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High mortality in orthotopic liver transplant recipients who require hemodialysis

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Abstract: Acute renal failure is a significant risk factor for death in patients with liver failure. The goal of this study was to analyze the impact of peri-transplant dialysis on the long-term mortality of liver transplant recipients. We performed a single-center, retrospective cohort study of 743 adult liver transplants; patients who received first liver transplants were divided into four groups: those who received more than one dialysis treatment (hemodialysis [HD], continuous veno-venous hemodialysis [CVVH]) pre-orthotopic liver transplantation (OLT), post OLT, pre- and post OLT, and those not dialyzed. There was no statistically significant difference in the mean survival time for patients who were not dialyzed or dialyzed only pre-OLT. Mean survival times were markedly reduced in patients dialyzed post OLT or both pre- and post OLT compared with those never dialyzed. Mortality risk in a Cox proportional hazards model correlated with hemodialysis post OLT, intra-operative vasopressin or neosynephrine, donor age >50 yr, Cr >1.5 mg/dL at transplant, and need for subsequent retransplant. Risk of post-OLT dialysis was correlated with pre-OLT dialysis, intra-operative levophed, pre-OLT diabetes, African American race, pre-OLT Cr >1.5, and male gender. We conclude that renal failure requiring hemodialysis post liver transplant, irrespective of pre-transplant dialysis status, is a profound risk factor for death in liver transplant recipients.

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Patients undergoing orthotopic liver transplantation have a high incidence of acute renal failure requiring peri-operative hemodialysis (1–6), often resulting in end-stage renal disease (7). In addition, acute renal failure in patients awaiting liver transplantation carries a greatly increased mortality compared to patients without renal failure (5, 8–10). Much less is known, however, regarding the impact of chronic renal insufficiency and hemodialysis after liver transplantation (1, 11–13). In this report, we analyze the effect of acute and chronic renal insufficiency on recipient survival in a large cohort of recipients of deceased and living donor liver transplants over a period of six yr.

Acute renal failure is common in the peri-operative period of liver transplantation. The inciting events appear to include hepatorenal syndrome, acute tubular necrosis (2, 6, 14), acute calcineurin inhibitor toxicity (15), tubular toxicity from hetastarch administration (16), IgA nephropathy, and cryoglobulinemia due to hepatitis C virus (17). A different profile occurs post transplant, with the most common causes of chronic renal failure being chronic calcineurin inhibitor arteriopathy (12, 16–18), diabetic nephropathy (12, 16–18), and acute or chronic thrombotic microangiopathy (12, 17).

Up to 60% of liver transplant recipients develop peri-operative acute renal failure (19) and 35% develop stage 3–5 chronic renal insufficiency (glomerular filtration rate [GFR] <30 mL/min per 1.73 m^2) or end-stage renal disease within five yr post-transplant. Acute renal failure in the intensive care unit setting, irrespective of liver transplantation, is associated with a high mortality rate, up to 50% at one yr (20). Chronic renal failure also is also a significant risk factor for increased morbidity and mortality (21). In this paper, we report on the incidence and long-term outcomes for a large cohort of deceased and living donor liver transplant recipients who received intermittent or continuous renal replacement therapy peri-liver transplant.

Methods

Study subjects and human subjects protection

This study was approved by the Research Subjects Review Board at the University of Rochester Medical Center. We reviewed the clinical course of 758 liver-only transplant recipients from 2000–2005 at the University of Rochester solid organ transplant program. The study population of interest included adult recipients of either deceased or living donor liver transplants. Recipients under the age of 18 (n = 7), lost to follow-up (n = 5), and those who received a combined liver–kidney transplant (n = 3) were excluded in both groups. Complete data were available on 743 liver transplants for 661 individual recipients, of which 653 having a first liver transplant were selected for the primary analysis. For a second analysis of the risk of acute renal failure post transplant, both first and second liver transplants were included, with the entire group of 743 patients used for the analysis.

Immunosuppression

During the study period, our center utilized tacrolimus, mycophenolate mofetil, and prednisone as the standard immunosuppression protocol for liver transplantation. No patient received antithymocyte globulin induction therapy, and only seven transplants were performed with basiliximab induction therapy. Post-transplant, all but n = 39 patients were maintained on tacrolimus, with n = 22 having switched to a cyclosporine-based regimen, and n = 17 undergoing a switch to sirolimus, all more than six months post transplant. Given the relative homogeneity of the overall immunosuppression regimen, and the small number of patients on cyclosporine and sirolimus, we did not attempt a comparison between groups of individuals with respect to immunosuppression regimen.

Data collection

Primary end points selected for the study were recipient death and the need for chronic hemodialysis. Data were collected from electronic and paper patient records, center specific SRTR data, and both in- and out-patient hemodialysis. Independent laboratory variables evaluated included blood urea nitrogen (BUN) and creatinine, at the time of transplant and one to five yr after transplant. Model for End Stage Liver Disease (MELD) scores were calculated for all patients at the time of transplant. MELD scores for those transplanted before February 2002 were calculated using laboratory values available within 48 h of the transplant. Clinical variables recorded included histological evidence of allograft rejection, maintenance immunosuppression, the use of intravenous pressors intra-operatively, pre-existing diabetes and hypertension, body mass index at the time of transplant, intra-operative blood loss, and colloid/crystalloid/packed red cell volume replacement. General demographic variables were used as confounders in our subsequent analysis and included gender, race, age at time of transplant, cause of liver failure, type of graft (deceased donor, living donor, split graft), liver donor characteristics donor risk index (DRI), donor age, donor health history (diabetes, hypertension), cause of death, retransplant, time on dialysis, and delayed hepatic graft function. DRI was calculated according to the method of Feng et al. (22) Independent variables were reviewed for a minimum of 24 months after transplant and outcomes over a range 2–7.3 yr post-transplant.

Statistical analyses

Continuous variables were compared with parametric or non-parametric tests as appropriate. Categorical variables were compared with the Mann–Whitney *U*-test. Variables with significant associations ($p < 0.3$) on univariate analysis were retained for multivariate analysis. Cox proportional hazard models were used to assess recipient survival, time to first post-operative hemodialysis, time to chronic hemodialysis, with adjustment for clinical and laboratory covariates. All terms were expressed as dichotomous variables, and multivariate retention criteria was set at $p < 0.05$. Variables not selected by the automated procedure were added back into the model individually to evaluate residual confounding. Recipient and graft survival were estimated by Kaplan–Meier analysis and significance assessed by the log-rank test. Analyses were performed using SPSS software (SPSS, Chicago, IL, USA). eGFR calculations were performed using the four variable MDRD formula in MATLAB (Mathworks, WA, USA), with least-squares univariate linear regression of eGFR vs. time calculated for transplants having two or more annual post-transplant creatinine values.

Results

Patient demographics

Patients were stratified into four cohorts based on their requirement for peri-operative hemodialysis: pre-operative dialysis only (PRD), post-operative

Table 1. Patient and group demographics

Dialysis status	None	Pre-only	p	Post-only	p	Pre + post	p
Patients with first liver txp	520	15		79		39	
Recipient factors							
Age at the time of transplant	51.2 ± 12.4	49.8 ± 14.9	n.s.	53.7 ± 8.7	**0.018**	54.6 ± 12.0	**0.041**
Male gender (%)	64.5	46.7	n.s.	71.7	n.s.	65.6	n.s.
African American (%)	5.5	6.7	n.s.	12	**0.020**	3.4	n.s.
Transplant number	1.1 ± 0.3	1.0 ± 0.0	n.s.	1.2 ± 0.4	n.s.	1.4 ± 0.6	**<0.001**
Waiting time (days)	259 ± 386	89 ± 127	**<0.001**	248 ± 432	n.s.	177 ± 416	n.s.
BMI (kg/m^2)	28.2 ± 6.2	30.8 ± 7.4	**0.100**	29.5 ± 5.8	**0.045**	29.5 ± 5.6	n.s.
Hypertension (%)	34	46.7	n.s.	53.3	**0.001**	41.8	n.s.
Tobacco abuse (%)	57.7	33.3	**0.046**	61.4	n.s.	35.6	**0.001**
Diabetes (%)	33.4	33.3	n.s.	49.4	**0.005**	59.3	**<0.001**
Coronary artery disease (%)	5.3	0	n.s.	14.3	n.s.	3.4	n.s.
Hepatitis C (%)	33.1	26.7	n.s.	44.6	**0.032**	25.4	**<0.001**
Hepatocellular carcinoma (%)	15.6	6.7	n.s.	18.5	n.s.	6.8	n.s.
Recipient renal factors and MELD							
Creatinine day of transplant (mg/dL)	1.33 ± 0.9	2.94 ± 1.7	**0.004**	2.06 ± 1.7	**0.001**	3.65 ± 1.9	**<0.001**
MELD at transplant	19.5 ± 9.5	33.8 ± 6.1	**<0.001**	23.8 ± 10.6	**<0.001**	34.4 ± 5.8	**<0.001**
Contribution of renal function (% of MELD)	6.0 ± 8.7	28 ± 12	**<0.001**	11 ± 6.4	**<0.001**	33 ± 14	**<0.001**
Donor and surgical factors							
Donor age (yr)	46.0 ± 18.0	37.8 ± 14.8	**0.054**	46.2 ± 17.1	n.s.	47.5 ± 17.7	n.s.
Living donor (%)	24.4	13.3	n.s.	10.9	**0.004**	0	**<0.001**
Split liver (%)	25.1	20	n.s.	10.9	**0.003**	0	**<0.001**
Cold ischemia (h)	9.8 ± 4.0	8.8 ± 2.6	n.s.	10.2 ± 3.2	n.s.	9.4 ± 3.1	n.s.
Intra-operative vasopressor use (n)	345	11	**<0.041**	68	n.s.	33	**<0.001**
Number of intra-operative pressor agents (%)	1.3 ± 0.6	1.6 ± 0.7	n.s.	1.4 ± 0.7	n.s.	1.7 ± 0.7	**0.001**
Donor risk index	2.04 ± 0.54	1.69 ± 0.34	n.s.	2.05 ± 0.50	n.s.	1.89 ± 0.44	**0.042**
Male donor (%)	51.1	53.3	n.s.	58.7	n.s.	61	n.s.
Donor diabetes (%)	10.1	0	n.s.	17.6	**0.034**	18.6	**0.044**
Donor hypertension (%)	33.6	26.7	n.s.	45.1	**0.035**	35.6	n.s.
Donor coronary artery disease (%)	9.4	0	n.s.	8.8	n.s.	16.9	n.s.
Post-operative biliary complications (%)	39	18.2	n.s.	33.9	n.s.	22	n.s.
Post-operative hepatic artery thrombosis (%)	12.3	21.4	n.s.	11.9	n.s.	15.8	n.s.
One or more rejection episodes (%)	26.3	20	n.s.	23.9	**0.021**	8.5	n.s.

Bold items indicate those with a statistical significance of $p < 0.10$

dialysis only (POD), combined pre- and post-operative hemodialysis (CD), and those who never received hemodialysis (ND). Pre-operative hemodialysis was defined as the need for any number of dialysis treatments within the 30 d prior liver transplant, and post-operative hemodialysis was defined as the need for any number of hemodialysis treatments post transplant, including prior to or after a second or third liver transplant. In addition, patients were further stratified for some analyses by the MELD era in which they received their transplant (pre- or post-February 2002).

Table 1 shows the demographics and a univariate comparison of significant variables between the primary liver transplant patients who did not require any pre- or post-transplant hemodialysis, and the 133 (20%) patients who required some form of pre- or post-transplant hemodialysis (PRD, POD, or CD), with the largest number in the POD group. In only 15 (2.3%) was dialysis restricted to the pre-operative interval. Those in the POD (39; 6.0%) or CD groups (79; 12.1%) were slightly older, had a higher incidence of pre-transplant diabetes, and received proportionately fewer living donor or split liver transplants compared to the ND group. Patients in the PRD group had significantly shorter waiting times, and more of these transplants occurred in the post-MELD era.

Mortality of liver transplant recipients requiring hemodialysis

We next compared the survival of the four groups of patients who received a first liver transplant only ($n = 653$ total) by Kaplan–Meier analysis. Patients who required post-transplant hemodialysis (POD, CD), irrespective of the need for pre-transplant dialysis, had strikingly poorer long-term survival than the ND or PRD groups (Fig. 1). The three-yr post-transplant mortality in the POD group was 48%, in the CD group was 40%, compared with 81% and 80% in the PRD and CD cohorts, respectively ($p < 0.0001$).

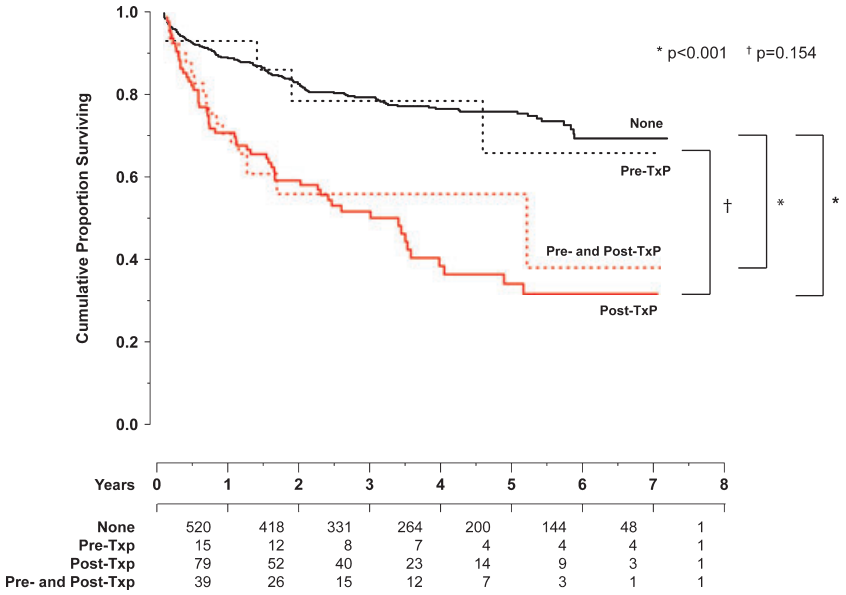

Fig. 1. Survival of first orthotopic liver transplant recipients stratified by the need for any hemodialysis treatment pre-transplant (- - - -; black), post-transplant (————; red), both pre- and post-transplant (- - - -; red), and neither pre- nor post-transplant (None, ————; black).

Table 2. Causes of death

Sepsis	111 (50.7)
Bacterial	103 (47)
Fungal	6 (2.7)
Fungal + viral	1 (0.5)
Mycobacterial	1 (0.5)
Cancer	31 (14.2)
Liver primary	25 (11.4)
Not liver primary	6 (2.7)
Cardiac arrest	18 (8.2)
Unknown	14 (6.4)
Graft failure	11 (5.0)
HCV reoccurrence	6 (2.7)
Hepatic artery thrombosis	2 (0.9)
Rejection	2 (0.9)
Non-adherence	1 (0.5)
Intracranial hemorrhage	8 (3.7)
Multiple organ system failure	6 (2.7)
Adult respiratory distress syndrome	3 (1.4)
Hemorrhage	3 (1.4)
Myocardial infarction	3 (1.4)
Renal failure (declined dialysis)	3 (1.4)
Overdose	1 (0.9)
Care withdrawn	1 (0.5)
Endocarditis	1 (0.5)
Intracranial thrombosis (stroke)	1 (0.5)
Pneumonia	1 (0.5)
Post-transplant lymphoproliferative disorder	1 (0.5)
Thrombotic thrombocytopenic purpura	1 (0.5)

The values in parenthesis are expressed as percentages.

Causes of death for all patients are listed in Table 2. Sepsis attributable to bacterial infection was responsible for the majority of deaths in the study cohort, followed by malignancy. Cause of death distributions between the groups were not significantly different with two exceptions. Death because of reoccurrence or primary hepatic malignancy, primarily hepatocellular carcinoma, occurred mainly in the ND group (n = 21), with few cases in the PRD (n = 2), POD (n = 1), and CD (n = 2) groups ($p < 0.001$ ND vs. each of the three groups). Death because of sepsis occurred primarily in the ND (n = 51), POD (n = 30), and CD (n = 20) groups, with only one death due to sepsis in the PRD group ($p < 0.001$ PRD vs. each of the three groups).

Table 3. Univariate analysis for mortality

	p-Value
Pre-transplant diabetes	0.001
Total pressors intra-operatively	0.001
Cryoglobulins	0.021
Creatinine >1.5	0.024
Hypertension	0.037
Donor hypertension	0.042
Donor age	0.043
Hepatocellular carcinoma	0.046
Required re-transplantation	0.051
MELD score	0.060
Creatinine clearance <40 mL/min	0.067
African American race	0.114
Male	0.227
Hepatitis C virus	0.253
Donor gender	0.307
Coronary artery disease	0.410
Cold ischemic time hours	0.536
Donor risk index	0.637
Warm ischemic time	0.661
Rejection episode	0.674
BMI	0.970
Tobacco use	0.979

Table 3 shows the univariate analysis used to select variables for the Cox proportional hazards model, and Table 4 shows the results of a Cox proportional hazards model of post-liver transplant mortality risk for patients receiving a first

Table 4. Cox proportional hazards models

	HR	Range	p
A. Death post first transplant			
Intra-operative vasopressin	2.2	1.1–4.2	0.003
Dialysis post transplant	2.2	1.5–3.2	<0.001
Donor age >50 yr	1.8	1.2–2.5	0.002
Cr >1.5 at transplant	1.7	1.1–2.6	0.014
Intra-operative neosynephrine	1.7	1.2–2.4	0.003
Required retransplant	1.7	1.1–2.6	0.026
B. Chronic dialysis after first transplant			
Dialysis (<90 d post txp)	30.5	11.4–81.1	<0.001
Diabetes (pre-txp)	2.1	1.0–4.1	0.038
HTN pre-transplant	2.0	1.0–4.1	0.045
Cr >1.5 at transplant	2.0	1.0–3.8	0.045
C. Acute dailysis post transplant (<90 d post txp)			
Dialysis pre-transplant	8.5	5.6–12.7	0.000
Intra-operative neosynephrine	4.1	1.0–16.9	0.048
African American	2.6	1.3–4.9	0.004
Intra-operative vasopressin	2.5	1.2–5.0	0.012
Previous transplant	2.1	1.5–2.8	<0.001
Cr >1.5 at transplant	2.0	1.3–2.9	<0.001
Age >60 yr	1.7	1.1–2.6	0.009
Diabetes	1.7	1.2–2.5	0.006
Male	1.7	1.1–2.5	0.013

liver transplant. Hemodialysis post liver transplant and the use of intra-operative vasopressin were associated with the highest relative risk (2.2). Donor age >50 (RR = 1.8), serum creatinine >1.5 mg/dL at the time of transplant (RR = 1.7), the need for subsequent retransplant (RR = 1.7), and use of intra-operative neosynephrine (RR = 1.7) were also risks for death. In this large series of patients, variables that were not significant in the Cox model included DRI, recipient age, need for retransplantation, hypertension, ethnicity, BMI, hepatitis C status, pre-transplant diabetes mellitus, waiting time, albumin, MELD score, tobacco use, other intra-operative pressor use (norepinephrine, dopamine), or type of transplant (living donor or split liver).

Effect of MELD era on dialysis related mortality

We next examined the influence of the MELD era on the pattern of dialysis-related mortality. Of the entire cohort of first liver transplant recipients (n = 653) where each patient received only a first liver transplant, 628 patients had complete data for calculating a MELD score prior to transplant. In this group, 217 (34%) were transplanted prior to the MELD era. There was no statistically significant difference between time-dependent mortality of the pre- and post-MELD cohorts (Fig. 2A), and the pattern of mortality in the PRD, POD, CD, and ND groups remained similar (Fig. 2C,D). The MELD score heavily weights renal insufficiency, and we were interested to see if the pre- and post-MELD groups differed at all in the contribution of Cr to the total MELD score at the time of transplant. We retrospectively calculated MELD scores for the 217 of the pre-MELD patients at the time of transplant. Compared with post-MELD patients, those who received transplants prior to the MELD era had calculated MELD scores that were slightly higher (21.9 ± 10.8 vs. 20.2 ± 9.3, $p = 0.029$) and with a smaller renal component ($6.1 \pm 9.8\%$ vs. 8.7 ± 11.4, $p = 0.003$). We then further stratified the data by dialysis cohort and performed a similar analysis (Fig. 2B). As expected, serum creatinine levels were higher in all dialysis requiring groups (PRD, POD, CD) compared with the ND group. Indeed, overall MELD scores in the PRD, POD, and CD groups were higher than the ND group, although only the differences between the CD and the POD ($p < 0.02$) and CO ($p < 0.05$) groups reached statistical significance.

Chronic renal insufficiency and progression to permanent hemodialysis

We next examined progression to chronic hemodialysis (Fig. 3A). At five yr post liver transplant, 39% of CD and 51% of POD patients progressed to hemodialysis, compared with only 3% of patients in the ND group ($p < 0.0001$). Significantly, those patients in the POD and CD groups who remained off of chronic hemodialysis had markedly lower mean estimated GFRs ($p < 0.01$ compared with ND), corresponding to DOQI Stage 3 or greater chronic kidney disease by two yr post transplant (Fig. 3B). Only five of the CD patients were able to come off dialysis, all within four months after transplant.

Risk factors for acute post-transplant hemodialysis and progression to chronic hemodialysis

Finally, we performed a Cox regression analysis to determine those factors associated with progression to chronic hemodialysis post transplant (Table 4B), and need for acute post-transplant (within 90 d) hemodialysis (Table 4C). This analysis was performed by transplant and included the 743 patients who received one or more liver transplants. By a large margin, hemodialysis for any period within 90 d after a first liver transplant was the single greatest risk factor for progression to chronic hemodialysis (RR = 30.5). A history of diabetes (RR = 2.1) or hypertension (RR = 2.0) prior to first liver transplant was also associated with an increased risk of progression to

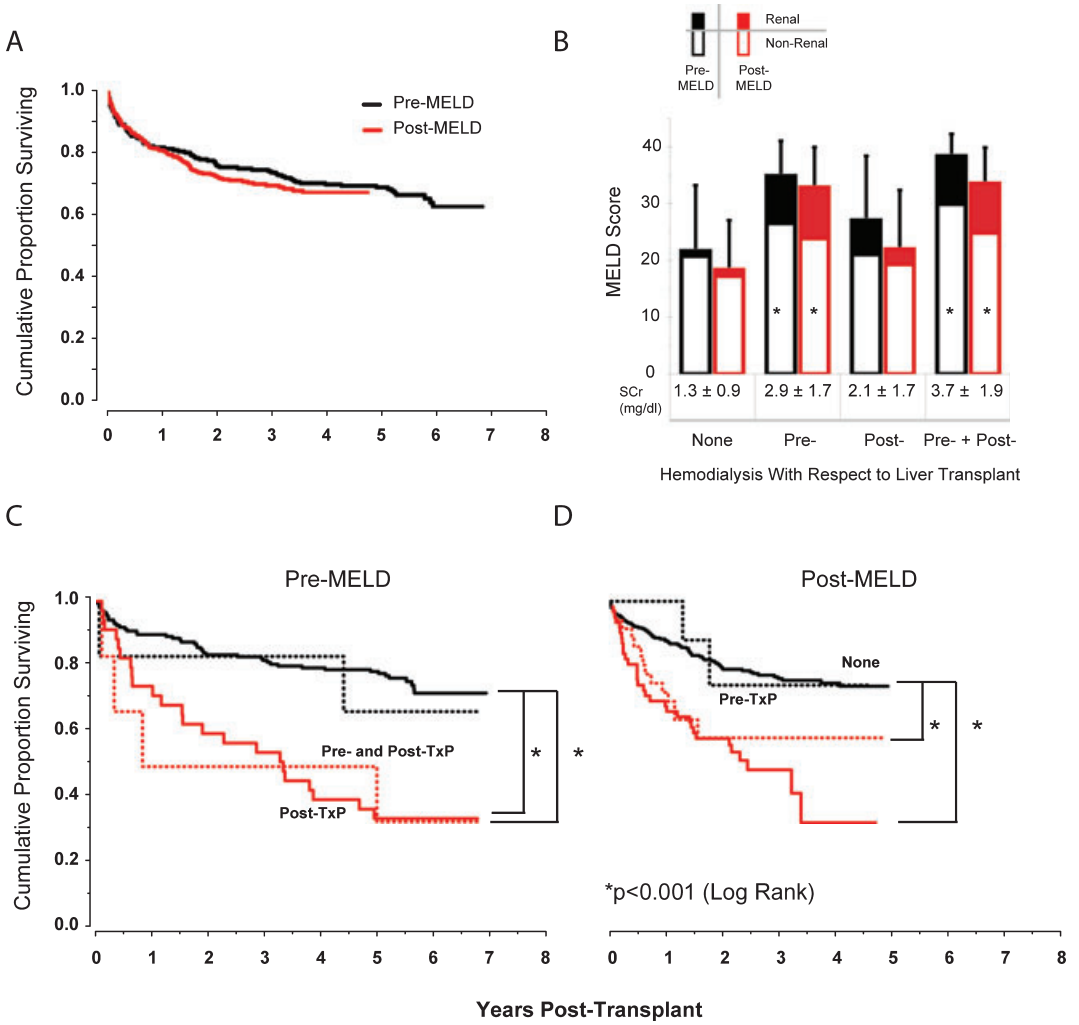

Fig. 2. Comparison of the effect of the MELD organ allocation system on patient survival, the proportion of the MELD score related to renal failure, and effect of dialysis on patient survival. (A) Kaplan–Meier analysis showed no difference between pre- and post-MELD implementation in the cumulative proportion of patients surviving after first orthotopic liver transplant. (B) Differences in MELD scores for patients receiving an orthotopic liver transplant either pre- (black) and post (red)-implementation of the MELD organ allocation system. Solid portions of the bar graphs indicate the amount of the MELD scores contributed by the serum creatinine/hemodialysis term. Error bars are mean ± standard deviation. (C,D) A comparison of patient survival stratified by need for hemodialysis in the era prior to MELD (C) and after MELD implementation (D). Statistically significant differences remained between patients who did not need hemodialysis (None, ———; black) and those who needed either post-transplant (————; red) or both pre- and post-transplant (- - - -; red) hemodialysis. There was no statistically significant difference between the no-dialysis group and those who required treatment pre transplant (- - - -; black).

end-stage renal disease and chronic hemodialysis. As might be expected, the presence of chronic renal insufficiency prior to first liver transplant (serum Cr >1.5 mg/dL) increased the likelihood of progression to chronic hemodialysis (RR = 2.0).

Finally, we studied factors associated the need for acute dialysis within 90 d of liver transplantation, given that this was the largest single risk factor for progression to end-stage renal disease and chronic hemodialysis. For this analysis, we examined all liver transplants performed during the study period. The need for hemodialysis pre-transplant was the largest single risk factor for receiving hemodialysis post transplant (RR = 8.5). In addition, recognized risk factors for acute renal failure were also risk factors for post-transplant hemodialysis, including Cr >1.5 at transplant (RR = 2.0), African American race (RR = 2.6), older age (>60 yr; RR = 1.7), pre-transplant diabetes mellitus (RR = 1.7), and male gender (RR = 1.7). Interestingly, the use of two pressors, neosynephrine (RR = 4.1) and vasopressin (RR = 2.5) intra-operatively was also associated with an increased risk of post-operative hemodialysis.

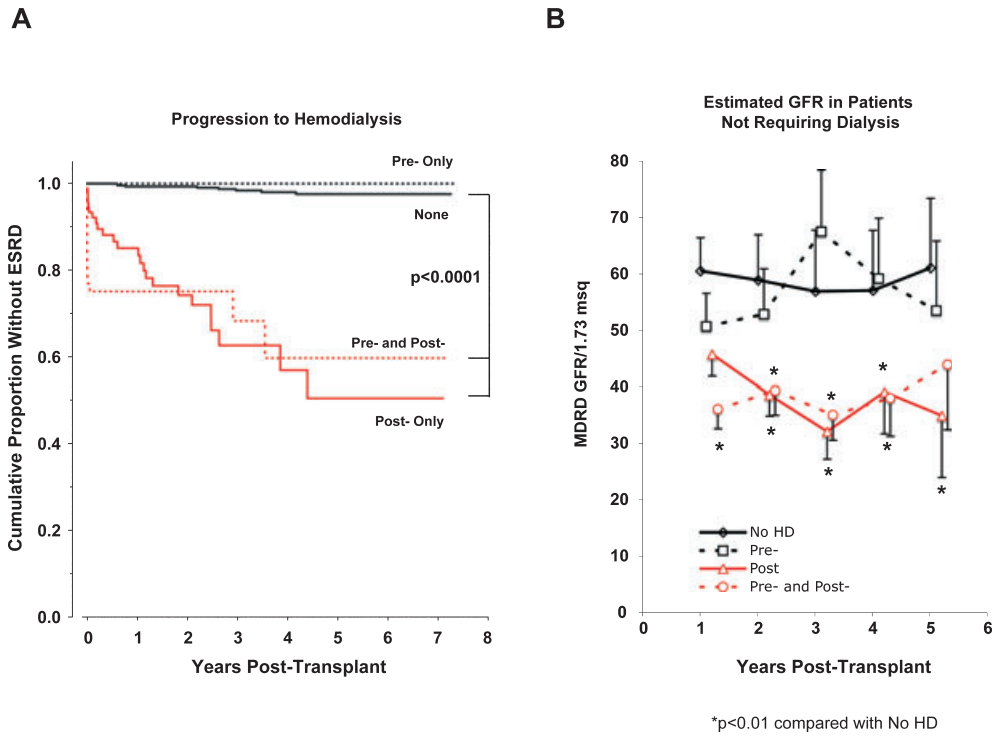

Fig. 3. Progression to end-stage renal disease and degree of chronic kidney disease by dialysis cohort. (A) Kaplan–Meier analysis of cumulative proportion of first orthotopic liver transplant recipients remaining free of end-stage renal disease stratified by the need for any hemodialysis treatment pre-transplant (- - - -; black), post-transplant (————; red), both pre- and post-transplant (- - - -; red), and neither pre- nor post-transplant (None, ————; black). (B) Estimated glomerular filtration rate (GFR) was calculated at one-yr intervals post-transplant for first orthotopic liver transplant recipients who did not have end-stage renal disease requiring renal replacement therapy. Data points are mean ± standard error of the mean.

Discussion

In liver transplantation, acute renal failure during the peri-operative period (4, 6, 7, 23–27), with subsequent chronic renal failure or end-stage renal disease (13, 17, 28, 29), are recognized and frequent complications. In this study, we demonstrate that post-operative hemodialysis is a substantial risk factor for long-term mortality, with only 37% patient survival at five yr after first liver transplant. Additionally, patients who received temporary post-transplant hemodialysis developed substantially impaired renal function, with a mean estimated GFR at one yr of 30 mL/min per 1.73 m^2, meeting criteria for chronic kidney disease stage 4 (30).

Outcomes studies of the association of the need for hemodialysis in liver transplant recipients have been difficult to undertake for several reasons. Large national database studies, such as used in the seminal work of Ojo et al., are excellent for tracking overall trends but are generally limited by the small number of endpoint variables available for analysis (17, 31). Single-center studies are able to collect substantially more detailed data but are often limited in statistical power by the number of study subjects and the length of follow-up (11, 12, 32). This study overcomes many pitfalls of single-center studies by examining detailed data on 743 liver transplant recipients over an extended period of time and a minimum of 24 months of follow-up.

Liver transplantation, chronic renal insufficiency, and dialysis dependence are all associated with increased long-term mortality. In general, increased mortality in patients with renal insufficiency is related to cardiovascular, peripheral vascular, and infectious sequelae of renal disease. This study identified a markedly increased mortality rate associated with acute renal failure requiring hemodialysis post liver transplant. In this cohort, the primary cause of death was sepsis due to bacterial infection, followed by malignancy largely from hepatocellular carcinoma. Risk factors for death in chronic renal disease are common post-liver transplant, including a chronic catabolic state, low body mass, edema, and increased risk of infection from dialysis catheters or uremia. It is not surprising, then, that infection accounted for almost 50% of deaths in this cohort. Sepsis was not a major cause of death in the PRD cohort, but the reason for this finding is unclear. One possible explanation may be that there were many fewer

patients in the PRD group as a whole (n = 13) with two deaths on the day of transplant and only two deaths post transplant.

It was unclear why the patients in the CD group had a lower incidence of progression to end-stage renal disease at five yr than the POD patients (39% vs. 51%). One possible explanation is that the demographics of these groups were different with respect to risk factors for renovascular disease. Compared with the CD group, the POD group had a higher proportion of patients who were African American ($p < 0.001$), had a history of hypertension ($p < 0.02$), used tobacco ($p < 0.001$), and had pre-transplant coronary artery disease ($p < 0.01$). However, diabetes was more prevalent in the CD group ($p < 0.02$). On balance, the POD group had more statistically significant risk factors for progression of renal disease than the CD group, which may explain this finding.

This study also addresses the question of whether implementation of the MELD classification increased the proportion of patients who developed acute or chronic renal disease. The MELD score weights renal insufficiency heavily and acute renal failure is common peri-liver transplant. Thus, it seems likely that liver transplant recipients of the post-MELD period would have a higher risk of acute, chronic, and end-stage renal disease. However, we found no difference in the proportion of patients who received peri-transplant hemodialysis, and any post-operative hemodialysis carried a substantial mortality risk independent of MELD era.

This work, and that of others, begs the question of whether combined kidney–liver transplant should be recommended for patients at high risk of requiring hemodialysis post-operatively, and when this should occur. Our study is unable to answer this question, as we excluded the three patients who received combined kidney–liver transplants during the time period of this study. This rate of kidney–liver transplantation may be low compared to other centers as only patients who were on chronic hemodialysis at the time of liver transplantation were considered for a combined kidney–liver transplant. Other limited studies have noted that patients with combined liver–kidney transplants have a higher initial mortality (33) but may have better survival within the first two yr post transplant (34–37). However, one-yr renal allograft survival appears to be substantially lower with combined kidney–liver transplantation compared with a kidney transplanted into a patient without liver failure (35). Unfortunately, pre-transplant hemodialysis alone is not a predictor of mortality, and post-transplant hemodialysis cannot currently be predicted with certainty. For this reason, some have suggested delaying kidney transplantation until 30–60 d after the liver transplant (38). This study does not directly support or refute this recommendation in general. However, our data do suggest that patients with diabetes, hypertension, and chronic renal insufficiency who require pre-liver transplant hemodialysis have a very high risk of post-transplant hemodialysis and increased mortality, and should therefore be considered for combined liver–kidney transplantation. We would suggest that chronic renal insufficiency, for the purpose of considering combined liver–kidney transplantation, be defined as an estimated GFR of <30 mL/min per 1.73 m^2 demonstrated over a period of at least two months, with other objective evidence of non-reversible parenchymal renal damage such as ultrasound or renal biopsy.

Our results also suggest that modifying some intra-operative factors, such as minimizing intra-operative pressor use, could prevent acute peri-operative renal failure and the need for post-operative hemodialysis. We did not examine the impact of duration of pre-liver transplant hemodialysis on the development of post-liver transplant need for acute or chronic hemodialysis or patient survival. A prospective, multi-center study of risk factors for post-transplant hemodialysis would be highly desirable to address these issues.

Finally, we propose that more comprehensive informed consent may be necessary when pursuing liver transplantation in patients with substantial pre-transplant renal dysfunction, and when pursuing aggressive post-operative measures in critically ill liver transplant recipients requiring hemodialysis. Patients should be provided with information regarding the risks of temporary or permanent renal failure following liver transplantation, the potential need for renal transplantation, as well as the mortality risk if they do require post-transplant hemodialysis.

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Conflict of interest

None.

Authorship

M.Z. designed the study, analyzed the data, created the figures and tables, and wrote the manuscript. A.B., M.A., P.A, G.T., R.K., S.P., and A.J. helped design the study,

collected data and contributed to the writing of the manuscript.

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