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Clinical Outcome of Residual Liver Volume and Hepatic Steatosis After Right-Lobe Living-Donor Hepatectomy

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Background: We examine how residual liver volume (RLV) and hepatic steatosis (HS) of living liver donors affect the regeneration process and clinical outcomes.

Material/Methods: We longitudinally studied 58 donors who underwent right-lobe hepatectomy during the period February 2014 to February 2015 at a single medical institution. The patients were classified based on RLV (30–35%, 35–40%, 40–50%) subgroups and HS (<10%, 10–30%, 30–50%) subgroups. Clinical parameters such as clinical outcome, liver volumetric recovery (LVR,%) rate and remnant left-liver (RLL,%) growth rate were collected for analysis.

Results: The clinical features of postoperative peak total bilirubin (p=.024) were significant in the 3 RLV subgroups. Body mass index (p=.017), preoperative alanine transaminase (p<.001), and pleural effusion (p=.038) were significant in the 3 HS subgroups. The LVR rate and RLL growth rate equations showed significant variation in regeneration among the 3 RLV subgroups. The LVR rate and RLL growth rate equations did not show significant variation in regeneration among the 3 HS subgroups.

Conclusions: Hyperbilirubinemia was a risk factor in the small-RLV group, and a large amount of pleural effusion was a risk factor in the steatosis 30–50% group. Hepatic steatosis subgroups did not show significantly different degrees of regeneration. The safety of living donors was a major concern while we compiled the extended living-donor criteria presented in this paper.

MeSH Keywords: Donor Selection • Liver Regeneration • Living Donors

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Background

Many studies have shown that a residual liver volume (RLV) of up to 30% after a living-donor hepatectomy can be a safety concern [1,2]. After donor hepatectomies, the 30–40% residual liver volume group and the 30–50% hepatic steatosis group slowly recovered liver functionality [3,4]. The prevalence in developing countries of nonalcoholic fatty livers has increased as more patients develop a sedentary lifestyle, have high caloric intakes without exercising, and have body mass indexes indicating obesity. However, with the increasing trend of hepatic steatosis or fatty change in living donors, different medical centers may want to change their donor selection criteria. Our study supposes that residual liver volume and hepatic steatosis affect the regeneration process and clinical outcome in living-donor hepatectomy; it is important that we share our experience of care with other transplant teams.

Material and Methods

All donors had preoperative evaluations, including blood typing, liver function surveys, heart and lung function tests, and other laboratory tests. Abdominal computed tomography (CT) scans were performed to assess liver vascular anatomy and liver volume. Liver volumes were estimated on computed tomography scans using 3D reconstruction software (IQQA-Liver, EDDA Technology, Inc.). Magnetic resonance cholangiopancreatographies were performed to evaluate biliary anatomy. All donors with right hepatectomies were eligible for inclusion in the study. Participants in this prospective longitudinal study were 59 donors who underwent donor hepatectomy during the period February 2014 to February 2015 at a single medical institution. A left-lobe hepatectomy was excluded, leaving 58 donors in the study. Approval was granted by the Changhua Christian Hospital Institutional Review Board (No. CCH 140708). Informed consent was given by the patients. This is a secondary data analysis study.

Design

The study's sample was liver donors classified based on RLV and hepatic steatosis. CT scans were analyzed using 3D reconstruction software to estimate liver regeneration. The RLV ratio was defined as the ratio of remnant left-liver (RLL) volume and preoperative total liver volume (TLV). We distinguished 3 subgroups based on the following RLV ranges: 30–35%, 35–40%, and 40–50%. All steatotic donors were measured preoperatively with the normal liver function survey. After a hepatectomy, a small sample of liver tissue was used to confirm fatty degree by pathology. We distinguished 3 subgroups based on the following ranges of steatosis: 0–10%, 10–30% and 30–50%.

We collected data on clinical parameters such as age, sex, body mass index, platelet count, alanine transaminase (ALT), total bilirubin (TB), ascites, hepatic steatosis, RLV, liver volumetric recovery (LVR,%) rate, remnant left-liver (RLL,%) growth rate, and postoperative complications (bile leak and pleural effusion). Liver regeneration was assessed by computed tomography scans 1 week, 1 month, 3 months, and 1 year after the operation. The liver regeneration was expressed with the following 2 equations: (1) Liver volumetric recovery (LVR) rate (%)=RLL after hepatectomy/the preoperative TLV)×100, and (2) Remnant left-liver (RLL) growth rate (%)=(liver volume at postoperative day X-preoperative RLL)/preoperative RLL×100. Some fluids of importance were ascites and pleural effusion. The reported ascites was the collected drainage amount during hospitalization. The reported pleural effusion was obtained on postoperative day 7 by using computed tomography scans and 3D reconstruction software.

Statistical analysis

Results were collected for analysis. Continuous variables are presented as mean±standard deviation (SD). The Pearson chi-square test and one-way ANOVA test were used to examine differences in demographic and clinical characteristics within the 3 groups. Repeated-measures ANOVA was used to compare longitudinal measurements of liver regeneration between the RLV groups and steatosis groups. P values lower than 0.05 were considered to be statistically significant. All statistical analyses were performed using IBM SPSS Statistics, version 20.0.

Results

Among the 58 right-lobe living-donor hepatectomies enrolled into the present study, the mean donor age was 31.17±8.75 (range, 19 to 61 years), body mass index (BMI) was 23.77±3.51 (range, 18.38 to 34.48), RLV was 37.44±4.22 (range, 30.00% to 49.43%), blood loss was 213.79±256.80 (range, 50.00 to 1700.43 ml), length of stay was 9.79±2.91 (range, 8.0 to 30.0 days), and the rate of bile leakage complication was 6.9% (n=4). The demographic and clinical features of the patients were not significantly different in the 3 RLV subgroups (Table 1), but postoperative peak TB (p=.024) was significantly different. Post hoc comparisons analysis showed that the RLV 30–35% group had a significantly higher postoperative peak TB than the RLV 35–40% group (p=.019). Most demographic and clinical features of the patients were not significantly different in the 3 hepatic steatosis subgroups, but BMI (p=.017), preoperative ALT (p<.001), and pleural effusion from operative complications (p=.038) were significantly different (Table 2). Post hoc comparisons analysis showed some significant differences: in BMI between the steatosis <10% group and the steatosis 10–30% group (p=.025), in pleural effusion between the steatosis 10~<30% group and

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Table 1. Comparisons of demographic data and clinical features of residual liver volume groups of liver donors.

Demographic and clinical features	RLV 30–35% n=18	RLV 35–40% n=26	RLV 40–50% n=14	*p*
	Mean±SD (range)	Mean±SD (range)	Mean±SD (range)	
Age (years)	30.33±6.19 (22–42)	31.04±10.76 (20–61)	32.50±7.74 (19–43)	.787
Body mass index	23.25±3.37 (18.38–30.47)	24.00±3.75 (19.07–34.48)	24.02±3.40 (18.97–30.82)	.754
Preoperative platelet (×1000/μL)	240.28±47.00 (145.00–320.00)	251.81±43.46 (149.00–350.00)	243.43±60.57 (166.00–408.00)	.725
Preoperative ALT (U/L)	18.94±9.87 (8.00–44.00)	20.62±6.63 (11.00–34.00)	23.64±10.67 (11.00–50.00)	.326
Preoperative TB (mg/dL)	.83±.40 (.35–1.76)	.65±.30 (.33–1.36)	.67±.37 (.17–1.53)	.213
Blood loss (ml)	225.00±225.73 (50.00–1000.00)	175.00±118.53 (50.00–550.00)	271.43±434.44 (50.00–1700.00)	.552
Pleural effusion (cm^3)	138.11±158.33 (00.00–642.00)	166.69±150.07 (0.00–501.00)	301.14±297.72 (2.00–1142.00)	.057
Ascites (ml)	1126.94±655.95 (260.00–2800.00)	1163.69±580.55 (169–2453.0)	951.07±670.54 (169.00–2335.00)	.582
Postoperative platelet (×1000/μL)	162.61±38.45 (103.00–256.00)	172.65±34.95 (100.00–240.00)	173.79±42.77 (118.00–248.00)	.626
Postoperative peak ALT (U/L)	247.06±156.15 (79.00–625.00)	189.12±98.26 (60.00–497.00)	214.36±113.67 (94.00–551.00)	.311
Postoperative peak TB (mg/dL)	3.64±1.84 (1.36–8.32)	2.47±.95 (1.20–4.95)	2.79±1.31 (1.17–6.11)	.024
Length of stay (days)	9.67±1.46 (8.00–14.00)	9.42±.86 (9.00–13.00)	10.64±5.64 (8.00–30.00)	.445
	(%)	(%)	(%)	
Gender				.653
Male	8 (44.4)	15 (57.7)	8 (57.1)	
Female	10 (55.6)	11 (42.3)	6 (42.9)	
Hepatic steatosis				.158
<10%	13 (72.2)	9 (34.6)	6 (42.9)	
10–30%	4 (22.2)	12 (46.2)	5 (35.7)	
30–50%	1 (5.6)	5 (19.2)	3 (21.4)	
Bile leakage				.445
No	17 (94.4)	25 (96.2)	12 (85.7)	
Yes	1 (5.6)	1 (3.8)	2 (14.3)	

RLV – residual liver volume; ALT – alanine transaminase; TB – total bilirubin.

the steatosis 30–50% group (p=.029), and in preoperative ALT between the steatosis <10% group and the steatosis 30–50% group (p<.001) and between the steatosis 10–30% group and the steatosis 30–50% group (p=.007).

The 2 equations for liver regeneration were assessed 1 week, 1 month, 3 months, and 1 year after the operation (Figure 1). In RLV groups, the LVR rate equation showed significantly different degrees of regeneration when comparing the 30–35%

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Table 2. Comparisons of demographic data and clinical features of hepatic steatosis groups of liver donors.

Demographic and clinical features	Steatosis <10% n=28	Steatosis 10–30% n=21	Steatosis 30–50% n=9	*p*
	Mean±SD (range)	Mean±SD (range)	Mean±SD (range)	
Age (years)	28.82±7.108 (20–43)	33.57±10.51 (19–61)	32.89±7.81 (22–48)	.139
Body mass index	22.44±3.07 (18.38–28.40)	25.00±3.58 (19.98–34.48)	25.02±3.43 (18.97–30.47)	.017
Preoperative platelet (×1000/μL)	236.75±37.75 (145.00–297.00)	256.48±62.05 (149.00–408.00)	251.67±34.24 (225.00–334.00)	.352
Residual liver volume (%)	37.17±4.90 (30.00–49.43)	37.52±3.27 (32.20–45.47)	38.12±4.30 (32.19–45.90)	.840
Preoperative ALT (U/L)	17.11±7.16 (8.00–34.00)	21.48±6.70 (12.00–37.00)	30.89±10.13 (21.00–50.00)	<.001
Preoperative TB (mg/dL)	.77±.42 (.17–1.76)	.67±.29 (.33–1.27)	.64±.24 (.42–1.10)	.500
Blood loss (ml)	246.43±343.71 (50.00–1700.00)	176.19±107.96 (50.00–550.00)	200.00±185.41 (50.00–600.00)	.637
Pleural effusion (cm^3)	193.57±185.754 (00.00–674.00)	127.57±108.56 (2.00–327.00)	331.00±343.37 (36.00–1142.00)	.038
Ascites (ml)	1128.71±600.62 (260.00–2800.00)	1046.57±607.24 (254.0–2453.0)	1141.56±774.71 (169.00–2240.00)	.884
Postoperative platelet (×1000/μL)	162.32±33.16 (103.00–220.00)	178.90±45.19 (100.00–256.00)	171.89±29.434 (118.00–214.00)	.313
Postoperative peak ALT (U/L)	195.89±134.06 (60.00–625.00)	205.71±90.80 (87.00–497.00)	284.44±138.83 (133.00–551.00)	.161
Postoperative peak TB (mg/dL)	3.03±1.52 (1.20–8.32)	2.47±.96 (1.17–4.92)	3.52±1.89 (1.55–6.65)	.156
Length of stay (days)	9.61±1.34 (8.00–14.00)	9.24±.62 (8.00–11.00)	11.67±6.95 (9.00–30.00)	.098
	(%)	(%)	(%)	
Gender				.082
Male	11 (39.3)	13 (61.9)	7 (77.81)	
Female	17 (60.7)	8 (38.1)	2 (22.29)	
Bile leakage				.295
No	25 (89.3)	21 (100.0)	8 (88.9)	
Yes	3 (10.7)	0 (0.0)	1 (11.1)	

RLV – residual liver volume; ALT – alanine transaminase; TB – total bilirubin.

and 35–40% RLV subgroups (p=0.019) and when comparing the 30–35% and 40–50% RLV subgroups (p=0.005). The RLL growth rate equation showed significantly different degrees of regeneration when comparing the following pairs of subgroups by repeated-measures ANOVA: RLV 30–35% *vs.* 35–40% (p<0.001), RLV 30–35% *vs.* 40–50% (p<0.001), and RLV 35–40% *vs.* 40–50% (p<0.001) (Figure 2). Among the 3 hepatic steatosis subgroups, the LVR rate equation and RLL growth rate equation did not show significantly different degrees of regeneration as determined by repeated-measures ANOVA (Figure 3).

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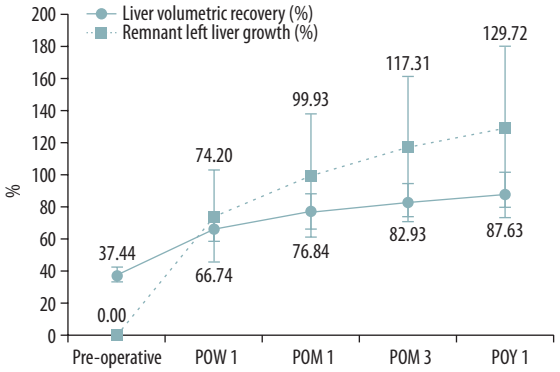

Figure 1. Liver volumetric recovery and remnant left-liver growth following right-lobe living-donor hepatectomy. The 2 equations for liver regeneration were assessed 1 week, 1 month, 3 months, and 1 year after the operation.

Discussion

Studies have shown that clinical parameters such as advanced age, male sex, high BMI, and the presence of moderate or severe steatosis have a significantly negative impact on liver regeneration after a donor's hepatectomy [5–9]. In our study, liver regeneration was 29.3% and 74.2% in the first postoperative week based on the LVR rate and RLL growth rate equations (Figure 1), respectively; average girth increased by 4.19% and 10.6% per day. Other average girth increases based on LVR rate calculations are 3.37% per week (1st postoperative week to 1st postoperative month), 3.05% per month (1st postoperative month to 3rd postoperative month), and 0.52% per month (3rd postoperative month to 1st postoperative year). For average girth increases based on RLL growth rate calculations, other values are 8.57% per week (1st postoperative week to

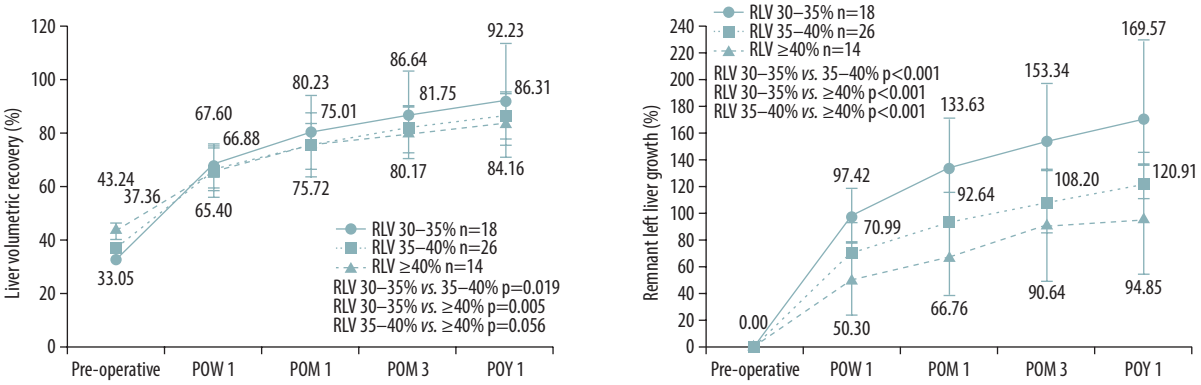

Figure 2. Comparisons of residual liver volume groups following right-lobe living-donor hepatectomy. In RLV groups, the LVR rate equation showed significantly different degrees of regeneration when comparing the 30–35% and 35–40% RLV subgroups (p=0.019) and when comparing the 30–35% and 40–50% RLV subgroups (p=0.005). The RLL growth rate equation showed significantly different degrees of regeneration when comparing the following pairs of subgroups by repeated-measures ANOVA: RLV 30–35% *vs.* 35–40% (p<0.001), RLV 30–35% *vs.* 40–50% (p<0.001), and RLV 35–40% *vs.* 40–50% (p<0.001).

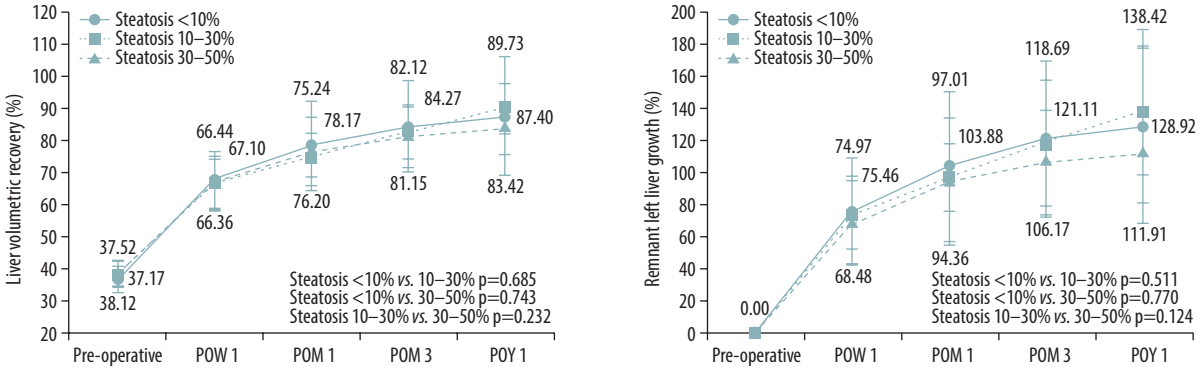

Figure 3. Comparisons of hepatic steatosis groups following right-lobe living-donor hepatectomy. Among the 3 hepatic steatosis subgroups, the LVR rate equation and RLL growth rate equation did not show significantly different degrees of regeneration as determined by repeated-measures ANOVA.

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1st postoperative month), 8.69% per month (1st postoperative month to 3rd postoperative month), and 1.38% per month (3rd postoperative month to 1st postoperative year). From 1 month to 1 year after hepatectomy, liver regeneration was moderate. The human liver has a remarkable capacity to regenerate after injury, with the most significant regeneration occurring within the first 3 months [10]. Studies have shown that the percent volumetric liver recovery ranges from 51.7% to 63.8% during the first postoperative week [6,7,11], from 64% to 71.3% after the fourth postoperative week [7,11], and from 74.0% to 81.5% approximately 12 weeks after surgery [6,7,11]. In our study, volumetric recovery rates were higher than those reported previously, possibly because our patients were younger (mean age, 31 years) than those in other studies (mean age, 32.9 to 39 years) and because our patients routinely received parenteral nutritional support after surgery. In the treatment of patients after major liver resection, branched-chain amino acids with parenteral nutrition promotes hepatocyte proliferation and improves liver regeneration and function [12–14]. In living donor after hepatectomy studies, significant rapid regeneration was observed in small-RLV groups, in males, and in younger patients [6–8,15]. However, there was no significant difference in regeneration when comparing mild steatosis and no steatosis groups and when comparing right-lobe hepatectomy and left-lobe hepatectomy groups [6,10]. In our study, the 30–50% steatosis group had poorer regeneration than the other steatosis groups, but the difference was not significant. Short-to-long-term regeneration was found to be significantly better in the small-RLV group. When a living donor needs adequate metabolic function after a hepatectomy, cytokines play an important role in cell cycles, growth factors, and regeneration [4].

Nonetheless, it is our belief that liver regeneration should not be the only metric to use when considering adequate liver functionality after a living-donor hepatectomy. Donor safety after a hepatectomy is the most important outcome. Among donors with a small RLV, many studies found increased risks, including delayed liver functions, postoperative complications, and longer hospital stays [16–18]. In our study, the small-RLV group appeared to have a high incidence of hyperbilirubinemia after hepatectomy, but there were no significant differences with regard to liver function, longer hospital stays, and ascites or bile leakage from postoperative complications. Pleural effusion from postoperative complications was a significant risk in the 30% to <50% steatosis group. A previous report suggested limits of 30% for RLV and 10% to 15% for steatosis. More reports regarding RLVs less than 30% found that to be safe, young living donors with no steatosis should be recommended [19,20]. Some publications reported nonalcoholic steatohepatitis donor mortalities after living-donor-related liver transplantations [21,22]; in them, moderate steatosis and severe steatosis were contraindications for donor selection. Some studies of mild steatosis found postoperative hyperbilirubinemia [23–25]. Our study found significantly higher levels of preoperative ALT and BMI. The largest postoperative peak ALT and TB appeared in the 30–50% steatosis group, but the 30–50% steatosis group had no significant delay in regaining liver functionality and did not have significantly longer hospital stays. We reduced the risks of postoperative complications and delayed liver functionality in our steatosis patients by adding branched-chain amino acids (BCAAs) to the parenteral nutrition routine. Research shows that BCAAs can improve the nutritional status, reduce protein loss, and support protein synthesis, insulin secretion, and liver regeneration [26,27]. BCAAs have potential to reduce the incidence of nonalcoholic fatty liver disease [28]. Reported preoperative steatosis workup protocols also included abdominal ultrasonography and either CT or liver magnetic resonance imaging [29–31].

When the imaging indicated severe steatosis, we should have rejected the living donation. However, liver function results were abnormal within steatosis grades by imaging, and liver biopsies for evaluating donor steatosis and hepatitis were considered when no other living-donor candidate was selected. Sometimes we had no choice but to use living donors with moderate steatosis; we screened them for normal liver functionality. Studies have shown that older hepatic steatosis patients have higher mortality and more postoperative complications after major hepatectomies compared to their younger counterparts [32,33]. We selected young living donors (≤45 years) in the 30% to 50% steatosis range. A right hepatectomy preserving the middle hepatic vein (>35% RLV) can be safely performed for these carefully selected steatotic living donors. This study has certain limitations. We did not evaluate any synthetic ability, such as albumin or INR of remnant liver function. Small amounts of clinical material and small groups and subgroups are limiting factors for the statistical analysis.

Conclusions

Small-RLV donors after hepatectomy had hyperbilirubinemia because their liver volumes were not sufficient, so bilirubin levels over 8 mg/dL should be closely monitored. The levels might decrease by the third to fourth postoperative day due to excellent regeneration. Although steatosis levels more severe than mild-to-moderate are not desirable when finding a good donor candidate, they are becoming more common as the number of obese donors with steatosis increases. Our study found that large pleural effusion was a significant post-hepatectomy complication, and hepatic steatosis subgroups did not show significantly different degrees of regeneration. Our criteria for living donors includes normal liver enzymes, young age (<50 years), and the ability to preserve the middle hepatic vein (RLV >35%) when a donor has hepatic steatosis.

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The safety of donors undergoing right hepatectomy is a very important reason to utilize these extended living-donor criteria.

Compliance with ethical standards

The study was approved by the Institutional Review Board of Changhua Christian Hospital (No. CCH 131234).

Conflict of interest

None.

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