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Original Article

Pretransplant mortality predictors in living and deceased donor liver transplantation

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Abstract

Background: Although there were some reports predicting postoperative morbidity and mortality in patients undergoing liver transplantation, most of them studied deceased-donor liver transplantation (DDLT). In this context, we performed this study to predict early mortality after liver transplantation from preoperative variables in both living-donor liver transplantation (LDLT) and DDLT.
Methods: We retrospectively reviewed the medical charts of 159 patients undergoing liver transplantation (LDLT, $n = 103$; DDLT, $n = 56$). Then, we identified the factors that independently predicted 30-day mortality using multivariable logistic regression models.
Results: The 30-day mortality and 1-year mortality for DDLT versus LDLT were 30% versus 6% and 39% versus 11%, respectively. In multivariate logistic regression analysis, pretransplant hepatic encephalopathy (odds ratio, 5.594; 95% confidence interval, 1.110–28.194; $p = 0.037$) in patients with DDLT and serum creatinine (odds ratio, 4.883; 95% confidence interval, 1.296–18.399; $p = 0.019$) in patients with LDLT were the independent risk factors for a composite of 30-day mortality.
Conclusion: In conclusion, hepatic encephalopathy in DDLT and serum creatinine level in LDLT were the significant pretransplant variables that were related with early death after LT.

Keywords: creatinine; hepatic encephalopathy; liver transplantation; mortality

1. Introduction

Liver transplantation (LT) for patients with hepatocellular carcinoma, cirrhosis, and fulminant hepatic failure is fairly common. However, this operation is not without risk—it carries a 5–10% incidence of 30-day mortality.[1] Identification of pretransplant risk factors that predict early mortality is important for postoperative management. It has been known that accuracy rates for pretransplant MELD (Model for End-stage Liver Disease) score and Child–Pugh classification are low as predictors of 3-month postoperative mortality.[2,3] The Child–Pugh score has been used to assess the prognosis of patients with liver cirrhosis. Although it was originally used to predict mortality during surgery, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity of liver transplantation. However, a limitation of the classification is that each variable is given the same weight. Multivariate analysis showed that the impacts of the different predictive factors on mortality were different.[4] Giving the same weight to different variables resulted in overestimating or underestimating their actual impact. In previously reported studies, the predictive values of survival explained by Child–Pugh scores were less than 50%.[5] The

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MELD score, originally created with the aim of predicting survival after transjugular intrahepatic portosystemic shunt,[4] has been also used for predicting pretransplant survival, but its usefulness as a model to predict survival following LT is still controversial.[6,7] Although there had been some reports predicting postoperative morbidity and mortality in patients undergoing liver transplantation including Child–Pugh classification, pre-LT renal insufficiency, malnutrition, technically complex surgery indexes,[8] and the MELD,[9] most of them have been studied in deceased-donor liver transplantation (DDLT).

The purpose of this study was to assess the predictive variables for posttransplant mortality and investigate the predictors of mortality for patients with living- and deceased-donor LT.

2. Methods

2.1. Participants

We retrospectively reviewed the medical charts of 159 consecutive LTs (living donor, $n = 103$; deceased donor, $n = 56$) that had been performed in our institute from March 2007 to October 2010. Patients were excluded if they had any history of advanced heart or lung conditions or aged <20 years.

2.2. Anesthesia and operative procedures

On arrival at the operating room, standard monitoring such as lead II and V5 of electrocardiography, arterial blood pressure, pulse oximetry, bispectral index, and cerebral oximetry were applied. A pulmonary artery catheter (Swan-Ganz CCOmbo CCO/SvO_2; Edwards Lifesciences LLC, Irvine, CA, USA) was inserted via the right internal jugular vein, and we monitored continuous cardiac output and mixed venous oxygen saturation and pulmonary arterial pressure. Anesthesia was induced with intravenous propofol, remifentanil, and atracurium, and then maintained with desflurane, remifentanil, and atracurium. Intravascular volume replacement was managed with crystalloid and colloid solutions to maintain the pulmonary capillary wedge pressure between 8 mmHg and 14 mmHg. The central blood temperature, which was measured using a pulmonary artery catheter, was maintained at about 36 °C with a warm mattress, a forced warm air blanket, and fluid warmer as necessary. During the surgical procedure, the mean arterial pressure was maintained above 70 mmHg with dopamine, norepinephrine, vasopressin, or epinephrine infusion. Allogenic-packed red blood cells were transfused when the hematocrit level was under 25% throughout the study period. Surgical procedures proceeded in the standard order used at our clinics. After mobilization of the recipient liver, the native liver was removed. Whole-size DDLT and right-lobe living-donor LT (LDLT) was performed in each group. For DDLT, donor age under 60 years and donation prior to cardiac death with Asian race without hepatic problems were selected.[10] After reperfusion, several anastomoses, hemostases, and closures were performed. All patients were transferred to the intensive care unit (ICU) after surgery. They received standardized ICU care at the discretion of the ICU staff according to the standard ICU protocols. Criteria for weaning from ventilatory support included an appropriate sensorium, hemodynamic stability (cardiac index, >2.2 L/min/m^2; pulmonary capillary wedge pressure, >60 mmHg; pulmonary capillary wedge pressure, <20 mmHg; and no significant arrhythmias), PaO_2/FiO_2 >200, minimal operation site drainage, no signs of hepatic failure or graft dysfunction, and temperature >35.5°C. Discharge criteria from the ICU were as follows: stabilized patient's clinical status without the need for ICU monitoring and care (including no further requirement for either inotropic or vasoactive agents), and no plan for further active intervention.

2.3. Statistical analysis

We identified factors that were independently associated with 30-day mortality with multivariate logistic regression models. The factors considered were age, sex, and components of Child–Pugh classification [hepatic encephalopathy (HE), ascites, total bilirubin, international normalized ratio (INR), serum albumin] and MELD score (serum creatinine, INR, total bilirubin),[11] as well as donor factors (age, sex, cold ischemic time, graft size in the LDLT, bile duct variation, macrovesicular steatosis, lymphocyte crossmatching).

Data were analyzed with SPSS version 18 (SPSS, Inc., Chicago, IL, USA) and expressed as mean ± SD or number of patients (%). Continuous variables were analyzed by independent t tests. Categorical data were analyzed with the Chi-square test. To determine the preoperative mortality predictor, an initial univariate analysis was used with logistic regression. Variables that showed p <0.1 by univariate analysis were included in the multivariable logistic regression model. A p value of <0.05 was considered statistically significant.

2.4. Ethics statement

This study was approved by the institutional review board of our hospital (Ref: 4-2010-0671).

3. Results

3.1. Characteristics of patients and mortality

Patients' characteristics and perioperative data are shown in Table 1. The overall 30-day mortality and 1-year mortality were 14% and 21%, respectively. The periodic difference of mortality from March 2007 to October 2010 was not found retrospectively. More patients with fulminant hepatic failure were in the DDLT group than in the LDLT group (18% vs. 4%, $p = 0.006$). The 30-day mortality (30% vs. 6%, p <0.001) and 1-year mortality (39% vs. 11%, p <0.001) were higher in DDLT than in LDLT. Patients with fulminant hepatic failure had higher 30-day mortality (43% vs. 12%, $p = 0.007$) and 1-year mortality (57% vs. 17%, $p = 0.002$) than patients without

Table 1
Patients' characteristics and mortality.

	DDLT (n = 56)	LDLT (n = 103)	p
Age (y)	49 ± 11	53 ± 9	0.031*
Sex (M/F)	39:17	83:20	0.070
Weight (kg)	70 ± 12	66 ± 12	0.041*
Height (cm)	167 ± 8	165 ± 12	0.361
Cause of LT			
Fulminant hepatic failure	10 (18)	4 (4)	0.006*
Hepatitis B	33 (59)	58 (68)	0.298
Hepatocellular carcinoma	3 (5)	17 (17)	0.047*
MELD score	24 ± 12	15 ± 9	<0.001*
Child–Pugh class C	36 (64)	29 (28)	<0.001*
HE grade 3	23 (41)	16 (16)	0.001*
Ascites grade 3	21 (38)	28 (27)	0.115
Total bilirubin (mg/dL)	2.3 ± 0.9	1.7 ± 0.9	<0.000*
Albumin (g/dL)	3.1 ± 0.7	3.0 ± 0.6	0.852
INR	1.8 ± 0.9	1.3 ± 0.6	0.000*
Serum creatinine (mg/dL)	1.4 ± 1.3	1.0 ± 0.5	0.022*
30-d mortality	17 (30)	6 (6)	<0.001*
1-y mortality	22 (39)	11 (11)	<0.001*

Data are presented as mean ± SD or n (%).
*Significant finding.
DDLT = deceased-donor liver transplantation; HE = hepatic encephalopathy; INR = international normalized ratio; LDLT = living-donor liver transplantation; MELD = Model for End-stage Liver Disease. HE grade: 1 = absent; 2 = mild; 3 = severe. Ascites grade: 1 = absent; 2 = mild–moderate; 3 = severe/refractory.

fulminant hepatic failure. The MELD score was significantly higher in the DDLT group than in the LDLT group (24 ± 12 vs. 15 ± 9, $p = 0.001$). The Child–Pugh class C was 64% in the DDLT group and 28% in the LDLT group ($p < 0.001$).

3.2. Mortality predictors in the DDLT and LDLT groups

In the analysis of the scoring system, Child–Pugh classification [odds ratio (OR), 15.200; 95% confidence interval (CI), 1.833–126.079; $p = 0.023$] but not the MELD score in the DDLT group, and MELD score (OR, 1.070; 95% CI, 1.024–1.119; $p = 0.003$) but not the Child–Pugh classification in the LDLT group were significant in the univariate analysis.

The logistic analysis of each component of Child–Pugh classification and MELD score are demonstrated in Tables 2 and 3. In the univariate analysis for 30-day mortality predictors, age, pretransplant HE, total bilirubin, INR, and cold ischemic time were the significant risk factors, and in the multivariable logistic regression analysis of these variables, only HE was an independent risk factor for a composite of mortality following DDLT (Table 2). In the LDLT group, pretransplant HE, total bilirubin, serum creatinine, and macrovesicular steatosis of donor liver were the significant risk factors in the univariate analysis, and in the multivariable logistic regression analysis, only serum creatinine was an independent risk factor for a composite of mortality (Table 3).

3.3. Intra- and postoperative courses

The intra- and postoperative courses are demonstrated in Table 4. The total anesthesia time, operative time, and anhepatic time were longer in the LDLT group than in the DDLT group. The amount of operative-site drainage, including ascites and blood, was higher in the DDLT group, and more transfusion was required in DDLT than in LDLT. The duration of intubation time and stay in ICU were longer in DDLT than in LDLT.

4. Discussion

In our study, HE after DDLT and serum creatinine level after LDLT were the only pretransplant variables that were significantly related to early death. Pretransplant MELD score was higher and more Child–Pugh class C patients were found following DDLT compared with LDLT. These differences in

Table 2
Logistic regression analysis for predictors of composite mortality in DDLT.

	Univariate regression			Multivariate regression		
	OR	95% CI	p	OR	95% CI	p
Recipient factors						
Age	0.935	0.882–0.992	0.026	0.986	0.915–1.063	0.715
Female sex	0.615	0.167–2.266	0.465			
Weight	1.018	0.970–1.068	0.468			
HE grade 3	13.533	3.209–57.078	<0.001	5.594	1.110–28.191	0.037*
Ascites grade 3	1.800	0.470–6.898	0.391			
Total bilirubin	1.070	1.019–1.124	0.007	1.005	0.924–1.093	0.913
Albumin	1.753	0.742–4.135	0.200			
INR	3.820	1.581–9.232	0.003	1.964	0.476–8.103	0.351
Serum creatinine	1.260	0.835–1.900	0.270			
Donor factors						
Female sex	0.982	0.253–3.806	0.979			
Cold ischemic time	4.986	1.184–20.997	0.028	3.265	0.589–18.091	0.176
Degree of macrovesicular steatosis	1.029	0.970–1.090	0.345			
Positive lymphocyte crossmatching	0.000	0.000–	0.998			

* Significant finding.
CI = confidence interval; DDLT = deceased-donor liver transplantation; HE = hepatic encephalopathy; INR = international normalized ratio; OR = odds ratio. HE grade: 1 = absent; 2 = mild; 3 = severe. Ascites grade: 1 = absent; 2 = mild–moderate; 3 = severe/refractory.

Table 3
Logistic regression analysis for predictors of composite mortality in LDLT.

	Univariate regression			Multivariate regression		
	OR	95% CI	*p*	OR	95% CI	*p*
Recipient factors						
Age	0.954	0.875–1.039	0.279			
Weight	0.989	0.931–1.050	0.712			
HE grade 3	6.462	1.176–35.497	0.032	4.270	0.442–41.298	0.210
Ascites grade 3	0.741	0.261–2.104	0.574			
Total bilirubin	1.058	0.990–1.131	0.098	0.998	0.906–1.100	0.974
Albumin	0.716	0.221–2.319	0.577			
INR	2.061	0.844–5.036	0.113			
Serum creatinine	4.286	1.613–11.386	0.004	4.883	1.296–18.399	0.019*
Donor factors						
Donor age	1.010	0.949–1.074	0.764			
Female sex	0.508	0.102–2.531	0.408			
Cold ischemic time	1.006	0.362–2.798	0.991			
Graft size	1.002	0.996–1.007	0.560			
Degree of macrovesicular steatosis	1.125	1.003–1.265	0.044	1.161	0.991–1.361	0.064
Positive lymphocyte crossmatching	1.208	0.135–10.788	0.865			

* Significant finding.
CI = confidence interval; HE = hepatic encephalopathy; INR = international normalized ratio; LDLT = living-donor liver transplantation; OR = odds ratio. HE grade: 1 = absent; 2 = mild; 3 = severe. Ascites grade: 1 = absent; 2 = mild–moderate; 3 = severe/refractory.

pretransplant patients' condition made a difference in the prognosis after LT including poor ICU course and higher mortality.

In Asia, the incidence of hepatitis B virus-related cirrhosis and carcinoma is high.[12] However, for various social and cultural reasons, deceased-donor organ allocation remains below 5 per 1 million population per year in Asia.[13] With the limited supply of deceased donors, the large number of patients who are on the waiting list for LT represents a problematic issue in Asia. Overall, LDLT accounts for more than 90% of all LTs in Asia compared with less than 5% in the United States.[14]

LDLT may reduce the waiting time and enable the optimal timing of transplantation compared with DDLT especially in patients with tumors, cholestatic diseases, or blood type O, and those who require retransplantation. Also, normal liver function with short ischemic time improves the success rate with respect to primary nonfunction of graft.[15] However, the surgical procedures involved in adult LDLT are more complex than those of whole-size DDLT because a partial graft has smaller and shorter hepatic arteries and bile duct. Thus, the incidence of biliary complications increases with partial grafts and the small-for-size syndrome could be problematic in LDLT.[16] Despite the differences between LDLT and DDLT mentioned above, there has been no study that evaluated the mortality predictors in both LDLT and DDLT. Hence, we analyzed both LDLT and DDLT for mortality prediction.

This study identified pretransplant HE grade 3 as a unique predictor of survival. HE is a serious complication of decompensated cirrhosis that manifests as a wide range of neuropsychological clinical findings ranging from minimal cognitive dysfunction to coma.[17] Liver allograft allocation changed in the United States with the implementation of the MELD-based system in 2002. As a result, HE is not used as a criterion to prioritize patients on the transplantation waiting list. In a previous large cohort study, the episode of HE was not an independent factor that influenced short-term survival in patients with cirrhosis.[18] However, little is known about the effect of encephalopathy on posttransplant morbidity and mortality. The risk of post-LT neurological complication is greater in patients who have pretransplant HE after DDLT.[19] Also, it has been observed that individuals with severe pretransplant HE have experienced more prolonged posttransplant altered mental status and infectious complications and

Table 4
Intraoperative data and postoperative courses.

	DDLT (n = 56)	LDLT (n = 103)	*p*
Intraoperative			
Anesthesia time (h)	11 ± 2	14 ± 2	<0.001*
Operative time (h)	9 ± 2	13 ± 2	<0.001*
Anhepatic time (h)	1.5 ± 0.4	2.0 ± 0.6	<0.001*
Infused fluid (mL/h)	1251 ± 762	1026 ± 483	0.628
RBC transfusion (mL)	2000 (1000–3750)	1250 (500–2750)	0.055
Estimated blood loss (mL)	6200 (3600–10,650)	4785 (2887–9675)	0.131
Urine output (mL/h)	130 ± 114	145 ± 120	0.021*
Postoperative ICU course			
RBC transfusion (mL)	1750 (750–3250)	750 (500–1000)	0.001*
Op-site drainage (mL)	9172 (3506–16,465)	4277 (2295–8400)	0.007*
Urine output (mL/h)	66 ± 50	106 ± 61	<0.001*
Total admission (d)	43 ± 36	47 ± 37	0.500
ICU admission (d)	11 ± 9	8 ± 7	0.020*
Intubation time (h)	119 ± 109	60 ± 86	0.001*
Reoperation for any cause, n (%)	7	6	0.223
Re-endotracheal intubation, n (%)	7	8	0.398

Data are presented as mean ± SD, median (interquatile range), or n (%).
*Significant finding.
DDLT = deceased donor liver transplantation; ICU = intensive care unit; LDLT = living donor liver transplantation; RBC transfusion = packed red blood cell transfusion.

were more likely to have prolonged hospital stays.[20] In our study, HE was a predictor of survival following only DDLT, but not LDLT. This might be attributable to the difference in the number of HE cases between the two groups. Although 24% of patients experienced HE prior to transplantation in the LDLT group, 52% of patients experienced HE in the DDLT group, and the overall incidence of severe HE was 41% in the DDLT group and 16% in the LDLT group ($p = 0.001$).

In our study, pretransplant serum creatinine was a predictor of short-term survival following LDLT, but not DDLT. Serum creatinine is one of the key components of a MELD scoring system. One study reported the impact of individual MELD components, especially creatinine, on survival benefit after DDLT. The investigators concluded that pretransplant serum creatinine was an important predictor of LT survival benefit independent of the MELD score of 15−17 or 24−40.[21] However, in certain categories of MELD score, patients with higher serum creatinine levels meant lower bilirubin levels and/or INR in comparison with their counterparts with lower serum creatinine levels. By contrast, there was a report that pretransplant renal function had no effect on patient survival after DDLT.[22] We could not find any report that evaluated the correlation between preoperative renal function and postoperative survival in LDLT. Furthermore, we could not exclude the possibility of overestimation of renal function in the LDLT group compared with the DDLT group. Creatinine is influenced by sex, age, and muscle mass, and many patients with cirrhosis have muscle wasting. In our analysis, age was significantly high ($p = 0.031$) and body weight was significantly lower in the LDLT group than in the DDLT group ($p = 0.041$). Despite the absence of the periodic difference of the mortality rate during the study period, the overall mortality rate was higher in our institute than that in previous reports (8.2%).[12] In this study, we included fulminant hepatic failure and patients with higher severity, especially in the DDLT group. So the mortality rate might be comparable with that in previous reports.

In conclusion, pretransplant HE in the DDLT group and serum creatinine level in the LDLT group might be potential markers predicting 30-day mortality.

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