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# Emergent right lobe adult-to-adult living-donor liver transplantation for high model for end-stage liver disease score severe hepatitis

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#### Keywords

acute liver failure, living-donor liver transplantation, severe hepatitis.

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# **Summary**

The aim of this study was to explore the feasibility of emergency right lobe adult-to-adult living-donor liver transplantation (LDLT) for high model for end-stage liver disease (MELD) score severe hepatitis. Consecutive 10 high MELD score severe hepatitis patients underwent emergency right lobe adult-toadult LDLT in our hospital from April to December 2007. The MELD score was  $34.50 \pm 2.088$ . The outcomes of these recipients were retrospectively analyzed. Among them, eight cases of ABO blood group were identical and two cases compatible, one case was Rh negative. Two recipients died and the rest of the recipients and all donors are safe; perioperative and 2-year survival rate was 80%. The mean graft-recipient weight ratio (GRWR) was 1.27%  $\pm$  0.25%, and graft volume to recipient standard liver volume ratio (GV/ESLVR) was  $56.7\% \pm 6.75\%$ . Of the 10 patients, three received right lobe grafts with middle hepatic vein (MHV), four without MHV, three without MHV but followed by V and VIII hepatic vein outflow reconstruction. An encouraging outcome was achieved in this group: elevated serum creatinine, serum endotoxin, decreased serum prothrombin activity, and Tbil returned to normal on postoperative days 3, 7, 14, and 28, respectively. One-year survival rate was 80%. Outcomes of emergency right lobe adult-to-adult LDLT for high MELD score severe hepatitis were fairly encouraging and acceptable. Emergency right lobe adult-toadult LDLT is an effective and life-saving modality for high MELD score acute liver failure patients following severe hepatitis.

# Introduction

The survival rate for nonsurgical management of acute liver failure caused by various etiologies is approximately 10–40% [1,2]. Patient and graft survival for living-donor liver transplantation (LDLT) in acute liver failure patients ranges from 70% to 88% [3–5]. As a result of the cadaveric organ shortage and the availability of a living-related liver graft, the rationale for the use of living-related liver grafts to rescue acute liver failure patients following severe hepatitis is obtaining increased acceptance in the community, even in China. In this study, we report the results of

10 consecutive cases of emergent right lobe LDLT performed in our center from April to December 2007.

#### Patients and methods

#### Patients' selection and evaluation

A total of 10 consecutive cases of emergent right lobe LDLT have been performed in our center from April to December 2007. They had chosen LDLT because of the unavailability of cadaveric liver organ in emergency and the progressive deterioration of the situation. Of these, five cases were acute hepatitis B liver failure, four cases

were acute liver failure resulting from chronic hepatitis B, and the other one was acute liver failure induced by drug. All the 10 cases received intensive treatment before operation, but there was no improvement in the condition or in controlling deterioration. The main parameters related to the severity of disease are shown in Table 1. The patients' weight and height were measured to calculate the patients' estimated need of graft volume. The patients and their families subscribed the written informed consent of the operation if the patients were mentally conscious; otherwise it was subscribed only by their legal guardian.

#### Donors' selection and evaluation

The procedures involved in donor selection and evaluation conformed to the guidelines of the Regulation of Human's Organ Transplantation of China and were approved by the Hospital Ethics Committee. All donors were adults aged 18–55 years with knowledge of civil rights. The evaluation was performed only after the donor expressed willingness to donate, after learning about the advantages and risks of the operation. The detailed evaluation methods, including psychologic evaluation, followed

the programmes of Queen Mary Hospital, Hong Kong University [6]. Liver fine needle biopsy was performed routinely under the guidance of ultrasonography on each potential donor in our institution one day prior to the surgery, after the donor confirmed willingness of donation. CT and MRI, including liver volumetric analysis and hepatic vasculature three-dimensional reconstruction, were very important to plan the graft procurement procedure and to allocate the liver volume precisely between donor and recipient. To shorten the waiting time of patients requiring emergency surgery, we usually completed the donors' selection and evaluation procedure within 48–72 h.

# Donors' operation and perioperative management

The donors' operations were performed based on the procedure described by Fan *et al.* [7,8]. Liver parenchyma was cut by Cavitron Ultrasonic Surgical Aspirator (CUSA) and the cell saver was routinely used.

Both the donors' minimum need on residual liver volume [Donors' Residual Liver Volume to recipient standard liver volume (ESLV) ratio must more than 30%, or Donor Residual Liver weight to Donor body weight ratio

Table 1. Preoperative data on 10 cases of severe hepatitis.

No.	Gender	Age	Pathogens	Total bilirubin (μmmol/l)	Prothrombin activity (%)	Prothrombin International Normalized Ratio (PT INR)	Serum creatinine (µmol/l)	MELD†	Endotoxin level (pg/ml)
1	Male	26	Acute hepatitis B liver failure	868.5	nonagglutination	nonagglutination	85.0	>40	>9999
2	Female	64	Acute on chronic hepatitis B liver failure	308.3	nonagglutination	nonagglutination	844.0	>40	2.23
3	Male	45	Acute on chronic hepatitis B liver failure	365.8	26.700	2.280	58.0	23	2.23
4	Male	29	Acute hepatitis B liver failure	703.0	29.950	3.145	245.0	>40	4.882
5	Female	39	Acute hepatitis B liver failure	412.4	23.350	3.509	47.6	27	20.3
6	Female	43	Acute on chronic hepatitis B liver failure	586.5	10.680	8.665	58.0	40	803.7
7	Male	40	Acute hepatitis B	112.0	22.900	3.578	117.0	30	98.7
8	Male	41	Acute on chronic hepatitis B liver failure	539.9	24.368	3.030	62.0	29	289.6
9	Female	21	Acute liver failure (induced by drug)	398.0	10.560	8.126	47.0	36	620.5
10	Male	25	Acute hepatitis B	971.0	11.260	4.850	129.0	>40	72.6
Median		39.5		476.15	17.08	4.214	73.5	40	85.65
Mean ± SD		37.30 ± 12.66		526.54 ± 263.37	>19.971 ± 7.883	>4.648 ± 2.426	169.26 ± 244.6	34.50 ± 2.088	>1191.37 ± 3107.64

†Model for end-stage liver disease (MELD) score =  $[0.957 \times ln(serum\ creatinine) + 0.378 \times ln(serum\ bilirubin) + 1.120 \times ln(lNR) + 0.643] \times 10$ , cited from http://www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older

must more than 0.5%] for safety (with high priority) and the recipients' minimum need on liver graft volume (Graft Liver Volume to Recipients' ESLV ratio or Graft Liver Weight to Recipient Weight ratio must more than 1.0%) were the decisive factors to determine whether or not to harvest the right lobe with middle hepatic vein (MHV). Besides these factors, the applied anatomy of donors' MHV also contributes to the decision making in this regard, and the resection line identified using an ultrasound scan of the MHV was also useful. Based on the donor's liver volumetric analysis by CT and the calculation of the patients' estimated need of graft volume, the graft weight to recipient weight ratio (GW/RW) was guaranteed to be not <1%, especially for emergency cases. The intra-operative cholangiography of every donor was performed using 60% Meglumini Diatrizoate transcystic duct to confirm if there was or no aberrance of the bile duct that magnetic resonance cholangiopancreatography (MRCP) neglected. Iodine anaphylaxis test was performed before the operation to avoid any potential anaphylactic reaction risk during intra-operative cholangiography, and it is a routine in our institution. To minimize donor disadvantages, the right hepatic bile duct and right branch of portal vein were reserved long enough and double-continuous suture, using 6-0 and 5-0 prolene suture, was employed to avoid biliary and portal vein strictures. Re-cholangiography was necessary to confirm that the donor had no biliary stricture after the right liver lobe was harvested. The hepatic vein branch was reconstructed if its diameter was more than 5 mm, to reserve enough functional remnant liver volume during the implantation of the liver graft. After harvesting operation, the donor was kept in the surgical intensive care unit for 3-5 days for close surveillance and rehabilitation.

#### Back-table

The right branch of the portal vein, the right hepatic artery, and the biliary duct of the harvested right lobes were perfused with cold Histidine-Triptophane-Ketoglutarate solution (HTK) at a low temperature (0–4 °C). The necessary reconstructions of the hepatic vein, biliary duct, and portal vein were performed before implantation in the recipients.

# Patients' operation and perioperative management

Patients' operations were also performed following the procedure similar to that described by Fan *et al.* [7,8], using a large right hepatic vein outflow reconstruction. The hepatic vein branch of the resection plane was reconstructed if its diameter was more than 5 mm to reserve enough functional liver volume. The portal vein, hepatic artery, and bile duct reconstruction adopted end-to-end anastomosis. If the bile duct and artery were too thin to

anastomose, the microscopical surgery technologies were employed. Perioperative critical care management was carried out in the surgical intensive care unit. To improve coagulation function, reduce serum endotoxin level, and inactivate the expression of inflammatory mediators, preoperative plasma exchange was conducted routinely using 50–80 ml/min per kilogram of plasma. In the event of perioperative anuria or oliguria, continuous renal replacement therapy (CRRT) was performed until the urine output reached greater than 100 ml per hour.

#### Follow-up

All donors' and patients' data have been enrolled in China Liver Transplant Registry (CLTR) hosted in Hong Kong University and their follow-up protocol has been compiled (https://www.cltr.org/en/). Doppler ultrasound testing was routinely required for donors and recipients. MRCP and cholangiography were needed in some conditions to investigate the biliary tract. The immunosuppressive protocol of recipients included simulect immunosuppression induction, followed by calcineurin inhibitor, mycophenolate mofetil (MMF), and steroid-based triple immunosuppressive regimen. The HBV prophylaxis protocol included nucleoside analog (Entecavir) combined hepatitis B immunoglobulin (HBIG) prophylaxis for the prevention of hepatitis B relapse. This was audited and approved by the Hospital Ethics Committee.

## Statistic methods

The data are reported as mean ± standard deviation and median. Survival rates after LDLT were calculated according to the Kaplan–Meier method. All statistical analyses were performed using spss 11.0 version (SPSS Inc. Chicago, Illinois USA).

#### **Ethics**

All procedures involving donors and patients followed the medical ethics and the Declaration of Helsinki.

# Results

# Donors' results

A total of 16 candidates were evaluated for liver organ donation. Of these, 10 donors (seven men and three women, median age: 38 years, range: 27–54 years) were chosen, who absolutely agreed with the conditions of liver organ donation. The donation rate was 62.5% (10/16). The other six potential donors were excluded because of age (>55 years), viral hepatitis, or blood type incompatibility. The liver fat content of the 10 donors was all

55.91575

54.1050 53.2545

51.3682

.344444 .185484

1.065

57.7265 47.7129

> 53.9970 54.7060

0.984615

0.988

640 650

1435.068

605

1244.041

163/166

73/65

60/45

-0/+0

3rother-sister

Aother-son

0

Mean ± SD

70/62

158/172

0.897

1428.218

181/165 168/173 173/176

70/74

B/AB 0/0

Wife-husband

**3rothers** 

Vephew-aunt

Brother-sister

92/71

8/8 0/0 0/0

Father-son

Vephew-aunt

Sister-brother

.081081

43.9861

50.3677

56.7488

46.6801 ±

7.0065

0.249506

0.896 ± 0.047

114.51

749.50

1412.886 ±

107.870

 $169.70 \pm 7.48/$   $171.10 \pm 4.09$ 

767.5

1407.173

69.5/172

 $74.40 \pm 9.11/$ 62.8 ± 8.82

72/63.5

.184654

45.6967

44.0168

<10% by liver biopsy, and the biopsies reveal any complications in donors. In three donors, right lobes were harvested with the middle hepatic vein and in seven donors, without the middle hepatic vein. All of the donors' remnant liver segment hepatic vein reconstructions were not needed. The ratio of the donor's residual liver volume versus donor's ESLV was 46.6801% ± 7.0065%, and the donor's residual volume to body weight ratio (RVDBWR) was 0.896% ± 0.047% (median: 0.861%), as shown in Table 2. The median duration of the donor operation was 8 h, and the mean operative blood loss volume of donors was 500 ml, all of them did not require extra blood or blood products transfusion. The mean time of donors' hospitalization was 14 days. The donors' liver function became normal soon after operation, as shown in Fig. 1. There was no donor mortality at a median follow-up of 20 months (range 17-24 months). There were minor complications in four donors, which are presented in Table 3. Among them, two patients developed a right pleural effusion and one had a subphrenic fluid collection, which were all of Clavien grade I. Another patient developed a pulmonary infection, which was categorized as Clavien grade II. There were no Clavien grade III, IV, and V complications. There were no hepatic vein obstruction and no portal vein obstruction according to the definitions of hepatic vein obstruction and portal vein obstruction (HV outflow obstruction was entertained when HV flow velocity was <10 cm/s and when monophasic waveform was seen on Doppler ultrasound, and PV outflow obstruction was entertained when PV flow velocity was <12 cm/s) [9], and also no hepatic artery thrombosis and biliary complications. All donors were in good condition, with normal liver function on subsequent follow-up.

# Recipients' results

Among the 10 recipients who underwent LDLT during the study period, there were six men and four women with a median age of 39.5 years (range, 21-64 years). The median preoperative waiting time for LDLT was 3 days. Details of the clinical parameters of patients are listed in Table 1. Of these recipients, three (30%) were on life support before operation. As shown in Table 2, the median graft's weight to recipient's weight ratio was 1.184654% (range 0.984615-1.45614%), the median graft's weight to recipient's estimated standard liver volume ratio was 55.9158% (range 47.7129-66.8775%). Three grafts of the right lobe with the middle hepatic vein, four grafts of the right lobe without the middle hepatic vein, and three grafts of the right lobe without the middle hepatic vein were implanted, but followed by a V and VIII segment hepatic vein reconstruction. The median cold ischemic

weight ESLV† (ml) 1423.133 Donors' recipient's neight (cm) Jonor's/ 65/172 weight (kg) recipient's Donor's/ recipient poold Relationship Father-son of donorecipient

recipients'

residual liver volume/ESLV

recipient weight

residual liver volume/donor

weight (%)

(GW/RW) (%)

.295775

.096491

Graft weight/

/olume/

ESLV (%)

62.6468

50.3596

54.8318 40.4750 66.8775

45.6933

.456140

.183824

0.810

1629.838 1528.357

352.372

164/175 180/176 171/168

74/168

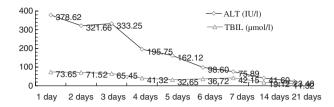
0.812

45.7001

Recipient standard liver volume (ESLV) = 706.2 × BSA(m²) + 2.4; 1 g GW 🛎 1 ml GW (Urata K, Hashikura Y, Ikegami T, et al. Standard liver volume in adults. In Elsevier Science Inc, 2000: 41: 1583.)

Table 2.

Donor-recipient-related



**Figure 1** Donor liver function studies. The highest mean level of postoperative total bilirubin is 73.65  $\mu$ mol/l. The highest mean level of glutamate-pyruvate transaminase is 378.6 IU/ml. Bilirubin levels return to normal 3 weeks later. Glutamate-pyruvate transaminase levels return to normal 2 weeks later.

**Table 3.** Clavien classification of surgical complications of donors and recipients.

Clavien grade	Donors	Recipients
I	2 cases of pleural effusion 1 case of subphrenic fluid collection	No
II	1 case of pulmonary infection	No
Illa	No	1 case of biliary anastomotic leak treated by an endoscopic procedure
IIIb	No	2 cases of bile leak treated by T-tube placement
IVa	No	1 case of anuria needed CRRT
IVb	No	No
V	No	1 patient died of acute renal failure secondary to a vena cava thrombosis 1 patient died of liver failure resulting from hepatic artery thrombosis

CRRT, continuous renal replacement therapy.

time of liver grafts was 98 min (range 72–114 min), the median time required for graft implantation was 196 min (range 148–264 min). The median operative blood loss volume of recipients was 1800 ml; because of a worse clotting profile before transplantation, all recipients required blood transfusion.

The results of the liver function, renal function, coagulation profile, and serum endotoxin levels are shown in Figs 1–5. The 2-year recipients' survival rate and grafts' survival rate was 80% at a median follow-up of 20 months (1–24 months). Perioperative mortality was 20%; one case developed acute renal failure secondary to a vena cava thrombosis and died one week later, one case developed liver failure because of hepatic artery thrombosis and died two weeks later because of not getting a chance to cadaveric liver transplantation. The biliary complication rate was 30%. Two cases required graft

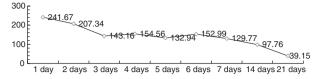


Figure 2 Recipient postoperative bilirubin.

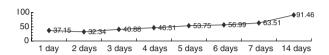


Figure 3 Recipient postoperative Prothrombin activity (PTA).

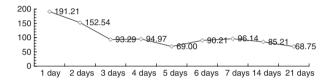


Figure 4 Recipient postoperative serum creatinine.

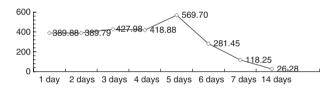


Figure 5 Recipient postoperative endotoxin.

resection for a bile leak located on the surface, which was then treated by T-tube placement. One biliary anastomotic leak occurred, which was successfully treated by an endoscopic procedure. A 64-year-old female recipient became anuric 1 day prior to the operation. CRRT was conducted prior to surgery, intra-operatively, and on the 5th postoperative day. No hepatic vein obstruction (excluding the recipients who developed acute renal failure secondary to a vena cava thrombosis) and no portal vein obstruction were reported. There were no extra hepatic artery complications except one, as described above in recipients.

#### Discussion

Severe hepatitis means acute liver failure or deterioration of liver function caused by various etiologies based on the presence or absence of chronic liver diseases. The early experiences [3–5,10] with LDLT have shown that the perioperative survival rate of LDLT and the graft volume are positively correlated, especially in the case of acute liver

failure [11-13]. As a result of the various types of severe hepatitis that are always accompanied by organ insufficiency, sepsis, or endotoxemia, and sometimes severe inflammatory response syndrome (SIRS), the exacerbated metabolic burden [14,15] requires a more functional graft volume; hence the ratio of graft-recipient weight ratio (GRWR) usually exceeds 1%. One of the following four strategies could be adopted or combined to meet this need in clinical practice: (i) choosing a heavier or bigger donor; (ii) harvesting the right lobe of the donor with the middle hepatic vein [16,17]; (iii) segments V and VIII hepatic vein reconstruction [18,19] of the liver graft; and (iv) the technique [20,21] of dual liver grafts. Avoiding the smallfor-size syndrome is extremely important, which relies on both a perfect graft outflow reconstruction [22,23] and the modulation of portal vein inflow.

In this study, in all patients with poor function reserve because of acute or chronic liver failure, enough graft volume was particularly crucial in providing sufficient functional liver volume with good venous drainage to meet the high metabolic demand of the recipients to result in favorable survival outcomes. Graft size mismatch and the resulting small-for-size syndrome have been described as predisposing factors for the development of graft failure in animal models and human transplantation, which could cause an inferior operative outcome in LDLT. The mean GRWR ratio in this group was nearly 1.26, which provides enough functional liver graft for this group of recipients to restore their liver function and to avoid small-for-size syndrome. As the graph shows, the liver function, such as total bilirubin, transaminases, prothrombin activity, etc., recovered in a brief period of time. In addition, the endotoxin level also obtained a rapid decline, which is greatly desired as the endotoxemia plays an important role in the possible development of the systemic inflammatory response syndrome postoperatively. Overall, the recovery of function of the liver graft was ideal.

In addition, to avoid small-for-size syndrome, the liver graft must include middle hepatic vein to guarantee enough graft volume. In this series, three cases of the right lobe liver graft with middle hepatic vein harvest were carried out because the size of the recipient was greater than the donor (No. 1, 3, and 7). Using the right lobe liver graft without middle hepatic vein would not achieve a GW/RW ratio > 1.0; therefore, the decision was made to harvest the middle hepatic vein simultaneously. In addition, we were convinced that, except in the case of a recipient's minimum demand for liver graft volume, the other two determined factors to decide whether to harvest the middle hepatic vein or not are the anatomy [24,25] of the donor's middle hepatic vein and the minimum residual liver volume, which is essential for the donors' life. Sometimes, the reconstruction of segment hepatic vein outflow was necessary to reserve enough functional liver volume. In LDLT, a perfect graft outflow was another condition to avoid small-for-size syndrome, so the big triangle anastomosis was necessary to ensure that the hepatic venous outflow was flowing sufficiently without occlusion. In this study, there was no small-for-size syndrome.

Biliary complications in LDLT were usually significantly higher than that in cadaveric liver transplantation. We performed biliary tract reconstruction based on the comprehensive estimation of donor's and recipient's biliary tract obtained by MRCP and intra-operative cholangiography. Of the 10 recipients, six had duct-to-duct biliary anastomosis without biliary drainage tube, three had duct-to-duct biliary anastomosis with biliary drainage tube, and one had Roux-en-Y choledochojejunostomy. Paries posterior bilary tract was anastomosed using continuous suture, and paries anterior bilary tract was anastomosed using discontinuous suture. The biliary complication rate was 30%, even though the micrological surgery technologies were used.

Currently, the model for end-stage liver disease (MELD) score is used to evaluate the severity of candidates waiting for LTx and the allocating scale for cadaveric liver donors [26]. The mean MELD score for this group of patients was greater than 35. Among them, five patients had a MELD score greater than 40. Higher MELD scores represent a higher mortality rate, with longer hospitalizations and increased medical expenses. Several authors have suggested that patients with MELD scores greater than 25 should be considered as a relative contraindication for transplantation because of the poor outcomes [27]. This group of recipients, with the exception of one patient, exceeded this criterion but still experienced satisfactory outcomes. These illustrative cases are as follows. The second case was that of a 64-year-old woman with collapse of her hemagglutination mechanism and an undetectable International Normalized Ratio (INR). She was anuric for 36 h with a serum creatinine level greater than 800 µmol/l preoperatively. Another case also had collapse of the hemagglutination mechanism with gastrointestinal hemorrhage. The seventh case had a combination of grade III HE and complicated aspiration pneumonia. They all survived the operation and recovered without complications postoperatively. The limited experience mentioned above in our single center shows that the height of the preoperative MELD score is not the only determining criterion to decide for or against transplantation. We suggest that with the exception of severe irreversible injury to vital organs, such as severe bilateral lung infection and cerebral herniation, it is worthwhile to consider urgent right lobe LDLT for acute liver failure following severe hepatitis.

Perioperative plasma exchange was found to have no direct influence on the survival rate, but it did improve the hemagglutination mechanism, reduce serum endotoxin level, and provide the optimum environment for surgery and recovery of vital organs postoperatively, which is undeniable [1,28]. Continuous renal replacement therapy (CCRT) is also important for eliminating excessive body water in vivo, lowering the endotoxin level, providing renal function, and preventing acute lung injury and pulmonary edema [29]. Early enteral tube feeding and micro-ecology preparation with enzymes produced by microorganisms have a positive effect in reducing the occurrence of systemic infection [30], improving the ecological environment of the intestinal tract, reducing intestinal bacterial translocation, and even promoting liver regeneration.

# Conclusions

Emergent right lobe adult-to-adult LDLT for high MELD score severe hepatitis is a determined treatment modality because of its availability and efficacy. This procedure should be recommended for high-risk acute liver failure cases following severe hepatitis in case of unavailability of cadaveric liver donor.

## **Authorship**

L S-C, W M-L, LN, ZY: designed research/study. L S-C, W M-L, LN, LW, CP, L J-N, DJ, ZZ, W J-S, L D-D, G Q-L, ZY: performed research/study. L S-C, LW, DJ, ZZ: collected data. L S-C, LW, DJ, ZZ: analyzed data. L S-C, LW, DJ: wrote the paper.

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