Original Article

Comparison of liver regeneration between donors and recipients after adult right lobe living-donor liver transplantation

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Background: Living-donor liver transplantation (LDLT) is recognized as the standard treatment for end-stage liver diseases. The regeneration of the residual liver and graft after LDLT is important in evaluating surgical success. Previous studies have attempted to elucidate mechanisms, principles of liver regeneration after LDLT, or influencing factors. However, they have not ruled out patients with complications and reached a uniform conclusion. In this study, for the first time, we unified measurement methods of liver volumes and eliminated patients with complications to compare liver regeneration trends between donors and recipients after LDLT and search for potential influencing factors.

Methods: A total of 61 donors and 62 recipients without complications after adult right lobe LDLT were included in this retrospective observational cohort study. The liver regeneration ratios (LRRs) at different time points in donors and recipients after LDLT were calculated and compared. Factors that affect LRRs include gender, age, graft with or without the middle hepatic vein (MHV), initial remnant liver (IRLV)/estimated standard liver volume (ESLV), initial graft volume (IGV)/ESLV, Child-Pugh grade, and model for end-stage liver disease (MELD) score of the recipients. Analysis of variance, independent-sample *t*-test, and correlation analysis were performed for statistical analyses.

Results: Significant differences were found in LRRs between the donors and recipients after LDLT (all P<0.05). The LRRs of donors at 0.5, 1, 3, and 6 months were 80.80%±24.12% (72.87%, 88.73%), 98.62%±37.47% (75.97%, 121.26%), 103.34%±23.47% (83.73%, 122.96%), and 130.18%±17.68% (102.04%, 158.32%), respectively. The LRRs of recipients at 0.5, 1, 3, and 6 months were 58.49%±26.67% (49.04%, 67.95%), 50.16%±27.25% (40.94%, 59.38%), 44.36%±26.75% (35.30%, 53.41%), and 31.19%±22.57% (20.91%, 41.47%), respectively. The former values were higher than the latter. The LRRs of recipients with the MHV was higher than those without MHV at 1 and 3 months (P<0.05). The LRRs at 1 month were 59.63%±27.48% and 41.68%±24.73%, and at 3 months were 57.25%±25.42% and 32.81%±22.79%, respectively. The IRLV/ESLV and IGV/ESLV were negatively correlated with LRRs at several times [r=−0.419 (−0.646, −0.134), −0.608 (−0.832, −0.318), respectively; P<0.05]. At 0.5 month, significant difference was found between Child-Pugh score of ≤9.55 and >9.55 (P<0.05) and MELD score of ≤14 and >14 (P<0.05).

Conclusions: After LDLT, donors had more significant and faster liver regeneration than the recipients. Graft with or without MHV, initial liver volume, and preoperative liver function status of the recipients significantly affect liver regeneration.

Keywords: Living-donor liver transplantation (LDLT); X-ray computed tomography; volume measurement; liver regeneration

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Introduction

Living-donor liver transplantation (LDLT) is recognized as the standard treatment for end-stage liver diseases. To overcome the problem of small-volume transplantation, the right lobe graft is usually preferred to provide greater liver quality. The regeneration of the residual liver and graft after LDLT is an important basis for judging surgical success. For decades, numerous reports (1,2) have attempted to elucidate mechanisms or principles of liver regeneration after LDLT; most of which considered postoperative 1–2 weeks as the peak of regeneration, followed by a constant level. However, the results of the above studies are inconsistent, and a study (3) showed a stage of volume reduction in the regeneration of the remnant liver.

Previous studies (4-7) have explored various factors that potentially influence the liver regeneration ratio (LRR), such as the graft volume (GV), graft with or without the middle hepatic vein (MHV), and age and gender of the donors or recipients. However, they have not reached a uniform conclusion. Thus, it is worth exploring whether regenerations in the two parts derived from the same liver were the same after LDLT. A European multicenter study (8) prospectively characterized growth patterns common to donors and recipients after LDLT. Some retrospective reports (9,10) have compared liver regeneration trends in donors and recipients after LDLT. They all found that liver regeneration in recipients occurred earlier and was more pronounced than that in donors. However, measurement methods of the initial remnant liver (IRLV) and initial graft volume (IGV) varied in the above studies. Furthermore, they did not rule out the donors and recipients with postoperative complications.

In this study, for the first time, we unified the method for measuring the IRLV and IGV and eliminated patients with complications to evaluate and compare liver regeneration trends of donors and recipients and to search for potential factors that affect remnant liver and graft regeneration. Herein, we present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1077/rc).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The cohort study was approved by the Medical Ethics Committee of Tianjin First Central Hospital, and all patients signed informed consent forms.

From March 2015 to November 2017, 96 pairs of donors and recipients who underwent adult right lobe LDLT were included in this study. The standards of patient enrollment are shown in *Figure 1*.

Multi-slice computed tomography (MSCT) parameter settings

CT was performed using a dual-source CT scanner (Siemens, Germany). All patients were fasting for more than 6 h and took a negative contrast medium (500–800 mL of water) before the examination. During abdominal enhancement examination, the non-ionic contrast agent Omnipaque (1.5 mL/kg, 3 mL/s; 350 mgI/mL, GE, USA) was injected into the anterior cubital vein with a high-pressure syringe. Contrast-enhanced images were obtained during the arterial, venous, and delayed phases at 25–30 s, 60–75 s, and 300 s after the injection of the contrast medium. Then, the standard reconstruction algorithm was applied to reconstruct the enhanced image with 2.5 mm thickness and 1.25 mm interval and transmitted to the liver CT image interpretation and analysis system (IQQA-liver workstation, EDDA, USA). The venous phase images were selected for liver volumetric measurement. The imaging acquisition parameters were as follows: voltage, 120 kV; electric current, 280 mAs; pitch, 1.375:1; matrix, 512×512; thickness, 10 mm; and spacing, 10 mm.

Liver volumes and LRRs

Given the large individual differences in the liver volume, this study did not compare the absolute value of the liver

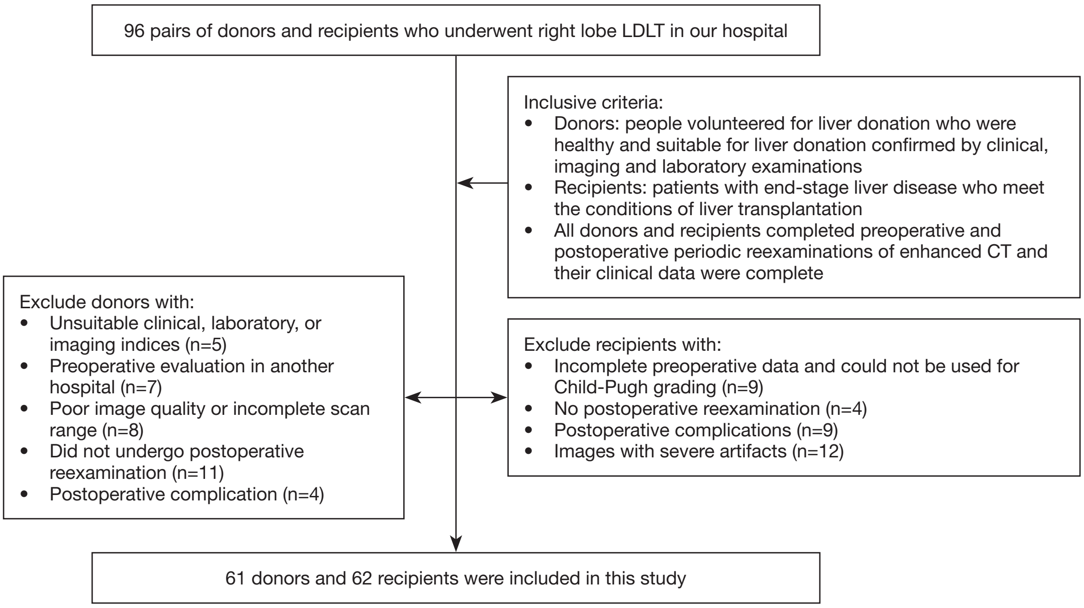

Figure 1 Summary of the inclusion and exclusion criteria. LDLT, living-donor liver transplantation; CT, computed tomography.

volume after liver regeneration but compared the LRRs.

(I) Donor group. The total liver volume (TLV) and right liver volume were measured by MSCT preoperatively. The difference between the TLV and right liver volume was taken as IRLV postoperatively. The remnant liver volume (RLV) measured by MSCT was reexamined at 0.5, 1, 3, and 6 months after LDLT. The LRRs at different times after surgery were calculated using the following formula: LRR (%) = (RLV − IRLV)/IRLV × 100%.

(II) Recipient group. The right liver volume of the donor group was taken as the IGV. The GV was measured by MSCT at 0.5, 1, 3, and 6 months, and the LRR was calculated using the following formula: LRR (%) = (GV − IGV)/IGV × 100%.

Statistical analyses

All statistical analyses were performed using SPSS 26.0 statistical software package (IBM Corp., Armonk, NY, USA). Variables that conform to a normal distribution are represented as mean ± standard deviation. The Mann-Whitney U test, chi-square test, and independent-sample *t*-test were used to compare the general conditions of all patients. The analysis of variance (ANOVA), post-hoc least significant difference test, and independent-sample *t*-test were used to compare the differences in LRRs at different times after LDLT of the donors and recipients. The Pearson or Spearman correlation analysis was used to explore the correlation between age or IRLV (IGV)/estimated standard liver volume (ESLV) and LRRs in donors and recipients. Differences in the LRRs among recipients with different preoperative Child-Pugh scores and model for end-stage liver disease (MELD) scores were compared by ANOVA and Mann-Whitney U test. The difference was significant with $P<0.05$.

Results

In total, 61 donors and 62 recipients met the requirements, and the general information is shown in *Table 1*. A significant age difference was found between donors and recipients, and no differences were noted in other factors.

Comparison of postoperative LRR between donors and recipients

For donors, significant differences in LRRs in the residual liver were noted at different times after LDLT ($P<0.05$, *Table 2*). For recipients, significant differences in the LRRs of the graft were found at different times postoperatively ($P<0.05$, *Table 2*).

After LDLT, the LRRs of donors showed a sustained growth trend, and the maximum LRR was observed at

Table 1 Comparison of general conditions of living donors and recipients.

Variable	Donors	Recipients	P value
Age (years)*	26 (24, 39)	46 (42, 53)	<0.001^
Gender#			0.787
Male	48	50	
Female	13	12	
Height (cm)*	172.00 (167.00, 175.00)	170.00 (165.00, 174.25)	0.088
Weight (kg)*	65.00 (60.5, 76.75)	67.00 (62.30, 75.75)	0.525
ESLV (cm^3)&	1267.99±109.70	1262.07±124.06	0.780
IRLV/ESLV (100%)	37.79 (34.87, 43.49)	–	
IGV/ESLV (100%)	–	65.29 (58.45,71.93)	
MHVs#			0.507
With	38	28	
Without	23	34	
Child-Pugh grades			
Grade A	–	9	–
Grade B	–	20	–
Grade C	–	33	–
Child-Pugh score	–	9.55±2.71	
MELD score	–	14 (9.75, 19.00)	–

^, P<0.05; *, Mann-Whitney U test was used; #, Chi-square test was used; &, independent-sample *t*-test was used. ESLV, estimated standard liver volume; IRLV, initial remnant liver volume; IGV, initial graft volume; MHV, middle hepatic vein; MELD, model of end-stage liver disease.

Table 2 Comparisons of donor and recipient liver regeneration at different periods after LDLT

Postoperative time	Liver volume (cm^3) (95% CI)		LRR% (95% CI)		t value	P value
	RLV	GV	Donors	Recipients		
0.5 month	913.34±213.03 (844.29, 982.40)	1,305.20±263.27 (1,211.85, 1,398.55)	80.80±24.12 (72.87, 88.73)	58.49±26.67 (49.04, 67.95)	3.700	<0.001*
1 month	993.47±166.04 (893.13, 1,093.81)	1,240.70±199.96 (1,173.04, 1,308.36)	98.62±37.47[a] (75.97, 121.26)	50.16±27.25 (40.94, 59.38)	4.961	<0.001*
3 months	981.91±86.59 (909.52, 1,054.30)	1,149.71±203.85 (1,080.73, 1,218.68)	103.34±23.47[a] (83.73, 122.96)	44.36±26.75[a] (35.30, 53.41)	5.753	<0.001*
6 months	1,076.47±72.28 (961.46, 1,191.50)	1,137.08±220.73 (1,036.61, 1,237.56)	130.18±17.68[ab] (102.04, 158.32)	31.19±22.57[ab] (20.91, 41.47)	9.862	<0.001*
F value	–	–	7.015	4.930	–	–
P value	–	–	<0.001*	0.003*	–	–

*, P<0.05. Compared with 0.5 month after LDLT, [a]P<0.05; compared with 1 month after LDLT, [b]P<0.05. LRR, liver regeneration ratio; LDLT, living-donor liver transplantation; RLV, remnant liver volume; GV, graft volume; CI, confidence interval.

6 months, while the maximum LRR in recipients was observed at 0.5 month, and then it showed a downward trend subsequently (*Figure 2*).

Different factors affecting LRRs

Gender

For both donors and recipients, no significant difference in LRRs was found between the male and female patients at all postoperative times (all P>0.05).

Age

The Spearman correlation analysis did not show an association between donor age and LRR, as well as between recipient age and LRR (all P>0.05).

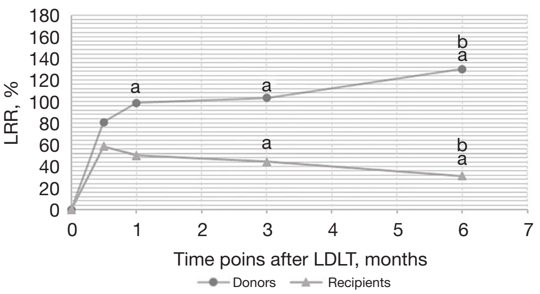

Figure 2 LRRs in donors and recipients at different times after LDLT. Compared with 0.5 month after LDLT, [a]P<0.05; compared with 1 month after LDLT, [b]P<0.05. LRR, liver regeneration ratio; LDLT, living-donor liver transplantation.

Graft with or without MHV

For donors, no significant difference in LRR was noted between groups with MHV and without MHV at different times after LDLT (all P>0.05). For recipients, the LRR of the group with MHV was higher than that of the group without MHV at 1 and 3 months after surgery, and the difference was significant (P<0.05, *Table 3*). There were 34 recipients without MHV; of these patients, 17 underwent vascular reconstruction and 4 underwent vascular bypass.

IRLV/ESLV, IGV/ESLV

Significantly negative correlations were found between IRLV/ESLV [r=−0.419 (−0.646, −0.134)] IGV/ESLV [r=−0.608 (−0.832, −0.318)], and LRR (all P<0.05) (*Figure 3*).

Preoperative liver function status of the recipients

According to the calculated Child-Pugh and MELD scores, the recipients were classified into two groups, that is, below the mean score and above the mean. At 0.5 month, significant differences were found between the Child-Pugh score of ≤9.55 and >9.55 [P<0.05; the LRRs were 47.14%±26.44% (33.07%, 61.24%), 69.17%±22.76%

Table 3 Comparison of liver regeneration rate between donors and recipient with or without MHV at different times after LDLT

MHV	LRR (%) (95% CI)			
	0.5 month	1 month	3 months	6 months
Donor				
With	87.14±22.66 (73.44, 100.83)	105.95±24.26 (83.51, 128.38)	112.47±24.84 (81.62, 143.31)	137.40±14.09 (102.40, 172.40)
Without	77.50±24.64 (67.33, 87.67)	90.07±50.01 (37.58, 142.55)	88.14±11.76 (58.93, 117.35)	122.96±20.65 (71.66, 174.27)
t	1.174	0.747	1.557	1.000
P	0.248	0.470	0.170	0.374
Recipient				
With	65.57±27.02 (51.68, 79.46)	59.63±27.48 (45.51, 73.76)	57.25±25.42 (44.18, 70.33)	42.64±29.35 (18.10, 67.17)
Without	50.98±24.94 (37.69, 64.27)	41.68±24.73 (29.76, 53.60)	32.81±22.79 (21.83, 43.80)	24.15±14.34 (15.48, 32.82)
t	1.609	2.064	3.042	1.664
P	0.118	0.047*	0.005*	0.130

*, P<0.05. LRR, liver regeneration ratio; LDLT, living-donor liver transplantation; CI, confidence interval; MHV, middle hepatic vein.

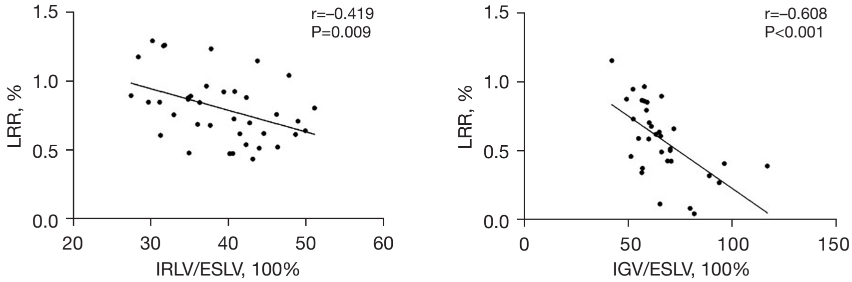

Figure 3 Correlation between IRLV/ESLV, IGV/ESLV, and LRRs (P<0.05). LRR, liver regeneration ratio; IRLV/ESLV, ratio of the initial remnant liver volume to the estimated standard liver volume; IGV/ESLV, ratio of the initial graft volume to the estimated standard liver volume; LRR, liver regeneration ratio.

Table 4 Comparison of LRRs among recipients with diverse scores at various times after LDLT

Score	LRR at different times after LDLT (%) (95% CI)			
	0.5 month	1 month	3 months	6 months
Child-Pugh				
≤9.55	47.14±26.44 (33.07, 61.24)	38.12 (31.66, 74.52) (31.69, 73.21)†	43.96±28.76 (27.35, 60.56)	25.86±15.28 (14.93, 36.79)
>9.55	69.17±22.76 (57.46, 80.87)	54.80 (31.96, 71.37) (32.63, 70.11)†	44.61±26.09 (33.04, 56.17)	36.04±27.47 (17.59, 54.50)
t/Z	−2.568	−0.143	−0.070	−1.034
P value	0.015*	0.887	0.944	0.314
MELD				
≤14	41.70±22.40 (28.77, 54.63)	48.93±29.15 (34.87, 62.98)	38.01±25.24 (24.56, 51.46)	24.35±16.49 (13.27, 35.43)
>14	70.87±22.83 (59.87, 81.87)	51.53±25.77 (38.28, 64.78)	49.43±27.47 (36.58, 62.29)	38.72±26.64 (19.66, 57.78)
t	−3.657	−0.283	−1.284	−1.502
P value	0.001*	0.779	0.208	0.150

†, the data were represented as the median (lower quartile, upper quartile) (95% CI); *, P<0.05. LRR, liver regeneration ratio; LDLT, living-donor liver transplantation; CI, confidence interval; MELD, model of end-stage liver disease.

(57.46%, 80.87%), respectively] and between MELD score of ≤14 and >14 [P<0.05; the LRRs were 41.70%±22.40% (28.77%, 54.63%), 70.87%±22.83% (59.87%, 81.87%), respectively], but no significant differences were found at other time points (*Table 4*).

Discussion

Many studies (8-10) have reported the liver regeneration of donors and recipients after LDLT. However, for the first time, we excluded patients with complications and unified the calculation of IRLV and IGV. This study suggested that the liver volume of donors and recipients increased rapidly after LDLT; however, the liver regeneration of donors was faster and more obvious than that of recipients.

A small liver volume will affect the recovery of liver function and reduce the survival rate; the most common factor limiting LDLT is the small-for-size syndrome (SFSS) (11). It is generally believed that IRLV/ESLV should be greater than 30%, and the graft size should be greater than 35% of ESLV (12,13). However, a report has also proposed that IRLV/ESLV should not be used as a contraindication when it is between 28% and 30% and that donation is also feasible without better options (14). In our study, the IGV/ESLV of recipients was 65.29% (58.45%, 71.93%), the lowest IGV/ESLV was 42%, the IRLV/ESLV of donors was 37.79% (34.87%, 43.49%), only the IRLV/ESLV of one donor was less than 30%, which was 28% (the donor recovered well after LDLT), and the others were greater than 30%. This ensured the recovery of liver function and normal regeneration of donors and recipients.

In our study, for donors, RLV showed an overall upward trend after LDLT, and the largest increase was within 0.5 month. It may be due to the increased portal blood flow after partial hepatectomy, vascular bed dilation, and parenchyma edema. With the disappearance of congestion and edema, the liver volume increased rapidly in 0.5–1 month after surgery, and the degree of growth decreases after 1 month. It was consistent with the three-stage liver regeneration process reported by Haga *et al.* (3,15), whereas the GV of recipients increased rapidly with the maximum LRR of 58.5% at 0.5 month and then decreased slowly. The rapid increase may be associated with the increased portal blood flow postoperatively (16). After 0.5 month, the GV and LRR began to decrease as the general condition of the recipients stabilized and the congestion and edema of the graft decreased (5), which was similar to the previously reported trend of graft regeneration (17). In our study, remnant liver regeneration showed a different trend from the graft; moreover, the former was faster and more observable than the latter. Kamel *et al.* (9) reported that the liver volume of both donors and recipients increased immediately; however, the LRRs of the recipients were significantly faster than that of the donors. Our conclusions differ from above studies, which may be due to the different calculation methods of LRR used and the number of cases included. Considering the results of our study, all donors may have a good liver function and strong tolerance to surgery and well capacity of liver regeneration, whereas recipients were all patients with end-stage liver disease, had poor tolerance to ischemia–reperfusion injury, and suffered from the effects of surgery and immunosuppressants (17).

Based on previous studies (18-20), various factors affect liver regeneration. Pomfret *et al.* (2) reported that donor age did not affect liver regeneration, while gender did. Shirabe *et al.* (21) proposed that LRR was negatively correlated with age. In our study, age or gender of donors and recipients did not significantly affect postoperative liver regeneration. It may be attributed to the relatively young age of the patients and similar hormone levels. The MHV is one of the most important drainage veins in segments IV/V/VIII of the liver. The right lobe grafts without the MHV were generally preferred by most transplant centers to ensure the safety of donors (22). Some studies (23) have shown that right liver transplantation with the MHV had the best venous outflow tract, which can improve the prognosis of the recipients. In addition, portal venous hemodynamics and good hepatic outflow can promote liver regeneration (24). Our results demonstrated that the LRRs of the recipients in the group with the MHV were significantly higher than that of the group without the MHV at 1 and 3 months after surgery, presumably because MHV drainage alleviated liver tissue congestion and promoted liver regeneration with hepatic cell edema subsided. In this study, although 27/38 donors (graft with the MHV) showed S4 congestion after LDLT, the volume of the congestion area was only 186.50±84.95 cm^3, accounting for 19.89%±6.07% of the RLV, which had little effect on the recovery of donors postoperatively. There are 34 recipients without the MHV (32/62); of these patients, 17 underwent vascular reconstruction and 4 underwent vascular bypass, which effectively improved the venous return of segments V and VIII. Moreover, the results revealed a difference in the LRRs between different Child-Pugh scores or MELD scores at 0.5 month, suggesting that the preoperative liver function status of the recipients affects liver regeneration within 0.5 month after surgery: liver regeneration was more observable in patients with poor preoperative liver function. The possible reason was that patients with worse liver function required larger volume and higher metabolism to match liver regeneration with metabolic needs in the early postoperative period. Half a month later, with the stabilization and improvement of the recipient's general condition, the effect of preoperative liver function status on liver regeneration disappeared. A very small liver volume will significantly affect the recovery of liver function and decrease the survival rate. Chen *et al.* (15) reported that the remnant liver regeneration capacity showed linear relationships with the resected liver volume or RLV. This study showed that the ratio of the initial liver volume of the donors or recipients to the ESLV was negatively correlated with the LRRs, indicating that the smaller liver volume regenerated faster (25).

The study has some limitations. First, a small number of patients was included and lost to follow-up, and related complications were excluded at the beginning of this study. In others words, we mainly examined the normal liver regeneration mode without complications after LDLT. Second, some patients were lost to follow-up, and we directly eliminated relevant data. In the future, the number of cases, observation cycle, and observation scope should be further increased to evaluate the effect of different complications on graft regeneration. Third, some other studies (8,26) reported that portal hemodynamics, vascular outflow, and graft quality are all related to liver regeneration. Hence, in future studies, we are determined to evaluate and explore more factors.

In summary, the liver regeneration pattern after LDLT is dissimilar between donors and recipients. Numerous factors influenced remnant liver and graft regeneration in each time after the operation. For surgeons, understanding the liver regeneration pattern in donors and recipients and the influencing factors appear crucial in preoperative donor selection, postoperative liver function assessment, and vigilance for postoperative complications.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-1077/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1077/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The cohort study was approved by the Medical Ethics Committee of Tianjin First Central Hospital and all patients signed informed consent forms.

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