ANNALS of Hepatology

ORIGINAL ARTICLE

July-August, Vol. 11 No.4, 2012: 471-477

Risk factors for in-hospital mortality of patients with high model for end-stage liver disease scores following living donor liver transplantation

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ABSTRACT

Background. Living donor liver transplantation (LDLT) for patients with high model for end-stage liver disease (MELD) scores is controversial due to its poor outcome. However, there is little information regarding which factor would negatively impact the outcome of patients with high MELD scores. The aim of this study was to identify factors associated with the in-hospital mortality of patients with high MELD scores after LDLT. **Material and methods.** All patients with an MELD scores ≥ 20 who received LDLT from 2005 to 2011 were recruited for the present study. Pre- and intra-operative variables were retrospectively and statistically analyzed. **Results.** A total of 61 patients were included in the current study. The overall 3-month survival rate was 82% for patients with high MELD scores. Preoperative renal dysfunction, hyponatremia, starting albumin level < 2.8 g/dL, preoperative renal replacement for severe renal failure, anhepatic period > 100 minutes and intraoperative red blood cell (RBC) transfusion ≥ 10 units were identified as potential risk factors by univariate analysis. However, only hyponatremia, preoperative dialysis and massive RBC transfusion were independent risk factors in a multivariate analysis. The 3-month survival rates of patients with two or more independent risk factors and patients with none or one risk factor were 91 and 25%, respectively. A significant difference was observed (P < 0.001). **Conclusion.** Hyponatremia, preoperative dialysis and massive RBC transfusion were related to poor outcome for sicker patients. Patients with two or more of the above-mentioned risk factors and high MELD scores may exhibit extremely poor short-term survival.

Key words. Living donor liver transplantation. Model for end-stage liver disease. Risk factor.

INTRODUCTION

The model for end-stage liver disease (MELD) score, which is based on three biochemical variables (total bilirubin (TB), creatinine, and internationalized normalized ratio (INR)), was first described to predict patient survival rates and complications after the transjugular intrahepatic portosystemic shunt (TIPS) procedure.[1] Because the MELD scores only include three objective variables, it was adopted by the United Network for Organ Sharing as the standard priority rule for determining who should receive liver transplantation in 2002.[2] Patients with high preoperative MELD scores were in extremely poor condition. Previous investigations confirmed that high MELD scores may be associated with a higher postoperative mortality, a higher postoperative complication rate, a prolonged intensive care unit (ICU) stay, the transfusion of more intraoperative blood products, a longer hospital stay, and an increase in transplant costs and so forth.[3] Accordingly, some investigators suggested that sicker patients may not be suitable candidates for partial liver transplantation due to the need for greater liver mass and their low tolerance to postoperative complications.[4] Moreover, the New York State Committee on Quality Improvement in living donor donation recommended that living donor liver transplantation should not be performed in patients with MELD scores > 25.[5] However, high MELD scores in LDLT are controversial. Recently, some investigators suggested that high preoperative MELD scores may not be an absolute contraindication to LDLT.[5]

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Manuscript received: February 02, 2012.
Manuscript accepted: March 21, 2012.

LDLT is under ethical debate due to the potential surgical risks imposed on donors.

Both donor and recipient outcomes are considered in evaluating LDLT. Determining who will benefit from LDLT is a realistic problem that is of concern not only to transplant surgeons but also to donors and recipient families, especially in the case of patients with high preoperative MELD scores. However, there is little information about which factor would negatively impact the outcomes of patients with high MELD scores following LDLT. To examine this issue further, we performed this study to determine which pre- and intra-operative variables were related to in-hospital death for patients with high MELD scores after LDLT.

MATERIAL AND METHODS

All adult patients with MELD scores ≥ 20 who received LDLT from 2005 to 2011 at our centre were considered in the present study (N = 61). Transplantations were approved by the ethics committee of West China Hospital, Sichuan University. We evaluated the recipients, grafts, donors and intraoperative variables including gender, age, body mass index (BMI), graft-to-recipient weight ratio (GRWR), MELD score, preoperative renal dysfunction, hyponatremia, hypokalemia, TB, albumin level, INR, intraoperative red blood cell (RBC) transfusion and intraoperative fluid infusion.

Patient 3-month survival rates will be also calculated and compared according to the number of identified risk factors. High pretransplant MELD scores were defined as MELD scores ≥ 20.[6] Postoperative complications were classified using Clavien-Dindo classification system.[7-9]

Potential risk factor selection

Potential risk factor selection, including pre- and intra-operative variables, was reviewed on the basis of previous investigations. Variables that may negatively impact the outcomes of liver transplantation were considered to be potential risk factors. Preand intra-operative factors included a GRWR < 0.8%, age, female-to-male gender match, BMI, starting TB, creatinine level, INR, albumin level, platelet level, hyponatremia, hypokalemia, hypocalcemia, need for a massive RBC transfusion, need for a massive intraoperative fluid infusion, pretransplant renal dysfunction and preoperative dialysis for severe renal failure.[10] The MELD score was calculated according to the formula:[3]

MELD score = 9.57 x Ln creatinine (mg/dL) + 11.2 x (Ln INR) + 3.78 x Ln bilirubin(mg/dL) + 6.43.

Preoperative renal dysfunction was defined as a serum creatinine level > 1.5 mg/dL.[10] Hyponatremia was defined as a serum sodium concentration of < 130 mEq/L.[11] A potassium level < 3.5 mEq/L was considered as hypokalemia.[12] The decision to proceed with intraoperative blood product transfusion was based on the laboratory tests. Usually, RBCs were used to maintain the haemoglobin level above 7.0 g/dL. Platelet concentrates were used when platelet count decreased to 50 x 10^9/L. Massive intraoperative fluid infusion was defined as a fluid infusion volume ≥ 10 L. An intraoperative RBC transfusion > 10 units was considered as a massive blood transfusion. A massive fresh-frozen plasma transfusion was defined as transfusion of 10 units. In-hospital mortality was defined as any death within the same hospital admission for LDLT, regardless of the number of days after transplantation.[13]

Immunosuppression protocol

The standard immunosuppression protocol in our center included tacrolimus, mycophenolate mofetil, and steroid. Tacrolimus is usually initiated within posttransplant 24 h. For patients with severe renal dysfunction, tacrolimus was replaced with sirolimus. Tacrolimus was administrated to such patients when renal function has stabilized. Steroid therapy was tapered off rapidly whenever possible. Steroid pulse therapy was conducted in patients with rejection.

Statistical analysis

All statistical analyses were performed using SPSS 16.0 for Windows. Categorical variables were assessed using the Chi-square test or Fisher's exact test. All continuous variables are expressed as the mean ± SD and were compared using one-way analysis of variance. Independent risk factors were identified by Cox regression. Factors significant at $P < 0.10$ in the univariate analyses were involved in the multivariate analyses. Post-transplant survival was estimated using the Kaplan-Meier method with the log-rank test. The diagnostic accuracy of the identified risk factors was evaluated using the receiver operating curve (ROC). We considered a P value < 0.05 to be significant.[14]

RESULTS

Demographic data

A total of 61 patients were included in the current study. The MELD scores of recipients ranged from 20 to > 40, with a mean of 29.39 ± 8.43. The mean age of recipients was 40.56 ± 7.90 years, whereas the mean age of donors was 36.85 ± 9.91 years. Sixteen patients received a massive RBC transfusion. Seventeen patients underwent massive intraoperative fluid infusion. Sixteen patients suffered from pretransplant renal dysfunction. Six patients received preoperative dialysis for severe renal dysfunction. Seven recipients receive a graft that was < 0.8% in area (GRWR ranged from 0.74 to 0.77%). The indications for transplantation included hepatitis B (n = 53), hepatocellular carcinoma (n = 3), alcoholic liver disease (n = 3), trauma (n = 1), and hepatitis C (n = 1). Eleven patients (18.03%) died during hospitalization. The causes included renal failure (n = 4), infection (n = 4), multiple organ dysfunction syndrome (n = 2), and cerebral haemorrhage (n = 1).

Donor outcomes

All postoperative complications, classified according to Clavien-Dindo classification, were listed in the table 1. A total of 14 (22.95%) donors suffered from various postoperative complications. No death, organ failure and cardiac events occurred. One donor received ultrasound-guided abdominocentesis for bile leak. Two donors suffered from thoracocentesis for severe plural effusion. One donor had pneumonia. Wound infections were observed in three donors. One donor had stress ulcer. Three donors suffered from mild plural effusion. Three donors had transient bile leak.

Table 1. Complications of the donors.

Complications	N
• Grade I	
Pleural effusion	3
Bile leak	3
• Grade II	
Pneumonia	1
Wound infection	3
Stress ulcer	1
• Grade IIIa	
Thoracentesis	2
Abdominocentesis	1
• Grade IIIb	0
• Grade IV	0
• Grade V	0
Total	14

Risk factors for in-hospital mortality

As shown in table 2, according to the univariate analysis, preoperative renal dysfunction, severe hypoalbuminemia, massive intraoperative RBC transfusion, preoperative dialysis for severe renal failure, anhepatic phase over 100 minutes and hyponatremia were determined as potential risk factors. However, only massive intraoperative RBC transfusion, hyponatremia and preoperative renal dialysis showed prognostic power in multivariate analysis (Table 3).

When the number of risk factors was analyzed and confirmed by multivariate analysis with an ROC, the best cut-off value for the number of risk factors was determined to be 2. The corresponding area under the ROC was 0.811 (Figure 1).

Postoperative survival

The overall 3-month survival for all recipients was 82% (Figure 2). However, patients with two or more of the above-mentioned risk factors had a significantly lower 3-month survival rate than those with one or zero risk factors (25 *vs.* 91%, P < 0.001) (Figure 3).

DISCUSSION

LDLT for sicker patients is controversial due to the associated ethical issues. Some investigators have even suggested that whole liver transplantation was the best option for some sicker patients.[15] However, in our current study, the in-hospital mortality of patients with high MELD scores following LDLT was 18.02%; this result is similar to previous reports.[13] This finding indicated that patients with high MELD scores may be appropriate candidates for LDLT. Moreover, our study also confirmed that massive intraoperative blood transfusion, preoperative dialysis for severe renal failure and preoperative hyponatremia were independent risk factors for in-hospital mortality following LDLT. Patients with two or more of the above-mentioned risk factors may have an extremely poor 3-month survival.

It is logical that massive allogeneic RBC transfusion was associated with poor outcome. Benson, *et al.*[16] confirmed that RBC transfusion contributed to the development of postoperative infection, which may increase in-hospital mortality.

Ramos, *et al.*[17] suggested that massive RBC transfusion was associated with a longer hospital stay and diminished survival. Hendriks, *et al.*[18] reported that an intraoperative requirement for blood products was associated with postoperative

Table 2. Univariate analysis of factors associated with patient survival.

Variables	Survived	Died	P
• Donor variables			
Age	37.06 ± 9.91	35.91 ± 10.36	0.731
Gender (female)	26	7	0.526
BMI	22.98 ± 3.01	23.08 ± 2.53	0.917
• Recipient variables			
Age	40.32 ± 7.93	41.64 ± 8.09	0.621
Gender (female)	5	1	0.706
BMI	22.51 ± 3.21	22.05 ± 4.14	0.67
MELD score	29.29 ± 8.06	30.09 ± 10.66	0.779
Starting TB level > 20 mg/dL	22	5	0.594
Starting INR > 3.5	8	2	0.58
Starting albumin level < 2.8 g/dL	11	6	0.039
Starting fibrinogen level < 1.5 g/L	32	7	0.619
Preoperative renal dysfunction	10	6	0.028
Preoperative dialysis	3	3	0.066
Hepatic encephalopathy	4	1	0.644
Hyponatremia	8	6	0.013
Hypokalemia	12	4	0.457
Hypocalcemia	18	6	0.315
MELD score > 30	21	6	0.514
• Donor-recipient match			
ABO disparity	12	2	0.512
Female-male gender match	24	7	0.508
• Graft variable			
GRWR < 0.8%	6	1	0.63
• Intraoperative variables			
RBCs transfusion ≥ 10 units	9	6	0.019
FFP transfusion ≥ 10 units	20	4	0.553
Platelet transfusion	25	6	0.524
Massive fluid infusion	13	3	0.599
Anhepatic period > 100 min	13	6	0.081
Surgical duration > 12 h	12	2	0.512
• Indications for liver transplantation	/	/	0.809

BMI: body mass index. MELD: model for end-stage liver disease. TB: total bilirubin. INR: international normalized ratio. GRWR: graft-to-recipient weight ratio. RBC: red blood cell. FFP: fresh frozen plasma.

Table 3. Independent risk factors in Cox regression.

Variables	B	SE	Wald	P	Exp(B)	95% CI	
			Lower	Upper			
RBCs transfusion	1.532	0.621	6.086	0.014	4.626	1.370	15.619
Dialysis	1.422	0.724	3.859	0.049	4.144	1.003	17.116
Hyponatremia	1.969	0.662	8.857	0.003	7.164	1.959	21.201

RBC: red blood cell. CI: confidence interval.

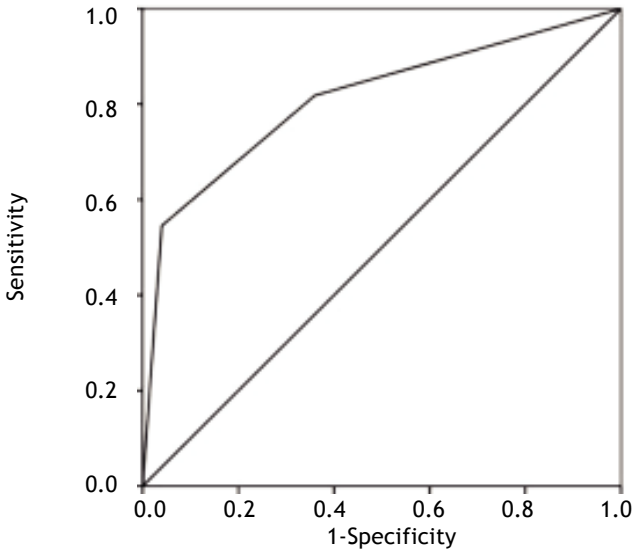

Figure 1. ROC curve for the risk factors that were identified by Cox regression.

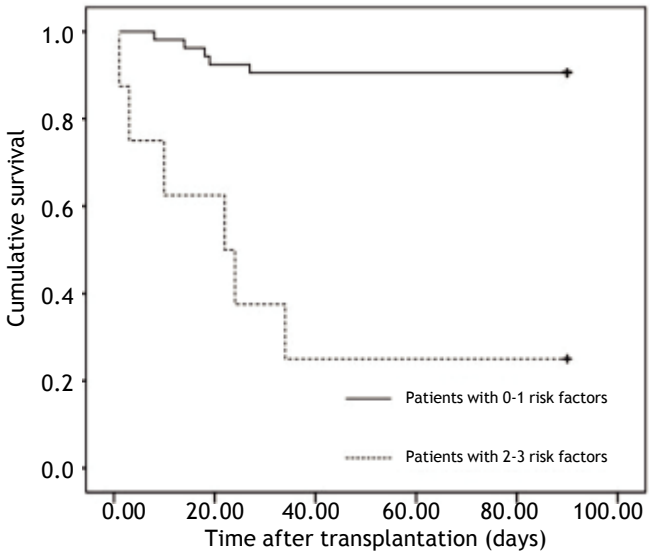

Figure 3. Cumulative survival curves for patients with none or one risk factor and two or more risk factor (P < 0.001).

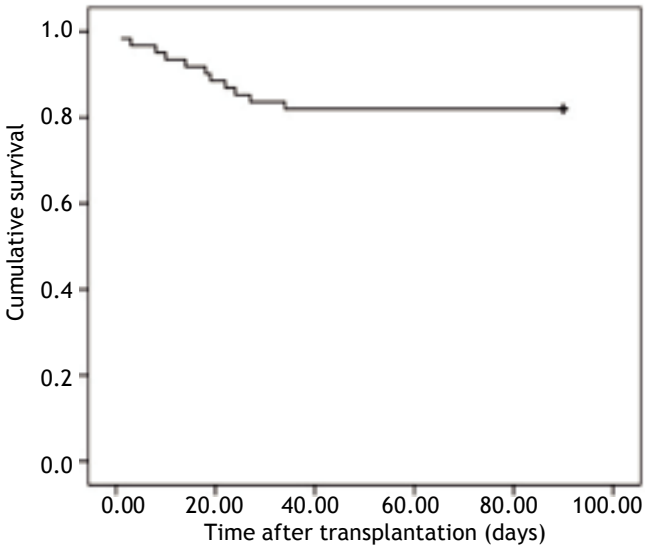

Figure 2. The 3-month survival curve for all patients.

reintervention after liver transplantation. Moreover, a number of studies confirmed that massive RBC transfusion may negatively impact long-term survival after liver transplantation. This finding suggests that effective intraoperative management may improve the outcome of patients with high MELD scores following LDLT. In contrast to massive RBC transfusion, FFP and platelet transfusion were not risk factors for in-hospital mortality in the current study. However, previous studies suggested both FFP and platelet transfusion may be related to acute lung injury and will increase postoperative mortality in liver transplantation.[16] Recently, a study performed by Kim *et al.*[19] suggested that platelet transfusion can be related to liver regeneration following LDLT. Tomimaru, *et al.*[20] confirmed that FFP transfusion will not negatively impact the outcomes of patients who undergo hepatic resection.

Preoperative renal dialysis was another independent risk factor in our study. Renal dysfunction was common and ranged from 10 to 20% among patients who underwent liver transplantation.[21] Moreover, renal function can be impaired after liver transplantation for various causes, such as prolonged surgical duration and immunosuppressive regimens.[22] However, previous studies suggested that preoperative renal replacement was associated with a high incidence of infection, intensive care unit stay and longer hospital stay.[23] Dellon, *et al.*,[24] even suggested that combined kidney and liver transplantation may be the best management for patients who are 65 years or older and who require renal replacement therapy during the preoperative period. Moreover, a number of investigations reported that preoperative renal dysfunction may also negatively influence long-term survival.[23] Although the timing of liver transplantation for patients with end-stage liver disease is still under debate, our finding suggested that liver transplantation should occur before patients develop severe renal dysfunction.

Hyponatremia is common in patients with decompensated liver function. Previous studies have

shown that hyponatremia was associated with hepatorenal syndrome, neurological complications, ascites and death from liver disease. In recent years, the debate as to whether the preoperative serum sodium concentration should be incorporated in the organ allocation policy continues. Kim, *et al.*[25] suggested that approximately 7% of waiting-list deaths could be prevented if the preoperative sodium concentration had been considered in the process of organ allocation. Carey, *et al.*[26] confirmed that hyponatremia will also increase mortality in paediatric patients awaiting liver transplantation. Our finding supports the influence of preoperative hyponatremia on the outcome of LDLT. Moreover, Balderramo, *et al.*[27] confirmed that not only preoperative factors but also postoperative hyponatremia were related to early calcineurin inhibitor-induced neurotoxicity. This condition was associated with a high incidence of infection, acute graft rejection and a longer hospital stay.

It was interesting that a GRWR < 0.8% was not a risk factor in our study. However, a number of studies suggested patients with a small-for-size graft may achieve poor outcomes, especially for patients with high MELD scores. Emiroglu, *et al.*,[28] even suggested that the GRWR should be at least 1.0% for patients with high MELD scores.

In our practice, splenic artery ligation or splenectomy was performed to prevent small-for-size syndrome. Moreover, efficient hepatic vein outflow was also emphasized in such situations. In addition, the GRWRs of small-for-size grafts ranged from 0.74-0.77% (slightly low than 0.8%). Although Yi, *et al.*[29] suggested that the outcomes of patients with high MELD scores and small-for-size grafts have been improved, due to the small sample size in the current study, we were not able to conclude that a GRWR < 0.8% was safe enough for patients with high MELD scores.

This issue requires further study.

Using preoperative MELD scores to predict postoperative survival is controversial. Some investigators have suggested that high MELD scores were associated with poor outcomes, whereas others deemed that MELD scores had no prognostic power. In the current study, we confirmed that MELD scores cannot predict postoperative survival among sicker patients. In contrast to the MELD score, patients with two or more of the above-mentioned risk factors may have an extremely poor 3-month survival rate.

This finding indicated that correcting the preoperative sodium concentration, an expedient operation and the appropriate intraoperative management could improve the outcomes of patients with high MELD scores following liver transplantation.

In conclusion, several factors related to in-hospital mortality after LDLT were identified by the current study. Preoperative hyponatremia, massive intraoperative RBC transfusion and preoperative hemodialysis were independent risk factors for in-hospital mortality following LDLT. Our finding reinforces the role of pre- and intraoperative management and transplant time selection.

FUNDING

This work was supported by a grant from the National Science and Technology Major Project of China (2012ZX10002-016 and 2012ZX10002017-006).

Ethical approval: Not needed.

Contributors: Li C and Wen TF proposed this study. Li C collected the data. All listed authors contributed to the transplantations. Wen TF revised the final version of this manuscript.

COMPETING INTEREST

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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