

ORIGINAL ARTICLE

Ratio of remnant to total liver volume or remnant to body weight: which one is more predictive on donor outcomes?

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Abstract

Background: Right lobe donations are known to expose the donors to more surgical risks than left lobe donations. In the present study, the effects of remnant volume on donor outcomes after right lobe living donor hepatectomies were investigated.

Methods: The data on 262 consecutive living liver donors who had undergone a right hepatectomy from January 2004 to June 2011 were retrospectively analysed. The influence of the remnant on the outcomes was investigated according to the two different definitions. These were: (i) the ratio of the remnant liver volume to total liver volume (RLV/TLV) and (ii) the remnant liver volume to donor body weight ratio (RLV/BWR). For RLV/TLV, the effects of having a percentage of 30% or below and for RLV/BWR, the effects of values lower than 0.6 on the results were investigated.

Results: Complication and major complication rates were 44.7% and 13.2% for donors with RLV/TLV of $\leq 30\%$, and 35.9% and 9.4% for donors with RLV/BWR of < 0.6 , respectively. In donors with RLV/TLV of $\leq 30\%$, RLV/BWR being below or above 0.6 did not influence the results in terms of liver function tests, complications and hospital stay. The main impact on the outcome was posed by RLV/TLV of $\leq 30\%$.

Conclusion: Remnant volume in a right lobe living donor hepatectomy has adverse effects on donor outcomes when RLV/TLV is $\leq 30\%$ independent from the rate of RLV/BWR with a cut-off point of 0.6.

Keywords

liver transplantation, living donor, remnant, right lobe, donor outcome, body weight

Received 25 January 2012; accepted 12 April 2012

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Introduction

Liver transplantation is a well-established and widely used treatment method for end-stage liver disease. In countries where cadaveric organ supply is problematic, living donor liver transplantation is prioritized. During this process, small-for-size syndrome experienced in left lobe grafts results in more frequent use of right lobe donations.¹ For right lobe donations, donor morbidity is reported to be 0–67% whereas the main drawback is the percentage of donor remnant.^{2–8} In most human beings, right lobe volume is 45–80% of the total liver volume; left lobe volume on the other hand is 15–45% of the total volume.⁹ In general, remnant liver volume after right hepatectomies is known to be around 20–40%.^{2,10,11} Together with

increasing experience and graft needs, transplant centres are guided towards using donors with smaller remnant volumes, i.e. $< 30\%$ total liver volume, that qualify as marginal.² In previous studies, remnant volume was expressed as the percentage of the remnant volume to the total liver volume. To the best of our knowledge, the present study is the first to evaluate donor morbidity after living donor right lobe donation based on the remnant liver volume to donor body weight ratio.

Whether remnant liver volume (RLV) to donor body weight ratio (BWR) (RLV/BWR) had any impact on outcome of the donors in addition to the widely used RLV to total liver volume (TLV) ratio (RLV/TLV) by the transplant centres was assessed which is generally accepted to be $\geq 30\%$.

Patients and methods

From January 2004 to June 2011, 262 consecutive living liver donors who had undergone a right hepatectomy at Florence Nightingale Hospital Organ Transplant Center were included in the study. In the present study, the remnant liver after a right lobe living donor hepatectomy was expressed both as the percentage of total liver volume (RLV/TLV) and as a ratio of donor body weight (RLV/BWR) and the effects of both on donor postoperative outcomes were investigated. Cut-off points were determined by receiver-operating curve (ROC) analysis. For RLV/TLV, 30% and below, and for RLV/BWR the value of under 0.6 were assigned as cut-off points. Donors were studied for age, gender, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin and international normalized ration (INR) levels, and complications within the first 7 post-operative days.

In order to assess the effects of the copresence of both instances on the results, the donors were divided into four subgroups: A (RLV/TLV \leq 30% and RLV/BWR $<$ 0.6), B (RLV/TLV \leq 30% and RLV/BWR \geq 0.6), C (RLV/TLV $>$ 30% and RLV/BWR $<$ 0.6) and D (RLV/TLV $>$ 30% and RLV/BWR \geq 0.6).

Remnant and total liver volume measurements were performed with multidetector computed tomography (CT). Operative details were published elsewhere.¹² Minor and major complications were categorized according to the modified Clavien's classification.³ The problems in Clavien 1 and 2, which resolved without invasive interventions, were accepted as minor complications. The problems in Clavien 3 and 4 that required radiological, endoscopic or surgical interventions were accepted as major complications. A post-operative total bilirubin level of $>$ 5 mg/dl was accepted as hyperbilirubinemia.

CT protocol and volume calculation

Multidetector computed tomography (MDCT) was performed on a 16-slice CT scanner (Sensation 16; Siemens Medical Solutions, Erlangen, Germany) using a three-phase contrast-enhanced protocol with a 1.0 mm slice thickness. For volumetric assessment, the hepatic venous phase was used with reconstructions of 5 mm thickness. Volumes were calculated using a software package (StereoInvestigator, version 6.0; Microbrightfield, Colchester, VT, USA) that uses a point counting technique based on the Cavalieri principle. Large vessels such as the extrahepatic portal vein in the area of the porta hepatis and the inferior vena cava, as well as larger fissures, and the teres hepatic ligament were excluded from volumetric markings. MDCT measurements were conducted on the middle hepatic vein (MHV) with the marking line passing 5 mm lateral (towards right lobe) to the MHV thereby leaving MHV on the remnant.

Donor evaluation

Individuals between 18–65 years of age who did not have any health problems and who were relatives of the recipients until fourth degree were accepted as donor candidates.

Donor candidates were checked for ABO blood group match, biochemical analyses, a viral hepatitis profile, factor 5 and prothrombin gene mutations. Examinations were carried out by a team consisting of a hepatologist, a transplant surgeon and a psychiatrist. Donor candidates who were found acceptable were evaluated with an abdominal ultrasound. Donor candidates having liver steatosis of more than 10% in radiological evaluation, a body mass index of $>$ 30 and anti-HBc positivity underwent routine liver biopsy. Candidates who were found to be eligible were assessed with volumetric computerized tomography and CT angiography. Bile duct anatomy was assessed with MR cholangiography.

In the first 100 live donor liver transplantations, as the deceased donor option was very limited, and when the recipients did not have any other live donor candidates, individuals with calculated remnant volumes of less than 30% were occasionally accepted for donations. After publishing the results of those data suggesting higher complication rates with remnant volumes $<$ 30%, donors with $<$ 30% remnant volumes were not accepted; however, donors with 30% remnant volumes continue to be accepted.¹³ With this limit of 30% in mind, the effects of RLV/BWR with different cut-off points, if any, on the post-operative course and complications in donors in addition to RLV/TLV of 30% were assessed.

Statistical analysis

Values of measured variables were expressed as means \pm standard deviation or as ranges. Categorical variables were expressed as frequencies and percentages. For statistical analysis, continuous parameters in each group were compared using an independent sample *t*-test, and categorical parameters were compared with the chi-square test. ROC curve analysis was used to determine sensitivity and specificity of the values for RLV/TLV, RLV/BWR and hyperbilirubinemia. The differences between continuous variables in subgroups were assessed using the ANOVA test. Tukey's test or Tamhanes's T2 test was used according to the variances of the groups. As group 4 had a much greater sample size compared with the other groups, the Welch statistic was used to assess the differences.

All analyses were performed with SPSS 16.0 for Windows (SPSS, Chicago, IL); a value of $P <$ 0.05 was considered significant.

Results

Donor's characteristic features and post-operative outcome according to the RLV/TLV and RLV/BWR rates are shown in Table 1.

Mean radiological measurement of the grafts and mean actual graft weight were 900 ± 184 g and 880 ± 168 g; radiologically measured weight and actual weight of the grafts were significantly correlated ($r = 0.75$, $P = 0.0001$). The mean radiological/actual graft weight was 1.04 and 0.98 in patients with grafts with MHV ($n = 77$) and without MHV ($n = 184$) ($P = 0.01$).

Table 1 Patient's characteristic features and post-operative outcome according to the RLV/TLV and RLV/BWR

		RLV/TLV ≤ 30% (n = 38)	RLV/TLV > 30% (n = 224)	P	RLV/BWR < 0.6 (n = 64)	RLV/BWR ≥ 0.6 (n = 198)	P
Age		38.8 ± 10.5	36.1 ± 10.4	NS	39.2 ± 11	35.6 ± 10	NS
Gender (M/F)		23/15	127/97	NS	36/28	114/84	NS
BMI		25.9 ± 4	25.1 ± 3.4	NS	26.1 ± 3.6	24.6 ± 3.2	NS
# of grafts with MHV/without MHV		9/29	68/156	NS	19/45	58/140	NS
RLV/BWR		0.61 ± 0.22	0.73 ± 0.22	0.003	0.54 ± 0.19	0.77 ± 0.2	0.000
RLV/TLV (%)		29.2 ± 1.0	35.8 ± 3.3	0.000	31.8 ± 2.8	35.8 ± 3.7	0.000
ALT (IU/L)	Day 7	65 ± 26	80 ± 45	NS	78 ± 37	78 ± 45	NS
	Peak	260 ± 191	229 ± 124	NS	263 ± 171	224 ± 121	0.047
AST (IU/L)	Day 7	44 ± 15.3	53.8 ± 24	0.03	52 ± 22	52 ± 24	NS
	Peak	234 ± 177	201 ± 102	NS	228 ± 152	198 ± 101	NS
INR	Day 7	1.2 ± 0.2	1.1 ± 0.1	NS	1.2 ± 0.18	1.1 ± 0.18	0.036
	Peak	1.91 ± 0.2	1.73 ± 0.26	0.000	1.8 ± 0.25	1.7 ± 0.26	NS
Bilirubin (mg/dl)	Day 7	3.1 ± 2.6	1.6 ± 1.5	0.000	2.5 ± 2.7	1.6 ± 1.2	0.002
	Peak	5.1 ± 2.8	3.9 ± 2.2	0.002	4.7 ± 2.9	3.9 ± 2	0.016
Hospital stay (day)		9.8 ± 3.5	9 ± 4.7	NS	10.9 ± 7.9	8.5 ± 2.5	0.000
No. of complications		17	61	0.029	23	55	NS
No. of major complications		5	15	NS	6	14	NS

Data were expressed mean ± standard deviation.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; F, female; INR, international normalized ratio; M, male; MHV, middle hepatic vein; Peak, highest value in the postoperative 7 days; POD, post-operative day. NS, not significant; RLV/BWR, remnant to body weight ratio; RLV/TLV, remnant to total liver volume.

The number and types of post-operative complications are shown in Tables 1 and 2, respectively.

In donors with RLV/TLV ≤ 30%, day 7 and peak total bilirubin levels, day 7 AST and peak INR values, and the number of complications were statistically significantly higher compared with donors with RLV/TLV > 30%.

Donors with RLV/BWR < 0.6 had significantly higher values for day 7 and peak total bilirubin, day 7 INR, peak ALT and hospital stay compared with donors with RLV/BWR ≥ 0.6. Post-operative INR and bilirubin levels according to RLV/TLV and RLV/BWR rates are demonstrated in Figs 1–4, respectively.

In the ROC curve analysis, having a RLV/BWR of less than 0.6 predicted major complications and hyperbilirubinemia with a sensitivity of 70% and a specificity of 76% (area under curve 0.47, $P > 0.05$). Having a RLV/TLV of 30% or below predicted major complications with a sensitivity of 90% and specificity of 93% (area under the curve 0.60, $P < 0.05$), whereas it predicted hyperbilirubinemia with a sensitivity of 84% and a specificity of 96% (area under curve 0.58, $P < 0.05$).

The post-operative course of donors according to the subgroups are shown in Table 3.

Donors with a RLV/TLV ≤ 30% (with or without RLV/BWR < 0.6) had significantly higher rates of hyperbilirubinemia. In donors with a RLV/TLV of ≤ 30%, having a RLV/BWR of 0.6 and above or below did not influence the results.

Bilirubin levels on days 3 ($P = 0.03$), 5 ($P = 0.02$) and 7 ($P = 0.004$), and peak INR ($P = 0.01$ and INR day 3 ($P = 0.0001$) levels

Table 2 Types of complications

Complication	Number of episodes in donors	Number of episodes in donors
	RLV/TLV ≤ 30%	RLV/BWR < 0.6
Minor wound infection	5	6
Fever	4	4
Mild pleural effusion	2	3
Biliary leak resolving spontaneously	–	2
Parenteral nutrition	–	2
Abdominal collection	3	3
Bleeding requiring blood transfusion	–	1
Pleural effusion/ percutaneous drainage	1	2
Evantration/re-operation	–	1
Biliary stricture/ERCP, sphincterotomy or stent placement	2	1
Biliary leak/ERCP, sphincterotomy or stent placement	1	1
Biliary leak/re-operation	–	1
Intra-abdominal bleeding/re-operation	2	1

RLV/BWR, remnant to body weight ratio; RLV/TLV, remnant to total liver volume; ERCP, endoscopic retrograde cholangiopancreatography.

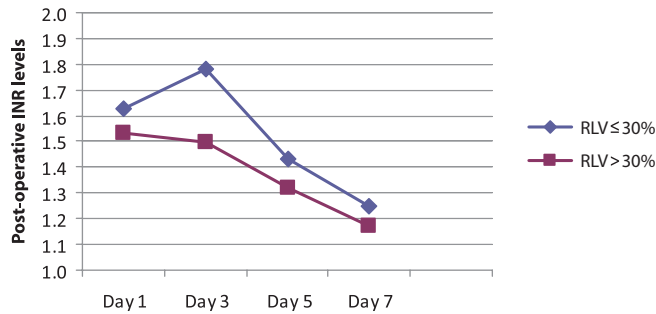


Figure 1 Post-operative international normalized ratio (INR) levels of donors according to the remnant liver volume (RLV)

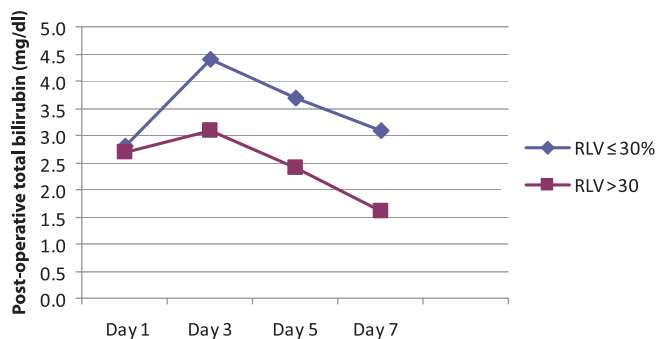


Figure 2 Post-operative bilirubin levels of donors according to the remnant liver volume (RLV)

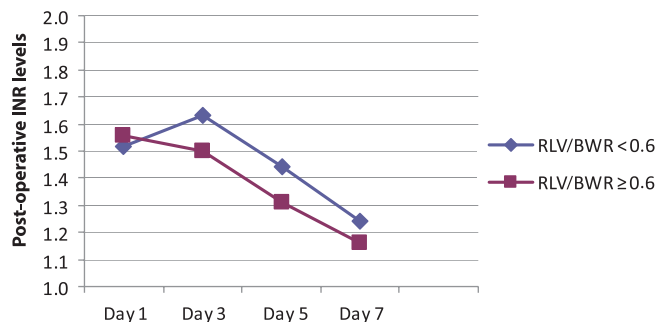


Figure 3 Post-operative international normalized ratio (INR) levels of donors according to the remnant liver volume to donor body weight ratio (RLV/BWR)

in Group A were significantly higher than Group D. Bilirubin levels on days 5 ($P = 0.005$), 7 ($P = 0.01$) and peak INR ($P = 0.01$), and INR day 3 ($P = 0.0001$) levels in Group B were significantly higher than in Group D (P -values are given according to Tukey's or Tamhane's test where appropriate).

To include the middle hepatic vein in the graft had no significant effect in either case, with the cut-off points of 30% and 0.6 of RLV/TLV and RLV/BWR, respectively (Tables 1 and 3). The length of hospital stay was significantly increased by RLV/BWR < 0.6

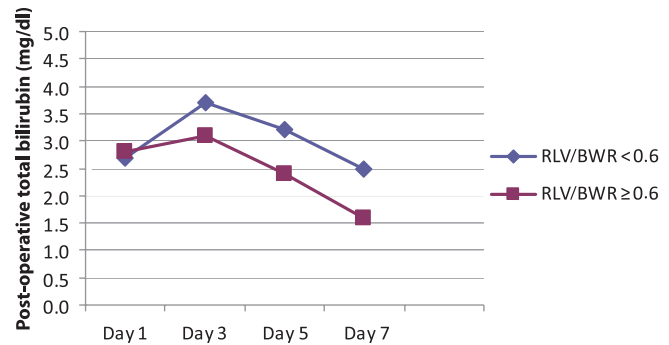


Figure 4 Post-operative bilirubin levels of donors according to the remnant liver volume to donor body weight ratio (RLV/BWR)

(Table 1); however, when assessed together with RLV/TLV (\leq or $>30\%$), its effect disappeared (Table 3).

Discussion

In living donor liver transplantations, to avoid small-for-size syndrome and insufficient graft function, the minimum value of graft to recipient body weight ratio is generally accepted to be 0.8 or above.⁵ However, in emergency transplantations, lower ratios such as 0.6 have been used successfully. In previous studies conducted on donor morbidity, the main points of discussion were MHV harvesting, age, steatosis and per cent remnant volume.¹²⁻¹⁸ The effects of volume calculation based on body weight in donors as is the case for the recipient were not analyzed. That is why we approached remnant volume from two perspectives, namely the ratio of remnant liver volume to total liver volume and the ratio of remnant liver weight to total body weight of the donors.

The key to donor safety is to ensure the presence of sufficient well functioning remnant liver volume. In previous studies performed on normal livers after a hepatectomy, a remnant volume of at least 27% was mentioned as being safe for the prevention of liver failure.^{2,19-21} Remnant volumes at or above 30% for donor safety should be maintained.

Small-for-size syndrome might develop as a result of small remnants after major hepatectomies, and lead to liver dysfunction characterized by lengthened cholestasis and coagulation disorders.²² After major hepatectomies, increased portal hypertension caused by transient sinusoidal narrowing and parenchymal loss gives rise to deterioration of parenchymal functions, furthermore damages in sinusoidal endothelial cells and Kupfer cells result in the secretion of inflammatory cytokines.²³⁻²⁶

In the past, knowledge of the effects of remnant volume on outcome was based on resections owing to tumours and on experimental studies. Together with the widespread utilization of living donor liver transplantation worldwide, increasing experience on donor hepatectomy resulted in a better understanding of the issue. It should be kept in mind that, in resections performed for tumours, most of the excised mass is non-functional, there is no healthy liver tissue and the other lobe might develop contralat-

Table 3 Post-operative course of donors according to the subgroups of different combinations of RLV/TLV and RLV/BWR

	Group A RLV/TLV \leq 30% plus RLV/BWR < 0.6 (n = 23)	Group B RLV/TLV \leq 30% plus RLV/BWR \geq 0.6 (n = 15)	Group C RLV/TLV > 30% plus RLV/BWR < 0.6 (n = 41)	Group D RLV/TLV > 30% plus RLV/BWR \geq 0.6 (n = 183)	P
Mean age	38.4 \pm 10.6	39.5 \pm 10.8	39.6 \pm 11.3	37.3 \pm 10	NS
Hyperbilirubinemia n (%)	10 (43.5)	7 (46.7)	10 (24.4)	39 (21.3)	0.026
Right-lobe graft with MHV, n (%)	7 (30.4)	2 (13.3)	12 (29.3)	56 (30.6)	NS
Mean hospital stay (day)	10.4 \pm 4.3	8.8 \pm 1.4	10 \pm 9.4	8.5 \pm 2.6	NS
Complications n (%)	12 (52.2)	5 (33.3)	11 (26.8)	50 (27.3)	NS
Major complications n (%)	3 (13%)	2 (13.3)	3 (7.3)	12 (6.6)	NS
Bilirubin day1 mg/dl (mean \pm SD)	2.8 \pm 2.0	2.9 \pm 1.1	2.6 \pm 1.5	2.7 \pm 1.5	NS
Bilirubin day3 mg/dl (mean \pm SD)	4.4 \pm 3.3	4.5 \pm 2.2	3.4 \pm 1.9	3.0 \pm 1.8	0.006
Bilirubin day5 mg/dl (mean \pm SD)	3.5 \pm 2.8	4.0 \pm 2.3	3.1 \pm 2.6	2.3 \pm 1.5	0.00
Bilirubin day7 mg/dl (mean \pm SD)	3.0 \pm 2.8	3.2 \pm 2.2	2.2 \pm 2.6	1.4 \pm 1.0	0.00
Bilirubin peak mg/dl (mean \pm SD)	5.0 \pm 2.9	5.4 \pm 2.5	4.5 \pm 3.0	3.8 \pm 1.9	0.005
INR day1	1.5 \pm 0.2	1.7 \pm 0.2	1.4 \pm 0.2	1.5 \pm 0.2	NS
INR day3	1.7 \pm 0.1	1.8 \pm 0.3	1.5 \pm 0.2	1.4 \pm 0.2	0.00
INR day5	1.4 \pm 0.1	1.4 \pm 0.1	1.4 \pm 0.3	1.3 \pm 0.1	NS
INR day7	1.2 \pm 0.2	1.2 \pm 0.1	1.2 \pm 0.1	1.1 \pm 0.1	NS
INR peak	1.9 \pm 0.2	1.9 \pm 0.2	1.7 \pm 0.2	1.7 \pm 0.2	0.002

P-values are the results of the one-way ANOVA test. The significance of differences among the groups (Tukey's or Tamhane's test, where applicable) are expressed in the text.

RLV/BWR, remnant to body weight ratio; RLV/TLV, remnant to total liver volume; SD, standard deviation.

eral hypertrophy. On the contrary, in donor hepatectomy procedures, totally healthy liver volumes are being lost. Taking into consideration that volumetric CT measurements have a deviation rate of 13% to 20%,^{27–29} ensurance of sufficient remnant volume that would not put the donor under risk becomes increasingly important.

Fatty liver is more prone to injuries by anaesthesia, ischaemia or reperfusion damage.^{30,31} For this reason, in donors with steatosis, calculation of remnant liver volume becomes more important. No candidates with steatosis of 10% or more as donors were accepted. As a result, hepatosteatosis did not become a factor that influenced remnant liver volume and associated results.

In a previous study, RLV/BWR was expressed as being more specific in predicting post-operative liver function in liver resections.³² A different study by Chun *et al.*³³ identified cut-off values of RLV/TLV of 20% and RLV/BWR of 0.4 for hepatic dysfunction. The same study found that patients with RLV/BWR ratios of 0.4–0.5 and RLV/TLV of 20–25% were more prone to hepatic dysfunction. As leaving these remnant rates would not be realistic in clinical practice for the safety of the living donors, the values of 30% for RLV/TLV and 0.6 for RLV/BWR were assessed.

When the present results were analyzed, both donors with a RLV/TLV of \leq 30% and with a RLV/BWR of < 0.6 had significant deteriorations in their post-operative courses. Donors with RLV/TLV of \leq 30% had complication and major complication

rates of 44.7% and 13.2%, whereas these values were 35.9% and 9.4% for donors with RLV/BWR of < 0.6. Complication and major complication rates of the whole series were 29.7% and 7.6%, respectively.

In donors who had a RLV/TLV of \leq 30%, having a RLV/BWR of < 0.6 or \geq 0.6 did not influence the results in terms of hyperbilirubinemia and complications. All the statistical differences concerning post-operative bilirubin and INR levels appeared in donors having a RLV/TLV of \leq 30%. The real impact on the outcome was created by a RLV/TLV of \leq 30%. As an exception, only those donors who had both a RLV/TLV of \leq 30% and a RLV/BWR of < 0.6 had higher complication rates of 52.2%. However, this difference was not of statistical significance. Moreover, problems such as a pleural effusion, atelectasis and wound infections that constitute most of the postoperative complications may not be directly related to the donor remnant liver. However, in donors with small remnant volumes, as has been shown by several previous studies, the post-operative process is more difficult and these donors had longer hospital stays.

Likewise, the age of the donor and MHV harvesting are two other parameters whose effects have been shown both on complications and post-operative liver function tests. The previous studies have demonstrated that live donors above the age of 50 years had increases in the incidence of major complications.¹⁴ In the present study, inclusion of MHV and age had no significant effect on outcome.

In conclusion, having a remnant liver volume to total liver volume percentage of equal or lower than 30% as well as a remnant to body weight ratio of less than 0.6 have adverse effects on post-operative liver function tests and complications after live donor hepatectomies when taken into account separately. However, when the two parameters of RLV/TLV and RLV/BWR are combined, it is shown in the present study that the cut-off point of remnant to body weight ratio of 0.6 has no significant effect on post-operative course, a RLV/TLV of $\leq 30\%$ is, by itself, a significant indicator of increased complications and a more difficult post-operative course.

Addendum

O.Y. designed the study. O.Y. and M.D. wrote the first draft. G.A., L.U., T.D., N.G. and M.A. collected the data. G.A., Y.Y. and Y.T. analysed the data, G.A. critically reviewed and revised the draft together with O.Y.

Conflicts of interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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