Right hepatectomy for living donation: Role of remnant liver volume in predicting hepatic dysfunction and complications

Marcelo Facciuto, MD, MPH,[a] Alan Contreras-Saldivar, MD,[a] Manoj K. Singh, MD, MPH,[a] Juan P. Rocca, MD,[a] Bachir Taouli, MD,[b] Irina Oyfe, MBA,[c] Dianne LaPointe Rudow, DNP,[a] Gabriel E. Gondolesi, MD,[d] Thomas D. Schiano, MD,[a] Leona Kim-Schluger, MD,[a] Myron E. Schwartz, MD,[a] Charles M. Miller, MD,[e] *and* **Sander Florman, MD,[a]** *New York, NY, Buenos Aires, Argentina, and Cleveland, OH*

Background. *Extensive attention has been placed on remnant liver volume (RLV) above other factors to ensure donor safety.*

Methods. *We performed a retrospective review of 137 right hepatectomies in live donors between June 1999 and November 2010.*

Results. *Median right lobe volume was 1,029 cm^3, which correlated with its actual weight ($r = 0.63$, $P < .01$); median RLV was 548 cm^3. Of the donors, 32 (24%) developed postoperative hepatic dysfunction (bilirubin >3 mg/dL or prothrombin time >18 s on postoperative day 4). RLV did not predict postoperative hepatic dysfunction (*$P = .9$*), but it was associated with peak international normalized ratio (INR) (*$P = .04$*). Donor age and male gender were predictors of increased bilirubin at postoperative day 4 (age,* $P = .03$*; gender,* $P = .02$*). Of the donors, 45 (33%) experienced complications, and 24 donors had RLVs <30%; 42% experienced complications compared to 31% of donors whose RLVs were greater than 30% (*$P = .3$*). Cell-saver utilization and aspartate-aminotransferase (AST) levels (OR = 3) were associated with complications. Volumetric assessment can predict RLV accurately.*

Conclusion. *Although no demonstrable association between RLV <30% and complications was found, an RLV of 30% should remain the threshold for donor safety. Age and gender should be balanced in donors with a near threshold RLV of 30%. Surgical complexity, suggested by the need for intraoperative autoinfusion of blood and postoperative levels of AST, remained the independent predictor of complications. (Surgery 2013;153:619-26.)*

From the Recanati/Miller Transplantation Institute,[a] and the Department of Radiology,[b] Mount Sinai Medical Center, New York, NY; the Department of Radiology,[c] New York Presbyterian Hospital, Columbia University, New York, NY; the Multiorgan Transplant Institute,[d] the University Hospital-Favaloro Foundation, Buenos Aires, Argentina; and the Department of Hepato-Pancreato-Biliary and Transplant Surgery,[e] Digestive Disease Institute, Cleveland Clinic, Cleveland, OH

THE OPTIMAL GOAL in living liver donation is to achieve a balance between optimal recipient outcomes and maximal safety for the donors. Even in this healthy population, donor right hepatectomy is considered a major surgery, and complications may occur regardless of suitable precautions. In pursuing this dictum, particular attention has been placed on the donor remnant liver volume (RLV) as a key factor in ensuring donor safety.[1,2] Preoperative volumetric assessment of the remnant liver has been considered a valuable tool in evaluating functional liver parenchyma reserve, and its accuracy in predicting postoperative hepatic dysfunction and complications has been extensively evaluated in oncologic liver surgery.[3,4]

It is considered that living donor hepatectomy can be performed safely when RLV is no less than 30% of the estimated total liver volume,[5] but this variable alone may not be enough to predict postoperative hepatic dysfunction and complications in these healthy donors.[2]

Given this controversy, we retrospectively examined the accuracy of estimating RLV and its utility,

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Reprint requests: Marcelo Facciuto, MD, MPH, Recanati/Miller Transplantation Institute, One Gustave L. Levy Place, Box 1104, New York, NY 10029. E-mail: marcelo.facciuto@mountsinai.org.

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along with other relevant risk factors, in predicting postoperative hepatic dysfunction and complications after right hepatectomy in healthy living donors.

MATERIALS AND METHODS

Medical records from living liver donors who underwent right hepatectomy between 1999 and 2010 were reviewed. Preoperative, intraoperative, and postoperative data were collected. Donor selection criteria and operative techniques have been reviewed previously.[6,7] Liver biopsy was performed to exclude liver steatosis that was suspected on history and physical examination. Donors with 20% to 25% of steatosis were excluded; in donors with steatosis of 10% to 20%, diet was recommended, and they were reassessed after weight reduction. Donors with less than 10% of hepatic steatosis were considered acceptable candidates for living donation.

Volumetric measurements of the right liver and left liver in milliliters were obtained using computed tomography (CT) or magnetic resonance imaging (MRI).[8] In addition, the standardized liver volume (SLV) was calculated from the patient's body surface area (BSA) using a mathematical formula:

SLV = $-794.41 + 1{,}267.28 \times$ BSA (m^2).[3,9,10] The ratio of the left RLV was expressed as a percentage of the estimated total liver volume (TLV) (RLV/TLV). The actual right-liver weight in grams was recorded on the back table after flushing the graft with Custodiol HTK (histidine-tryptophan-ketoglutarate) solution (Essential Pharmaceuticals, Newtown PA), and then was compared to the preoperative estimated right liver volume.[11]

Variables previously shown to affect outcome in hepatic resection were studied, including age, gender, body mass index (BMI), BSA, intraoperative autoinfusion (Cell Saver; Haemonetics, Braintree, MA), utilization, hospital length of stay, and postoperative liver function tests. Based on published data, and for the purpose of this study, postoperative hepatic dysfunction was defined as bilirubin level >3 mg/dL or prothrombin time >18 s on postoperative day 4.[3,4,12,13] Complications were defined as any unexpected event deviant from a normal recovery course. Severity of complications was graded using the Clavien scoring system.[14]

Statistical analysis. Continuous variables were expressed as means ± standard deviation (SD). Categorical variables, expressed as frequencies and percentages, were compared using the Fisher exact test. Linear correlations among variables were assessed using the Spearman rank correlation coefficient. To assess the agreement between the pairs of measures, the method comparison approach used was the Bland-Altman analysis. The difference in paired variables, which is the amount of disagreement, was plotted against their average. Bivariate and multiple regression analysis were used to examine the relationship between quantitative outcome variables and single or multiple predictors. Logistic regression analysis was performed to predict the probability of complications as a binary-outcome variable. Statistical differences were considered significant at $P < .05$. All statistical analyses were performed using Stata 11 Statistics/Data Analyses (StataCorp, College Station, TX).

RESULTS

Between June 1999 and November 2010, 137 right hepatectomies for living liver donation were performed. Patient demographics are presented in Table I. The median age was 38 years; 63% were males, and the median weight was 78 kg, with a median BMI of 26 kg/m^2.

Liver volume assessment. Volumetric assessment of the donor livers is outlined in Table II. Estimated median TLV, right liver volume, and left RLV were 1,593 cm^3, 1,029 cm^3, and 548 cm^3, respectively.

The median RLV was 35% of the TLV, and corresponded to 0.7% of donor body weight. The RLV was also expressed as a percentage of the SLV and corresponded to 33% of the SLV. The Bland-Altman comparison method was used to analyze the difference between the ratio of RLV to TLV and the ratio of RLV to SLV and did not detect a significant difference (mean difference, 0.7%). Of the donors, 24 had an RLV <30% of the TLV. The median RLV in these 24 donors was 27.5%, with an SD of 2.8%.

Volumetric assessment of the right liver by CT or MRI correlated with its actual weight (Spearman rank correlation coefficient r = 0.63, $P < .01$), allowing accurate estimation of volumetric measurements of RLV. By linear regression analysis, a statistically significant relationship between volumetric assessment of the right liver and its actual weight (regression coefficient: 0.47, $P < .01$, 95% CI 0.36, 0.58) was found. To measure the strength of the relationship, the $r^2 = 0.38$, explaining 38% of the variance in the right livers' actual weights. Also, the SD around the regression line (the root mean squared error, root MSE = 155 cm^3) was 25% closer to the mean right liver actual weight than the SD around the overall mean of the right liver actual weight (198 g). A smaller SD around

Table I. Donor demographic data

N	*137*
Age (y, median)	38
Gender: male/female	87/50
Weight (Kg, median)	78
Height (cm, median)	173
BSA (m^2, median)	1.94
BMI (kg/m^2, median)	26

Table II. Volumetric liver assessment

	Median	*Range*	*SD*
SLV by BSA (cc)	1,668	1,054–2,332	256
TLV by imaging (cc)	1,593	980–2,456	325
Right lobe volume by imaging (cc)	1,029	601–1,793	250
Actual right lobe weight (gm)	800	338–1,430	198
RLV by imaging (cc)	548	262–937	130
RLV/donor weight ratio (%)	0.7	0.35–1.33	0.18
RLV/TLV (%)	35	20–51	6
RLV/SLV (%)	33	17–59	8

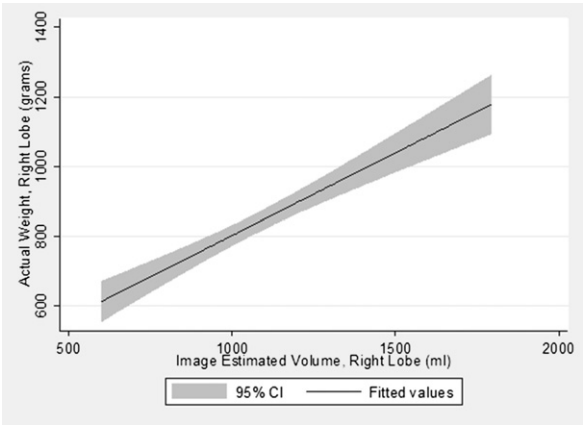

Fig 1. Confidence band around the regression line predicting actual liver weight by volumetric assessment.

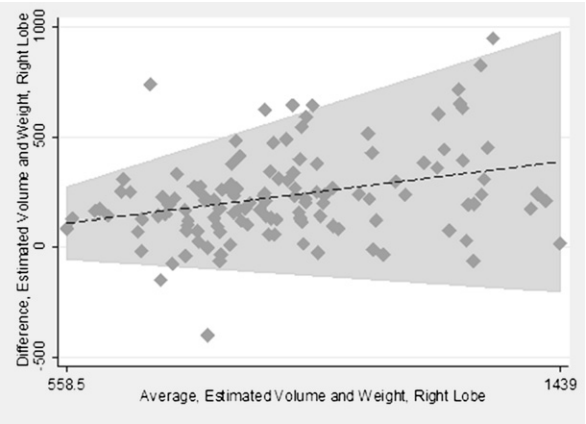

Fig 2. Bland-Altman plot of the differences in paired variables versus their average. The *line* represents the regression between the differences and the average and then alters the limits of agreement accordingly. This is particularly useful when the 2 variables are measured on different scales; hence, a straight conversion factor would recalibrate the 2 variables.

the regression line suggests that the observations were close to this line, hence the regression line does improve our actual weight prediction. The regression equation would be written as: actual weight (g) = 328 + 0.47 (radiologic volume, cm^3), and let us estimate the actual weight depending on the radiologic volume. For example, the median right liver volume (1,029 cm^3) would have had a predicted actual weight of 812 g. This represents a 21% volumetric overestimation. The confidence interval around the regression line is shown in Fig 1. The band around the regression line represents 95% confidence; it is narrowest near the middle of the distribution of the volumetric assessment and widest at the ends. The regression line is not as accurate at the extremes, usually because there are few people at the extremes of distribution. The Bland-Altman comparison method was used to analyze the difference in volumetric assessment of the right liver and the corresponding actual weight of individual cases. The mean and SD of disagreement was 232 ± 200 cm^3. Fig 2 shows the plot of the difference of paired variables versus their average.

Operative data and postoperative liver function. Donor clinical data are detailed in Table III. Most donors had right hepatectomy, preserving the middle hepatic vein with the left lobe (129/137); in only 8 cases did the right hepatectomy include the middle hepatic vein. Of the donors, 30 required cell-saver autoinfusion, and only 2 donors required heterologous blood transfusion.

Of the 137 donors, 32 (24%) developed postoperative hepatic dysfunction as previously defined. By logistic regression analysis, RLV was not able to predict postoperative hepatic dysfunction in this specific donor population ($P = .9$). Other variables, such as donor age and gender, were unable to predict defined hepatic dysfunction. To further evaluate the role of different independent variables, postoperative liver function tests were assessed individually as outcome variables. Using multiple linear regression analysis, RLV was inversely and independently associated with peak

Table III. Donor clinical data

Graft type without MHV- no. of donors, (%)	129/137 (94%)
CellSaver usage- no. of donors, (median units)	30/137 (2)
PRBC- no. of donors, (median units)	2 (1)
Bilirubin at day 4 (mg/dL, median), (SD)	2.0 (1.3)
Prothrombin time at day 4 (seconds, median), (SD)	16 (2.6)
Peak INR (international normalized ratio, median), (SD)	1.8 (0.46)
Peak AST (aspartate-aminotransferase IU/mL, median), (SD)	243 (185)
AST at day 4 (IU/mL, median), (SD)	96 (41)
Peak ALT (alanine-aminotransferase IU/mL, median), (SD)	251 (170)
ALT at day 4 (IU/mL, median), (SD)	132 (71)
Defined post operative hepatic dysfunction, *n* (%)	32 (24%)
Length of stay (days, median), (SD)	6 (2)
Complications, *n* (%)	45 (33%)

INR ($P = .04$, $R^2 = 0.32$) (Fig 3, *A*). No association was shown between RLV and other liver chemistry tests evaluated (aspartate-aminotransferase, alanine-aminotransferase, and serum bilirubin). In addition, donor age and male gender were independent predictors of higher serum bilirubin at postoperative day 4 (age: $P = .035$, male gender: $P = .02$, $R^2 = 0.47$) (Fig 3, *B* and *C*).

Postoperative complications. Among the 137 donors, 45 experienced postoperative complications (an overall morbidity rate of 33%). Complications were classified based on the Clavien scoring system[14] and are shown in Table IV. Of all complications, 75% were grade 1 or 2. One donor experienced gas gangrene of the stomach, leading to death (mortality rate of 0.7%).[15]

When comparing donors with RLV <30% to RLV >30%, the rate of complications was not statistically different (42% in RLV <30% vs 31% in RLV >30%, $P = .3$).

Logistic model to predict complications. Univariate analysis of all covariates was performed first. For continuous variables, the assumption of linearity in the model was confirmed by the lowess smoothed univariable scatterplot. Variables in which the univariate test had a P value < .25 or known clinical importance were included in the multivariable model (age: $P = .4$; gender: $P = .8$; aspartate-aminotransferase (AST) levels at day 4: $P = .02$; use of cell saver: $P = .07$; BMI: $P = .28$;

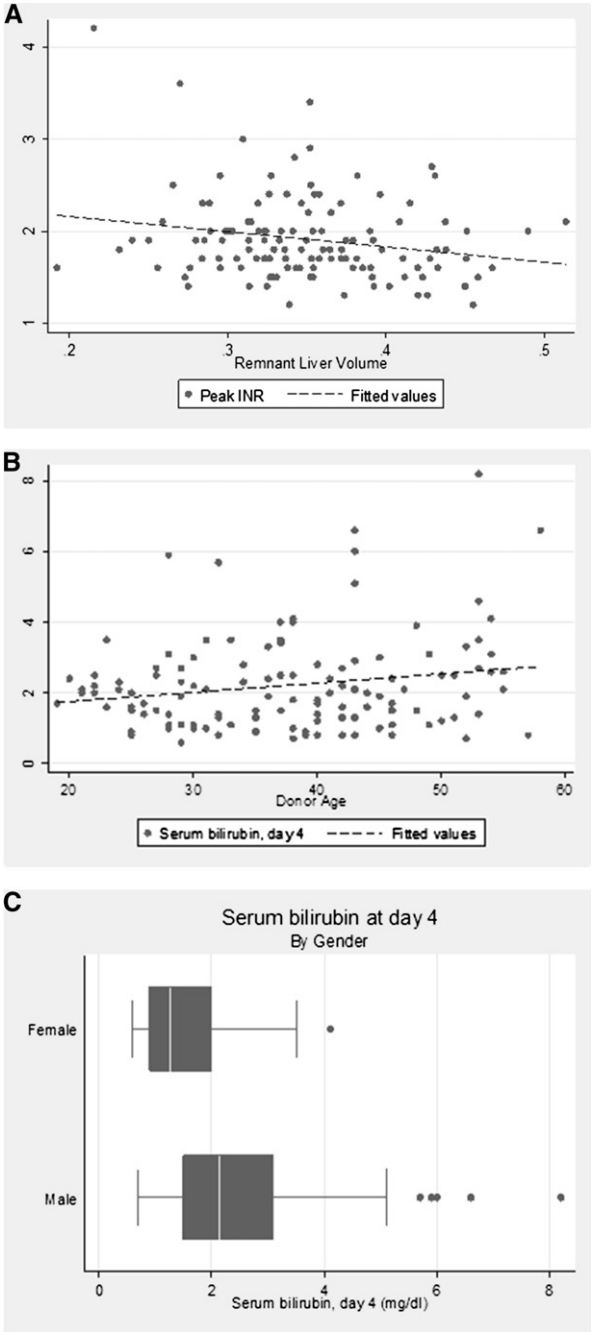

Fig 3. Impact of remnant liver volume, donor age, and gender on postoperative liver function tests. (*A*) Correlation between peak INR (*vertical axis*) and remnant liver volume (*horizontal axis*). (*B*) Correlation between serum bilirubin at postoperative day 4 (*vertical axis*) and donor's age (*horizontal axis*). (*C*) Box plot of serum bilirubin at postoperative day 4, by gender. The *white vertical line* in the *dark-gray boxes* is the median. The *left* and *right* sides of the *dark-gray box* are the 25th and 75th percentiles. *Lines* extending from the edge of the *dark-gray box* represent 99% of the sample. Beyond this, there are *dots* representing outliers, or extreme values.

Table IV. Summary of operative morbidity and mortality following live donor right hepatectomy

Complications	*Grade according to Clavien's classification*					
	I	*II*	*IIIA*	*IIIB*	*V*	*Total (%)*
Wound infections		6	1			7 (5%)
Biliary		2	3	1		6 (4%)
Fluid retention: Pleural/ascites/edema	1	2				3 (2%)
Readmission: Abdominal pain	8	2				10 (7%)
Fever	1	2				3 (2%)
Intra-abdominal abscess			2			2 (1.5%)
Small bowel obstruction	2	1		2		5 (4%)
Deep vein thrombosis		3				3 (2%)
Pneumonia		2				2 (1.5%)
Altered mental status	1					1 (0.7%)
Urinary tract infection		1				1 (0.7%)
Median nerve palsy				1		1 (0.7%)
Gas gangrene of stomach					1	1 (0.7%)
Total (%)	13 (9%)	21 (15%)	6 (4%)	4 (3%)	1 (0.7%)	45 (33%)

Table V. Logistic regression analysis of factors associated with complications

Variable	*Coefficient*	*Standard error*	P *value*	*Odds ratio (95% CI)*
CellSaver utilization (vs not)	1.1040	0.4846	.023	3 (1.2–7.8)
AST at Postop. day 4 (IU/mL)	0.0118	0.0051	.020	3*(1.2–8.8)

*Odds ratio for a 100-IU change in AST.

RLV: $P = .58$; prothrombin time at day 4: $P = .24$). Wald test statistics were used to delete variables 1 by 1, the least significant first, until all variables were significant. The likelihood-ratio test comparing 2 models with and without each deleted variable was performed to test that the reduced model was as good as the full model. Also, the variable-confounding effect was checked based on a <15% change in the beta coefficient for the variables of AST at day 4 and the use of a cell saver in order to exclude the variable from the model. At this point, variables not included in the model were entered, their statistical significance was tested using the Wald test, and their confounding effect was assessed based on the impact on the coefficients for the other variables in the model. Interactions among the variables in the model were checked by creating interaction variables as the arithmetic product of the pair of main effect variables (AST at day 4 and use of a cell saver). The result of adding the interaction variable to the preliminary model was not significant and thus was excluded.

The final model is shown in Table V. Cell-saver utilization ($P = .02$) and AST at postoperative day 4 ($P = .02$) were significantly associated with postoperative complications. Of outcome events (donors who had complications), 45 provided a ratio between outcome events and number of independent variables selected for retention in the final model of >10, enough to prevent model overfitting.

Evaluation of the fit of the model. A link test for model specification was used to understand how the model explained the association between the independent variables (cell-saver utilization and AST at day 4) and complications. The results showed $P = .94$, meaning that there was no unexplained association with outcome.

To test model performance by discrimination, a receiver operating characteristic (ROC) curve was performed to provide a measure of discrimination between subjects with and without complications. The area under the curve was 0.71, which is considered an acceptable discrimination.

To test model performance by calibration, a goodness-of-fit test (the Hosmer-Lemeshow test) was used, and the model fit reasonably well. Under the null hypothesis that the model fits the data, a $P = .8$ did not allow us to reject the null hypothesis and, hence, the model.

DISCUSSION

Donors' well-being must be the principal consideration in liver transplantation involving living liver donation. As a center that experienced the

tragic event of a living donor's death, we are in constant awareness of the delicate balance between donor risks and recipient benefits.

Anticipating appropriate function of donor remnant hepatic mass after right hepatectomy is an initial step toward donor safety. Currently, there is no way to measure liver weight accurately in vivo in healthy human subjects. Three-dimensional radiologic imaging by CT or MRI has been the method of choice to assess liver volume. The accuracy of CT has been evaluated ex vivo by scanning livers harvested from cadavers. Under these circumstances, radiographic volume and mass agreed within 5%.[16,17] In vivo, radiologic volume has been shown to correlate with liver weight.[4,18] However, estimated liver volume by volumetric analysis is often an overestimation of liver mass weighed on the back table. Chan et al[19] showed that CT volumetric assessment of the liver often overestimates liver weight by 20% in healthy Chinese adults.

In line with previous reports, we found a correlation between right hepatectomy mass and volume, which allowed us to detect, by regression equation, a 21% mass overestimation of the median volumetric value in this cohort of healthy donors from the United States. Of note, the accuracy of radiologic volumetric estimation can diminish with liver volumes further away from the mean liver volume, as previously shown by Schiano et al[20] and Van Thiel et al.[11] The discrepancy between radiologic volume and mass may be attributed to the space occupied by blood-perfused vessels as opposed to the weight of an in situ perfused liver. This can also explain the high accuracy of radiographic volume in ex vivo livers with collapsed vessels, even when using water-displacement methods.[17]

In extrapolating to the left liver, these findings allowed us to accurately correlate RLV and mass of the left liver, but left us with the assumption that we were also overestimating the mass of remnant left liver. Estimating RLV is the closest approximation we currently count on to predict functioning hepatic mass. RLV, although a virtual variable, can be accurately and directly measured by current imaging techniques, and hence stands as an independent variable to predict outcome.

Previous experiences in extended hepatic resections have shown the relevance of RLV in predicting postoperative hepatic dysfunction and complications.[3,4,12,13] It is considered, overall, that an RLV of 25% to 30% is adequate for spontaneous recovery after major liver resection.[12,21,22]

To define postoperative liver failure and predict complications after hepatectomy, Balzan et al[13] analyzed 775 elective liver resections and observed that a PT <50% of normal and bilirubin >3 mg/dL on postoperative day 5 were predictors of complications.

In the current study, RLV failed to show an association with the predetermined definition of hepatic dysfunction. However, it did have an inverse association with peak INR values. Other variables were also correlated with individual abnormal liver function tests in this study: age and male gender were associated with higher serum bilirubin levels postoperatively. Donor age has previously been associated with liver graft function following living-donor liver transplantation.[23,24] This same variable may also have an influence on remnant donor liver itself. Experimental studies after two-third partial hepatectomy in rats have shown proliferation in the remnant liver involving 99% of the hepatocytes in young rats, compared to 30% in older rats.[25] In regard to the effects of gender on postoperative liver function, it has been hypothesized that females with less fat-free mass for a given body weight may require less liver mass to meet the body's metabolic needs.[19,26,27]

As opposed to what is considered an acceptable risk for hepatic dysfunction and complications in oncologic liver surgery, the same degree of acceptance may not apply to living donors, a highly selected group of subjects with no comorbid conditions. Even though an RLV of 27% was considered the lowest limit to support survival in a nonfatty liver, Fan et al[5] recommended an RLV of 30% to increase donor safety. Several publications have addressed the controversy regarding donor safety, complications, and the RLV in right-lobe living donation. Taner et al[1] reported a greater relative risk for morbidity in donors with an RLV <30%. On the other hand, Ibrahim et al[2] showed no difference in postoperative liver function and complications in donors with RLV <30%. He based his results on the fact that those donors in the RLV <30% group had a mean RLV of 28% and probably were more highly selected donors, having complete preservation of tributary veins to segment 4 of the remaining left lobe. Among the 137 donors in this study, in only 8 was the middle hepatic vein (MHV) retrieved with right liver graft. This small number of cases precluded us from making any rational analysis of the impact of venous outflow drainage in the remnant left liver. In addition, it is possible that unplanned donor selection biases could have contributed to the lack of apparent differences in outcomes for donors in whom the middle hepatic vein was removed. Retrospectively, donors in whom the MHV had been

removed had bigger RLV (RLV 39% vs 35%, $P = .053$), and there were proportionally more females (75% vs 33%, $P = .02$) compared to donors whose MHV was preserved. In addition, 40% of the donors in whom the MHV had been removed had a preserved independent segment 4 vein draining into the left hepatic vein.

This study failed to demonstrate a correlation between RLV, predefined postoperative hepatic dysfunction, and the occurrence of complications. When we compared the 24 donors with RLV <30% against the group having large RLV, no statistical difference in complications was found. In agreement with Ibrahim et al,[2] this result can be supported in part by a very close to 30% RLV (27.5%) and a biased selection of donors. Although no demonstrable association between RLV<30% and complications was found, we routinely weigh the risk for potential postoperative complications and aim for a minimum of 30% RLV when selecting donors. The predefined postoperative hepatic dysfunction in this study did not translate into a complication event for these healthy subjects, but we raise the concern that lower RLVs may ultimately lead to clinically relevant hepatic dysfunction and complications. In light of the proven independent association between RLV, liver dysfunction, and complication rate in oncologic liver surgery, the minimal acceptable RLV may be a few percentage points away from what is currently recommended (30%) in healthy donor subjects. However, it is difficult to justify further search for an independent minimal acceptable RLV at the expense of donor safety. When considering donors with a near-threshold RLV of 30%, other donor variables, especially age and gender, should also be taken into consideration independently. Steatosis in the liver is also an important consideration when calculating the RLV, because the functional RLV will be proportionally less than the measured volume.[20]

The current study showed that the need for intraoperative autoinfusion of blood products and the postoperative serum levels of AST were independent predictors of postoperative complications. The need for intraoperative blood transfusion has been associated with postoperative complication in liver surgery.[28-30] When comparing live donor hepatectomies with and without vascular inflow occlusion, Miller et al[28] described a higher incidence of major complications in living donors who had great need for blood transfusion and increased parenchymal damage (reflected by peak alanine aminotransferase (ALT) and AST serum levels). Ibrahim et al[31] showed that intraoperative blood loss is an independent predictor of postoperative complications after living-donor hepatectomy. It is logical to assume that the need for autoinfusion of blood products and the degree of parenchymal damage based on AST levels are reflections of surgical complexity, which directly impact on the occurrence of postoperative donor complications.

Refinements in techniques for hepatectomy are essential to maintain safety and decrease morbidity in the donor. We previously described our experience with single upper-midline incision for living donor hepatectomy (data presented in part at ATC 2012).[32]

Since May 2010, 31 consecutive living donors underwent right hepatectomy via a supraumbilical upper-midline incision. Liver mobilization, hilar dissection, and parenchymal transection were performed through a single upper-midline incision with a mean length of 12.5 cm. This approach consolidates the steps of liver mobilization, hilar dissection, and parenchymal transection in a single exposure method. The upper-midline approach avoids the morbidity of conventional subcostal, J, or Mercedes-Benz incisions, using incision lengths comparable to those used in the laparoscopy-assisted modality.

In conclusion, RLV can be predicted accurately by volumetric assessment in healthy living donors. Although no demonstrable association with postoperative hepatic dysfunction and complications was found, RLV remains an important factor in donor evaluation and safety, but it is not exclusive. When approaching the established RLV of 30%, the risks associated with increasing donor age and male gender should be carefully balanced. From a surgical perspective, upgrading the standards of donor surgery remains our most important effort to decrease the risks for postoperative complications. Detailed surgical planning based on preoperative radiologic imaging, ensuring excellent anesthetic care, and taking advantage of technologic improvements in surgical techniques are essential considerations in planning for uneventful donor-liver surgery.

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