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Liver Transplantation in Recipients Receiving Renal Replacement Therapy: Outcomes Analysis and the Role of Intraoperative Hemodialysis

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The Model for End-Stage Liver Disease (MELD) system has dramatically increased the number of recipients requiring pretransplant renal replacement therapy (RRT) prior to liver transplantation (LT). Factors affecting post-LT outcomes and the need for intraoperative RRT (IORRT) were analyzed in 500 consecutive recipients receiving pretransplant RRT, including comparisons among recipients not receiving IORRT (No-IORRT, n = 401), receiving planned IORRT (Pl-IORRT, n = 70), and receiving emergent, unplanned RRT after LT initiation (Em-IORRT, n = 29). Despite a median MELD of 39, overall 30-day, 1-, 3- and 5-year survivals were 93%, 75%, 68% and 65%, respectively. Em-IORRT recipients had significantly more intraoperative complications (arrhythmias, postreperfusion syndrome, coagulopathy) compared with both No-IORRT and Pl-IORRT and greater 30-day graft loss (28% vs. 10%, p = 0.004) and need for retransplantation (24% vs. 10%, p = 0.099) compared with No-IORRT. A risk score based on multivariate predictors of IORRT accurately identified recipients with chronic (sensitivity 84%, specificity 72%, concordance-statistic [c-statistic] 0.829) and acute (sensitivity 93%, specificity 61%, c-statistic 0.776) liver failure requiring IORRT. In this largest experience of LT in recipients receiving RRT, we report excellent survival and propose a practical model that accurately identifies recipients who may benefit from IORRT. For this select group, timely initiation of IORRT reduces intraoperative complications and improves posttransplant outcomes.

Keywords: Hemodialysis, liver transplantation, outcomes, pretransplant renal failure, renal disease in liver transplantation

Abbreviations: ALF, acute liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CIT, cold ischemia time; CRRT, continuous renal replacement therapy; c-statistic, concordance-statistic; DCD, donation after circulatory death; Em-IORRT, emergent IORRT; ESLD, end-stage liver disease; ICU, intensive care unit; INR, international normalized ratio; IOHD, intraoperative hemodialysis; IORRT, intraoperative renal replacement therapy; LOS, length of stay; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; No-IORRT, not receiving IORRT; OLT, orthotopic liver transplantation; OR, odds ratios; Pl-IORRT, planned IORRT; PRS, postreperfusion syndrome; ROC, receiver operator characteristic; RRT, renal replacement therapy; uPRBC, packed red blood cell units; WIT, warm ischemia time

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Introduction

Implemented in 2002 as the standard for deceased donor liver allocation in the United States, the Model for End-Stage Liver Disease (MELD) score (1) is an accurate predictor of 3-month waitlist mortality in patients with end-stage liver disease (ESLD). With serum creatinine weighing heavily in MELD score calculations, the transplant community has seen a dramatic increase in the number of recipients with renal failure requiring pretransplant hemodialysis, a threefold increase in the number of simultaneous liver–kidney transplants, and overall sicker recipients with greater MELD scores (2,3).

While pretransplant renal dysfunction and the MELD score are important predictors of outcome after liver transplantation (LT) (2,4), few studies have systematically examined the factors that affect perioperative outcomes in recipients with renal insufficiency of sufficient severity to require renal replacement therapy (RRT). In these sick recipients, the

intraoperative course can be complicated by major hemodynamic changes, electrolyte and acid–base derangements and coagulation abnormalities, which have been shown to increase intraoperative complications such as cardiac arrhythmias and postreperfusion syndrome (PRS) (5,6). While the use of intraoperative RRT (IORRT) to manage such metabolic derangements in recipients receiving pretransplant RRT has physiologic justification and may theoretically reduce these intraoperative complications, data on the use of IORRT in this patient population are scarce, with the few reports limited either by small study size (7–9) or a narrow focus on feasibility and safety (5,10). Consequently, there are no guidelines to identify the subset of liver recipients on pretransplant RRT that would benefit from IORRT. Routine use of IORRT may add unnecessary risk to recipients without a clear benefit, and significantly increases health-care costs and resource utilization in an economically burdened health-care system (11,12).

This study was undertaken to (1) analyze intraoperative and perioperative outcomes in our single-center experience with 500 liver transplants performed in recipients receiving pretransplant RRT; (2) characterize the effects of the use of IORRT on these outcomes and (3) develop a practical clinical risk score to identify recipients who would benefit from IORRT.

Methods

Using a prospectively collected transplant database, we performed a retrospective review of all adults (ages 18 years and older) who received RRT prior to orthotopic LT (OLT) at the University of California, Los Angeles between January 2004 and September 2012. The study was approved by the Institutional Review Board of the University of California, Los Angeles.

Pretransplant RRT included single-pass hemodialysis or continuous RRT (CRRT). CRRT included continuous veno-venous hemodialysis (solute removal by diffusion across the filter with the dialysate but no replacement fluid) or continuous veno-venous hemodiafiltration (solute removal by diffusion across the filter with the dialysate and with replacement fluid prefilter or postfilter allowing for adequate solute removal even with zero or net-positive fluid balance). CRRT was utilized when a recipient's hemodynamic, metabolic (acid/base and or electrolyte disturbances) and/or fluid status precluded the use of single-pass hemodialysis for maintenance of an adequate systemic blood pressure, and/or fluid, acid/base and electrolyte homeostasis. The decision for the type of pretransplant RRT was made by consensus of the primary transplant and consulting nephrology teams.

Contraindications to LT included uncontrollable pretransplant acidosis refractory to RRT, and volume overload and pulmonary edema requiring mechanical ventilation with an inspired fraction of oxygen (FiO_2%) greater than 50% or a positive end-expiratory pressure requirement greater than 5 cm H_2O to maintain adequate oxygenation.

The subset of patients requiring IORRT were identified, and three groups were characterized based on their need for IORRT: Group 1, no IORRT (No-IORRT); Group 2, planned IORRT (Pl-IORRT), with need for IORRT anticipated, and IORRT initiated at the start of OLT and Group 3, emergent IORRT (Em-IORRT), with unanticipated need for IORRT after initiation of OLT. The decision to utilize IORRT was based on our institutional consensus guidelines developed by the surgical, anesthesia and nephrology teams. Pl-IORRT RRT was *recommended* in recipients with (1) pretransplant serum potassium >5 mmoL/L; (2) pretransplant arterial blood gas base deficit of greater than −8 and (3) need for either CRRT or vasopressors for maintenance of systemic mean arterial pressures. For recipients requiring Em-IORRT, reasons to initiate intraoperative dialysis included (1) the development of significant hyperkalemia (potassium >5.5 mmoL/L) with corresponding electrocardiographic changes and (2) severe acidosis (base deficit greater than −10) refractory to treatment with intravenous bicarbonate and with corresponding hemodynamic instability and resistance to vasopressors. All patients requiring IORRT were connected to a continuous dialysis circuit via a dedicated dual-lumen central venous hemodialysis catheter.

Data on recipient demographics, comorbidities, pretransplant acuity and donor and operative characteristics were compared to identify the important predictors of the need for IORRT. Intraoperative complications and postoperative outcomes were analyzed, and the effects of IORRT on these measures were assessed. Complications related to the utilization of IORRT were reported.

Variables collected for analysis for both recipients and donors included age and gender; for recipients, BMI, etiology of liver disease, retransplantation, obesity (BMI > 30), diabetes, hypertension, hyperlipidemia, metabolic syndrome, history of smoking and for donors, graft type, including heart-beating cadaveric, donation after circulatory death (DCD) and cadaveric split grafts. Recipient acuity measures included the MELD score at transplantation (1), hospitalization status, pretransplant length of stay (LOS), pretransplant duration of RRT, pretransplant blood urea nitrogen (BUN), bilirubin and potassium, arterial blood gas base deficit, international normalized ratio (INR) and need for preoperative CRRT versus single-pass hemodialysis, mechanical ventilation and vasopressors.

Operative variables included combined liver and kidney transplantation, cold ischemia time (CIT), warm ischemia time (WIT), use of veno-venous bypass, operative transfusion requirement of packed red blood cell units (uPRBC) and core body temperature at the beginning and end of transplantation. Variables collected as intraoperative outcome measures included serum base deficit and potassium levels, and the occurrence of intraoperative complications including PRS, cardiac arrhythmias and severe coagulopathy requiring intra-abdominal packing. PRS was defined as a decrease in the mean arterial pressure of more than 30% of the value observed in the anhepatic stage for more than 1 min during the first 5 min after reperfusion of the graft (13). Intraoperative cardiac arrhythmias were defined as (1) bradycardia with heart rate less than 60 requiring treatment with atropine, glycopyrolate, dopamine, epinephrine or cardiac pacing; (2) new-onset atrial fibrillation or sustained sinus tachycardias of greater than 30 min duration with heart rate >120 greater than requiring treatment with atrioventricular nodal blocking agents and (3) ventricular arrhythmias (bigeminy, trigeminy, wide complex rhythms, ventricular tachycardia), ventricular fibrillation or pulseless electrical activity arrest. Severe coagulopathy was defined by the need for intra-abdominal packing after arterial reperfusion and deferral of the biliary reconstruction. The fraction of patients with any complication (at least 1) and multiple complications (more than 1) were compared. Variables collected as postoperative outcome measures included the peak aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the first 24 h after OLT, posttransplant intensive care unit (ICU) and LOS, 30-day graft and patient survival, need for early retransplantation (<30 days or same hospitalization) and overall graft and patient survival.

Statistical analysis

For descriptive and bivariate analyses, continuous variables were compared using the Student's t-test and summarized as means, while categorical variables were compared using Fisher's exact test and summarized as

percentages and frequencies. Graft and patient survival curves were computed using the Kaplan–Meier methods and compared using log-rank tests. Two distinct multivariate analyses, described below, were performed using 28 recipient (age, gender, diagnosis, BMI, MELD, retransplantation, diabetes, hypertension, hyperlipidemia, smoking, metabolic syndrome, pretransplant ICU or ward hospitalization and total and ICU LOS, CRRT, mechanical ventilation, vasopressors, serum BUN, potassium, bilirubin, INR and arterial blood gas base deficit) and donor (age, gender, graft type, combined liver/kidney transplantation and CIT) variables. For these analyses, a backward step-down technique was used, with $p < 0.15$ used as retention criteria.

A multivariate discriminant analysis was performed to identify the pretransplant variables that were simultaneously significant in discriminating the three groups. The first two canonical component scores representing the weighted sum of these significant variables were computed and plotted to generate 50% prediction ellipses, where the degree of overlap indicates the degree of similarity between the groups in a multivariate fashion.

A multivariate logistic regression using the 28 pretransplant variables was used to construct a model to predict the need for IORRT in patients receiving pretransplant RRT, analyzing recipients with ESLD and acute liver failure (ALF) separately. The model was derived based on the No-IORRT and PI-IORRT groups and then applied to the Em-IORRT group to determine whether it accurately predicted the need for IORRT in this independent group. A nonparametric receiver operator characteristic (ROC) analysis was carried out using the logit scores from the final model. The concordance statistic (c-statistic) was computed under this nonparametric ROC as a measure of model accuracy. A cumulative IORRT risk score was computed based on the weighted sum of the logistic model regression coefficients (log odds ratios[OR]) for each significant variable, with a conversion factor of $8.13 \times \log$ OR to best round the risk score points. The threshold risk score was set at the maximum unweighted accuracy for each of the models.

The sensitivity and specificity of our institutional guidelines and our new multivariate models in identifying recipients requiring IORRT were compared.

Results

Of the 1517 adults who underwent OLT during the study period, 500 (33%) received pretransplant RRT (Figure 1). Of these 500 patients, 99 (20%) required IORRT, planned in 70 patients (71%) and emergent in 29 (29%).

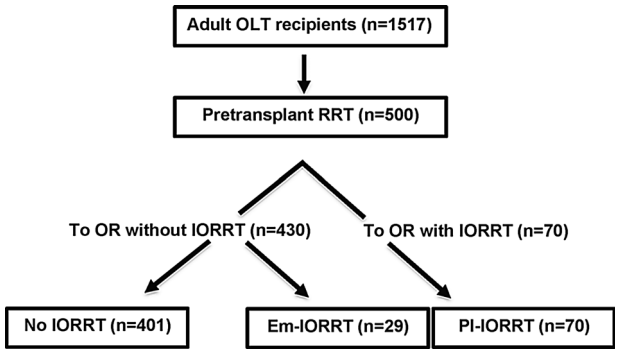

Figure 1: Overview of the 1517 adult recipients who underwent liver transplantation during the study period, including 500 consecutive patients who received pretransplant renal replacement therapy. Em-IORRT emergent intraoperative renal replacement therapy; No-IORRT, not receiving IORRT; OLT, orthotopic liver transplantation; OR, operating room; PI-IORRT, planned IORRT; RRT, renal replacement therapy.

Recipient characteristics

Recipient characteristics are compared in Table 1. Em-IORRT and PI-IORRT recipients were significantly more likely to be undergoing retransplantation compared to No-IORRT recipients (31% vs. 10%, $p = 0.024$ and 21% vs. 10%, $p = 0.006$), with no difference between Em-IORRT and PI-IORRT (31% vs. 21%, $p = 0.315$). The PI-IORRT recipients were more likely to have ALF compared with No-IORRT (20% vs. 9.5%, $p = 0.006$). There were no significant differences among the three groups in etiology of chronic liver disease, age, gender, and prevalence of obesity, diabetes, hypertension, hyperlipidemia, metabolic syndrome or smoking.

Recipient acuity is compared in Table 2. No significant differences in any acuity measures were seen for recipients in the Em-IORRT and PI-IORRT groups. Compared to the No-IORRT group, PI-IORRT recipients had significantly longer pretransplant ICU hospitalization (11 vs. 7 days, $p = 0.032$); higher pretransplant K^+ (4.1 vs. 3.9, $p = 0.024$), MELD scores (39 vs. 37, $p = 0.013$) and total bilirubin (30 vs. 23, $p = 0.006$) but lower BUN (32 vs. 38, $p = 0.045$); and were more likely to be receiving CRRT (70% vs. 37%, $p < 0.001$), mechanical ventilation (70% vs. 44%, $p < 0.001$) and vasopressors (55% vs. 27%, $p < 0.001$). Similarly, Em-IORRT recipients had significantly longer pretransplant hospitalization, both total (24 vs. 16 days, $p = 0.005$) and ICU (15 vs. 7 days, $p < 0.001$), and were more likely to be receiving CRRT (62% vs. 37%, $p = 0.014$), compared to No-IORRT.

Donor and operative characteristics

Comparison of donor and operative characteristics revealed no differences in donor age, gender, graft type and CIT and WIT between the three groups (Table 3). Em-IORRT recipients were more likely to be receiving a combined liver/kidney transplant compared to PI-IORRT patients (31% vs. 11%, $p = 0.018$). Compared to the No-IORRT group, both Em-IORRT and PI-IORRT were significantly more likely to require veno-venous bypass (83% vs. 50%, $p = 0.002$ and 73% vs. 50%, $p = 0.001$, respectively) and more transfusions (40 vs. 20 uPRBC, $p < 0.001$ and 29 vs. 20 uPRBC, $p < 0.001$).

Multivariate group discriminant analysis

Bivariate analysis of pretransplant recipient demographic and acuity measures demonstrated that the Em-IORRT and PI-IORRT groups were very similar to one another and significantly different from the No-IORRT group. To demonstrate this more rigorously, a multivariate discriminant analysis was performed and identified 11 simultaneous factors (recipient BMI, fulminant diagnosis, retransplant, pretransplant CRRT, vasopressors, bilirubin, potassium, ICU status, ICU LOS, donor DCD and CIT) that

Table 1: Comparison of recipient characteristics

Variables	No-IORRT (n = 401)	Em-IORRT (n = 29)	p-Value	No-IORRT (n = 401)	PI-IORRT (n = 70)	p-Value	Em-IORRT (n = 29)	PI-IORRT (n = 70)	p-Value
Etiology of liver disease									
Hepatitis C, N (%)	158 (39)	12 (41)	0.976	158 (39)	23 (33)	0.555	41	23 (33)	0.709
Alcohol, N (%)	67 (17)	8 (28)	0.302	67 (17)	14 (20)	0.784	8 (28)	14 (20)	0.642
NASH, N (%)	53 (13)	3 (10)	0.892	53 (13)	5 (7.1)	0.325	3 (10)	5 (7.1)	0.898
Acute liver failure, N (%)	38 (9.5)	2 (6.9)	0.645	38 (9.5)	14 (20)	0.009	2 (6.9)	14 (20)	0.109
Cholestatic, N (%)	23 (5.8)	1 (3.5)	0.849	23 (5.8)	1 (1.4)	0.280	1 (3.5)	1 (1.4)	0.908
Hepatitis B, N (%)	16 (4.0)	1 (3.5)	0.988	16 (4.0)	1 (1.4)	0.540	1 (3.5)	1 (1.4)	0.876
Age (years)	54	52	0.344	54	50	0.013	52	50	0.615
Male (%)	62	52	0.307	62	51	0.101	52	51	0.979
Retransplant (%)	10	31	0.024	10	21	0.006	31	21	0.315
BMI (kg/m^2) >30 (%)	33	45	0.198	33	28	0.364	45	28	0.098
Diabetes (%)	33	24	0.330	33	24	0.153	24	24	0.988
Hypertension (%)	34	38	0.681	34	31	0.656	38	31	0.537
Hyperlipidemia (%)	12	21	0.157	12	11	0.944	21	11	0.233
Metabolic syndrome (%)	11	17	0.618	11	10	0.933	17	10	0.563
Smoking (%)	48	45	0.771	48	36	0.065	45	36	0.401

Em-IORRT emergent intraoperative renal replacement therapy; NASH, nonalcoholic steatohepatitis; No-IORRT, not receiving IORRT; PI-IORRT, planned IORRT.
Cholestatic liver disease includes primary biliary cirrhosis and primary sclerosing cholangitis.

independently discriminated among the three groups. These 11 factors were summarized into the two canonical components that represent the weighted sum of these 11 variables and are shown in Figure 2. The 50% prediction ellipses show that even on multivariate analysis, the Em-IORRT and PI-IORRT groups were much more similar for these 11 pretransplant variables, compared to the No-IORRT group.

Patient and graft survival

Compared to the 1017 recipients not requiring pretransplant RRT, the 500 patients requiring pretransplant RRT had significantly inferior 1-, 3- and 5-year overall survival (75%, 68% and 65% vs. 86%, 75% and 72%, $p < 0.001$; Figure 3). Kaplan–Meier patient and graft survival estimates for all 500 patients receiving pretransplant RRT are shown in Figure 4. Overall patient and graft survival rates at 30 days and 1-, 3- and 5 years were 93%, 75%, 68% and 65% and 89%, 69%, 60% and 57%, respectively. Compared to PI-IORRT and Em-IORRT recipients, No-IORRT patients had superior overall patient (Figure 5A) and graft (Figure 5B) survival rates. Compared to Em-IORRT, a trend for better early graft survival was observed for the PI-IORRT recipients.

Table 2: Comparison of pretransplant recipient acuity

Variables	No-IORRT (n = 401)	Em-IORRT (n = 29)	p-Value	No-IORRT (n = 401)	PI-IORRT (n = 70)	p-Value	Em-IORRT (n = 29)	PI-IORRT (n = 70)	p-Value
Hospitalization (%)	93	83	0.064	93	94	0.599	83	94	0.071
Non-ICU (%)	23	21	0.947	23	14	0.220	21	14	0.762
ICU (%)	69	66	0.669	69	80	0.070	66	80	0.129
Pretransplant stay									
Total (days)	16	24	0.005	16	18	0.337	24	18	0.127
ICU (days)	7	15	<0.001	7	11	0.032	15	11	0.110
Duration of RRT (days)	15	26	0.188	15	15	0.928	26	15	0.113
Pretransplant K^+ (mmol/L)	3.9	4.1	0.116	3.9	4.1	0.024	4.1	4.1	0.845
Pretransplant base deficit	−1.6	−1.3	0.591	−1.6	−2.0	0.509	−1.3	−2.0	0.395
Pretransplant BUN	38	33	0.184	38	32	0.045	33	32	0.775
MELD score	37	39	0.275	37	39	0.013	39	39	0.747
Total bilirubin (mg/dL)	23	29	0.067	23	30	0.006	29	30	0.814
INR	2	1.9	0.374	2	2	0.698	1.9	2	0.443
Continuous RRT (%)	37	62	0.014	37	70	<0.001	62	70	0.448
Mechanical ventilation (%)	44	50	0.543	44	70	<0.001	50	70	0.070
Vasopressors (%)	27	35	0.452	27	55	<0.001	35	55	0.064

BUN, blood urea nitrogen; Em-IORRT emergent intraoperative renal replacement therapy; ICU, intensive care unit; INR, international normalized ratio; No-IORRT, not receiving IORRT; PI-IORRT, planned IORRT; RRT, renal replacement therapy.

Table 3: Comparison of donor and operative characteristics

Variables	No-IORRT (n = 401)	Em-IORRT (n = 29)	p-Value	No-IORRT (n = 401)	PI-IORRT (n = 70)	p-Value	Em-IORRT (n = 29)	PI-IORRT (n = 70)	p-Value
Donor age (years)	37	34	0.240	37	35	0.300	34	35	0.715
Donor male (%)	63	69	0.520	63	59	0.515	69	59	0.352
DCD graft (%)	2.7	7.1	0.171	2.7	6	0.146	7.1	6	0.833
Split graft (%)	1	0	0.590	1	1.4	0.746	0	1.4	0.523
Liver/kidney (%)	19	31	0.206	19	11	0.109	31	11	0.018
Cold ischemia time (min)	386	433	0.085	386	426	0.065	433	426	0.858
Warm ischemia time (min)	41	43	0.388	41	44	0.059	43	44	0.730
Veno-venous bypass (%)	50	83	0.002	50	73	0.001	83	73	0.628
Starting temperature (°C)	35.7	35.8	0.347	35.7	35.6	0.223	35.8	35.6	0.116
Ending temperature (°C)	35.9	35.6	0.122	35.9	35.0	<0.001	35.6	35.0	0.017
Change in temperature (°C)	0.18	−0.14	0.194	0.18	−0.49	<0.001	−0.14	−0.49	0.216
Transfusions (uPRBC)	20	40	<0.001	20	29	<0.001	40	29	0.064

DCD, donation after circulatory death; Em-IORRT emergent intraoperative renal replacement therapy; No-IORRT, not receiving IORRT; PI-IORRT, planned IORRT; uPRBC, packed red blood cell units.

Intraoperative complications and postoperative outcomes

These are shown in Table 4. Compared to No-IORRT recipients, patients requiring Em-IORRT had a significantly greater frequencies of PRS (38% vs. 20%, p = 0.027), IOP arrhythmias (43% vs. 23%, p = 0.021), coagulopathy requiring intraabdominal packing (54% vs. 8%, p < 0.001), any intraoperative complication (76% vs. 39%, p < 0.001), multiple intraoperative complications (38% vs. 10%, p < 0.001), worse intraoperative base deficit (−10.3 vs. −8.3, p = 0.002), higher intraoperative potassium (6.1 vs. 5.2, p = 0.001), higher postoperative AST (1741 vs. 1040, p = 0.005) and ALT (904 vs. 550, p = 0.014), longer posttransplant ICU hospitalization (34 vs. 19 days, p = 0.003) and higher 30-day graft loss (28% vs. 10%, p = 0.004) leading to more frequent retransplantation (24% vs. 10%, p = 0.099). Despite having similar pretransplant acuity to recipients undergoing PI-IORRT, Em-IORRT recipients also had a greater frequency of PRS (38% vs. 17%, p = 0.026), intraoperative arrhythmias (43% vs. 19%, p = 0.012), coagulopathy (54% vs. 21%, p < 0.001), any intraoperative complication (76% vs. 41%, p = 0.002), multiple intraoperative complications (38% vs. 11%, p = 0.002), worse intraoperative base deficit (−10.3 vs. −8.6, p = 0.042) and higher intraoperative potassium (6.1 vs. 5, p < 0.001). Postoperative AST, ALT, 30-day graft loss and retransplantations were also higher in the Em-IORRT group compared to PI-IORRT but did not reach statistical significance. Although the PI-IORRT group demonstrated significantly increased acuity compared to No-IORRT, no differences in any of the adverse intraoperative and postoperative outcomes were observed, except for more coagulopathy requiring abdominal packing (21% vs. 8%, p < 0.001) and longer posttransplant

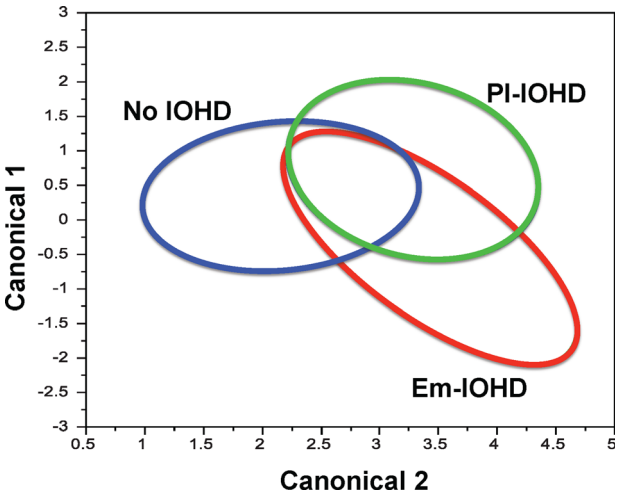

Figure 2: Fifty percent prediction ellipses of the 11 independently significant pretransplant factors from the multivariate discriminant analysis are shown, demonstrating greater similarity among recipients requiring intraoperative RRT (PI-IORRT and Em-IORRT) compared with recipients not requiring IORRT (No-IORRT). Em-IORRT emergent intraoperative renal replacement therapy; IOHD, intraoperative hemodialysis; No-IORRT, not receiving IORRT; PI-IORRT, planned IORRT; RRT, renal replacement therapy.

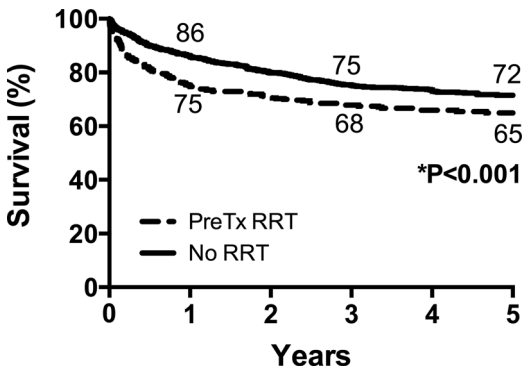

Figure 3: Kaplan–Meier patient survival estimates after liver transplantation comparing 1017 recipients not requiring pretransplant renal replacement therapy to 500 recipients receiving pretransplant renal replacement therapy.

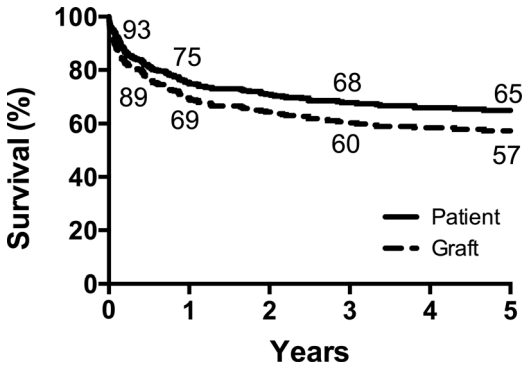

Figure 4: Kaplan–Meier patient and graft survival estimates after liver transplantation for all 500 recipients receiving pretransplant renal replacement therapy.

hospitalization, both total (70 vs. 42 days, $p = 0.001$) and ICU (36 vs. 19 days, $p = 0.001$).

Utilization of IORRT was safe, with no intraoperative access related complications, and no instances of air- or thromboembolism in the 99 recipients undergoing IORRT. One recipient developed clotting of the dialysis circuit that required replacement with no adverse events.

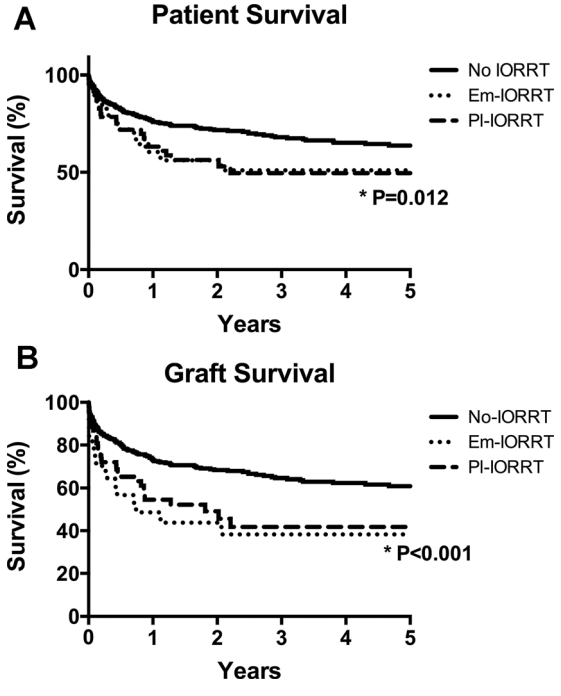

Figure 5: Kaplan–Meier survival estimates after liver transplantation comparing overall (A) patient and (B) graft survival among recipients not receiving intraoperative RRT (No-IORRT), receiving planned IORRT (PI-IORRT) and receiving emergent IORRT (Em-IORRT). RRT, renal replacement therapy.

Multivariate model to predict need for intraoperative renal replacement therapy

A multivariate logistic regression based on the No-IORRT and PI-IORRT is shown in Table 5 and reported separately for recipients with ESLD and ALF. For recipients with ESLD, eight independent predictors of the need for IORRT included DCD donors (OR 3.46, $p = 0.084$), retransplantation (OR 3.06, $p = 0.005$), pretransplant potassium (OR 2.86, $p < 0.001$), pretransplant vasopressor (OR 2.36, $p = 0.012$), continuous pretransplant RRT (OR 2.09, $p = 0.054$), CIT (OR 1.18, $p = 0.008$), pretransplant serum bilirubin (OR 1.02, $p = 0.023$) and recipient BMI (OR 0.95, $p = 0.045$). For recipients with ALF, six independent predictors of the need for IORRT included continuous pretransplant RRT (OR 31.3, $p = 0.009$), DCD donors (OR 3.46, $p = 0.084$), pretransplant vasopressor (OR 2.36, $p = 0.012$), pretransplant base deficit (OR 1.25, $p = 0.051$), CIT (OR 1.18, $p = 0.008$) and pretransplant serum bilirubin (OR 1.02, $p = 0.023$).

An intraoperative dialysis risk score based on these models is reported for recipients with ESLD and ALF (Table 6). For recipients with ESLD, a threshold score of 42 indicated a high risk for requiring IORRT, compared to a threshold score of 38 in recipients with ALF (Figure 6A). The risk score models for ESLD and ALF had an excellent sensitivity (83.9% and 92.9%) and specificity (72.2% and 60.5%) in identifying recipients that would require IORRT, with a c-statistic of 0.829 and 0.776, respectively (Figure 6B and C). When applied to the independent group of 29 Em-IORRT patients, the model correctly predicted that 22 of the 29 patients (75.9%) would have required IORRT (19 of 26 ESLD, 73.1% and 3 of 3 ALF, 100%).

Compared to our multivariate models described above, our institutional guidelines had inferior sensitivity in identifying both PI-IORRT (58 of 70, 82.9%) and Em-IORRT (18 of 29, 62.1%) recipients, and inferior overall specificity (52%).

Discussion

The landscape of LT has changed dramatically in the decade since the introduction of the MELD scoring system. The ''sickest first'' allocation principle has led to significant increases in recipient acuity and strongly favored liver candidates with renal insufficiency. This effect has been particularly dramatic at our center, where more than one-third of our adult recipients in the post-MELD era received pretransplant RRT, compared with 21% in other regional centers and 11% nationally (3,14). Although pretransplant renal function is a known important predictor of posttransplant outcomes (4), data regarding outcomes in the growing population of recipients requiring pretransplant RRT are limited (15). This study represents the largest single-institution experience with LT in high-acuity recipients receiving pretransplant RRT, with a detailed description of intraoperative and postoperative outcomes and a practical risk score to identify recipients who may benefit from IORRT.

Table 4: Comparison of intraoperative complications and postoperative outcomes

Variables	No-IORRT (n = 401)	Em-IORRT (n = 29)	p-Value	No-IORRT (n = 401)	Pl-IORRT (n = 70)	p-Value	Em-IORRT (n = 29)	Pl-IORRT (n = 70)	p-Value
Intraoperative									
Postreperfusion syndrome (%)	20	38	0.027	20	17	0.524	38	17	0.026
Arrhythmia (%)	23	43	0.021	23	19	0.380	43	19	0.012
Coagulopathy (%)	8	54	<0.001	8	21	<0.001	54	21	<0.001
Any complication (%)	39	76	<0.001	39	41	0.753	76	41	0.002
Multiple complications (%)	10	38	<0.001	10	11	0.771	38	11	0.002
Worst base deficit	−8.3	−10.3	0.002	−8.3	−8.6	0.431	−10.3	−8.6	0.042
Highest potassium (mmol/L)	5.2	6.1	0.001	5.2	5	0.705	6.1	5	<0.001
Postoperative									
Opening AST (U/L)	1040	1741	0.005	1040	1226	0.270	1741	1226	0.139
Opening ALT (U/L)	550	904	0.014	550	578	0.759	904	578	0.066
ICU LOS (days)	19	34	0.003	19	36	0.001	34	36	0.901
Total LOS (days)	42	49	0.059	42	70	0.001	59	70	0.496
30-day graft loss (%)	10	28	0.004	10	16	0.177	28	16	0.219
30-day mortality (%)	7	10	0.517	7	9	0.562	10	9	0.791
Retransplantation (%)	10	24	0.099	10	13	0.626	24	13	0.169

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Em-IORRT emergent intraoperative renal replacement therapy; ICU, intensive care unit; LOS, length of stay; No-IORRT, not receiving IORRT; Pl-IORRT, planned IORRT.

Despite their medical acuity, recipients in our study achieved a 75% 1-year and 65% 5-year overall survival, comparable to the reported survival in recipients with the highest MELD scores (2,16). Similar to the report by Petrowsky et al (17), the risk of mortality in these high-acuity recipients was greatest in the first year following OLT, with excellent long-term survival for patients surviving past the first year. Although the reasons for increased short-term mortality are multifactorial, we believe that intraoperative complications such as cardiac arrhythmias, PRS and coagulopathy have contributed. PRS (18) and intraoperative arrhythmias (19) have been shown to be risk factors for increased postoperative complications, poor liver allograft function, graft loss, retransplantation and mortality following LT (20,21). Patients with renal failure requiring RRT have an increased incidence of electrolyte and acid/base disturbances making them particularly susceptible to arrhythmias, PRS and coagulopathy during LT (22). It seems intuitive that IORRT, by correcting these metabolic derangements, may diminish these intraoperative problems and improve postoperative outcomes in recipients with pretransplant renal failure. However, it is important to emphasize that not all recipients receiving pretransplant RRT seem to require IORRT, as evidenced by the lack of intraoperative complications in the majority of our recipients not receiving IORRT.

Despite the increasing number of liver recipients with pretransplant renal failure, data regarding the use and efficacy of IORRT are lacking. Townsend et al (9) reported the successful use of IORRT in 41 patients undergoing OLT and concluded that it was feasible and safe. This study did not include a control group of patients with preoperative renal failure who did not receive IORRT, limiting the conclusions that can be drawn. In a matched control study comparing two groups of 36 recipients undergoing OLT with and without IORRT, Parmar et al (8) showed no difference in postoperative mortality or complications.

Table 5: Independent predictors of need for intraoperative renal replacement therapy in recipients with ESLD and ALF

	End-stage liver disease(ESLD)			Acute liver failure (ALF)		
Predictor of IORRT	OR	95% CI	p-Value	OR	95% CI	p-Value
DCD donor	3.46	0.9–14.2	0.084	3.46	0.9–14.2	0.084
Retransplant	3.06	1.4–6.6	0.005	–	–	–
Pretransplant K+ (per mmol/L)	2.86	1.6–5.1	<0.001	0.39	0.1–2.2	NS (0.285)
Vasopressor use	2.36	1.2–4.6	0.012	2.36	1.2–4.6	0.012
Continuous RRT	2.09	1.0–4.4	0.054	31.3	2.4–412	0.009
CIT (per h)	1.18	1.0–1.3	0.008	1.18	1.0–1.3	0.008
Bilirubin (per mg/dL increase)	1.02	1.0–1.04	0.023	1.02	1.0–1.04	0.023
BMI (per kg/m^2)	0.95	0.9–1.0	0.045	1.03	0.9–1.1	NS (0.603)
Base deficit (per unit increase)	1.03	1.0–1.1	NS (0.418)	1.25	1.0–1.6	0.051

CIT, cold ischemia time; DCD, donation after circulatory death; IORRT, intraoperative renal replacement therapy; NS, not significant; RRT, renal replacement therapy.

Table 6: Independent predictors of IORRT and assigned risk score points

	Risk score points	
Variables	End-stage liver disease	Acute liver failure
DCD donor	10	10
Retransplant	9	–
Pretransplant vasopressors	7	7
Continuous RRT	6	28
Pretransplant K^+ (mmol/L)	1 per 0.12 mmol/L	–
Cold ischemia time (h)	1 per 0.74 h	1 per 0.74 h
Bilirubin (mg/dL)	1 per 6 mg/dL	1 per 6 mg/dL
BMI (kg/m^2)	−1 per 2 U	–
Base deficit (negative)	–	1 per 0.5 U

DCD, donation after circulatory death; IORRT, intraoperative renal replacement therapy; RRT, renal replacement therapy; –, variable not assigned points in given diagnosis.

However, only 26% of recipients in the control group had received pretransplant RRT compared to 94% in the IORRT group, with no assessment of the intraoperative complications such as arrhythmias, PRS and coagulopathy. Most recently, Nadim et al (10) reported on 238 liver transplants performed with intraoperative hemodialysis (IOHD). While they showed that IOHD was safe and effective with excellent short- and long-term patient survival, they provided no further analysis of the intraoperative complications that may be averted by the use of RRT. Furthermore, the study did not have a control group because all recipients receiving pretransplant RRT were automatically placed on IOHD, limiting the conclusions that could be drawn regarding the benefit of intraoperative IORRT (10).

More than safety and feasibility of IORRT, our study is the first to address questions regarding efficacy and need. We provide details regarding the intraoperative complications of cardiac arrhythmias, PRS and coagulopathy, which are the immediate outcomes that may reasonably be affected by the use of IORRT. Moreover, our study is limited to patients who received pretransplant RRT, only some of whom received IORRT, allowing for reliable conclusions from the comparison of recipients who underwent OLT with and without IORRT.

Of the 500 patients receiving pretransplant RRT, 401 underwent OLT without the need for IORRT, while 99 received IORRT. Recipients receiving PI-IORRT (n = 70) had significantly greater acuity compared to No-IORRT patients as evidenced by greater frequency of retransplants, higher MELD scores, longer pretransplant hospitalizations and greater need for pretransplant CRRT, mechanical ventilation and vasopressors. These pretransplant factors undoubtedly influenced the clinical decision to utilize IORRT at the outset of OLT. Despite greater acuity compared to the No-IORRT group, PI-IORRT recipients experienced similar rates of intraoperative arrhythmias and PRS. Conversely, PI-IORRT recipients had significantly fewer intraoperative arrhythmias, lower rates of PRS and coagulopathy requiring packing, and a trend toward decreased 30-day graft loss and retransplantation compared to the Em-IORRT recipients, despite being extremely well-matched on many recipient, donor and operative characteristics. These ''better-than-expected'' intraoperative outcomes in the PI-IORRT provide a strong argument that the planned utilization of IORRT at the initiation of surgery may have avoided progression of the metabolic derangements that resulted in the increased intraoperative complications seen in the Em-IORRT group, where IORRT was not initiated until intraoperative factors dictated its need.

Although it is possible that a subset of No-IORRT recipients may have benefited from IORRT, and that some of the PI-IORRT recipients may have not required IORRT, the need for IORRT in the Em-IORRT recipients is undeniable, as they developed metabolic derangements that required initiation of IORRT. The inferior intraoperative outcomes observed in the Em-IORRT recipients may have partly been a

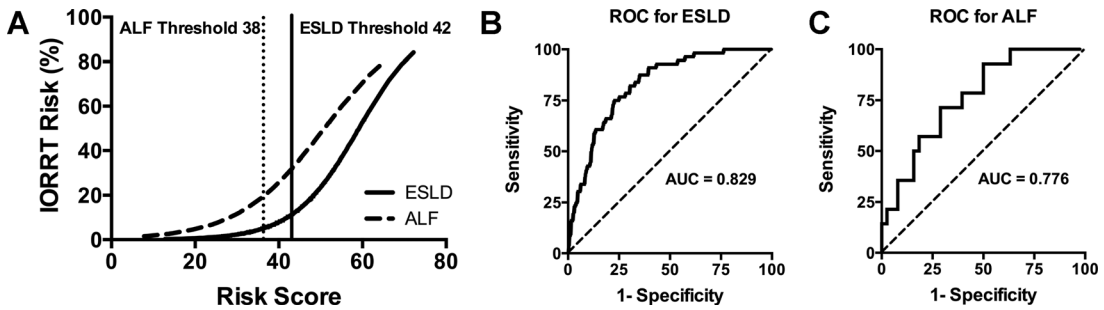

Figure 6: The multivariate logistic model predicts the need for intraoperative renal replacement therapy based on the cumulative risk score calculated from the eight independent predictors for ESLD and six independent predictors for ALF shown in Table 6. (A) The predicted intraoperative dialysis risk according to the cumulative risk score points for recipients with ESLD and ALF. A risk score of greater than 42 for ESLD and 38 for ALF identifies a recipient at high risk of requiring intraoperative RRT (IORRT), and should trigger the utilization of IORRT to be initiated at the start of OLT. The ROC curve of the IORRT risk model had a c-statistic of 0.829 for recipients with ESLD (B) and 0.776 for recipients with ALF (C). ALF, acute liver failure; c-statistic, concordance-statistic; ESLD, end-stage liver disease; OLT, orthotopic liver transplantation; ROC, receiver operator characteristic; RRT, renal replacement therapy.

consequence of not initiating IORRT in a timely fashion in recipients who proved that they required it during the course of transplantation, and may in fact have impacted their inferior postoperative outcomes. It is precisely this group of patients that must be identified prior to initiation of OLT.

A unique contribution of this study is the development of a practical risk score to identify recipients who will benefit from IORRT. We identified independent pretransplant predictors of the need for IORRT that were slightly different for recipients with ESLD (DCD donor, retransplantation, pretransplant potassium, pretransplant vasopressors, continuous RRT, CIT, serum bilirubin and BMI) and ALF (CRRT, DCD donor, pretransplant vasopressors, pretransplant base deficit, CIT and serum bilirubin). A practical risk score was constructed with thresholds of 42 and 38 to trigger the use of IORRT in recipients with ESLD and ALF. These models had an overall sensitivity and specificity of 84% and 72% in ESLD and 93% and 61% in ALF, respectively, significantly better than the sensitivity and specificity achieved when our institutional guidelines were utilized. In the independent group of 29 Em-IORRT recipients who demonstrated that they required IORRT, our multivariate models correctly predicted that 22 of the 29 (75.9%) Em-IORRT recipients would require IORRT. While it may be argued that the safest approach is to place all recipients who require pretransplant RRT on IORRT, our data clearly show that the majority of recipients not receiving IORRT did not experience any adverse intraoperative complications. Currently, approximately 10% of liver transplant recipients require pretransplant RRT nationally. With an average cost of $2000 for the utilization of IORRT and dialysis nursing and an average 6000 liver transplants per year, this amounts to an estimated $1 200 000 in annual intraoperative dialysis costs alone. The costs and resource utilization associated with such an approach are hard to justify in an economically burdened health-care system (11,12). Our risk score correctly identifies 85% of all recipients requiring IORRT and would decrease the unnecessary use of IORRT by 71% in an approach that advocates its indiscriminate use in all recipients receiving pretransplant RRT.

Our study's major limitations are that it is retrospective in nature. It is possible that factors unaccounted for may explain the inferior outcomes in recipients requiring Em-IORRT. However, short of a prospective trial randomizing IORRT to evaluate its potential utility, we feel that our large experience provides strong evidence that IORRT is in fact beneficial in a cohort of high-acuity recipients requiring pretransplant RRT.

In summary, we have presented the largest experience with LT in recipients receiving pretransplant RRT, describing their intraoperative complications and postoperative outcomes. Despite the high acuity of these patients, excellent long-term survival was achieved. The majority of patients requiring pretransplant RRT seem not to require IORRT. We propose a practical risk score that can be used to accurately identify the subset of recipients receiving pretransplant RRT that are likely to require IORRT. The selective and planned use of IORRT at the start of OLT may lead to reduced intraoperative complications and improved posttransplant outcomes in this challenging group of recipients.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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