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Liberation From Renal Replacement Therapy After Cadaveric Liver Transplantation

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Background. Renal failure requiring renal replacement therapy (RRT) is common in patients with end-stage liver disease (ESLD) and is associated with worse outcomes following liver transplantation (LT). We investigated the factors associated with liberation from posttransplant RRT and studied the impact of RRT on patient and graft outcomes. **Methods.** A 5-year retrospective study of ESLD patients who received pretransplant RRT was conducted. Variables associated with liberation from RRT at 30 days and at 1-year posttransplant were analyzed. We used propensity matching to compare patient and graft outcomes in the study cohort to those of a control group who underwent LT but not pretransplant RRT. **Results.** Sixty-four patients were included in the study. Twenty-four (38%) were liberated from RRT at 30 days posttransplant. Duration of pretransplant RRT (odds ratio [OR], 0.94; 95% confidence interval [CI], 0.89-0.98) and severe postreperfusion syndrome (OR, 0.26; 95% CI, 0.08-0.87) were significantly associated with continued RRT at 1-month posttransplant. At one year, 34 (53%) patients were liberated from RRT. Age was significantly associated with lack of liberation from RRT (OR, 0.933; 95% CI, 0.875-0.995). Compared with propensity matched controls, patients who received RRT pretransplant had worse graft and patient survival at 1 year (52% vs 82%; $P = 0.01$, and 53% vs 83%; $P = 0.003$, respectively). **Conclusions.** In ESLD patients who received pretransplant RRT, one third were liberated from RRT at 1 month, and half at 1 year. Longer duration of pretransplant RRT, postreperfusion syndrome, and older age were associated with lower likelihood of liberation from RRT. Patients who required pretransplant RRT had worse graft and patient survivals compared to matched patients who did not require RRT. Patients who were liberated from RRT post-LT had similar outcomes to patients who never required pre-LT RRT.

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Patients with end-stage liver disease (ESLD) awaiting liver transplantation (LT) can develop renal failure; some require renal replacement therapy (RRT). Traditionally, it has been thought that renal function will recover post-LT, especially if renal failure was caused by hepatorenal syndrome (HRS). Predicting liberation from RRT post-LT is important because renal failure with ongoing RRT may have a negative impact on graft and patient survivals.[1] Patients with renal failure requiring RRT may be eligible to receive simultaneous liver and kidney transplantation (SLKT); however, SLKT should ideally be performed only if recovery of renal function and liberation from RRT is not anticipated. Our primary aim was to determine the variables associated with liberation from RRT post-LT in a cohort of patients with ESLD receiving RRT at the time of LT. Secondary aims were to determine the effect of renal failure requiring RRT on patient and graft survival.

MATERIALS AND METHODS

Adult LT recipients who received pre-LT RRT from January 1, 2005, through December 31, 2011, were identified using an enhanced electronic medical record system that houses clinical and laboratory data specific to our transplant population. Data were prospectively collected by a dedicated research nurse. Patients were excluded if they received RRT for longer than 90 days at the time of LT, received SLKT,

had previous renal transplants, received a multiorgan transplant, or had fulminant hepatic failure.

Liberation from RRT was determined if patients were on RRT for more than 1 week and subsequently were taken off RRT for at least 1 week and never required RRT again. Liberation from RRT was determined at 2 different time points, 30 days and 1-year post-LT. Pre-LT variables included recipient demographics, etiology of ESLD, etiology of renal failure, MELD score, duration of pre-LT RRT, and type of RRT. Intraoperative data included duration of surgery, cold and warm ischemia time, type of allograft (extended donor criteria or conventional graft), development of postreperfusion syndrome (PRS), use of veno-venous bypass, use of antifibrinolytic agents, amount of blood products, and type and volume of intravenous fluid. Postoperative data included timing of RRT liberation, as well as graft and patient outcomes. Extended donor criteria grafts were defined as liver allografts from donors with any of the following criteria: age > 65 years old, sodium level greater than 150, liver graft with greater than 30% steatosis on biopsy, cold ischemia time > 16 hours, warm ischemia time > 90 min, and donation after cardiac death donors. PRS was defined as the presence of severe and persistent hypotension (blood pressure is 30% less than that preperfusion) resulting in the requirement for continuous vasopressor support intraoperatively and possibly extended into the postoperative period.

The study cohort was divided into 2 groups: group 1 included patients who were liberated from RRT up to 1 year post-LT and group 2 included patients who continued to require RRT post-LT. Preoperative and intraoperative data of the 2 groups were compared to identify factors associated with liberation from RRT.

Propensity score matching was performed to compare patient and graft survivals in the study cohort to those of the matched control group with normal renal function pre-LT. Each patient on RRT was matched with 1 control using propensity score analysis based on age, sex, race, preoperative diabetes mellitus, and coronary heart disease. Nearest neighbor matching without replacement was used for propensity score matching. Comparisons between each group and its corresponding matched control group were made using an appropriate matched pair's survival analysis technique (Klein and Moeschberger, 1997). The study was approved by the University of Pittsburgh Institutional Review Board.

Statistical Analysis

Descriptive statistics for the study cohort were summarized as frequencies and percentages, mean ± standard deviation (SD), or median (interquartile range) as appropriate. Examination of normal distribution assumption for continuous data was determined by q-q plots and histograms. Bivariate logistic regression was applied to assess the strength of association between predictor variables (preoperative and intraoperative data) and the dichotomous outcome of interest (liberation versus nonliberation from RRT). The predictor variables that showed independent association with the primary outcome (in terms of odds ratio [OR] and a significance level of $p < 0.20$) were selected for model fitting in a subsequent multiple logistic regression. Multiple logistic regression analysis was performed using a forward stepwise approach that included variables with p-value < 0.20 (age, MELD score, diabetes mellitus, PRS). The level of significance to enter or remain in the model was set to 0.15 and 0.10, respectively. The magnitude of association between the potential predictor variables and outcome was quantified using OR and the corresponding 95% confidence interval (CI). Performance of the model was tested using the Hosmer-Lemeshow goodness-of-fit test. Kaplan-Meier survival curves were used to describe overall 5-year liver allograft survival and patient post-LT survival for the study cohort. All statistical

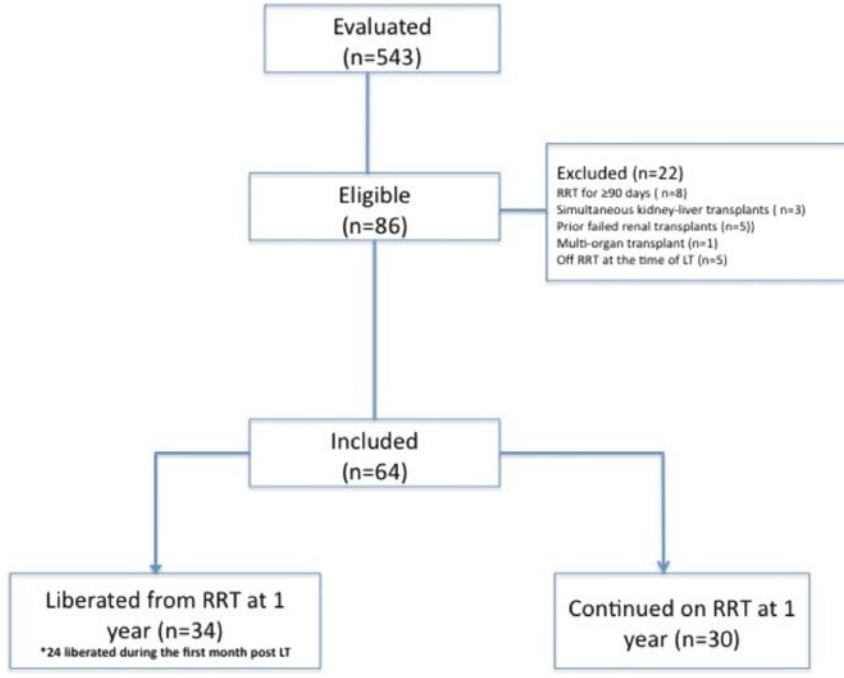

FIGURE 1. Study flowchart.

TABLE 1.

Perioperative variables based on liberation from RRT at 30 days postliver transplant (LT).

LT recipient data	Liberated from RRT at 30 days post-LT N = 24 (37.5%)	Continued RRT at 30 days post-LT N = 40 (62.5%)	*$P \leq 0.05$
Age, y	52.9 ± 10.4	58 ± 8.4	0.0444*
Male sex	15 (62.5%)	25 (62.5%)	0.603
Caucasian race	22 (91.7%)	37 (92.5%)	0.925
Weight, kg	90.1 ± 18.8	88.6 ± 18.4	0.748
MELD score	38 [34.5; 40]	35 [30.5; 40]	0.078
HRS	20 (83.3%)	34 (85%)	0.238
Diabetes mellitus	9 (37.5%)	19 (47.5%)	0.302
Coronary artery disease	1 (4.2%)	1 (2.5%)	0.613
Pretransplant RRT, d	7.5 [2; 18]	18.5 [13.3; 28.8]	0.0171*
Extended criteria donor	10 (41.7%)	20 (50%)	0.35
Total operative time, h	6.9 [6.2; 8.2]	7.7 [6.4; 8.8]	0.209
Cold ischemic time, h	8.73 ± 2.4	9.5 ± 2.5	0.224
Warm ischemic time, min	30 [23.5; 38.5]	28 [24; 35.5]	0.862
Veno-venous bypass	21 (87.5%)	36 (92.3%)	0.415
Aprotinin	3 (12.5%)	5 (12.8%)	0.645
Methylene blue	17 (70.8%)	24 (63.2%)	0.367
Crystalloid (L)	4 [3; 5.3]	4.3 [3.4; 5.9]	0.256
Albumin 5% (L)	1.75 [1.4; 2.5]	2 [1; 3]	0.936
Packed red blood cells, units	12 [8.5; 15]	10 [8; 13]	0.477
Fresh-frozen plasma, units	10 [5.5; 14.5]	8.5 [6; 12]	0.529
Platelets, units	2 [1; 3]	2 [1; 3]	0.463
Cryoprecipitate, units	0 [0; 1]	0.5 [0; 2]	0.805
Reperfusion syndrome	10 (41.7%)	24 (63.2%)	0.082

analyses were conducted using SAS, version 9.3 statistical software (SAS Institute Inc., Cary, NC).

RESULTS

In the study period, 543 liver transplants were performed. Eighty-six LT recipients required RRT before transplantation. Sixty-four patients were included in the study (Figure 1). We excluded 22 patients for RRT for > 90 days (n = 8), no longer on RRT at time of LT (n = 5), previous failed renal transplant (n = 5), combined kidney-liver transplant (n = 3), and multiorgan transplant (n = 1).

During the first month post-LT, 24 patients were liberated from RRT. Bivariate logistic regression analysis showed that patient age and duration of pre-LT RRT were significantly associated with liberation from RRT by the first month post-LT (OR, 0.94 and 0.94; 95% CI, 0.89-0.99 and 0.906-0.99; $P = 0.04$ and 0.017, respectively). Table 1 summarizes the results from the logistic regression analysis at the end of the first month post-LT.

In the multivariable logistic regression, both duration of pre-LT RRT (OR, 0.94; 95% CI, 0.89-0.98) and severe PRS (OR, 0.26; 95% CI, 0.08-0.87) were significant factors in continuing RRT post-LT. After adjusting by severe PRS, a 1 day increase in pre-LT RRT duration led to a lower likelihood of liberation from RRT (OR, 0.94). After adjusting by pre-LT RRT days, patients that had severe PRS had an approximately 74% decreased odds of liberation from RRT compared with those who did not have severe PRS.

At 1-year post-LT, 34 patients were liberated from RRT (Table 2). Bivariate logistic regression analysis demonstrated that age (OR, 0.93; 95% CI, 0.87-0.99; $P = 0.02$) and preoperative diabetes mellitus (OR, 0.37; 95% CI, 0.132-1.013, $P = 0.05$) were associated with continuing RRT post-LT. No other variable other than age remained in the final model.

The odds of continued requirement of RRT at 1-year post-LT was 1.07 higher for every 1-year increase in age.

Duration of pre-LT RRT was not significantly associated with the duration of post-LT RRT (OR, 0.99; 95% CI, 0.97-1.02, $P = 0.7$). Survival analysis demonstrated that the probability of liver allograft survival at 1-year was 70% and the probability of patient survival at 1-year was 72%.

Matched Control Analysis

Descriptive statistics for the matched control group are summarized in Table 3; the control group included patients who received cadaveric LT during the same study period and were never on RRT before LT. Each patient that received pre-LT RRT was matched with 1 patient from the control group using propensity score analysis based on age, sex, race, preoperative diabetes mellitus, and coronary heart disease.

Patient Outcomes

Compared with the matched control group who did not receive pre-LT RRT, patients receiving pre-LT RRT had lower 5-year patient survival (0.54 vs 0.83 p = 0.003)

TABLE 2.

Perioperative variables based on liberation from RRT at one-year post-LT

Recipient data	Liberated from RRT at 1 y post-LT, N = 34 (53.13%)	Continued RRT at 1 y post-LT, N = 30 (46.88%)	*$P \leq 0.05$
Age, y	53.3 ± 9.5	59.2 ± 8.5	0.0168*
Male sex	22 (64.7%)	18 (60%)	0.448
White race	32 (94.1%)	27 (90%)	0.775
Weight, kg	89.8 ± 15.9	88.4 ± 21.1	0.775
MELD score	38 [33.7; 40]	35 [29.7; 40]	0.288
HRS	30 (88.2%)	24 (80%)	0.288
Preexisting diabetes mellitus	11 (32.4%)	17 (56.7%)	0.0520*
Coronary artery disease	1 (2.9%)	1 (3.3%	0.722
Pretransplant RRT, d	14.5 [4.5; 23]	18 [6.8; 28]	0.336
Extended criteria donor	15 (44.1%)	15 (50%)	0.413
Total operative time, h	6.9 [6.2; 8.6]	7.7 [6.7; 8.7]	0.326
Cold ischemic time, h	9.1 ± 2.4	9.3 ± 2.6	0.781
Warm ischemic time	30 [23.8; 37.3]	28 [24; 36.3]	0.84
min	30 (88.2%)	27 (93.1%)	0.416
Veno-venous bypass	6 (17.6%)	2 (6.9%)	0.186
Aprotinin	20 (60.6%)	21 (72.4%)	0.239
Methylene blue	4.5 [3.1; 5.7]	4 [3.4; 4.9]	0.582
Crystalloid (L)	2 [1.5; 2.8]	1.5 [1; 2.8]	0.283
Albumin 5% (L)	11 [8; 15.3]	10.5 [8; 13.8]	0.91
Packed red blood cells	9.5 [5;12.3]	9 [6.3; 14.8]	0.51
(units)	2 [1; 3]	2 [1; 3]	0.408
Fresh frozen plasma, units	0.5 [0; 1.3]	0 [0; 2]	0.884
Platelets, units	15 (45.5%)	19 (5.5%)	0.092
Cryoprecipitate, units			
Reperfusion syndrome			

TABLE 3.

Descriptive statistics for the matched data

	Required RRT (n = 64)	Never-required RRT (n = 64)	
Matched characteristic	Mean ± SD, N (%)	Mean ± SD, N (%)	*P*
Age, y	56 ± 9	56 ± 8	0.8176
Sex (Male)	40 (62.5)	42 (65.6)	0.7150
Race (white)	59 (92.2)	63 (98.4)	0.1025
Diabetes	28 (43.8)	30 (46.9)	0.7150
Coronary artery disease	2 (3.1)	2 (3.1)	1.0000

(Figure 2). When the study cohort was divided into the RRT liberated group (34 patients) and the RRT continued group (30 patients) and the patient survival of each group was compared to that of the corresponding matched control group, no significant difference was found (P = 0.4927) (Figure 3). However, patient survival in the RRT continued group was significantly lower than that in the corresponding matched control group (0.27 vs. 0.79; P = 0.0003) (Figure 4).

Graft Outcome

Graft survival in the study cohort was significantly shorter than in the corresponding matched control group (0.52 vs 0.82; P = 0.01) (Figure 5).

Liver graft 1-year survival for the RRT liberated group at the end of 1-year post-LT showed no significant difference from the corresponding matched control group (0.79 vs. 0.84, p = 1.0) (Figure 6). Finally, 1-year graft survival for the continued RRT group was significantly lower than that of the corresponding matched control group (0.27 vs 0.79, P = 0.0003) (Figure 7).

DISCUSSION

Liberation from RRT occurred by 30 days in 38% of patients; age, and duration of pre-LT RRT were factors associated with early liberation. These findings are somehow similar to findings by Sharma et al,[2] who investigated renal function outcomes at 6 months post-LT and concluded that duration of pre-LT RRT, age, and diabetes mellitus were all risk factors for nonrecovery. In another study, the older the recipient, the less likely a full recovery of preexisting acute kidney injury.[3] Using multivariable regression, age and PRS were factors that adversely affected early liberation from RRT. In PRS with hemodynamic instability, it is possible that renal blood flow is negatively impacted, leading to ischemic insult that jeopardizes renal recovery.[4] However, the association of PRS with continuing RRT post-LT has not previously been described.

Iglesias et al[5] reviewed data from the United Network for Organ Sharing to investigate the frequency of renal function recovery in patients with pre-LT renal impairment and factors that impacted recovery/nonrecovery for the first 29 days post-LT. They found that factors that affected recovery included absence of allograft dysfunction and the use of anti-thymocyte globulin as an induction agent (tacrolimus- and cyclosporine-sparing). Unfortunately, we cannot confirm this finding since our study group received tacrolimus and no 1 in the group suffered significant graft dysfunction. However, Iglesias et al concluded that duration of pre-LT renal dysfunction or duration of RRT did not affect renal function recovery post-LT, a finding that our results contradicted. The Iglesias et al study was an older investigation (1989-2005), while both our study and the study by Sharma et al examined more recent data. Our study demonstrated that age was the only significant factor associated with late liberation from RRT at 1-year post-LT. Our study cohort had worse graft and patient survival when compared to a propensity matched control group of patients who never received RRT pre-LT. One-year graft and patient survivals in our study cohort were 70% and 72%, respectively. When the study cohort was stratified into RRT liberated and RRT continued groups, the results were interesting. The RRT continued group

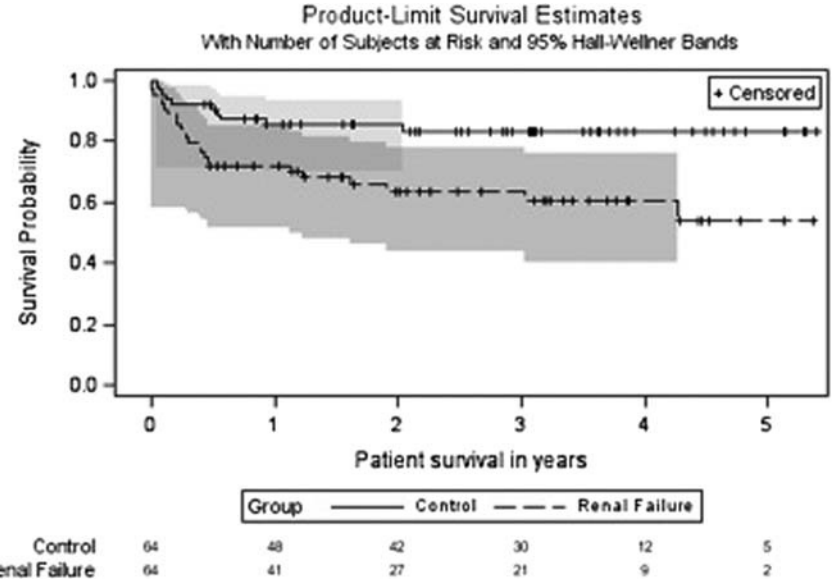

FIGURE 2. Kaplan-Meier curve comparing patient survival curves in LT recipients with pre-LT renal failure receiving RRT (64 patients) and the corresponding matched-control group of cadaveric LT recipients without pre-LT renal failure (P = 0.003).

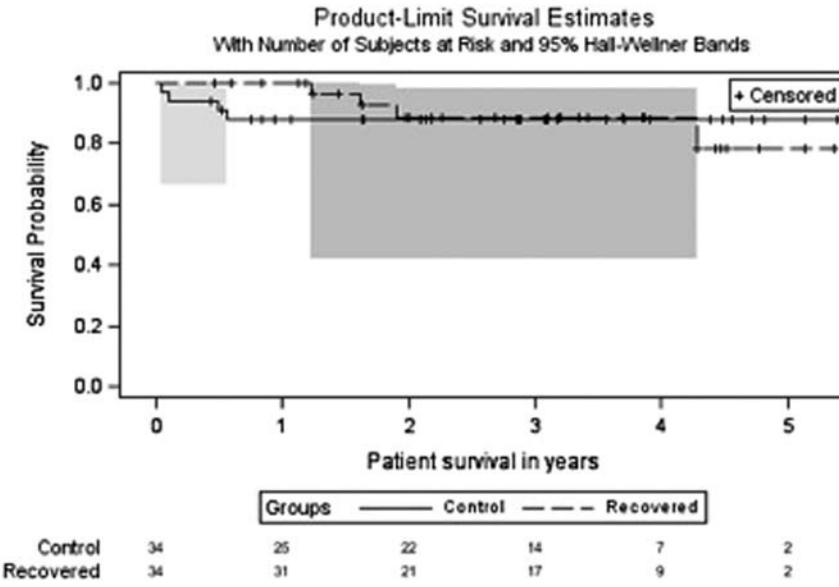

FIGURE 3. Kaplan-Meier survival curve for patients who recovered renal function at the end of the first year (34 patients) compared with the corresponding matched-control group ($P = 0.49$).

had significantly lower 1-year patient and graft survivals when compared to the control group, while the RRT liberated group had similar graft and patient survivals when compared to the control group that never required RRT. These results point to the impact of renal failure on patient and graft survival, a fact that has been described previously[6] and confirmed in our study. Despite their large study samples, neither Sharma et al nor Iglesias et al[2,5] presented any data on the effects of persistent post-LT renal failure on patient and graft survival.

The persistence of RRT in post-LT recipients can impose end-organ damage by provoking chronic inflammation and activation of pro-inflammatory biomarkers.[7] Mortality increased in patients on hemodialysis who also have elevated serum levels of inflammatory biomarkers. The causes of inflammation are multifactorial and may be caused by patient-related factors, oxidative stress, infections, or induction of immune-related responses by the extra-corporal circulation; such responses can be persistent or episodic.[8] The decision to perform LT only in patients with pre-LT renal failure and on RRT or to proceed with SLKT transplantation is difficult; each center has its own criteria, which makes it challenging to compare the results of 1 center to another. In our institution, the transplant selection committee determines organ eligibility. In addition, continued discussions between the transplant surgeons and the transplant nephrologist play an important role in determining the criteria for SLKT. Although our study sheds some light on this topic, we think there is still work to do before reaching firm conclusions.

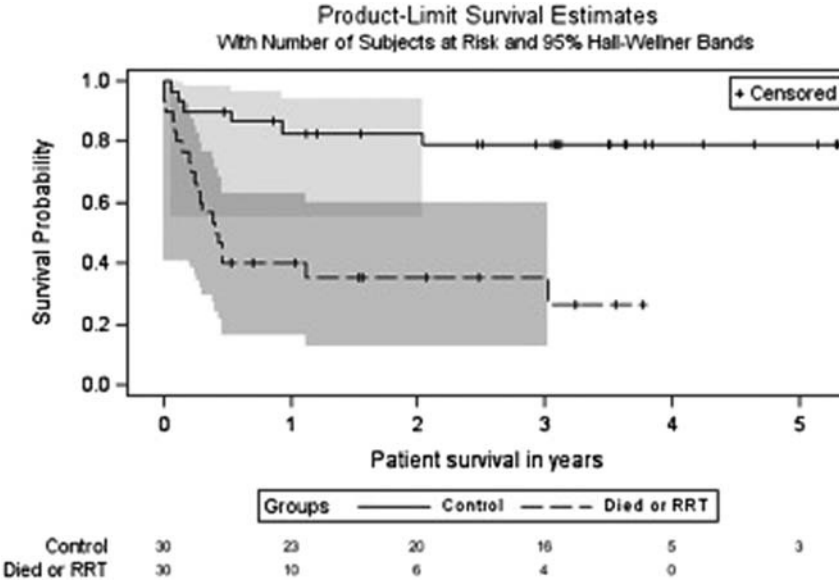

FIGURE 4. Kaplan Meier survival curve for patients with renal failure who did not recover renal function at the end of the first year (30 patients) compared with matched-controls ($P = 0.0003$).

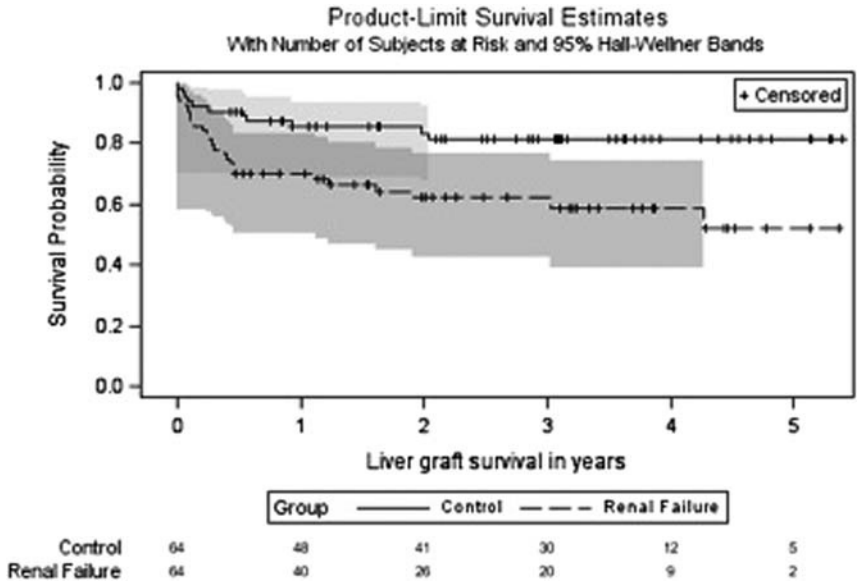

FIGURE 5. Kaplan-Meier curve comparing graft survival between the study cohort (64 patients) and the corresponding matched-control group (p = 0.01).

Although the number of patients investigated was small, our study suggests that pre-LT RRT that continued post-LT is associated with worse patient and graft survival. It is not surprising that the most common etiology of renal failure requiring RRT in our cohort was HRS, affecting 84.38% of the patients. HRS is the most common cause of acute kidney injury in cirrhotic patients,[9,10] with serious consequences on patient outcomes.

The timing of renal transplantation in patients who continue RRT post-LT is important, since delaying such a procedure can adversely affect patient survival; performing renal transplantation within a year of LT may prevent such devastating effects on patient and liver allograft survival. In our study, patients who continued on RRT post-LT were older and had higher cumulative days on RRT pre-LT. In an effort to establish criteria for SLKT for patients on LT wait lists, a panel of experts outlined certain clinical practice recommendations.[11] Our results should be interpreted with caution because our study was retrospective with a small sample size. Criteria to initiate or discontinue RRT may not be similar to those of other institutions, which can impact generalizability.

In conclusion, more than 50% of patients utilizing pre-LT RRT were liberated from RRT at the end of 1-year post-LT. Duration of pre-LT RRT, age, and PRS were factors associated with continued RRT post-LT. At 1-year post-LT, patients who continued post-LT RRT had worse 1-year graft and patient survivals. Finally, patients who were liberated from RRT had similar outcomes to patients who never required RRT pre-LT.

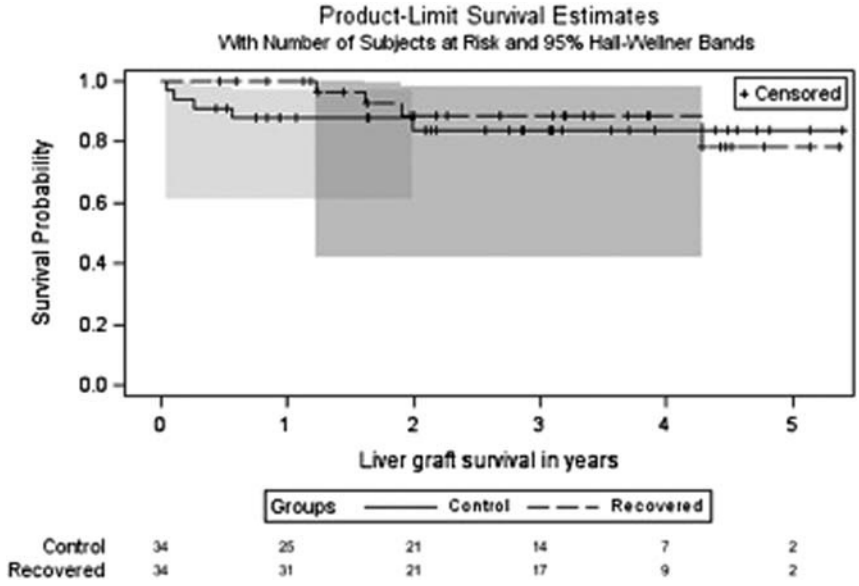

FIGURE 6. Kaplan-Meier curve comparing graft survival for the 34 patients with recovered renal function and the corresponding matched-control group (p = 1.0).

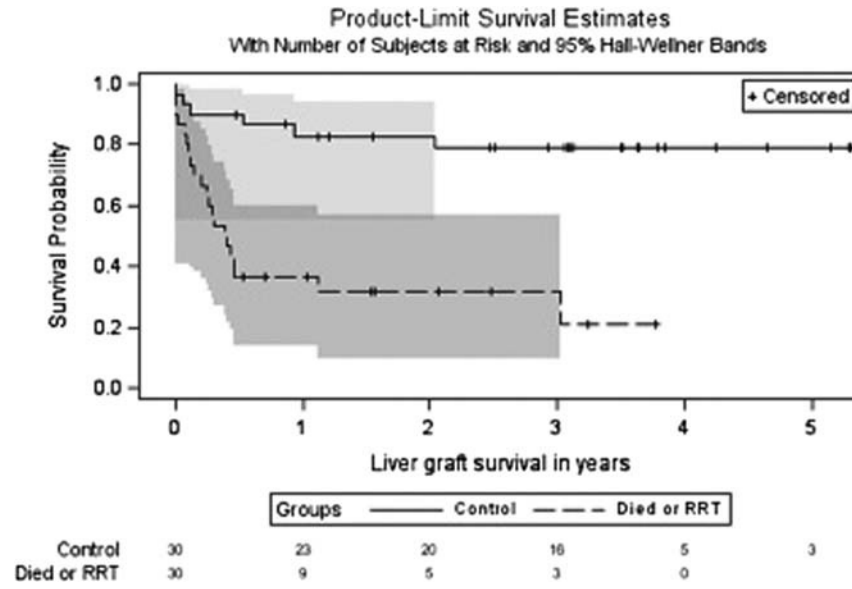

FIGURE 7. Kaplan-Meier curve comparing graft survival for the 30 patients with nonrecovered renal function and the corresponding matched-control group (p = 0.0003).

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