



O-1

Maintenance of Allograft Function May Reduce the Risk of Cerebrovascular Disease Events after Kidney Transplantation

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Aims: The risk of cardiovascular disease, broadly categorized as the leading cause of morbidity and mortality among patients with renal failure, appears to improve with kidney transplantation. However, there are limited data on the epidemiology of cerebrovascular disease events (CVE) in end-stage renal disease or the potential for modification of CVE risk with transplantation. We examined the incidence and mortality implications of CVE after kidney transplant within national data, and compared variations in risk on the transplant waitlist and after allograft failure.

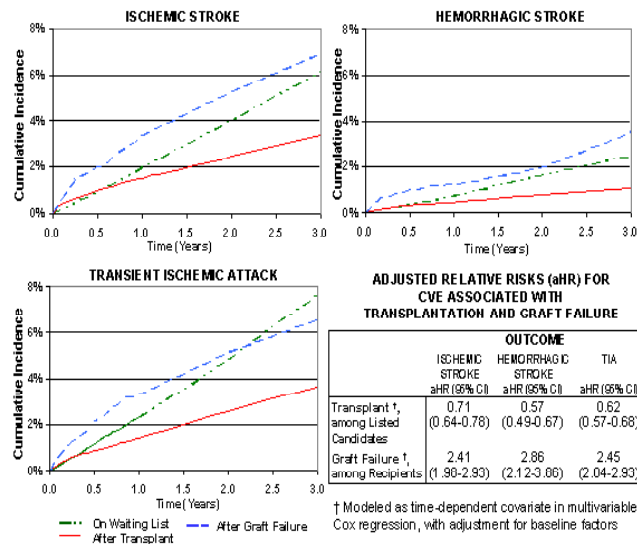
Methods: Data describing kidney transplant candidates and recipients in 1995-2002 were drawn from the United States Renal Data System. CVE including ischemic stroke, hemorrhagic stroke and transient ischemic attacks (TIA) were ascertained from billing records, and participants were followed until Medicare end or December 31, 2002. We used multivariable survival analysis to compare new-onset CVE incidence and risk profiles among 51,501 wait-listed candidates, 29,614 transplant recipients, and 2,594 recipients after allograft failure in the same period.

Results: Observed incidences of individual CVE types by kidney transplant status are shown below (Figure). The cumulative, 3-year incidence of any de novo CVE after transplant was 68% (95% confidence interval (CI) 65–72%), and was lower than 3-yr estimates of 118% (CI 113–122%) on the waitlist and 112% (CI 93–131%) after graft loss that included adjustment for baseline factors. In time-dependent regression, transplantation predicted a 34% reduction in subsequent, overall CVE risk compared to remaining on the waitlist (adjusted HR (aHR) 0.66, CI 0.62–0.71), whereas risk of CVE increased >150% after graft failure (aHR 2.58, CI 2.26–2.94). Similar relationships were observed for each CVE type (Table).

Recipient factors associated with increased risk of ischemic events, TIA and the composite outcome after transplant included older age (aHR 6.33 for age >60 vs 18-30 yrs), ESRD due to diabetes (aHR 2.37), pre-transplant coronary artery disease (aHR 1.36) and female gender (aHR 1.15). Pretransplant smoking predicted approximately 45% increased risk of both ischemic stroke (aHR 1.46) and TIA (aHR 1.44).

The risk of acquiring any CVE diagnosis was modestly higher with transplant from donors aged >60 yrs (aHR 1.27) and in cases with delayed graft function (aHR 1.12).

All forms of CVE diagnoses after transplant predicted increased mortality: Adjusted HRs for death were 1.056 (CI 889–1253) after hemorrhagic stroke, 1.515 (CI 453–585) after ischemic stroke, 1.236 (CI 201–278) after TIA, and 1.467 (CI 422–518) for the CVE composite.



Summary: 1) CVE diagnoses are common after kidney transplant and predict increased mortality. 2) The risk of post-transplant CVE is associated with recipient factors including age, cause of ESRD and coronary disease history, as well as donor age and delayed graft function. Women are not protected, and smoking may be a potentially modifiable correlate of CVE. 3) The risk of all CVE types is lower among transplant candidates who receive organs compared to those who remain on the waitlist, but risk increases markedly if the allograft fails.

Conclusions: Cerebrovascular events should be considered in the post-transplant monitoring and management of higher-risk renal allograft recipients. Along with known benefits for diverse complications of ESRD, maintenance of allograft function may reduce the risk of vascular disease involving the cerebral circulation, further supporting the importance of long-term preservation of renal function as the central focus of post-transplant care.



The High Risk Recipient

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Gender Disparities in Access to Transplantation for Elderly Patients

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Aims: Over 50,000 patients over the age of 65 develop ESRD every year. Even for patients of this age, kidney transplantation has been shown to improve survival. Furthermore, elderly patients are more likely to utilize and benefit from kidneys from expanded criteria donors. Despite this, fewer than 7% of ESRD patients over the age of 65 are listed for transplantation. The goal of this study was to evaluate factors associated with access to transplantation and post-transplant survival in the elderly ESRD population, with specific attention to gender disparities.

Methods: We analyzed 288,481 patients over 65 captured in the USRDS dataset who developed ESRD between 2000 and 2005. A similar cohort of 80,153 patients between the ages of 18 and 45 was studied as a reference group. Access-to-transplantation (ATT) was defined as either registering for the deceased donor waiting list or receiving a kidney transplant, and was analyzed by multivariate logistic regression. Multivariate models were adjusted for age, BMI, diabetes, heart disease, hypertension, malignancy, cerebrovascular disease, pulmonary disease, peripheral vascular disease, functional status, ethnicity, cause of renal failure, insurance coverage, and smoking. Post-transplant survival was analyzed by Kaplan-Meier and multivariate Cox proportional hazards models adjusted for the above recipient factors as well as significant donor factors.

Results: Of 10,831 patients over 65 who had ATT, only 37% were female. Even after adjusting for all other factors associated with ATT, women over 65 had profoundly lower odds of ATT than their male counterparts (multivariate odds ratio [MOR] 0.64, $p < 0.0001$). This disparity persisted for both live donor transplantation (MOR 0.73, $p < 0.0001$) as well as deceased donor transplantation (MOR 0.69, $p < 0.0001$). Conversely, post-transplant survival was significantly better in women over 65, with a 5-year 62% survival in women (compared with 57% in men) and a 13% lower risk of death after adjusting for all donor and recipient factors associated with survival (multivariate hazard ratio 0.87, $p = 0.01$). In comparison, of patients aged 18-45 who had ATT, gender disparity in ATT was not seen (MOR 0.95).

Furthermore, interaction term analyses showed that having certain comorbidities (such as diabetes, ischemic heart disease, or a previous myocardial infarction) or lacking private insurance decreased ATT in women to a significantly greater extent than having the same characteristics in men, yet these factors affected post-transplant survival equally in men and women.

Conclusions: Despite good outcomes, women over 65 were significantly less likely to have access to transplantation, even in multivariate models that adjusted for all other associated factors. We theorize that a perceived frailty in women, particularly women with comorbidities, might contribute to their limited ATT. More research is needed to determine if this bias arises at the level of the patient, family, dialysis center, or transplant center.



The High Risk Recipient

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A Comparison of Living Donor and Deceased Donor Liver Transplantation for Hilar Cholangiocarcinoma

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Aims: We have achieved excellent results with neoadjuvant radiotherapy, chemosensitization and orthotopic liver transplantation (OLT) for patients with early stage hilar cholangiocarcinoma (CCA) Our initial experience (2001 – 2002) with living donor (LD) liver transplantation for CCA was poor and we reassessed recipient criteria, changed the timing of the staging operation, and resumed LD transplantation for CCA in 2004 We reviewed our experience since 2004, with the specific aim to compare survival and CCA recurrence for LD versus DD liver transplant recipients

Methods: We reviewed records for all patients enrolled in the combined treatment protocol that underwent liver transplantation between 2004 and September 20, 2007 Patients with living donors underwent operative staging within a few days of LD liver transplantation Those without potential living donors underwent staging as soon as possible after completion of brachytherapy per an existing agreement between UNOS Region 7 transplant centers Patients received an appealed MELD score of 20 after a negative staging operation with incremental increases equivalent to a 10% increase in mortality every six months We compared actuarial survival and disease recurrence after LD versus DD liver transplantation We also compared survival after LD transplantation for CCA versus non-CCA patients

Results: Sixty-one patients underwent OLT for CCA – 22 with LDs and 39 with DDs Mean waiting list registration-to-transplant times were 118 days for LD patients and 265 days for DD patients (p<0001) One and three year actuarial survival from the time of registration and the time of transplant were excellent for both groups, similar to patients transplanted with LD for all other indications (Table 1) DD patients experienced 5 recurrences and 5 deaths There were 2 recurrences and 3 deaths in the LD patients Mean time to recurrence was 440 days in the DD group and 217 days in the LD group (p=NS) There was a trend toward an increase in loco-regional recurrences in the DD group (Table 2) Twenty-one patients underwent transplantation within 105 days of registration (12 LD and 9 DD), and none have yet developed recurrent disease The other 40 patients (10 LD and 30 DD) transplanted beyond that interval have had 7 recurrences

Table 1 Patient survival: DD vs LD for CCA and LD for non-CCA

	1 Year	3 Years
DD-CCA (n=39)	95%	81%
LD-CCA (n=22)	81%	81%
LD-non CCA (n=23)	96%	96%

Table 2 Recurrences and Deaths after Transplantation for CCA: LD vs DD

	Recurrences	Sites of Recurrence	Deaths	Causes of Death
DD	5	1 Liver, abdomen 2 Duodenum, Porta 3 Duodenum, Porta 4 Colon, Small bowel 5 Bone	5	Recurrent disease - 5
LD	2	1 Bone 2 Adrenal, Porta	3	Recurrent disease – 2 Technical complication – 1

Conclusions: Living donor liver transplantation achieves comparable patient survival to deceased donor transplantation following neoadjuvant therapy for CCA Survival is inferior to results achieved with LD liver transplantation for patients without CCA Decreasing the interval between registration and transplantation may reduce locoregional recurrence.

Saturday, 1.26.08



The High Risk Recipient

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Renal Transplantation from Restored Kidneys: Renal Allografts from Unrelated Donors/patients with Intrinsic Renal Disease

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Introduction: In Japan, more than 260,000 people are on chronic hemodialysis, and only 150-200 deceased donors are available yearly. The average waiting time for kidney transplantation is 16 years. Because of the grave shortage of deceased kidney allografts in Japan, we have embarked on a new source of organs; "Restored kidneys" from living patients.

Methods: From January 1991 through February 2007, 42 kidneys (8 benign tumors, 8 small renal cancers, 8 ureteral cancers, 6 pseudoaneurysms, 8 severe nephrotic syndrome from 4 patients, and 4 ureteral stenoses) were obtained from 38 patients/donors after extensive discussion of treatment modalities and risks. All patients/donors agreed to undergo total nephrectomy. The lesions were removed/repared on the back table, and those restored kidneys were transplanted into 42 recipients. All recipients were notified of all possible risks including donor disease recurrence.

Results: Donor demographics: male 22, female 16, ages 20 to 77 years (mean 62.8). Recipient demographics: male 30, female 12, ages 23 to 69 years (mean 46.7). The follow-up was 9 to 200 months (mean 67.1 months). One, 3, 5, and 10 year graft survival rates of all transplants were 78.3%, 69.3%, 51.5% and 41.6%, respectively. One, 3, 5, and 10 year patient survival rates of all transplants were 92.8%, 89.8%, 79.3% and 63.3%, respectively. There was one recurrence of ureteral cancer in the transplanted kidney 15 months after operation, treated with partial resection of the tumor at the patient's request. The patient developed fatal squamous cell lung cancer 3 years later. Four of 8 recipients of kidneys from patients with nephrotic syndrome experienced transient proteinuria but did not develop nephrotic syndrome and are doing well.

Conclusion: In countries where deceased donors are scarce, such as Japan, the restored kidneys can be a last resort for renal allografts.



The High Risk Recipient

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Combined Liver-Kidney and Liver Transplantation in Patients with Renal Failure Outcomes in the MELD Era

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Background: With the implementation of MELD for liver donor allocation the number of combined liver-kidney transplants (LKT) has increased dramatically Controversy exists as to the effect of LKT on outcomes This study compares the outcomes of LKT with isolated liver transplantation (LT) to determine the optimal strategy for donor allocation

Methods: The UNOS liver transplant dataset was analyzed for all adult, non-status-1, liver transplants occurring in recipients with renal failure in the US from February 2002 to April 2006 This group was subdivided into subjects undergoing transplantation while on hemodialysis (HD) and to those in renal failure not on HD prior to transplantation Subjects receiving LKT were compared to those receiving LT alone Univariate analyses and multivariate survival models were constructed to analyze independent predictors of death or re-transplantation

Results: All recipients in renal failure at the time of transplantation were included (creatinine >25 mg/dL or on HD at the time of transplantation) 1,397 subjects were in renal failure but not on HD, and of those 18% received a LKT while 82% underwent LT 1,740 subjects were on HD prior to transplantation, and of those 41% received a LKT while 59% received a LT

Hemodialysis Cohort: In recipients on HD, those receiving LKT compared to LT alone had longer waiting times (236 days vs 187 days, $p<0.02$), significantly lower MELD scores (31 vs 36, $p<0.0001$), lower bilirubin levels (85 mg/dL vs 109 mg/dL $p<0.0001$), and lower INR levels (18 vs 22, $p<0.0001$) Donor characteristics in the LKT were more favorable compared to LT: including donor age (34 yrs vs 38 yrs, $p<0.0001$) and donor creatinine (10 mg/dL vs 13 mg/dL, $p<0.0001$) Cox regression analysis demonstrated LKT had an independent protective effect in the HD patients: HR 0.775 (CI 0.604-0.995, $p<0.045$) In subjects on HD, LKT had improved survival at one year (69.6% vs 61.0%, $p=0.003$)

Renal failure non-dialysis cohort: For subjects in renal failure without HD, LKT days on waiting list was not significantly different than LT LKT had significantly lower MELD scores (28 vs 34, $p<0.0001$), lower bilirubin levels (85 mg/dL vs 161mg/dL $p<0.0001$), and lower INR levels (17 vs 22, $p<0.0001$) LKT subjects had greater mean serum creatinine (42 mg/dL vs 37mg/dL, $p<0.0001$) Donor characteristics in the LKT were more favorable compared to LT: donor age (36 yrs vs 40 yrs, $p<0.0004$), donor creatinine (11 mg/dL vs 14 mg/dL, $p<0.0008$) LKT was not protective in the non-HD cohort using Cox regression analysis LKT subjects had a non-significant difference in survival compared to LT at one year (71.1% vs 69.6%)

Conclusions: In subjects undergoing combined liver-kidney transplantation there was improved survival at one year compared to liver transplantation alone if the subjects were on hemodialysis at the time of transplantation; however, in the cohort in renal failure, but not on hemodialysis, there was no difference in survival when comparing combined liver-kidney transplant to liver transplantation alone This data suggests subjects in renal failure but not on hemodialysis should not be considered for combined liver-kidney transplantation given the current organ shortage.

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The High Risk Recipient

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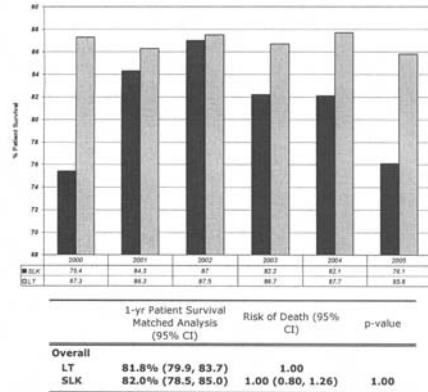
Declining Outcomes in Simultaneous Liver Kidney Transplantation in the MELD Era: Ineffective Utilization of Renal Allografts

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Background: When the United Network for Organ Sharing (UNOS) changed its algorithm for liver allocation to the Model for End Stage Liver Disease (MELD) system in 2002, highest priority shifted to patients with renal insufficiency as a major component of their end-stage liver disease (ESLD). An unintended consequence of the new system was a rapid increase in the number of simultaneous liver-kidney transplants (SLK) being performed yearly. In this study, we review recent national trends in SLK after introduction of the MELD system and examine whether simultaneous kidney transplantation in patients undergoing liver transplant is associated with long-term benefit.

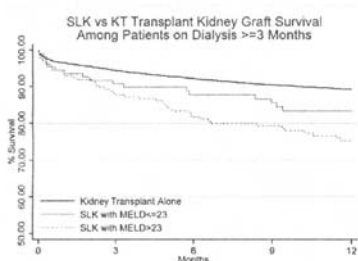
Methods: Adult recipients of deceased donor liver transplants alone (LT), kidney transplants alone (KT), and SLK transplants between 1987 and 2006 were evaluated based on UNOS data. Recipients were stratified by donor subgroup, MELD score, pre vs post MELD era, and length of time on dialysis. Recent dialysis was defined as <3 months, and long-term dialysis was defined as 3 months. Kidney and liver graft survival (KiGS and LiGS) and patient survival (PS) were analyzed by Kaplan-Meier (unadjusted) and Cox proportional hazards analyses (matched control analyses: matched for donor age, race, cause of death, split/partial; recipient final meld score and dialysis status; and further adjusted for share type and cold ischemic time).



Results: MELD era outcomes demonstrate a decline in PS after SLK, while PS after LT remains unchanged (Figure A). Utilizing matched control analysis we are unable to demonstrate an overall benefit in the SLK cohort conferred by the addition of kidney transplantation, despite the fact that higher quality allografts are being utilized for SLK. Subgroup analysis of the cohort that underwent SLK demonstrate an increase in overall PS and LiGS only in those patients on long-term dialysis (>3 months) when compared to LT [845% vs 708%, p=0008; HR 0.57 (0.34, 0.95), p=003] (Figure B). Further, in order to demonstrate KiGS comparable to KT recipients, SLK transplantation would have to be restricted to those end-stage liver disease patients on long-term dialysis with MELD scores<23 [892 vs 834, p=02; HR 1.32 (0.84, 2.06), p=02] (Figure C). Interestingly, of the more than 1,000 SLK transplants performed in the MELD era, only 318 went to a patient on long-term dialysis and only 110 went to a patient on long-term dialysis with a MELD<23.



Length of Dialysis (months)	Risk of Death (95% CI)	p-value
>0 - 1	1.00	-
1 - 2	1.34 (0.66, 2.72)	0.42
2 - 3	1.02 (0.37, 2.77)	0.89
≥3	0.46 (0.21, 1.00)	0.05



MELD	Risk of Graft Loss (95% CI)	p-value
15 - 20	1.00	-
20 - 21	1.2 (0.32, 4.46)	0.79
21 - 22	2.43 (0.76, 7.75)	0.13
22 - 23	2.74 (0.82, 9.09)	0.1
≥3	3.15 (1.17, 8.48)	0.02

Conclusion: These findings call into question the benefit of SLK in the MELD era as it is currently practiced and suggest that current prioritization of kidney grafts to these patients results in wasting of limited resources.

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The High Risk Recipient

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The Outcome of Heart Transplant Recipients Bridged with Combined Mechanical Cardiorenal Support

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Introduction/Objectives: Although the cumulative impact of end-stage heart and renal failure portends a grim prognosis, current strategies of aggressive dual system mechanical support may help to alter these poor outcomes. We examined the fate of patients who were heart transplant recipients and that were bridged with ventricular assist device (VAD) and continuous renal replacement therapy (CRRT).

Methods: A retrospective review was conducted of all patients with VAD who subsequently received CRRT during the last 8 years (January 1, 1999 to December 31, 2006). VAD and CRRT patients who were successfully bridged to heart transplant were identified. Database examination was supplemented with chart review.

Results: Of 53 VAD + CRRT patients, 17 (32%) were successfully bridged to heart transplant. Post-cardiotomy shock (37%) was the most common etiology of heart failure. Males comprised 70% of the population. The mean age was 55.1 years (range 30 to 72 years). None required long-term hemodialysis. Twelve (70.6%) patients were alive at follow-up.

Conclusion: Against traditional wisdom, heart transplant recipients who were bridged with combined mechanical cardiorenal support have acceptable results in the means of mortality in the short/midterm follow up.



The High Risk Recipient

O-8 Do High Model-for-End-Stage-Liver-Disease (MELD) Recipients of Extended Criteria Donors (ECD) Have Worse Patient or Graft Survival Than Similar Recipients of Standard Donors (SD)?

A Single Center 5-Year Report among 628 Adult Cadaveric Liver Recipients

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Objective: The purpose of this study is to examine the effect of donor quality on patient-survival and graft-survival of high-risk adult liver transplant recipients. The hypothesis of the study is that first-time adult isolated whole-liver cadaveric recipients with a MELD score of 35 or above have lower patient-survival and graft-survival when they receive organs from ECD's compared to SD's.

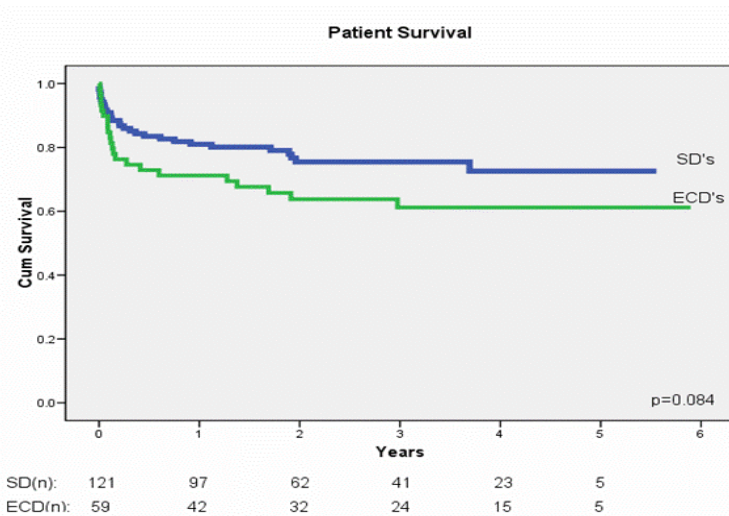
Methods: After obtaining approval from Institutional Review Board for human studies, a retrospective review of a prospectively maintained database of 4287 transplanted livers at a single center was conducted to identify 628 MELD-prioritized first-time adult recipients of isolated whole livers from cadaveric donors from Feb of 2002 to Dec of 2006. Recipients were categorized as Low MELD (score <27), Moderate MELD (score 28-34), and High MELD (score \geq 35). Donors were deemed SD's if their age was \leq 55 years, their hospital length-of-stay was \leq 5 days, and their cold ischemia time was \leq 10 hours. Donors were considered ECD's if they did not meet at least 1 of the above 3 criteria. Kaplan Meier log rank (Mantel-Cox) survival analysis and Pearson Chi-Square test were used for statistical analysis.

Table: Distribution of Donor Type among MELD Groups.

MELD Groups		Count	Donor Type		Total
			SD's	ECD's	
Low (<28)	Count		131	142	273
	% within MELD Groups		48.0%	52.0%	
	% within Donor Type		37.4%	51.1%	
Mod (28-34)	Count		98	77	175
	% within MELD Groups		56.0%	44.0%	
	% within Donor Type		28.0%	27.7%	
High (35 or greater)	Count		121	59	180
	% within MELD Groups		67.2%	32.8%	
	% within Donor Type		34.6%	21.2%	
Total			350	278	628

MELD: Model for End-stage Liver Disease; SD: Standard Donor; ECD: Extended Criteria Donor

Figure: High MELD recipient survival according to donor type.



Results: Median (range) follow-up was 23 (0-59) years. Of the 628 donors, there were 350 SD's and 278 ECD's. Of the recipients, there were 273 Low MELD, 175 Mod MELD, and 180 High MELD patients. Among the High MELD group, 121 received grafts from SD's while 59 received grafts from ECD's (Table). As shown in the figure, High MELD recipient 1-yr, 3-yr, and 5-yr survival rates were 81%, 76%, and 73% in the SD group, compared to 71%, 61%, and 61% in the ECD group ($p=0.084$). Graft survival results were similar, although 86% of High MELD recipients of ECD grafts required a re-transplant compared to 25% of similar recipients of SD grafts ($p=0.063$).

Conclusion: High MELD recipients of ECD's have acceptable patient and graft survival compared to similar recipients of SD's. The process of recipient-donor matching is critical in attaining acceptable results, specially in the high-risk liver transplant recipient patients.