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Original Article

In-hospital mortality after adult living donor liver transplantation: single-center experience

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Abstract: Objectives: To identify the preoperative risk factors associated with in-hospital mortality after living donor liver transplantation (LDLT). Materials and methods: Between November 2001 and May 2015, LDLT were performed in 276 consecutive adult recipients in our hospital. Medical data were collected from the Chinese Liver Transplant Registry. Indications for transplantation and causes of death were analyzed. Potential risk factors for in-hospital mortality after LDLT were analyzed by using univariate and multivariate in this study. Results: From November 2001 to May 2015, 276 consecutive adult recipients underwent LDLT in our hospital. Recipients who received dual grafts or repeat transplant were excluded. A total of 263 LDLT recipients were indentified with an overall in-hospital mortality of 13.7%. The most frequent cause of death was infections (47.2%), which was followed by multiple organ failure (25.0%) and renal failure (8.3%). Associated risk factors included D-MELD more than 600 ($P<0.05$), preoperative ICU stay ($P<0.05$) and the Charlson comorbidity index of 1 or higher ($P<0.05$). Conclusion: Our study indentified that being ICU-bound before LDLT, with a D-MELD score more than 600 and the CCI of 1 or higher were the independent factors that associated with in-hospital mortality after LDLT. These findings could help in patients consulting, donor selection and decision making.

Keywords: Living donor liver transplantation, in-hospital mortality, D-MELD, preoperative ICU stay, charlson comorbidity index

Introduction

Liver transplantation (LT) is the only way to cure end-stage liver diseases. Despite of advances achieved in surgical techniques, immunosuppression and perioperative managements, the shortage of donor continues to be the top issue of LT. Compared to most western countries, Asian has a scarcity of deceased donors as a result of cultural belief and lack of the 'brain death law' [1-3]. Some Asian countries and regions have focused on the promoting LDLT as a response of organ shortage. Despite of technical complexity, issues of donor safety, higher rates of the biliary complication and retransplantation compared to deceased donor liver transplantation (DDLT), living donor liver transplantation (LDLT) plays a crucial role even as standard procedure somewhere [4, 5].

Since we performed the first adult-to-adult LDLT in mainland China in 2001 [6], there are already 276 adult cases till May 2015 in our center. In contrast to other procedures in hepato-surgery, much more factors are negatively influence the outcomes of LDLT and lead to a relatively high in-hospital mortality [7-11]. However such factors have not been well established. In the present study, we performed a retrospective review of medical records to analyze risk factors associated with in-hospital mortality as well as causes of death after LDLT in a single center.

Materials and methods

Patients and methods

From November 2001 to May 2015, 276 consecutive adult recipients underwent LDLT in our hospital. The data were collected from the Chinese Liver Transplant Registry (CLTR). Patients were excluded from the study if they received retransplantation, dual grafts or combined liver and kidney transplantation. All the liver donations and transplantations were ap-

proved by the Liver Transplantation Committee of our hospital. The current study was approved by the Ethics Committee of our hospital. All the protocols were carried out in accordance with ethical principles of the Declaration of Helsinki and performed after informed consent were obtained from the patients.

Donor evaluation

All the living liver donors were voluntary and healthy relatives within the third degree of consanguinity or spouse. Donor with an age <18 years, known medical disorders that had significantly influence on perioperative risk or contraindicated donation were excluded. The ABO blood type of donor and recipient should be identical or compatible. Computed tomography scan with contrast was performed to evaluate graft volume, vessel anatomy and the size of the future remnant donor liver. Donors with a estimated remnant liver volume less than 40% of the total liver for were excluded for donations.

Operative techniques

Both donor and recipient operative techniques has been detailed described previously [12]. The abdominal cavity is exposed through a right subcostal incision with an extension to the upper midline. Then a liver biopsy was performed after abdominal exploration to exclude donors with severe hepatic steatosis. Cholecystectomy was performed after the result of biopsy showed normal. Then evaluation of biliary anatomy was done by intraoperative cholangiography via the cystic duct if the preoperative MRCP shows variations. After dissection and isolating the vessels and ducts at hilar, the transection line was confirmed after a temporary inflow occlusion and marked by electrocautery on the surface of the liver. Liver transection was performed without inflow occlusion and done by using a combination of clamp fracture, ultrasonic dissector (CUSA®), suture ligation and electrocautery. As the transection approaches the hilar, right hepatic duct and surrounding tissue were sharply divided. Once the transection was completed, the right hepatic artery, portal vein and hepatic vein were divided after systemic heparinization and then transferred to the back table. The grafts were preserved and flushed by using either the University of Wisconsin or HTK solution. The inferior vena cave of the recipients was preserved and no venovenous bypass was performed during the transplantation. After native liver of recipient was removed, stumps of the middle and left hepatic veins were closed and a venoplasty of the right hepatic vein (RHV) was performed to ensure a wide outflow. Then the graft hepatic vein was anastomosed to the stump of the right hepatic vein of the recipient. Additional anastomosis to IVC was required if a wide size inferior RHV or major branch of MHV were encountered. Reconstruction of the remained tubes were performed in the following order: portal vein, hepatic artery and bile duct. If the hepatic artery of the recipient was inadequate for reconstruction, a jump graft of recipient's saphenous vein to the aorta was required. A Rou-en-Y hepaticojejunostomy was performed while duct-to-duct anastomosis cannot be achieved.

Postoperative managements

Standard immunosuppression regimen consists of calcineurin inhibitor (tacrolimus or cyclosporine), mycophenolate mofetil and prednisone. For those patients with renal dysfunction, sirolimus was given instead of calcineurin inhibitor. Steroids were tapered off within a month while the graft function was stable well. Steroid pulse therapy was taken after diagnosis of rejection was made by liver biopsy. Hepatitis B immune globin was given intraoperation and combined with lamivudine post-transplant in order to prevent recurrence of HBV in the recipients with positive HBsAg.

In-hospital mortality

The in-hospital mortality was studied and causes of death were analyzed. In-hospital death was defined as death occurred during the same hospitalization for LDLT regardless of causes and the length of hospital stay (LOS). Data from donors and recipients were obtained and analyzed to determine the variables associated with in-hospital death. The donor factors included age, sex and body mass index (BMI). The recipients factors included the following: age, sex, BMI, indication for LDLT, graft-recipient weight ratio, being ICU-bound before LDLT, model of end-stage liver disease (MELD), D-MELD which is the product of MELD score and donor age, Child-Turcotte-Pugh, the Charlson comorbidity index (CCI), complications of primary disease (gastrointestinal bleeding and encephalopathy), prior abdominal surgery, pre-

Table 1. Romano adaptation of the Charlson index

Comorbidity	Points
AIDS	6
Cerebrovascular disease	1
Chronic pulmonary disease	1
Congestive heart failure	1
Connective tissue/rheumatic disease	1
Dementia	1
Diabetes	
Without end organ damage	1
With end organ damage	2
Hemiplegia	1
Myocardial infarction	1
Peripheral vascular disease	1
Renal disease	2
Ulcer disease	1

Table 2. Indications for living donor liver transplantation

Indications	Number of cases
Hepatocellular carcinoma	130
Hepatitis B virus cirrhosis	68
Acute-on-chronic liver failure	22
Cholestatic diseases	9
Cholangiocarcinoma	8
Alcoholic cirrhosis	6
Budd-Chiari syndrome	5
Hepatitis C virus cirrhosis	4
Fulminant hepatic failure	3
Hepatic echinococcosis	2
Polycystic liver disease	1
Wilson disease	1
Autoimmune hepatitis	1
Hepatic epithelioid hemangioendothelioma	1
Cirrhosis due to schistosomiasis	1
Trauma	1

transplant portal vein thrombosis, dialysis before transplantation and combined splenectomy. The CCI was applied for classifying patients at different risk stage according to the comorbidities by using a simple weighted scoring system [13, 14]. The CCI was assigned by the sum of the points for the conditions presented for each case except the comorbidities of 'liver diseases' and 'malignancy' (**Table 1**). Splenectomy were performed while patients were suffered from a very severe portal hypertension with a platelet count $<30\times10^9$/L.

Statistical analysis

The categorical variables were compared by Chi-square test or Fisher exact test when appropriate. Risk factors which were significant in the univariate analysis were then subjected to multiple logistic regression analysis. Level of $P<0.05$ was considered significant. All the statistical analysis was performed by using SPSS Version 19 statistical analysis software (SPSS Inc., Chicago, Illinois, USA).

Results

Between November 2001 and May 2015, LDLT were performed in 276 consecutive adult patients at our center. Of all the LDLT recipients, 13 were excluded because of re-transplantations (n=5) or had received dual grafts (n=8). Therefore, 263 recipients were included in the current study and 159 (60.5%) were males. The mean age of the recipients was 42.86±8.87 years. Indications for LDLT included hepatocellular carcinoma (n=130), hepatitis B virus cirrhosis (n=68), acute-on-chronic liver failure (ACLF, n=22), cholestatic diseases (n=9), cholangiocarcinoma (n=8), alcoholic cirrhosis (n=6), Budd-Chiari syndrome (n=5), hepatitis C virus cirrhosis (n=4), fulminant hepatic failure (n=3), hepatic echinococcosis (n=2), polycystic liver disease (n=1), Wilson disease (n=1), autoimmune hepatitis (n=1) hepatic epithelioid hemangioendothelioma (n=1), cirrhosis due to schistosomiasis (n=1) and trauma (n=1) (**Table 2**). The mean MELD score was 15.87±9.42 and mean D-MELD score was 570.45±442.71. The median LOS after LDLT was 30 days (range from 1 to 146 days). A total of 36 recipients died after LDLT with an overall in-hospital mortality of 13.7% (**Figure 1**). Causes of in-hospital death after LDLT included the following: infections (17), MOF (n=9), renal failure (n=3), vascular complications (n=3), intra-abdominal hemorrhage (n=3), intracranial hemorrhage (n=1) (**Table 3**). Among the 36 recipients, 26 (72.2%) were died within 30 days after LDLT and the remained 10 (27.8%) were died after more postoperative days.

Risk factors which might associate with in-hospital mortality after LDLT were investigated in the univariate analysis (**Table 4**). The significant factors included: ACLF as indication for LDLT ($P=0.014$), the CCI of 1 or higher ($P<0.001$), being ICU-bound before LDLT ($P<0.001$), a D-MELD score more than 600 ($P<0.001$), recip-

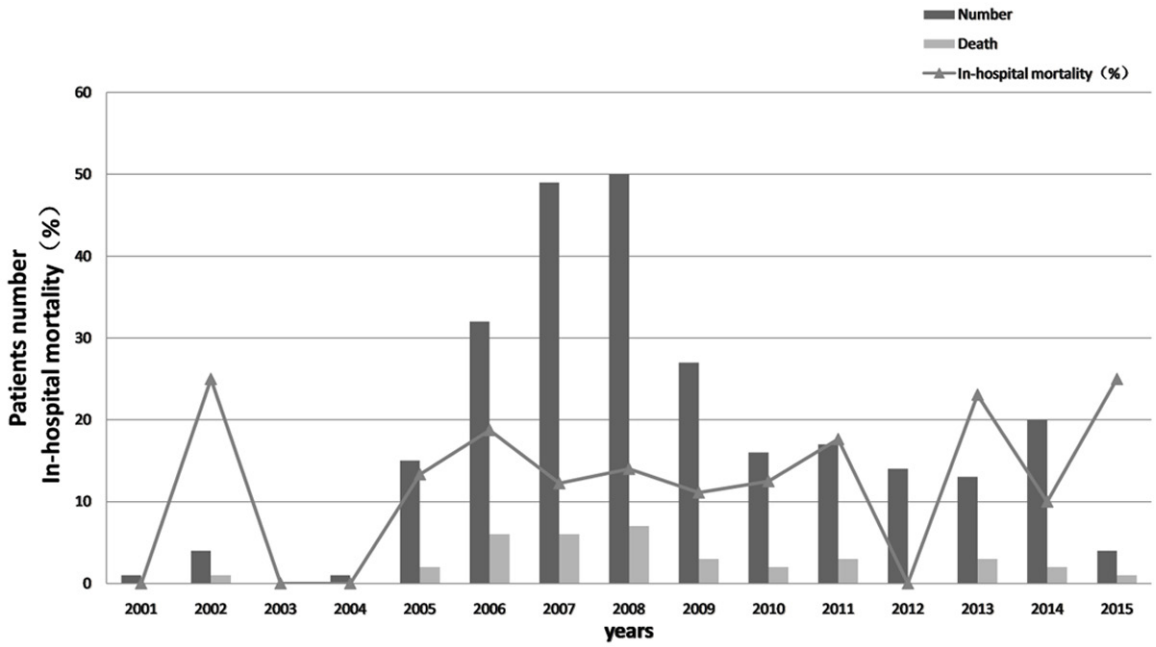

Figure 1. Annual number of cases and in-hospital mortality.

Table 3. Causes of in-hospital death after liver donor liver transplantation

Cause	Number of death
Infection	17
Multiple organ failure	9
Renal Failure	3
Vascular complications	3
Intraabdominal bleeding	3
Intracranial hemorrhage	1

ient age older than 49 years (P=0.031) and a BMI of 28 Kg/m^2 or higher (P=0.044). Then the potential risk factors mentioned above were subjected to the multiple logistic regression model and the results showed that CCI of 1 or higher (P=0.018), being ICU-bound before LDLT (P=0.009) and a D-MELD score more than 600 (P=0.006) were independent adverse prognostic factors for in-hospital mortality (**Table 5**). Among the three factors, being ICU-bound before transplant had the greatest association on rising the odds of in-hospital mortality with a odds ratio (OR) of 6.286; 95% confidence interval (CI), 1.582-24.981, P=0.009.

Discussion

Like other countries and regions in the world, mainland China also faced the continuing organ shortage crisis [3]. In 2010, the liver activity per million of the population were 17.00 for Korea, 16.00 for Taiwan, 7.00 for Hong Kong, 4.00 for Japan and 0.07 for mainland China respectively [3, 15]. According to the China Liver Transplant Registry (CLTR) 2011 annual scientific reports, there were a total cases of 20,877 LT performed up to December 2011 in mainland China and only 7.37% of them (n=1,539) were LDLT. Despite of a higher rate of surgical complications compared to DDLT, LDLT has emerged as an alternative because of the potential benefits of short waiting time and optimal graft at right time. No significant difference was observed in preoperative mortailty and long-term survivals between LDLT and DDLT recipients [4, 16, 17]. Excellent outcomes of recipients and a decreased postoperative complication rates can achieved as centers gain greater experience with LDLT [10, 17, 18]. In the current condition of no laws of brain death [19], traditional Chinese culture of sacrifice for the family and increased morbidity and high mortality associated with DCD grafts [20, 21], LDLT might be the optimum choice for liver transplantation of mainland China like in any other Asian countries and regions.

Outcomes of recipients undergoing LDLT were associated with many preoperative factors. The current study identified the preoperative risk factors and causes of in-hospital death at a single center in mainland China. The overall in-hospital mortality (13.7%) and median LOS

Table 4. Univariate analysis of factors associated with in-hospital mortality after LDLT

Variables before LDLT	Survived (n=227)	Died (n=36)	P
Donor			
Age ≥50 years	24 (10.6%)	4 (11.1%)	0.922
Male sex	138 (60.8%)	21 (58.3%)	0.779
Recipients			
Age ≥50 years	40 (17.6%)	12 (33.3%)	0.031*
Male sex	194 (85.5%)	28 (77.8%)	0.24
BMI ≥28 Kg/m^2	11 (4.8%)	5 (13.9%)	0.044*
ACLF as an indication	15 (6.6%)	7 (19.4%)	0.014*
HBV cirrhosis as an indication	69 (30.4%)	9 (25.0%)	0.511
HCC as an indication	115 (50.7%)	15 (41.7%)	0.318
GRWR <0.8%	55 (24.2%)	11 (30.6%)	0.417
ICU-bound before transplant	6 (2.6%)	6 (16.7%)	<0.001*
MELD score ≥25	27 (11.9%)	6 (16.7%)	0.435
CTP score ≥9	94 (41.4%)	16 (44.4%)	0.336
Charlson score ≥1	31 (13.7%)	16 (44.4%)	<0.001*
GI bleeding	34 (15.0%)	3 (8.3%)	0.294
Encephalopathy	22 (9.7%)	7 (19.4%)	0.089
Prior abdominal surgery	55 (24.2%)	12 (33.3%)	0.247
Portal vein thrombosis	21 (9.3%)	5 (13.9%)	0.39
Dialysis	3 (1.3%)	2 (5.6%)	0.112
Combined splenectomy	7 (3.1%)	2 (5.6%)	0.742
D-MELD >600	62 (27.3%)	22 (61.1%)	<0.001*

Abbreviations: BMI, body mass index; ACLF, acute-on-chronic liver failure; GRWR, graft-recipient weight ratio; MELD, Model for End-Stage Liver Disease; D-MELD, the product of Model for End-stage Liver Disease score and donor age; CTP, Child-Turcotte-Pugh; CCI, Charlson Comorbidity Index; GI, gastrointestinal. *P<0.05.

Table 5. Multivariate analysis of factors associated with in-hospital mortality after living donor liver transplantation

Variables	OR	95% CI	*P*
D-MELD			
>600	3.285	1.418-7.611	0.006
≤600	1		
Charlson score			
≥1	2.883	1.204-6.904	0.018
0	1		
Preoperative ICU stay			
<90	6.286	1.582-24.981	0.009
≥90	1		

after LDLT (30 days, range from 1 to 146 days) appeared to be higher compared to others. Liu et al. [17] reported a very low in-hospital mortality of 1.6% in 124 LDLT cases with a median LOS of 19 days (range from 7-114 days). In their study, all the recipients except 1 had received grafts with middle hepatic vein and patients with hepatic tumor were excluded from LDLT. The mortality (18.9%) reported by Kaido et al. [10] seemed a little higher. However about 15.0% of the recipients received ABO-incompatible grafts and more than one third recipients had conditions of MELD score of 25 or higher. Therefore the in-hospital mortality is associated with preoperative conditions of recipients and indications. Prolonged LOS could not only increase the risk of nosocomial infections, but also lead to a waste of medical resources. However, rehabilitation facilities for allograft recipients after discharge have not yet been established in our country. Lacking of rehabilitation facilities after discharge is the reason why recipients had a longer LOS compared to others in our center. Besides reasonable long LOS could avoid premature discharge and reduce the possibility of readmission by enable managements of early complications after LDLT [22, 23].

Infections remain the main risk factors of mortality early after transplantation [24-26]. This finding was confirmed in our study as well. The incidence of infectious complications is especially high in liver recipients because of the poor health conditions, complex surgical procedures, transfusion and use of immunosuppression [10, 27-29]. Kim et al. [26] stated that most of the infections were catheter-related and primary bacteremia that occurred more frequently within 1 month after LDLT. Appropriate managements and early removal of catheters are important to reduce infections within 1 month of transplantation. Parenteral nutrition has been associated with increased postoperative infection rates and more metabolic complications compared to enteral feeding [29-31]. Different from the recipients in US or Europe who might eat sufficient food 5 days after transplantation, it takes about 2 weeks for Japanese patients because of appetite loss and weakness [10]. Therefore

Kaido et al. started a research of routine use of postoperative early enteral nutrition via tube jejunostomy with a mean period of 21 days from 2003. It is more feasible and comfortable compared with feeding via a transnasal feeding tube for such a long time. After introduction of enteral feeding, the periods of using central venous catheter had decreased from 2 weeks to less than 5 days and eliminated 70% of the infection risk. However, the surgical procedures of jejunostomy may increase the risk of infections.

Our study confirmed that CCI of 1 or higher, being ICU-bound before LDLT and D-MELD score more than 600 were independent preoperative risk factors for in-hospital mortality after LDLT. Comorbidities such as hypertension, chronic obstructive pulmonary disease or diabetes may have negative effects on outcomes after LDLT [32-35]. The CCI was used to evaluate comorbidities according to their prognostic significance and calculated by the sum of the points for the comorbidities [13, 14, 36]. The reliability of the CCI in predicting outcomes of liver transplantations had already been previously proved [37, 38]. The 2 studies both have suggested that the CCI was a useful tool in risk prediction. However the ability in predicting early (1-month) mortality after LT was suggested poor [39]. There was only about 17.8% of recipients experienced comorbidities with a mean age of 42±9 years in our study while the proportion was 30% with a mean age of 50±10 years in the study by Wasilewicz et al. Also they only evaluated the ability to predict 1-month mortality after LT with a limited number of 169 recipients.

MELD score has been widely used in quantifying the severity of primary liver diseases for patients on the LT waiting list and predicting outcomes after LT [10, 40]. However, some investigations suggested that MELD score had poor ability in predicting outcomes after LT [41-43]. In the current study, MELD score showed poor predictive power for in-hospital mortality after LDLT. Factors which affect outcomes of transplantations should be considered together rather than alone. By considering that donor factors may also affect outcomes after LT, the D-MELD score which is the product of MELD score and donor age was introduced in predicting outcomes after LT by Halldorson et al. [40]. They suggested that D-MELD score cutoff of 1600 is associated with significantly poor survival and prolonged LOS in decreased donor liver transplantation. This viewpoint was in consistent with our finding in the current study. In our study, we confirmed that a D-MELD score ≥600 is an independent risk factor for in-hospital mortality after LDLT. This finding might be explained by the different donor types and healthy conditions of recipients. For example, donors aged over 60 years were excluded from transplantation in our center. Recipients with high MELD score were easier to get organs from decreased donors because they are at the forefront of the waiting list. Toru et al. reported that for those LDLT recipients, D-MELD is a useful predictor of in-hospital mortality as well [44].

There are several inherent strengths and weaknesses in this study. The outcomes after LDLT are associated with factors peri-, intra- and post-operative. We only indentified the preoperative factors which may limit its use in outcome prediction without considering factors intra- and post-operation. However these findings might be useful in patients consulting, donor selection and decision making. Another limitation is that the end point is death acquired in hospital. As we know there were only 2 recipients passed away within 3-month period after discharged. Another weakness is the retrospective and single-center design of current study. This hinders the external validity and generalizability of our findings.

Although with high rates of surgical complications after transplantation, LDLT facilitates access to liver transplantation made it an alternative to DDLT. This study indentified that being ICU-bound before LDLT, with a D-MELD score more than 600 and the CCI of 1 or higher were the independent factors that associated with in-hospital mortality after LDLT. We believe that our finding would be helpful in patients consulting, donor selection and decision making.

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Disclosure of conflict of interest

None.

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