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ORIGINAL ARTICLE

An outcome comparison between primary liver transplantation and retransplantation based on the pretransplant MELD score

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Summary

Survival after liver retransplantation (RLTX) is worse than after primary liver transplantation (LTX). We studied retrospectively the 2-year outcome in 44 patients who received RLTX more than 30 days after the primary transplant and in 669 after LTX performed between December 1993 and October 1999, focusing on the relation between the model for end-stage liver disease (MELD) score immediately pretransplant and post-transplant survival. A 2-year survival for RLTX was inferior to LTX (65.9% vs. 82.9%, $P \leq 0.01$). This difference was greatest with MELD scores < 25; survival within 2 years remained 11.3–18.2% less for RLTX than for LTX (6 months, $P = 0.002$; 12 months, $P = 0.029$, 24 months, $P = 0.123$). Mortality was mainly related to early vascular complications and sepsis. Two-year survival after RLTX was 81.8% if RLTX occurred < 2 years after LTX and 50% if the interval between LTX and RLTX was > 2 years ($P < 0.05$). MELD scores were similar in 2-year survivors and nonsurvivors after late RLTX ($P = 0.82$). Late RLTX is marked by poor survival regardless of the pretransplant MELD score. The MELD-based allocation system may not benefit patients who undergo retransplantation.

Introduction

The model for end-stage liver disease (MELD) score is currently the basis for organ allocation used by the United Network for Organ Sharing (UNOS) in patients with chronic disease awaiting liver transplantation. It provides an accurate estimate of survival without transplantation, and therefore, is a reasonable system for allocating organs to the sickest patients, given the accurate estimate of the mortality using the score in these patients awaiting liver transplantation [1–8]. Some studies have also suggested that the MELD score predicts post-transplant mortality, though this is controversial [3,9–15]. Our previous study showed that post-transplant mortality is higher in patients transplanted with high MELD scores, especially in patients with hepatitis C or other noncholestatic liver disease [16–17]. As with primary transplantation, the MELD score is an accurate predictor for mortality of patients waiting for RLTX but performs less consistent with regard to post-transplant outcome [18–19].

Currently, patients who require retransplantation for chronic or recurrent liver disease fall under the same allocation system as primary transplant candidates. However, patients who undergo retransplantation of the liver (other than for primary allograft nonfunction) have lower patient and graft survival [19–33]. This is particularly true in recipients with recurrent hepatitis C [18,34–37] and cholestatic disease [29]. Our aim was to check if the disease severity prior to transplantation, as measured by the MELD score, has impact on early survival after the retransplantation in our transplant center.

Material and methods

Six hundred and eighty-three adult patients underwent primary liver transplantation for chronic liver disease at Baylor University Medical Center in Dallas, Texas, USA, between December 1993 and October 1999. Ten patients who died in the first 2 years after a primary liver transplant because of primary or recurrent solid malignant tumors were not included. We also excluded a patient who died in a motor vehicle accident. Three patients with post-transplant lymphoproliferative disease (PTLD) were not excluded. Another three patients in the primary transplant group did not have data available for the calculation of the pretransplant MELD score and were also excluded. The final study group included 669 patients who underwent primary transplantation (LTX). Fifty-five patients underwent retransplantation during the same period. Of these, 11 underwent emergency retransplant for primary graft nonfunction and are not included in this analysis. Another 44 patients underwent retransplantation for chronic allograft failure from 1 month to more than 12 years (152 months) after the first transplant (mean, 42 months; median, 24 months) and comprised the retransplant group (RLTX). Data on all patients were collected prospectively in the Baylor Liver Transplant Database and were studied retrospectively. Medical records were reviewed as necessary to complete data for the analysis. Follow-up data were collected for a minimum of 2 years or until death or retransplant occurred. The study was approved by the Institutional Review Board of Baylor University Medical Center and Baylor Health Care System in Dallas, Texas, USA.

As the patients included in this study were transplanted prior to implementation of the MELD allocation system, laboratory data obtained upon hospital admission for liver transplantation (within 12 h of transplant surgery) were used to calculate the MELD score, retrospectively. The MELD score was calculated as follows:

$$\begin{aligned}\text{MELD score} = [&0.957 \times \text{LN(creatinine)} \\ &+ 0.378 \times \text{LN(bilirubin)} \\ &+ 1.12 \times \text{LN(INR)} + 0.643] \times 10.\end{aligned}$$

Both serum bilirubin and creatinine were expressed in the formula as mg/dl.

MELD score values were capped at the lower and upper limit at 6 and 40, respectively, and the serum creatinine was capped at 4 mg/dl as an upper limit or for patients on dialysis. MELD scores were based on the laboratory testing only and no adjustments were made for hepatocellular carcinoma or other diseases.

Both LTX and RLTX groups were stratified according to the pretransplant MELD score: <15; 15–24; 25 and above. These MELD ranges were selected to roughly correlate within our Organ Procurement Organization with the former UNOS status 3, status 2B, and sick 2B or status 2A patients, respectively.

All patients completed 2 years of follow-up unless graft loss or patient death occurred. The observed patient and graft survival was analyzed at 1 month, 3, 6, 12, 18, and 24 months. Statistical analysis utilized the chi-squared test or the Fisher's exact test for nonparametric data.

Results

The primary liver transplant group (LTX) consisted of a total of 669 patients, 374 male and 295 female, with a mean age of 50.5 years (range: 15–72). The 44 patients in the retransplant group (RLTX) consisted of 26 males and 18 females with a mean age of 43.8 years (range: 19–64; Table 1). In contrast, the distribution of MELD scores in the two groups was quite different. The pretransplant MELD score was <15 in 340 LTX patients (50.8%), but only 11 of the RLTX group (25%) ($P < 0.01$). Patients undergoing retransplantation were more likely to have MELD scores equal to or exceeding 25 (40.9% vs. 15.4%, $P < 0.0001$). The differences in calculated MELD score were related to higher bilirubin levels in the RLTX group (16.7 ± 15.1 vs. 6.7 ± 9.4, $P < 0{\cdot}001$). Mean creatinine and International Normalized Ratio (INR) levels were not significantly different between the RLTX and LTX groups (creatinine, 1.9 ± 1.1 mg/dl vs. 1.4 ± 1.3 mg/dl; INR 1.3 ± 0.5 vs. 1.5 ± 0.6).

The etiology of liver disease in the LTX group was hepatitis C in 268 patients (40.1%), alcohol in 93 patients (13.9%), cryptogenic in 91 cases (13.6%), autoimmune hepatitis in 31 patients (4.6%) and hepatitis B in 23 patients (3.4%). Other causes included alpha-1-antitrypsin deficiency (17 cases), hemochromatosis (six cases), secondary biliary cirrhosis (six cases), Budd–Chiari syndrome (five cases), nonalcoholic steatohepatitis (four

Table 1. Characteristics of patients in the primary transplant (LTX) and retransplant (RLTX) groups.

	LTX	RLTX	
Number of patients	669	44	
Male gender	55.9%	59.1%	NS
Mean age (range)	50.5 ± 10.6 (15–72)	43.8 ± 10.0 (19–64)	NS
MELD < 15	340 (50.8%)	11 (25%)	$P < 0.001$
MELD 15 – 24	226 (33.8%)	15 (34.1%)	
MELD ≥ 25	103 (15.4%)	18 (40.9%)	
Mean creatinine	1.4 ± 1.3	1.9 ± 1.1	NS
Mean INR	1.5 ± 0.6	1.3 ± 0.5	NS
Mean bilirubin	6.7 ± 9.4	16.7 ± 15.1	$P < 0.001$

cases), sarcoidosis (four cases), Wilson's disease (two cases), polycystic liver disease (two cases), and one each with cystic fibrosis and giant cell hepatitis. Another 115 patients (17.2%) had cholestatic liver disease including 51 with primary sclerosing cholangitis and 64 with primary biliary cirrhosis. In the RLTX group, 14 patients (31.8%) had chronic rejection, nine (20.5%) had biliary duct strictures, nine (20.5%) had hepatic artery thrombosis, seven (15.9%) had recurrent hepatitis C, three had recurrent primary sclerosing cholangitis, and two had *de novo* hepatitis C.

In the patients who underwent RLTX <2years from LTX ($n = 22$), eight had chronic rejection, seven had hepatic artery thrombosis, four had biliary strictures, and three had recurrent hepatitis C infection. In the group retransplanted more than 2 years from LTX ($n = 22$), six had chronic rejection, five had biliary strictures, four had recurrent hepatitis C, three had recurrent primary sclerosing cholangitis, two had *de novo* hepatitis C and two had hepatic artery thrombosis.

Patient survival over the first 2 years post-transplant is shown in Fig. 1. Survival was significantly worse for RLTX at all time points over the 2 years of observation (6 months: $P \leq 0.025$; 1 year: $P \leq 0.025$; 2 years: $P \leq 0.01$). However, the difference in the slopes of the survival curves was similar after 3 months indicating that early mortality accounted for these differences. In the LTX group, post-transplant patient survival decreased progressively as MELD score increased with 2-year survivals of 85.9%, 82.3% and 74.8% for low, medium, and high MELD groups (Fig. 2a). Early post-transplant survival in the RLTX group actually appeared to be lower in the low MELD group, but these differences were not different after 6 months (3 months, $P = 0.789$; 6 months, $P = 0.449$; 12 months, $P = 0.651$; 24 months, $P = 0.332$) (Fig. 2b).

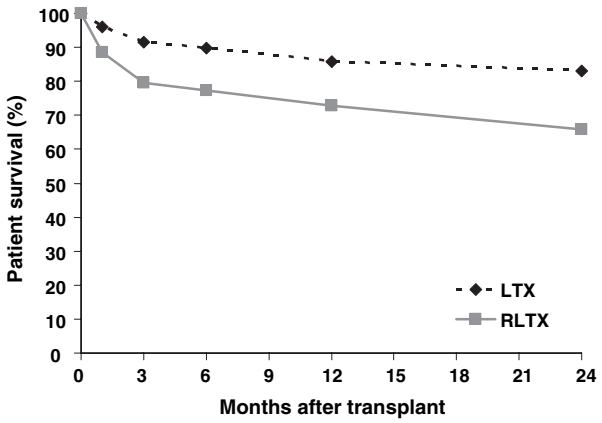

Figure 1 Actual patient survival of primary liver transplant recipients and retransplant recipients. Survival is significantly better in recipients of first liver transplants ($P < 0.05$ at 6 and 12 months, $P < 0.01$ at 24 months).

Causes of death are listed in Table 2. One hundred and twelve LTX patients (16.7%) died during the first 2 years after transplantation. Sepsis was the predominant cause of death followed by cardiovascular complications. Technical complications related to surgery were encountered in10 patients (seven vascular complications, including hepatic

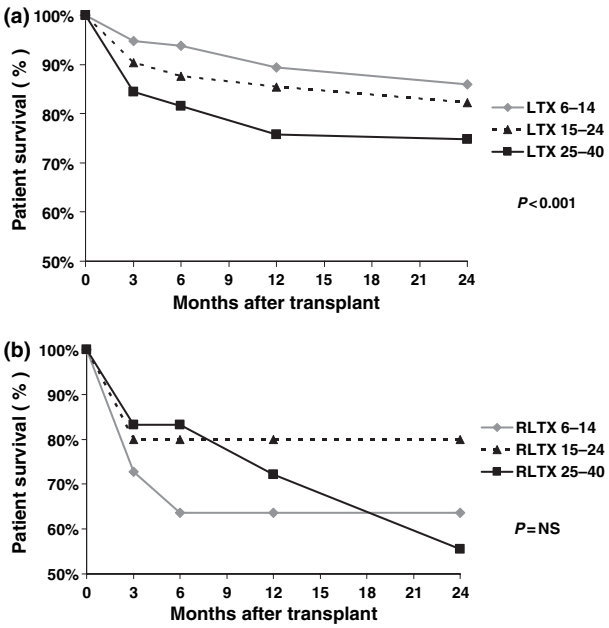

Figure 2 Post-transplant survival after primary liver transplant (LTX) (a) and RLTX (b). Actual survival of patients after LTX and RLTX by MELD score groups.

Table 2. Causes of death with primary liver transplantation and retransplantation (percent of total transplants in parentheses; none of these differences are significant).

	LTX $n = 669$	RLTX $n = 44$
Total deaths	112 (16.7)	15 (34.1)*
Sepsis	44 (6.6)	6 (13.6)
Cardiovascular	18 (2.7)	3 (6.8)
Neurologic	12 (1.8)	2 (4.5)
Surgical complications	10 (1.5)	3 (6.8)
Recurrent hepatitis	10 (1.5)	1 (2.3)
Gastrointestinal	5 (<1)	
PTLD	4 (<1)	
Chronic rejection	3 (<1)	
Graft versus host disease	3 (<1)	
Primary nonfunction	1 (<1)	
Acute renal failure	1 (<1)	
Medication overdose	1 (<1)	

LTX = primary liver transplant; RLTX = liver retransplant.
PTLD = post-transplant lymphoproliferative disease.
*$P = 0.007$ vs. LTX.

artery thrombosis (HAT), two biliary leaks with sepsis, one intraoperative bleeding).

In the RLTX group, 15 RLTX patients died in the first 2 years post-transplant (34.1%; $P = 0.007$ vs. LTX). Ten of 15 deaths in the RLTX group occurred within the first 2 months. Causes of death were sepsis in six patients (days 20, 21, 22, 34, 244, and 493), HAT in three patients with graft loss (days 2, 5, and 61), three cardiac (days 26, 31, and 61), neurological (3 months), meningitis (16 months), recurrent hepatitis C (9 months). All fatal complications were more common in the RLTX group than the LTX group though these differences did not reach significance (Table 2). However, among the surgical complications, hepatic artery thrombosis with graft loss was the cause of death in three patients in the RLTX group (6.8%) and seven out of the 669 LTX patients (1%) ($P = 0.019$).

MELD scores did not correlate with post-transplant survival in RLTX patients. In fact, those with MELD scores <15 had the highest mortality though survival was not significantly different among the three MELD groups (Fig. 2b). This appears to be related to early complications, part of them technical in nature. All three cases of hepatic artery thrombosis in the RLTX group occurred in the low MELD group. These patients underwent the second transplant 34, 109, and 152 months after the primary transplant (their reason for retransplant: recurrent primary sclerosing cholangitis, late hepatic artery thrombosis, and recurrent hepatitis). The risk for HAT was 27% in the RLTX low MELD group, compared with two out of 340 patients (0.6%) in the LTX low MELD group ($P = 0.0002$). However, among the sickest of the RLTX group with calculated MELD scores for 20 or more, mortality did increase as the MELD score rose. One-year mortality was 15.8% with MELD scores between 20 and 29 (3 of 19), 25% of the four patients with scores of 30–34, and 100% in the four patients with MELD scores of 35 or more. RLTX patients with MELD scores of 35 and above died at 22, 31, and 61 days, and 9 months post-transplant. By comparison, 2-year mortality in LTX patients with MELD scores above 20 was lower (11.0% for the 101 patients with MELD scores of 20–29, 25% of the 24 patients with scores of 30–34, 22.5% of the 40 patients with a MELD of 35 or more).

The time interval between the primary liver transplant and retransplantation was different in patients who died in the first 2 years after RLTX than in those who survived beyond 2 years post-RLTX. The mean time interval between transplants was 59.2 ± 41.9 months, with a median of 52 months in deceased patients, when compared with 33.1 ± 40 months with a median of 15 months in the patients alive 2 years after RLTX ($P = 0.053$).

Eighteen out of 22 patients retransplanted <2 years after the first transplant were alive 2 years after RLTX (81.8%), when opposed with 11 out of 22 (50%) of patients who underwent RLTX more than 2 years after the first transplant ($P < 0.05$). The 18 patients who underwent RLTX <2 years after the original transplant and survived had a mean MELD score of 20.1 ± 8.31 (median 19.5); the four patients who died had MELD scores of 24, 29, 33, and 37 (mean 30.8 ± 5.56, median 31) ($P = 0.025$). In contrast, the 11 patients who underwent RLTX more than 2 years after the primary transplant had a mean MELD score of 22 ± 11.2 (median 20), while in the 11 patients who died the mean MELD was similar, at 21.1 ± 6.83 (median 21) ($P = 0.82$).

Discussion

Our study shows that patients undergoing retransplantation of the liver are sicker and have higher MELD scores than patients undergoing primary transplantation. This is related to higher bilirubin and, to a lesser degree, creatinine levels [28]. Overall, patients who are retransplanted have lower overall survival than primary liver transplantation. This is related to not only high early mortality that is mostly related to infectious but also to technical problems that are not predicted by the preoperative MELD score. Retransplantation involves surgery in a previously operated abdomen of an ill and immunosuppressed patient with allograft failure.

This series does not include patients who underwent early retransplantation for primary allograft nonfunction or hepatic artery thrombosis. These patients are listed as Status 1 and are not subject to the MELD score. Notably, they have a better outcome than the patients retransplanted later (data not shown) [38]. In our series, patients who underwent retransplantation <2 years after the primary transplant had a 2-year postretransplant survival of more than 80%, and all patients who died in this group had significantly higher pretransplant MELD scores than the survivors. This group of patients had a similar outcome to patients who underwent primary transplantation, where the severity of liver disease pretransplant, as reflected by the MELD score, correlated with post-transplant survival [16–17]. Patients who underwent retransplantation beyond 2 years after their original transplant had a very poor outcome, only half of them survived more than 2 years after retransplant. In fact, among these patients, early survival was inversely related to the MELD score, and the mean pretransplant MELD score was almost the same in those who reached 2 years postretransplant and those who did not. A progressive increase in the MELD score reflected survival differences only in those retransplanted patients with a MELD score more than 20. In these patients, 1-year survival is approximately equivalent to primary liver transplant recipients.

The worse results with late retransplantation (after 2 years) may be because of a higher proportion of patients with biliary strictures, including recurrent primary sclerosing cholangitis, in this specific subgroup of patients.

These results reflect a time period when donor liver allocation was not based on the MELD score. Patients with MELD scores <15 would not have been transplanted today in the USA. We speculate that, under the MELD score-based allocation policy, many of these patients with MELD < 15 would have been transplanted later with much more advanced allograft failure. Implementation of the MELD score for allocation of deceased donor livers for transplantation led to reduction of the mortality on the liver transplant waiting list without deterioration in survival after primary liver transplant recipients [39–40]. However, candidates for retransplant with chronic allograft failure must compete for donors in the same MELD allocation system. Our data suggest that this system disadvantages retransplant candidates, particularly those who have lower MELD scores [41]. A longer waiting time seems to adversely impact survival after retransplantation. While retransplant candidates as a whole tend to have higher MELD scores as a result of higher bilirubin and creatinine levels [22,24,25,32,42], they have greater mortality than primary recipients for any given MELD score.

If the final goal of the allocation scheme is to improve outcomes for all patients [43], then a system that identifies those most likely to survive retransplantation and provides them with a MELD score to facilitate early transplantation is necessary. Such a system probably needs to limit the opportunity for retransplant in patients unlikely to achieve long-term survival, for example those with very high MELD scores [44–45]. Indeed, our series replicates what has been reported elsewhere; of our four patients with a MELD of 35 or more, none was alive at 1 year and only one survived the first 2 months after retransplantation.

At the present time, retransplantation should be considered to be high risk in all candidates. Every effort should be made to optimize hepatic and renal function in an effort to avoid retransplantation whenever possible. Given the technical challenges and high risk of retransplantation, candidates should undergo careful evaluation and selection to optimize their outcome. As retransplantation is associated with lower survival, the issue of organ allocation to these patients should be carefully considered on a local and national level. If retransplantation is a priority, then future efforts should be aimed at identifying those cases that would reap long-term survival benefit from the procedure.

Conclusions

Candidates for retransplantation of the liver are sicker than primary transplant candidates and especially if retransplantation occurs more than 2 years after the first transplant. MELD scores do not accurately predict survival after late retransplantation. Indeed, even retransplantation recipients with low MELD scores have complications similar to primary recipients with higher MELD scores. Because of technical difficulty and reduced survival, retransplantation should be carefully considered and would be best considered before patients become debilitated by prolonged and advanced allograft failure. Unfortunately, this is not possible with the current allocation of organs for retransplantation through the MELD system. Consideration should be given to defining which patients optimally benefit from retransplant and providing them with an appropriate exception within the MELD allocation system. However, given the current state of organ availability, this may not be a judicious use of organs, and it would be an ethical and political challenge to implement.

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