

# Adult to adult right lobe living donor liver transplantation: does biological relationship matter?

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## Abstract

The influence of the biological relationship between the donor and the recipient is rarely discussed in living donor liver transplantation (LDLT), although it is believed to be an important risk factor in other types of organ transplantations. A total of 272 consecutive patients undergoing adult to adult right lobe LDLT were retrospectively analyzed and stratified into a nonbiologically related (NBR) group (69 patients) and a biologically related (BR) group (203 patients). The preoperative data and postoperative outcomes of both recipients and donors were evaluated.

More than two-thirds of the recipients had histories of HBV infection, and hepatocellular carcinoma (HCC) was the main reason for the patients undergoing LDLT in both groups. The percentage of female donors in the NBR group was more than the percentage in the BR group ( $P=0.000$ ). There were no differences between the groups in postoperative laboratory testing or daily immunosuppression dose, and the complication rates in both the recipient and donor surgeries showed no significant differences. For patients with benign diseases, the cumulative 1-, 3-, 5-, and 10-year survival rate were 92.9% in the 4 periods in the NBR group and 89.1%, 87.6%, 83.7%, and 83.7%, respectively, in BR group, while for the patients diagnosed as HCC, if patients exceeding the Milan criteria were involved, the 5-year survival rate was 41.2%, compared to 82% for patients within the Milan criteria, which was nearly the same as for those with the benign disease. In conclusion, our findings suggested that the biological relationship between the donor and the recipient in adult to adult LDLT was not associated with the short- and long-term outcomes of recipients diagnosed with benign liver diseases and early stage HCC. Moreover, the criteria for patients diagnosed with HCC to undergo LDLT should be restrictively selected.

**Abbreviations:** BR = biologically related, HCC = hepatocellular carcinoma, HLA = human leukocyte antigen, INR = international normalized ratio, LDLT = living donor liver transplantation, LT = liver transplantation, NBR = nonbiologically related, POD = postoperative day, TB = total bilirubin.

**Keywords:** donor–recipient relationship, hepatocellular carcinoma, liver transplantation

## 1. Introduction

Liver transplantation (LT) is considered the best choice for end-stage liver disease and selected malignant liver tumors,<sup>[1–3]</sup> and it

provides recipients with an opportunity to receive a new liver, replacing a previously diseased organ. Since Starzl et al<sup>[4]</sup> performed the first LT successfully in 1967, this technique has been applied worldwide, and the demand for LT has increased as well. However, unfortunately, the available grafts are scarce, and there are far fewer grafts than the number of patients demanding LT, resulting in high mortality among patients on the waiting list.

Living donor liver transplantation (LDLT) was introduced by Raia et al in 1989.<sup>[5]</sup> Since then, LDLT has experienced a tremendous and flourishing development in the past 2 decades, especially in Asian countries. Due to the differences in culture, tradition, and politics, as well as the severe organ shortage because of the high infection rates with hepatitis B virus (HBV), hepatitis C virus (HCV), and related diseases, such as liver cirrhosis and hepatocellular carcinoma (HCC), living donors form an important part of the donor pool.<sup>[6]</sup> In some countries, LDLT even comprises more than 90% of the transplant activity.<sup>[7]</sup> Currently, there is no brain death law in our country, and donation after cardiac death is the only source of the deceased donor LT, which has promoted the development of LDLT. In our country, donor candidates are limited to the 3rd degree of consanguinity and spouse or to nonbiological-related donors with sentiments for the relatives. To expand the donor pool, marginal donors, such as small-size grafts and the older

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donors, have been used due to the lack of available grafts.<sup>[1,8,9]</sup> In transplantation, closely related donors and recipient pairs offer the theoretical advantage of a more favorable human leukocyte antigen (HLA) match, which could decrease accelerated rejection and early graft loss. However, the biological relationship between the donor and recipient has not been discussed before, and the postoperative complication and survival rates between groups remain controversial because some studies have reported that this relationship has some connection to vascular variation and early graft rejection,<sup>[10]</sup> especially among patients receiving right lobe LDLT.<sup>[11]</sup> In the present study, we collected the data of patients after LDLT and divided them into 2 groups based on the donor–recipient relationship, and we compared the short- and long-term outcomes as primary end points.

## 2. Methods

### 2.1. Study design

Between January 2001 and December 2015, 364 patients received LDLT at the Liver Transplantation Center of West China Hospital, Sichuan University, Chengdu, China. Among these patients, 286 patients received right lobe LDLT. We excluded 8 recipients younger than 18 years old and 6 patients who underwent LDLT before December 2004. A total of 272 consecutive patients who underwent adult to adult right lobe LDLT between March 2005 and November 2015 were involved in this study. Based on the relationship of the donor and recipient, we divided the subjects into 2 groups: the nonbiologically related (NBR) group (n=69) and the biologically related (BR) group (n=203). The protocol was approved by the West China Hospital Ethics Committee, and the study was in accordance with the ethical guidelines of the Declaration of Helsinki. The details of the relationships are described in Table 1.

The data were retrieved from our prospective surgical database, and we retrospectively analyzed factors including fundamental information about the donor and recipient,

**Table 1**

**The description of the donor relationship to the recipient.**

Biologically related	203
Parent, %	30 (15)
Offspring, %	24 (12)
Sibling, %	77 (38)
Cousin, %	30 (15)
Niece or nephew, %	42 (20)
Nonbiologically related	69
Spouse, %	46 (67)
Other nonbiological, %	23 (33)

operative characteristics, and the follow-up information, such as complications and survival rates.

### 2.2. Recipient data

The recipient data collected included patient age, sex, body mass index, pretransplant blood tests, including creatinine, total bilirubin (TB) and international normalized ratio (INR), and the model for end-stage liver disease score. The etiology was recorded as HBV infection history, malignant tumor history, and alcoholic history. In our center, all of the patients listed for LDLT are also listed for deceased donor liver transplant, and the time on the waiting list for a liver and the conditions of patients were counted from the day they were offered an attempt at transplantation (Table 2).

### 2.3. Donor selection and perioperative evaluation

Donors are voluntary and altruistic. In our country, donor candidates were limited to blood relatives up to the 3rd degree and spouses or NBR donors with sentiments for the relatives. Generally speaking, a healthy individual between 18 and 65 years of age, without a significant medical history, a long-term excessive alcohol drinking history, a cardiopulmonary history,

**Table 2**

**Preoperative characteristics of patients receiving from no-biologically related donor versus biologically related donor.**

	Nonbiologically related donor, n=69	Biologically related donor, n=203	P
Recipient age, year*	42 (±5.8)	42 (±9.6)	0.634
Recipient Male, %	62 (90)	168 (83)	0.181
Recipient BMI, kg/m <sup>2</sup> *	21.95 (±2.99)	22.72 (±3.11)	0.073
Pretransplant creatinine, μmol/L*	78.52 (±29.28)	80.40 (±46.34)	0.752
Pretransplant bilirubin, μmol/L*	90.37 (±147.46)	111.41 (±171.67)	0.364
Pretransplant INR*	1.47 (±0.56)	1.66 (±1.40)	0.295
MELD at Transplant*	14 (±7.2)	16 (±9.9)	0.251
Pretransplant hospital stay, %	43 (62)	118 (58)	0.573
Time on waiting list, day†	19 (10–30)	19 (10–35)	0.726
Etiology of liver diseases			
HBV infection, %	56 (81)	148 (73)	0.200
HBV related cirrhosis without tumor, %	17 (25)	50 (25)	1.000
HCC, %	36 (52)	99 (49)	0.625
Alcoholic cirrhosis, %	1 (1)	6 (3)	0.683
Fulminant hepatic failure, %	5 (7)	18 (9)	0.806
Patients with HCC			
In Milan criteria	16 (44)	34 (34)	0.282
In Chengdu criteria	17 (47)	50 (50)	0.736

BMI = body mass index, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, INR = indicates international normalized ratio, IQR = interquartile range, MELD = model for end-stage liver disease, SD = standard deviation.

\* Means (SD).

† Median (IQR).

**Table 3****Donor demographic data and operative characteristics of patients receiving from nonbiologically related donor versus biologically related donor.**

	Nonbiologically related donor, n=69	Biologically related donor, n=203	P
<b>Donor factors</b>			
Donor age, year*	37 (±8.9)	36 (±11.7)	0.757
Donor male, %	19 (28)	139 (68)	0.000
Donor BMI, kg/m <sup>2</sup> *	23.00 (±2.48)	22.98 (±2.67)	0.959
Graft weight, g*	561 (±104.65)	587 (±114.46)	0.097
GRWR*	0.924 (±0.19)	0.939 (±0.21)	0.610
Graft with middle hepatic vein, %	8 (12)	6 (3)	0.009
Cold ischemia time, minutes <sup>†</sup>	90 (25–192)	92 (20–195)	0.870
ABO-compatible, %	55 (80)	165 (81)	0.859
<b>Operative characteristics in recipient</b>			
Duration of anhepatic phase, minutes <sup>†</sup>	85 (65–105)	92 (70–122.25)	0.048
Duration of the operation, hour <sup>†</sup>	10.9 (9.1–12.5)	10.7 (9.3–12.2)	0.787
Estimated blood loss, mL <sup>†</sup>	1600 (1000–3000)	1500 (900–3000)	0.497
PRBCs transfusion, U <sup>†</sup>	6 (2–10)	5.5 (2–10)	0.563
Plasma transfusion, mL <sup>†</sup>	1200 (600–1650)	1000 (600–1800)	0.922
Platelet transfusion, U <sup>†</sup>	0 (0–0)	0 (0–1)	0.275
<b>Operative approach</b>			
Anastomosis between right portal vein (graft) and the main portal vein, %	50 (73)	155 (77)	0.521
Anastomosis between both right hepatic arteries, %	22 (32)	78 (38)	0.387
Anastomosis between right hepatic artery (graft) and proper or common hepatic artery, %	41 (59)	107 (54)	0.401
Reconstruction of hepatic artery, %	2 (3)	3 (2)	0.604
Duct to duct biliary anastomosis, %	61 (88)	182 (90)	0.822
Hepaticojejunostomy, %	6 (9)	22 (11)	0.819
<b>Immunosuppression</b>			
Tacrolimus, %	22 (32)	87 (43)	0.108
Mycophenolate, %	25 (36)	95 (47)	0.127

BMI=body mass index, GRWR=indicates graft-to-recipient weight ratio, IQR=interquartile range, PRBC=packed red blood cell, SD=standard deviation.

\* Means (SD).

<sup>†</sup> Median (IQR).

abnormal blood tests, fatty liver disease, or a vital hepatitis history, is suitable as a liver donor in our center. Preoperative estimation of the graft and the remnant liver volume and the status of the hepatic vessels were performed using 3-dimensional reconstructed images from multidetector computed tomography, and variation in the hepatic biliary duct was evaluated by magnetic resonance cholangiopancreatography. In addition, in the donors, after the abdomen was opened, a liver specimen was collected to determine whether hepatic steatosis existed, and after resection of the gall bladder, intraoperative cholangiography was also performed to evaluate the hepatic duct again. Intraoperative ultrasound was routinely used to confirm adequate hepatic venous anatomy and to verify the transaction plan before donor hepatectomy. The fundamental characteristics of the donor and the graft weight are listed in Table 3. In our center, the middle hepatic vein is not routinely taken along with the right lobe of the liver for the graft. We aimed to ensure that the recipients offered grafts with an estimated graft-to-recipient weight ratio of 0.8 or more and that the donors had a residual liver volume of 30% or more.<sup>[12]</sup>

#### 2.4. Surgical procedure

If the recipient was diagnosed with a malignant disease, surgical exploration was decided on for the recipient before surgery on the donor was conducted to exclude the possibility of distant metastasis. The surgical procedure performed on the donor has been described previously.<sup>[13]</sup> We analyzed the duration of the

operation and the anhepatic phase. In addition, we estimated the intraoperative blood loss and evaluated the count of transfusions. The operative approaches are listed in Table 3. If the artery was not sufficiently long, it could be lengthened by reconstruction with autogenous veins, such as great saphenous vein. If the biliary graft contained a single duct, duct-to-duct anastomosis was the preferred method for biliary reconstruction. In grafts with 2 ducts in close proximity, ductoplasty was performed to create a single duct for anastomosis. If these 2 approaches were not feasible, hepaticojejunostomy was performed.

#### 2.5. Postoperative outcomes

Complications were classified according to the Clavien-Dindo classification.<sup>[14]</sup> Pre-, intra-, and postoperative complications are described in Table 4. Pretransplantation complications were defined as symptoms occurred when the patients underwent LDLT. In the analysis of intra- and postoperative complications, if a patient had 2 or more complications, we evaluated them as one complication in total. Blood testing and ultrasound were routinely performed on postoperative days (PODs) 1 to 7 to monitor the evolution of the disease. Small-for-size syndrome was defined by a TB value >10 mg/dL on POD 14.<sup>[15]</sup>

After discharge, each patient was followed in our center every 3 months. Immunosuppression consisted of cyclosporine or tacrolimus and corticosteroids, with or without mycophenolate and sirolimus. Immunosuppressive treatment was recorded by daily dose and drug concentration. Long-term outcomes were

**Table 4****Complication description of patients receiving from nonbiologically related donor versus biologically related donor.**

	Nonbiologically related donor, n=69	Biologically related donor, n=203	P
Pretransplantation complications			
Encephalopathy, %	3 (4)	17 (8)	0.423
GI bleeding, %	9 (13)	11 (5)	0.058
Peritonitis, %	1 (1)	3 (2)	1.000
Uncontrolled ascites, %	7 (10)	24 (12)	0.828
Renal insufficiency, %	1 (1)	5 (3)	1.000
Intraoperative complications, %	2 (3)	4 (2)	0.645
Cardiac arrest, %	0 (0)	1 (0.5)	1.000
Massive hemorrhage, %	1 (1)	4 (2)	1.000
Hepatic vein stenosis, %	0 (0)	1 (0.5)	1.000
Portal vein stenosis, %	1 (1)	2 (1)	1.000
Hypotension, %	1 (1)	1 (0.5)	0.444
Early postoperative complications, %	26 (38)	76 (37)	1.000
Postoperative bleeding, %	3 (4)	11 (5)	1.000
Arterial thrombosis, %	3 (4)	3 (2)	0.173
Portal vein thrombosis, %	1 (1)	3 (2)	1.000
Hepatic vein thrombosis, %	0 (0)	1 (1)	1.000
Biliary leakage, %	4 (6)	3 (2)	0.071
Biliary stenosis, %	0 (0)	1 (1)	1.000
Intraabdominal collection, %	9 (13)	40 (20)	0.277
Bacterial pneumonia, %	6 (9)	12 (6)	0.410
Pleural effusion, %	13 (19)	37 (18)	1.000
Renal failure, %	1 (1)	6 (3)	0.683
SFSS, %	6 (9)	21 (10)	0.818
Late postoperative complications, %	11 (16)	34 (17)	1.000
Hepatic vein thrombosis, %	2 (3)	4 (2)	0.645
Arterial thrombosis, %	1 (1)	1 (0.5)	0.444
Portal vein thrombosis, %	1 (1)	8 (4)	0.456
Biliary leakage, %	4 (6)	4 (2)	0.116
Biliary stenosis, %	1 (1)	11 (5)	0.306
Chronic cellular rejection, %	1 (1)	1 (0.5)	0.444
Clavien-Dindo IIIb, IV within 30 days, %	11 (15)	32 (15)	1.000
30-day mortality, %	5 (7)	19 (9)	0.806

GI=indicates gastrointestinal bleeding, SFSS=small-for-size syndrome.

analyzed by survival rates at 1, 3, 5, and 10 years. For patients diagnosed with HCC, we compared the survival rate according to the Milan criteria (single tumor up to 5 cm or up to 3 tumors, each no larger than 3 cm, without macrovascular invasion or extrahepatic spread).<sup>[2]</sup> To expand the criteria for LT, we proposed our standard of total tumor size less than 9 cm without macrovascular invasion and metastases.<sup>[16]</sup> We also compared our criteria in this research.

## 2.6. Statistics

Statistical analysis was performed with IBM SPSS software, version 19.0 for Windows (Armonk, NY). Clinical data of the patients are expressed as counts, percentages, means, and standard deviations or as medians and ranges as appropriate. Continuous variables were compared using Student *t* test, while in abnormally distributed variables, the Mann-Whitney *U* test was used. Categorical variables were determined using the chi-square test or Fisher exact test. For the postoperative laboratory data, repeated measures analysis of variance (ANOVA) with Greenhouse-Geisser correction was used between groups at each observation. Survival was determined by the Kaplan-Meier method and was compared with the log-rank test. Differences were considered significant at  $P < 0.05$ .

## 3. Results

### 3.1. Recipient characteristics

The demographic characteristics of the recipients among LDLT patients are summarized in Table 2. Pretransplant biochemical profile (including creatine, bilirubin, and INR) showed no differences between the groups (Table 2). Recipient disease severity, measured by model for end-stage liver disease score, and pretransplant hospital stay showed no significant differences between the groups. More than two thirds of the recipients had histories of HBV infection (NBR group,  $n = 56$ , vs BR group,  $n = 148$ ), and HCC was the main reason (nearly half) for the patients undergoing LDLT in both groups (NBR group,  $n = 36$ , vs BR group,  $n = 99$ ). The median waiting time for LDLT was 19 days and was similar in both groups.

### 3.2. Donor factors and surgical procedures

The descriptions of the donors are shown in Table 3. The percentage of female donors in the NBR group was greater than in the BR group ( $P = 0.000$ ). The average age and body mass index were similar in both groups. The mean graft weight and median cold ischemia time showed no significant differences between the groups, and the median graft-to-recipient weight ratio was greater than 0.9. There were more grafts with the middle hepatic vein in the NBR group ( $n = 8$ , 12%) than in the BR group ( $n = 6$ , 3%) ( $P = 0.009$ ).

The durations of the operation and the anhepatic phase were similar in both groups (Table 3), and the estimated blood loss and transfusion of blood showed no significant differences. The right portal vein (graft) was usually anastomosed to the main portal vein. Nearly 90% of the recipient ducts were anastomosed to ducts directly, without ductoplasty or hepaticojejunostomy.

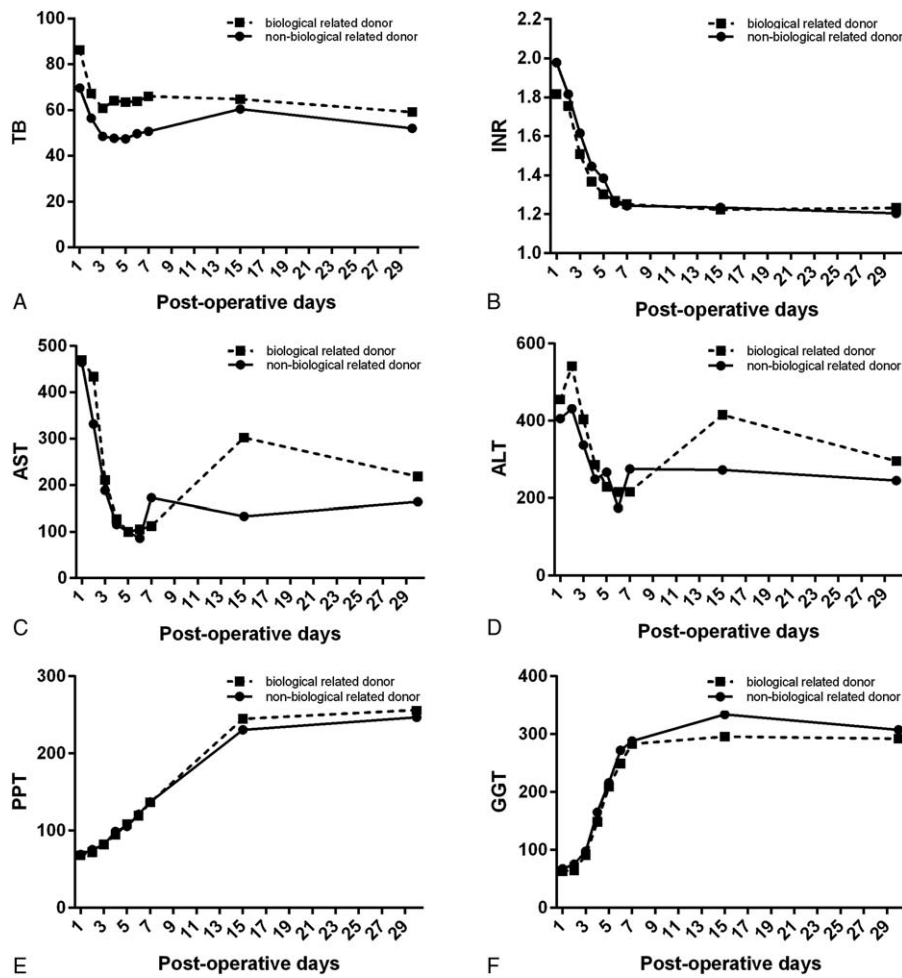
### 3.3. Postoperative laboratory tests and immunosuppression doses

Figure 1 shows the development of TB, INR, aspartic aminotransferase, alanine aminotransferase, alkaline phosphatase, and  $\gamma$ -glutamyl transpeptidase from the 1st to the 7th, 15th, and 30th PODs in the 2 groups. The levels of TB in the NBR group were lower than those in the BR group, albeit without significant difference ( $P = 0.173$ ). Similarly, there were no statistically significant differences observed in other factors (INR,  $P = 0.229$ ; aspartic aminotransferase,  $P = 0.344$ ; alanine aminotransferase,  $P = 0.309$ ; alkaline phosphatase,  $P = 0.852$ ;  $\gamma$ -glutamyl transpeptidase,  $P = 0.470$ ).

We selected the patients using only tacrolimus and mycophenolate as immunosuppression protocols to compare the postoperative doses on the 30th day and at 1, 2, and 3 years. There were no significant differences between the 2 groups in daily doses of the 2 drugs (Fig. 2).

### 3.4. Complications of recipients

Gastrointestinal bleeding and uncontrolled ascites caused by liver dysfunction were the most common complications for both groups. No differences were shown in intra- and postoperative complications. More than one-third of the recipients suffered from early postoperative complications. Intraabdominal collection and pleural effusion were the most common factors, and major complications, defined as Clavien-Dindo IIIb and IV, were similar in both groups at 15%. Biliary complications, including leakage and stenosis, were the most common among late postoperative complications.

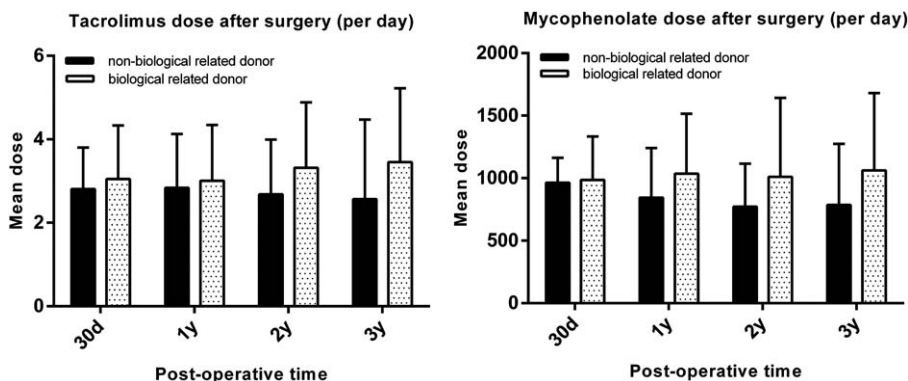


**Figure 1.** The development of postoperative TB, INR, AST, ALT, PPT, and GGT at 1st to 7th, 15th, and 30th POD of the NBR and BR group (TB,  $P=0.173$ ; INR,  $P=0.229$ ; AST,  $P=0.344$ ; ALT,  $P=0.309$ ; PPT,  $P=0.852$ ; and GGT,  $P=0.470$ ). ALT=alanine aminotransferase, AST=aspartic aminotransferase, BR=biologically related, GGT= $\gamma$ -glutamyl transpeptidase, INR=international normalized ratio, NBR=nonbiologically related, POD=postoperative day, PPT=alkaline phosphatase, TB=total bilirubin.

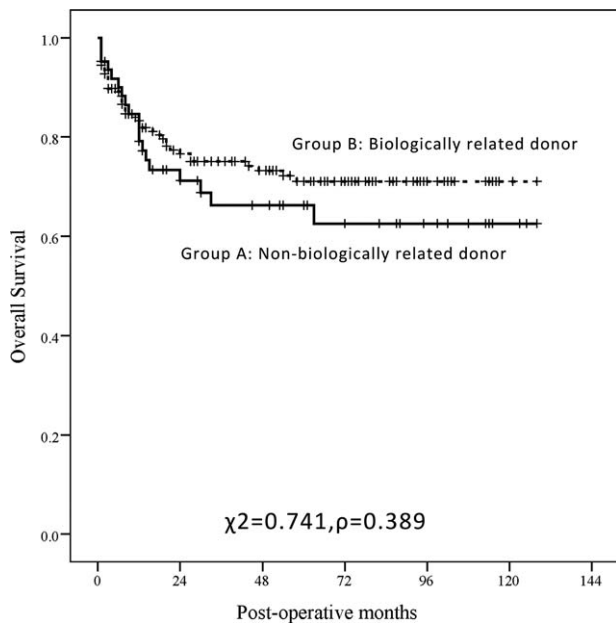
### 3.5. Recipient survival

As shown in Table 4, 24 patients died within 30 days after transplantation, and no difference was observed between the 2 groups (NBR: 7% vs BR: 9%;  $P=0.806$ ). Similarly, no significant differences were observed in patient survival between the NBR

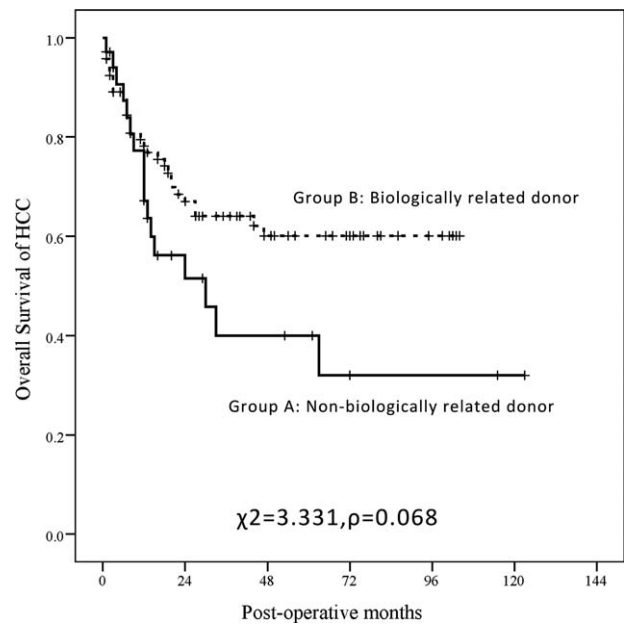
and BR groups at 1, 3, 5, and 10 years (79.1%, 66.2%, 66.2%, 62.5% vs 83.3%, 75.2%, 71%, 71%) ( $P=0.389$ ) (Fig. 3). For patients with benign diseases, the cumulative 1-, 3-, 5-, and 10-year survival rates were 92.9% in the 4 periods in the NBR group and 89.1%, 87.6%, 83.7%, and 83.7% in the BR group, respectively (Fig. 4), while for the patients diagnosed as HCC, the



**Figure 2.** Daily immunosuppression drug dose after liver transplantation in NBR and BR group ( $P=0.432$ , 0.639, 0.213, and 0.247 at 30 days, 1 year, 2 year, and 3 year in tacrolimus dose, and  $P=0.786$ , 0.14, 0.234, and 0.276 in mycophenolate dose, respectively). BR=biologically related, NBR=nonbiologically related.



**Figure 3.** Overall survival after LDLT in NBR group and BR group. BR=biologically related, LDLT=living donor liver transplantation, NBR=nonbiologically related.



**Figure 5.** Overall survival of HCC after LDLT in NBR group and BR group. BR=biologically related, HCC=hepatocellular carcinoma, LDLT=living donor liver transplantation, NBR=nonbiologically related.

survival rate was lower in the NBR group than in the BR group, albeit without a significant difference ( $P=0.068$ ) (Fig. 5). Thereafter, we compared the patients with HCC in the 2 groups both within and exceeding the Milan criteria. These patients would achieve a better outcome – the same as with benign disease – if the Milan Criteria were satisfied (Fig. 6A), and the same result was also evaluated with our Chengdu criteria. However, if patients exceeding the Milan criteria were involved, the outcome was not satisfied with a 41.2% 5-year survival rate, compared

with 82% for patients within the Milan criteria (Fig. 6C) ( $P=0.000$ ). More interestingly, the BR group would achieve a better survival rate compared to the NBR group if the Milan criteria were exceeded (Fig. 6B) ( $P=0.017$ ).

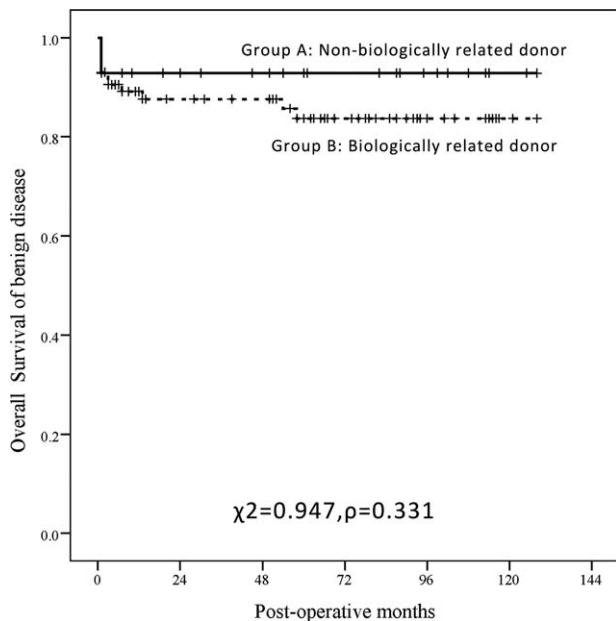
**3.6. Outcomes of donors after live donor hepatectomy**

There was no residual disability or death occurring in the donors, and all of the donors returned to their routine activities after surgery. The median hospital stay was approximately 14 days in both groups. Pleural effusion was the most common postoperative complication in donors (NBR group, 4% vs BR group 3%,  $P=0.697$ ). There was no significant difference between the 2 groups in other complication rates (Table 5).

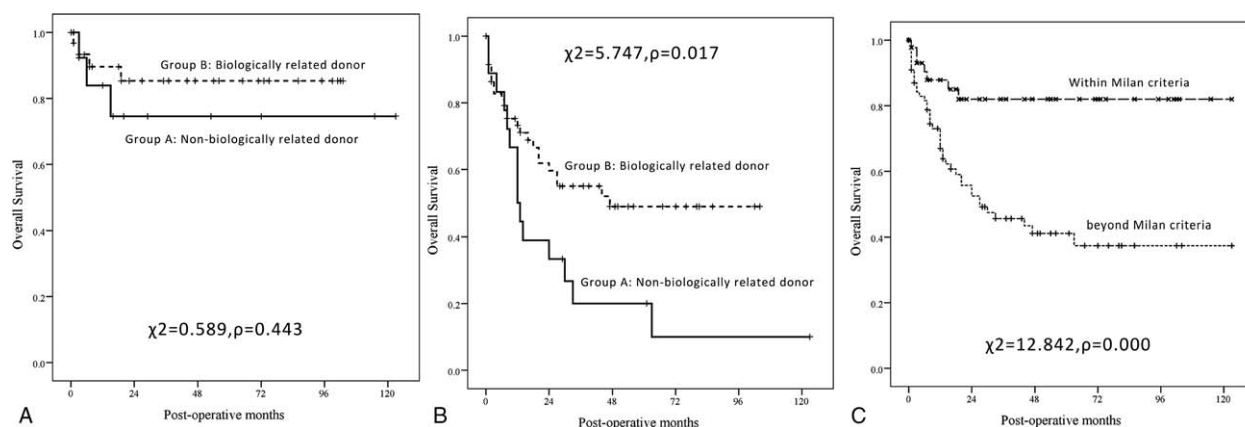
**4. Discussion**

This study was the first to discuss the characteristics and outcomes of LDLT based on the donor–recipient relationship, and as far as we know, it had one of the largest samples referring to NBR donors. This study was undertaken at a single Chinese institute with surgeons experienced for more than 10 years. Our study demonstrated that the recipients undergoing LDLT from NBR donors had good outcomes comparing to those with a BR donor, especially in cases of benign liver diseases and early stage HCCs.

In our study, most of the recipients were male – 90% in the NBR group and 83% in the BR group – which suggested a higher prevalence of liver disease in male patients, as some research has reported before.<sup>[17]</sup> In the NBR group, most of the donors were the spouses of the patients, showing a high rate of female donors. Although a statistically significant difference was found in the duration of the anhepatic phase, it could have been related to the small size of the sample, especially in the NBR group, because in every transplantation, we tried our best to shorten the time of the anhepatic phase to ensure the safety of the recipients.



**Figure 4.** Overall survival of benign disease after LDLT in NBR group and BR group. BR=biologically related, LDLT=living donor liver transplantation, NBR=nonbiologically related.



**Figure 6.** Overall survival of HCC after LDLT in NBR group and BR group based on the Milan Criteria (A) the HCC within Milan Criteria; (B) the HCC beyond Milan Criteria; and (C) comparing the overall survival rate of the patients with HCC within and beyond Milan Criteria. BR=biologically related, HCC=hepatocellular carcinoma, LDLT=living donor liver transplantation, NBR=nonbiologically related.

In transplantation, patients who have been exposed to HLA can experience accelerated rejection and early graft loss,<sup>[18]</sup> and closely related donor and recipient pairs might have the theoretical advantage of a more favorable HLA match. In 1995, Terasaki et al<sup>[19]</sup> conducted the 1st study demonstrating a high survival rate with spousal donors in renal transplantation, and soon the same result was reported by other centers in the benefit of unrelated donors only if prior cross-matching was satisfactorily performed.<sup>[20]</sup> However, HLA compatibility does not seem to have an important impact on LT, and this test seems to have been used sporadically.<sup>[21]</sup> In 1986, Gordon et al<sup>[22]</sup> conducted a study of more than 500 recipients and indicated that cross-matching was associated with neither hyperacute rejection of the liver nor decreased graft survival. Using data from the Organ Procurement and Transplantation Network, an American study of 631 patients, demonstrated that the degree of HLA match had no significant effect on graft failure and 5-y survival rates.<sup>[23]</sup> Unfortunately, however, some important specific causes of graft failure, such as surgical techniques, duration of the operation, the results of preoperative laboratory testing and disease severity, were missing, like most large multiinstitutional databases. However, more recently, a study in Italy demonstrated that HLA cross-matching was important if patients underwent retransplantation due to HLA class I antibodies having deleterious effects on regraft survival.<sup>[24]</sup> In the present study, HLA was not tested routinely in LT, and the effect of graft function was indicated by postoperative laboratory data, complication rates and immunosuppression doses, and no

obvious differences between the groups were observed using the indices above because: as an immunologically privileged organ, the overall postoperative rejection rate in LT is lower than with any other solid organ transplant, and a better prognostic factor is needed for comparing different modes of grafts as a response to the quality of the liver; although immune tolerance could theoretically be achieved easily in recipients after LT, it could not be judged by objective testing, and the occasion for immunosuppression decrease or withdrawal was only decided based on the experience of the surgeons, resulting in a deviation in the daily dose for each patient, especially in small samples; and in the BR group, both parents or offspring and siblings are blood related, but the HLA exposure is quite different, and the former is considered a surrogate for a higher closely matching HLA with a higher risk of recurrence of hepatitis and graft injury, while the latter is usually the best choice for transplantation. More evidence and multiple institutions are needed to evaluate the changes in immunologic function in LT.

Anatomic variants in hepatic vessels were common: approximately 45% in the hepatic artery and 20% in the portal vein in the general population;<sup>[25,26]</sup> portal vein variations were also associated with higher rates of biliary variations.<sup>[27]</sup> Some studies have even shown that the relationship between the donor and recipient might be connected to variations in vessels.<sup>[10]</sup> Right lobe grafts were generally preferred for a larger size in adult to adult LDLT. However, a high incidence of vascular and biliary variants occurs in the right lobe anatomy, compared to the left lobe,<sup>[28]</sup> which promoted the development of surgical techniques but with the possibility of postoperative complications or failure of the donor selection.<sup>[29]</sup> Kim et al<sup>[10]</sup> conducted a study to compare the variants in the hepatic artery and portal vein in selected donors, and they were divided into related and unrelated groups based on the donor-recipient relationship. As a result, they demonstrated that the donor-recipient relationship might have a correlation with the portal vein but no association with the hepatic artery. In the present study, although we did not provide direct information about the anatomic variants of the donors, according to the conditions of variant vasculature, we performed different anastomoses between the graft and recipient. The results suggested that there was no connection between the donor-recipient relationship and the surgical procedure. In the NBR group, the percentage of female donors was greater than that in the BR group, and usually, in our experience, the grafts from

**Table 5**  
Donor postoperative complication and hospital stay description.

	Nonbiologically related donor, n=69	Biologically related donor, n=203	P
Hospital stay <sup>†</sup>	14 (11–19)	14 (11–17)	0.618
Postoperative complications, %	4 (6)	13 (6)	1.000
Bacterial pneumonia, %	0 (0)	2 (1)	1.000
Pleural effusion, %	3 (4)	6 (3)	0.697
Postoperative bleeding, %	0 (0)	2 (1)	1.000
Hepatic failure, %	0 (0)	1 (0.5)	1.000
Postoperative ileus, %	1 (1)	2 (1)	1.000

<sup>†</sup> Median (interquartile range [IQR]).

female donors were smaller than the recipients', resulting in a higher percentage of the graft containing the middle hepatic vein in the NBR group.

In the present study, the patients diagnosed with HCC constituted nearly half of all of the patients undergoing LDLT. However, the overall survival rate was not as satisfactory, which could have been influenced by the different classifications of HCC. In 1996, Mazzaferro et al.<sup>[21]</sup> from Milan suggested that LT should be performed in patients with restrictive selection criteria, in whom the 5-year survival rate could increase to 70%. With the same result, the patients with HCC undergoing LDLT had an 82% 5-year survival rate in our center if the Milan criteria were satisfied, which was close to the outcome of patients with benign diseases. As we mentioned before, we expanded the criteria up to 9 cm of the total size of the tumor, and the 5-year survival rate also increased to 83%. Although there are several classifications of HCC to expand the criteria, LDLT is still available to be performed in smaller and early stage HCCs. The 5-year survival rate of HCC exceeding the Milan criteria was 41.2%, while in cases exceeding the Chengdu criteria, the rate was 27.8%. Interestingly, a difference in survival rate was observed between the NBR and BR groups among patients exceeding the Milan criteria ( $P=0.017$ ). Subsequently, we analyzed the disease-free survival (DFS) rate in this situation, and we found that the DFS rate was lower in the NBR group by 40% at 5 years, compared to 65% in the BR group, albeit with no significant difference ( $P=0.316$ ). Although HCC shows a genetic predisposition among populations, especially in 1 family tree, environmental factors and the hepatitis virus infection also play important roles in the occurrence of HCCs.<sup>[30]</sup> All of the donors were preferred without hepatitis virus infection histories; thus, genetic development was not present in the same biological related family. There were 20 patients exceeding the Milan criteria in the NBR group and 65 patients in the BR group; the small sample sizes in both groups might have resulted in the lower survival rate in the NBR group. Furthermore, for patients exceeding the Milan criteria, the risk factors, such as the size, the number, and the degree of invasion for microvessels, could not be consistent. As we mentioned before, if we limited the upper bound of the criteria, like with the Chengdu criteria, differences were not found between the 2 groups. Thus, we believe that the lower survival in the NBR group could be related to the expansion of the criteria for HCC.

Postoperative complications in recipients after LDLT remain a concern for surgeons. In our center, 38% patients experienced early period complications, and 15% experienced late complications. Except for abdominal collection and pleural effusion, biliary complications were the most common, especially among late postoperative complications. In other centers in Asia, the rates of biliary leaks have ranged from 2.7% to 18.2%, while the rates of biliary strictures have ranged from 7.3% to 31.7%.<sup>[31–33]</sup> This high rate of biliary leakage might be associated with the surgical procedure when performing dissection of the periductal tissues, which can influence the blood supplies of the donor and recipient bile ducts. Therefore, preserving Glisson's sheath to protect the optimal blood supply is an important approach for avoiding biliary leaks.<sup>[34]</sup>

There were some limitations to our study. First, it was a retrospective study with 1 center's experience, and certain biases could not be avoided completely. Second, we did not compare the doses or concentrations of postoperative antirejection drugs, which might have been related to chronic graft rejection. In addition, we did not estimate the level or volume of liver regeneration.

In conclusion, our findings suggested that the biological relationship between donor and recipient in adult to adult LDLT was not associated with the short- and long-term outcomes of recipients diagnosed with benign liver diseases and early stage HCC. NBR donor, especially spousal donors, could be a potential source for grafts in LDLT with changes in family structure. For patients diagnosed with HCC, the criteria for LDLT should be restrictively selected, and the Chengdu criteria, by expanding the standard, should yield the same results as the Milan criteria.

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