference between the two groups (decreasing in both groups with no shooting in group A).

Figure 6



Alanine aminotransferase pattern postoperatively (group 1=group A and group 2=group B).

Table 3 Clavien's scale of postoperative complications [2]

Grades	Definitions
I	Any deviation from the normal postoperative course without the need for medical treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens: use of drugs such as antiemetics, antipyretics, analgesics, diuretics, electrolytes and need for physiotherapy
II	Necessitating medical treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are included
III	Necessitating endoscopic, surgical or radiological intervention
	(a) Intervention without general anesthesia
	(b) Intervention with general anesthesia
IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
	(a) Single organ malfunction
	(b) Multiorgan malfunction
V	Patient death

Table 4 Comparison of type of complications

	Groups				*P* value
	Group 1		Group 2		
	Count	%	Count	%	
Complications					
No complications	4	21.0	14	31.8	0.499
Respiratory complications	0	0	5	11.6	
Cardiac complications	0	0	0	0	
Vascular complications	0	0	0	0	
Wound infection	2	10.5	4	9.0	
Intraperitoneal hematoma	0	0	3	6.8	
Biliary complications	0	0	0	0	
Pancreatitis	1	5.26	3	6.8	
Multiple complications	14	68.8	15	34.0	

This did not match with what was reported by Zheng Rong Shi *et al.* [10] in their study, which included 150 donors, with 50 donor with RLV less than 35% and 100 donors with RLV greater than 35. The volume of the remnant had a significant effect on the recovery of liver function and ICU time. In addition, the occurrence of complications, such as the peak of liver enzymes and duration of ICU admission, was more in group with residual volume less than 35%.

From this study, it could be suggested that reducing RLV in donors of LDLT does not affect them postoperatively or increase morbidities only with

precise preoperative evaluation. This is in accordance of what have been mentioned by Itamoto *et al.* and Burcin *et al.* [1,2].

Thus, we can suggest that good preoperative evaluation of donors as suggested by Itamoto and colleagues and Nugroho and colleagues will allow surgeons to choose donors with lower residual volumes in consideration with donor safety first and for the utmost benefit of the recipient.

Conclusion

Low residual volume up to 33% in donors of LDLT does not affect their safety, as there is no difference in increase in recovery period with good selection of donors. Moreover, there is no significant difference in postoperative complications rate compared with donors with RLV more than 35%. and at the same time increase the availability of liver graft for patients in need for transplantation.

Limitation

There has been a relative shortage of publications in English literature that focus on remnant volume and associated morbidity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Burcin T, Murat D, Baris A, *et al.* Donor safety and remnant liver volume in living donor liver transplantation. J Liver Transpl 2008; 14:1174–1179.

2 Itamoto T, Emoto K, Mitsuta H, *et al.* Safety of donor right hepatectomy for adult-to-adult living donor liver transplantation. J Transplant Internat 2006; 19:177–183.

3 Khaled EA, Ibrahim M. Living donor liver transplantation in Egypt. J Hepatobiliary Surg Nutrition 2016; 5:98–106.

4 Peter S, Waldemar U, *et al.* Living-donor liver transplantation: evaluation of donor and recipient. J Nephrol Dial Transplant 2004; 19:11–15.

5 Roberto FMJ, Paolo S, Marcelo BdR, *et al.* Liver transplantation: history, outcomes and perspectives. J Einstein 2015; 13:149–152.

6 Stefan F, Christina H, Hans JS. Overview of the indications and contraindications for liver transplantation. J Cold Spring Harb Perspect Med 2014; 4:a015602.

7 Chapman S. Clavien-Dindo classification of surgical complicaions: Star Surg. II 16th Septemper.

8 Nugroho A, Kim OK, Lee KW, *et al.* Evaluation of donor workups and exclusions in a single-center experience of living donor liver transplantation. Liver Transplantation 2017; 23:614–624.

9 Yoshizumi T, Taketomi A, Kayashima H, Harada N, Uchiyama H, Yamashita YIkegami T, *et al.* Successful treatment for a patient with hemophagocytic syndrome after a small-for-size graft liver transplantation. Hepatogastroenterology 2008; 55:359–362.

10 Shi ZR, Yan LN, Du CY. Donor safety and remnant liver volume in living donor liver transplantation. World J Gastroenterol 2012; 18:7327–7733.