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ORIGINAL ARTICLE

Renal Outcomes After Liver Transplantation in the Model for End-Stage Liver Disease Era

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The proportion of patients undergoing liver transplantation (LT) with renal insufficiency has significantly increased in the Model for End-Stage Liver Disease (MELD) era. This study was designed to determine the incidence and predictors of post-LT chronic renal failure (CRF) and its effect on patient survival in the MELD era. Outcomes of 221 adult LT recipients who had LT between February 2002 and February 2007 were reviewed retrospectively. Patients who were listed as status 1, were granted a MELD exception, or had living-donor, multiorgan LT were excluded. Renal insufficiency at LT was defined as none to mild [estimated glomerular filtration rate (GFR) $\geq$ 60 mL/minute], moderate (30-59 mL/minute), or severe ($<$30 mL/minute). Post-LT CRF was defined as an estimated GFR $<$ 30 mL/minute persisting for 3 months, initiation of renal replacement therapy, or listing for renal transplantation. The median age was 54 years, 66% were male, 89% were Caucasian, and 43% had hepatitis C. At LT, the median MELD score was 20, and 6.3% were on renal replacement therapy. After a median follow-up of 2.6 years (range, 0.01-5.99), 31 patients developed CRF with a 5-year cumulative incidence of 22%. GFR at LT was the only independent predictor of post-LT CRF (hazard ratio = 1.33, $P < 0.001$). The overall post-LT patient survival was 74% at 5 years. Patients with MELD $\geq$ 20 at LT had a higher cumulative incidence of post-LT CRF in comparison with patients with MELD $<$ 20 (P = 0.03). A decrease in post-LT GFR over time was the only independent predictor of survival. In conclusion, post-LT CRF is common in the MELD era with a 5-year cumulative incidence of 22%. Low GFR at LT was predictive of post-LT CRF, and a decrease in post-LT GFR over time was associated with decreased post-LT survival. Further studies of modifiable preoperative, perioperative, and postoperative factors influencing renal function are needed to improve outcomes following LT. ***Liver Transpl 15:1142-1148, 2009.*** © **2009 AASLD.**

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Liver transplantation (LT) has altered the natural history of end-stage liver disease and is now considered the preferred therapy for a wide range of previously fatal chronic liver diseases. Optimal timing of LT is important to avoid harm from intervening too early and futility from transplanting too late.

Serum creatinine, bilirubin, and the international normalized ratio of the prothrombin time are the components of the Model for End-Stage Liver Disease (MELD), which has served as the basis for liver allocation since February 2002.[1] An analysis of data from the Scientific Registry of Transplant Recipients showed that the proportion of candidates with creatinine $\geq$ 2.0 mg/dL or on renal replacement therapy (RRT) at the time of LT has increased significantly in the MELD era.[2] These candidates have significantly lower patient and graft survival in comparison with those with creatinine $<$ 2.0 mg/dL at the time of LT.[2]

Pre-LT renal insufficiency is also an important predictor of post-LT morbidity and mortality.[3,4] Many studies have shown that patients with renal insufficiency at the time of LT have increased sepsis, number

Abbreviations: CI, confidence interval; CNI, calcineurin inhibitor; CRF, chronic renal failure; DM, diabetes mellitus; GFR, glomerular filtration rate; HCV, hepatitis C virus; HR, hazard ratio; HTN, hypertension; LT, liver transplantation; MDRD, Modified Diet in Renal Disease; MELD, Model for End-Stage Liver Disease; RRT, renal replacement therapy.

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of days spent in the intensive care unit, need for postoperative dialysis, and overall costs.[3] Therefore, MELD, which was implemented to minimize pre-LT waitlist mortality, may be shifting mortality to the posttransplant period by assigning a higher priority to patients with renal insufficiency.

We have recently shown that serum creatinine is overweighted in the existing MELD formula.[5] At a given MELD score, candidates with higher creatinine levels have a lower waitlist mortality in comparison with candidates with lower creatinine levels (hazard ratio = 0.89, $P = 0.001$).[5] Given the fact that creatinine is heavily weighted in the MELD formula[5] and a higher proportion of candidates with renal insufficiency undergo transplantation in the MELD era,[2] we sought to evaluate the incidence of chronic renal failure (CRF) after LT in the MELD era and the factors associated with it. In addition, we set out to determine the effect of post-LT CRF on patient survival.

PATIENTS AND METHODS

Patient Population and Data Collection

Medical records of all adult patients (age $\geq$ 18 years) who underwent deceased-donor LT between February 28, 2002 and February 27, 2007 at the University of Michigan were reviewed. The study was approved by our institutional review board. Candidates who were transplanted as status 1, received a MELD exception, or underwent living-donor or repeat LT or multiorgan transplantation were excluded. Data on the demographics (age, gender, and race/ethnicity), the MELD score at the time of transplant, creatinine at the time of listing, 3 months and 1 month prior to LT, and at transplant, the duration of RRT before and after the LT, the history of diabetes and hypertension before LT, serum creatinine at months 1, 3, and 6, and years 1, 3, and 5 post-LT, the hospital status at the time of LT, the number of days spent in the hospital during the initial transplant admission, the type of calcineurin inhibitor (CNI), CNI-sparing strategies in the immediate post-LT period (delay in the introduction of tacrolimus and use of basiliximab), and the status of the patient and graft at the end of the follow-up period were recorded. The patients were followed up to February 29, 2008 or death.

The estimated glomerular filtration rate (GFR) was calculated at each time point with the Modified Diet in Renal Disease (MDRD) formula[6]:

$$\text{Estimated GFR (mL/minute/1.73 m}^2\text{ of body surface area)} = 186 \times (\text{Serum creatinine} \times 0.0113)^{-1.154} \times \text{Age (years)}^{-0.203} (\times 0.742 \text{ if female})$$

Renal insufficiency was defined as mild, moderate, or severe on the basis of the estimated GFR. Patients with an estimated GFR $\geq$ 60 mL/minute were categorized as normal to mild, patients with an estimated GFR of 30 to 59 mL/minute were categorized as moderate, and patients with an estimated GFR $<$ 30 mL/minute were categorized as severe.

Post-LT CRF was defined as an estimated GFR $<$ 30 mL/minute persisting for $\geq$3 months or initiation of RRT or listing for renal transplantation.[7] The definition of pre-LT diabetes included a history of diabetes or use of insulin or oral hypoglycemic medications. Pre-LT hypertension was defined as a history of hypertension or use of antihypertensive. Pre-LT renal dysfunction was defined as an estimated GFR $<$ 60 mL/minute on more than 2 occasions between listing and LT, and the duration of pre-LT dysfunction was calculated as the number of days with a GFR $<$ 60 mL/minute between listing and LT.[8] Graft failure was defined as listing for repeat LT or death. Time to post-LT CRF was calculated from the date of LT to the development of post-LT CRF. Time to death was calculated from the date of transplant to the date of death. Patients were censored at the last follow-up visit or at the time of graft failure.

Immunosuppression

The standard immunosuppression protocol at our center consists of tacrolimus, mycophenolate, and prednisone. Tacrolimus is usually initiated within 24 hours post-transplant at a starting dose of 0.05 mg/kg every12 hours. The target trough levels of tacrolimus are 12 to 15 ng/mL for the first postoperative month, 8 to 10 ng/mL for the second to sixth postoperative months, and 4 to 8 ng/mL subsequently. The introduction of tacrolimus is delayed for up to 7 days in patients with tenuous renal function. In such cases, 1 dose of basiliximab (20 mg) is given intravenously on the day of transplant and on postoperative day 4. Tacrolimus is initiated whenever renal function has stabilized or by postoperative day 7. Mycophenolate is started on day 1 at 1 g twice a day. Prednisone is usually discontinued after 6 months except for patients transplanted for autoimmune liver diseases and those who had experienced acute rejection. Patients are switched to cyclosporine if they develop adverse effects to tacrolimus.

Statistical Analysis

Continuous variables were expressed as the median and range, and categorical variables were expressed as proportions. The cumulative probabilities of post-LT CRF and post-LT patient survival were calculated with Kaplan-Meier analysis. The log-rank test was used to compare the probabilities in subgroups. Cox regression analysis was used to determine the predictors of post-LT CRF and post-LT survival. Covariates with a P value $<$ 0.1 in univariate analysis were included in the multivariable model. The effect of post-LT GFR on survival was assessed with time-dependent Cox regression. A P value $<$ 0.05 was considered significant. The Mann-Whitney test and chi-square tests were used to compare the groups.

RESULTS

Cohort Description and Baseline Characteristics

A total of 346 adult LT procedures were performed at the University of Michigan during the study period. One

TABLE 1. Cohort Characteristics at the Time of LT

Variable (n = 221)	Median (Range) or n (%)
Age (years)	54 (18–70)
Male	146 (66%)
Caucasian	196 (88.6%)
Black	5 (2.4%)
Others	20 (9%)
Hepatitis C	94 (42.5%)
RRT at LT	14 (6.3%)
Pre-LT diabetes	60 (27%)
Pre-LT hypertension	54 (24.4%)
MELD at LT	20 (7–40)
GFR at LT	
• Normal or mild ≥60 mL/min	109 (49%)
• Moderate, 30–59 mL/min	70 (32%)
• Severe, <30 mL/min	42 (19%)
Immunosuppression	
• Delay in introducing CNI at LT	66 (30%)
• Tacrolimus	183 (83%)
• Cyclosporine	38 (17%)

Abbreviations: CNI, calcineurin inhibitor; GFR, glomerular filtration rate; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; RRT, renal replacement therapy.

hundred twenty-five were excluded (status 1 = 16, MELD exceptions = 86, re-LT = 12, others = 11). The final cohort consisted of 221 patients. Table 1 shows the baseline characteristics of the patients at the time of LT. The median age of the cohort was 54 years, 66% were males, 89% were Caucasian, and 43% had hepatitis C. One hundred twelve (51%) patients had moderate to severe renal insufficiency at the time of LT, and 14 (6.3%) were on RRT at the time of LT.

Immunosuppression

All 221 patients received CNI-based triple immunosuppression. Sixty-six (30%) had a delay in the introduction of a CNI for 1 to 7 days because of tenuous renal function. Most patients (83%) were on tacrolimus, while 17% were on cyclosporine at the end of follow-up.

Outcomes of the Cohort

Patients with Pre-LT Renal Dysfunction

Eighty (36%) patients had pre-LT renal dysfunction; of these, 14 were on RRT at the time of LT. Forty-two were men, 92% were Caucasian, and 38% had hepatitis C as the etiology of liver disease. Compared to patients who did not have pre-LT renal dysfunction, this subset of patients was older (56 versus 53 years, $P = 0.01$) and had a higher median MELD score at LT (23 versus 19, $P = 0.001$). The median estimated GFR at listing and at LT was 45 (0-144) and 36 mL/minute (0-74), respectively. The median duration of pre-LT renal dysfunction was 51 days (4-890).

The patients with pre-LT renal dysfunction had a higher incidence of post-LT CRF than the patients who did not (26% versus 7%, $P = 0.01$). The 5-year cumulative incidence of post-LT CRF in patients with and without pre-LT renal dysfunction was 34% and 10%, respectively ($P = 0.0001$). However, the number of post-LT deaths [22 (28%) versus 29 (21%), $P = 0.167$] and the 5-year post-LT mortality (32% versus 23%, $P = 0.19$) in these 2 groups were similar. The duration of pre-LT renal dysfunction was associated neither with post-LT CRF ($P = 0.3$) nor with post-LT survival ($P = 0.7$). Similarly, the delay in the introduction of a CNI did not affect the risk of post-LT CRF ($P = 0.7$) in this subgroup.

Patients Receiving RRT at the Time of Transplant

Of the 14 patients who were on RRT at the time of LT, 8 (57%) had recovery of their renal function (Fig. 1). The median duration of pre-LT RRT was 10.5 days (2-64). The baseline characteristics of the patients who recovered their renal function were similar to those of the patients who did not except for a shorter duration of pre-LT RRT (6.5 versus 17 days, $P = 0.003$).

All 8 with recovered renal function required transient RRT during the immediate postoperative period. Four required RRT for 1 to 3 days only, while the other 4 required it for 11 to 48 days (median, 38). The median GFR at the last follow-up visit in these 2 groups was similar: 55.5 (43-120) versus 63.5 mL/minute (43-84). Four of these 8 patients had a GFR < 60 mL/minute at their last follow-up visit. All 8 were alive at the end of the follow-up period, that is, a median of 2.7 (1.3-4.4) years post-LT.

Among the 6 (43%) patients who did not recover their renal function, 4 died after a median follow-up of 8.5 months (4.5-37; Fig. 1). The cause of death in all 4 patients was multiorgan failure. Two patients were alive at the end of the follow-up period, 18 and 37 months post-LT. The observed post-LT mortality in this group was significantly higher than that in those who recovered their renal function ($P = 0.015$).

Patients Not Receiving RRT at the Time of Transplant

Two hundred seven patients were not on RRT at the time of LT, 109 (53%) had a GFR ≥ 60 mL/minute, 70 (34%) had a GFR between 30 and 59 mL/minute, and 38 (18%) had a GFR < 30 mL/minute. This group included 66 (32%) patients with pre-LT renal dysfunction.

Incidence of Post-LT CRF

Of the 207 patients who were not on RRT at the time of transplant, 31 (15%) developed post-LT CRF after a median of 2.6 years (0.01-5.99) post-LT (Fig. 1). Five of these patients required transient RRT (median, 88 days; range, 2-210 days) during the initial post-LT period; all 5 had post-LT CRF at the last follow-up. The incidence rate of post-LT CRF was 5.43 per 100 patient years. The cumulative incidence of post-LT CRF at 1, 3, and 5 years was 8%, 17%, and 22%, respectively (Fig.

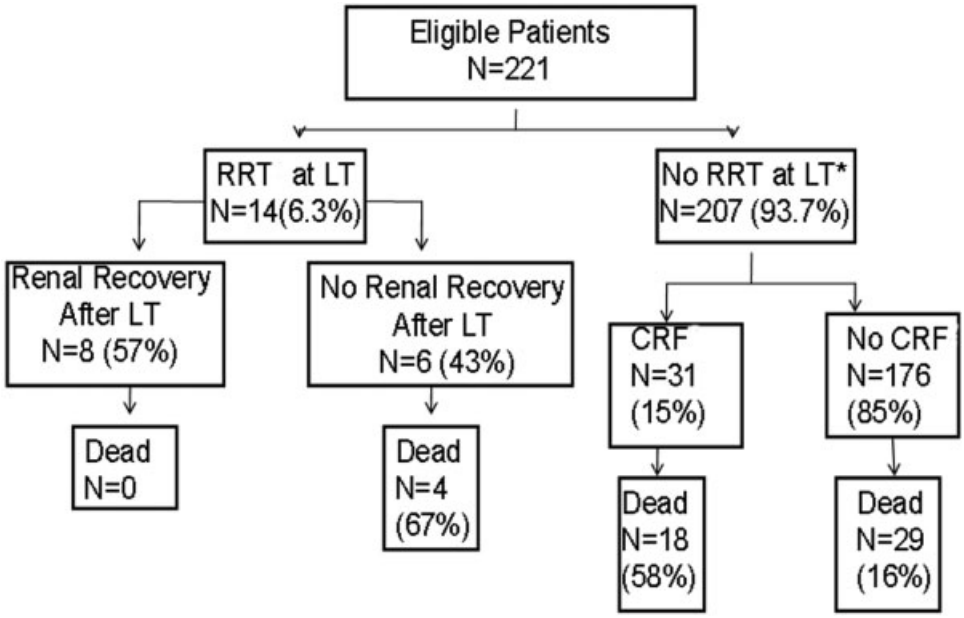

Figure 1. Post-LT outcomes of patients with and without RRT at the time of LT. The asterisk indicates the inclusion of 64 patients with pre-LT renal dysfunction. Abbreviations: CRF, chronic renal failure; LT, liver transplantation; RRT, renal replacement therapy.

2A). The cumulative incidence of post-LT CRF at 1, 3 and 5 years in patients with MELD < 20 and in those with MELD ≥ 20 at LT was 5%, 10%, and 17% and 11%, 23%, and 37%, respectively ($P = 0.03$).

Predictors of Post-LT CRF

On univariate analysis, age, pre-LT diabetes, MELD, delay in the introduction of a CNI, and estimated GFR at the time of LT showed a trend with a P value ≤ 0.1 (Table 2). The duration of pre-LT renal dysfunction was not significant ($P = 0.5$). The estimated GFR at the time of LT was the only independent predictor of post-LT CRF after adjustments for age, pre-LT diabetes, and MELD at the time of LT (Table 2). Every 10-mL decrease in the estimated GFR at the time of LT increased the hazard of post-LT CRF by 33%.

Figure 2B shows that patients with a GFR < 30 mL/minute at the time of LT had a higher probability of developing post-LT CRF than patients with a GFR of 30 to 59 mL/minute or a GFR ≥ 60 mL/minute at the time of LT ($P < 0.0001$). The 1-, 3- and 5-year cumulative incidence of post-LT CRF in these 3 groups was 5%, 8%, and 8% for patients with a GFR ≥ 60 mL/minute, 8%, 16%, and 27% for patients with a GFR of 30 to 59 mL/minute, and 20%, 42%, and 77% for patients with a GFR < 30 mL/minute at the time of LT. Even for patients with MELD ≥ 20 at LT, a lower pre-LT GFR was associated with a higher cumulative incidence of post-LT CRF ($P = 0.003$). Among the patients with an estimated GFR > 60 mL/minute at LT, the 1-year incidence of post-LT CRF was similar for patients with MELD scores < 20 or ≥ 20 at LT (4.8% versus 5.4%).

The median hospital length of stay (22 versus 10 days; $P = 0.005$) and intensive care unit length of stay (6 versus 3 days; $P = 0.003$) for the initial transplant admission were longer for patients who developed post-LT CRF.

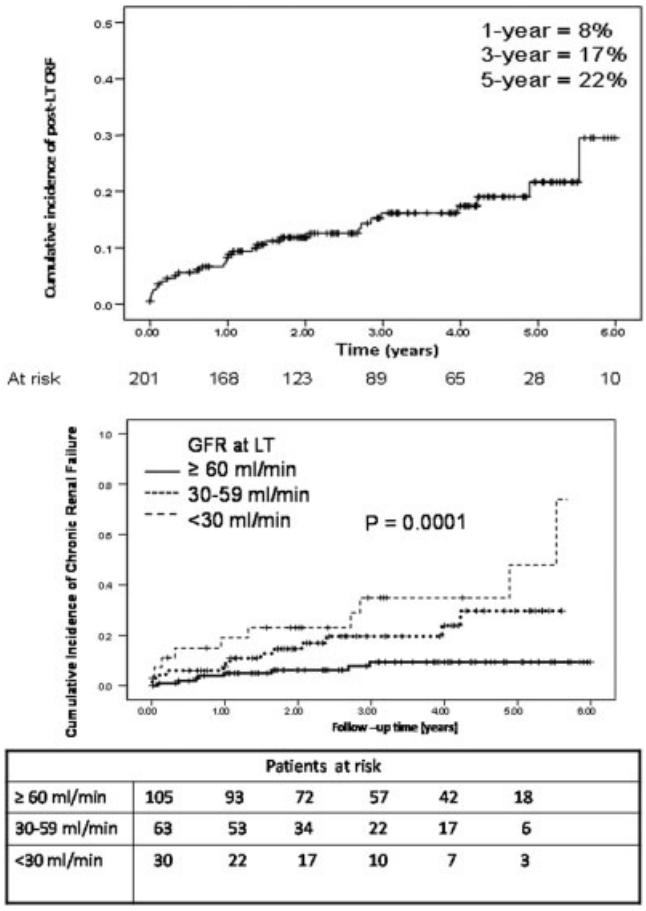

Figure 2. (A) Cumulative incidence of post-LT CRF. (B) Cumulative incidence of post-LT CRF according to the estimated GFR at LT. Abbreviations: CRF, chronic renal failure; GFR, glomerular filtration rate; LT, liver transplantation.

TABLE 2. Univariate and Multivariate Analysis: Predictors of Post-LT Chronic Renal Failure

Univariate Analysis		
Variable	HR (95% CI)	*P* Value
Age (every 10-year increase)	1.63 (1.29–2.05)	0.035
Hepatitis C	1.56 (0.77–3.16)	0.2
MELD at LT	1.05 (0.99–1.12)	0.07
Pre-LT DM	1.76 (0.87–3.57)	0.1
Pre-LT HTN	0.8 (0.37–1.73)	0.3
GFR at LT (every 10 mL/min decrease)	1.32 (1.23–1.42)	0.0001
Delay in introducing CNI at LT	1.86 (0.87–3.97)	0.1
Multivariate Analysis		
GFR at LT (every 10-mL decrease)	1.33 (1.11–1.58)	0.001

Abbreviations: CI, confidence interval; CNI, calcineutin inhibitor; DM, diabetes mellitus; GFR, glomerular filtration rate; HR, hazard ratio; HTN, hypertension; LT, liver transplantation; MELD, Model for End-Stage Liver Disease.

TABLE 3. Multivariate Analysis: Predictors of Post-LT Patient Mortality

Variable	Hazard Ratio (95% CI)	*P* Value
Etiology (non-HCV)	0.580 (0.34–1.04)	0.08
Age at LT	1.038 (0.99–1.02)	0.07
MELD at LT	1.00 (.95–1.05)	0.97
GFR at LT	1.00 (.99–1.02)	0.62
Post-LT GFR over time		
GFR <30 versus ≥60 mL/min	3.2 (1.19–8.67)	0.02
GFR <30 versus 30–60 mL/min	2.9 (1.3–6.4)	0.008

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; HCV, hepatitis C virus; LT, liver transplantation; MELD, Model for End-Stage Liver Disease.

Post-LT Survival and Its Predictors

A total of 51 patients died during the study period: 4 (29%) of the 14 patients with RRT and 47 (23%) of the 207 patients without RRT at the time of LT (Fig. 1). The overall post-LT survival at 1, 3, and 5 years was 88%, 76%, and 74%.

Patients who developed post-LT CRF had higher mortality ($P < 0.0001$) than those who did not. Univariate analysis showed that age, etiology, and post-LT CRF were associated with higher post-LT mortality, but pre-LT renal dysfunction was not ($P = 0.7$). The decrease in GFR during post-LT follow-up was the only independent predictor of post-LT mortality after adjustments for age, etiology, MELD, and GFR at LT (Table 3).

The median hospital length of stay for the initial transplant admission was longer for patients who died compared to those who survived after LT (15 versus 10 days, $P = 0.001$), but the median intensive care unit length of stay was similar (4 versus 3 days, P = not significant) in the 2 groups.

DISCUSSION

The results from this study show that post-LT CRF is common in the MELD era with a 5-year cumulative incidence of 22%. Although the estimated GFR at LT was the most important determinant of post-LT CRF, a decrease in post-LT GFR over time strongly predicted the post-LT mortality.

There are 2 cohort studies from the pre-MELD era that have evaluated the incidence of post-LT CRF.[7,9] The first study from the pre-MELD era, by Gonwa et al.,[9] included 834 patients from a single center who had LT between June 1985 and December 1994. The combined incidence of post-LT CRF, defined as sustained serum creatinine ≥ 2.5 mg/dL or end-stage renal disease (on RRT), was 4.3% at 5 years and 18% after 13 years of follow-up. It should be noted that the definition of CRF and the endpoint used in Gonwa et al.'s study were different from those of our study and Ojo et al.'s study.[7] The second, larger study analyzed the data from the Scientific Registry of Transplant Recipients for 36,849 adult patients who had LT in the United States between January 1, 1990, and December 31, 2000. The incidence of post-LT CRF was 18% at 5 years and 26% at 10 years.[7] This study, like ours, defined post-LT CRF as GFR ≤ 29 mL/minute/1.73 m^2 of body surface area or the development of end-stage renal disease, which was defined as initiation of RRT or listing for renal transplantation.

Because creatinine is one of the components of MELD, one would expect a higher incidence of post-LT CRF in the MELD era. Our data demonstrated a slightly higher cumulative incidence of post-LT CRF (ie, 22% versus 18% by Ojo et al.[7] from the pre-MELD era), but these differences were not significant. The most likely reason that an increase in the incidence of post-LT CRF was not observed is the small number of events and short duration of follow-up in the current study. The frequent use of a CNI-sparing strategy in our population (30%) may also have reduced the overall frequency of post-LT CRF, but this variable was not an independent predictor of renal outcomes (Table 2).

The definition of chronic kidney disease has evolved in the past few years. In fact, the Kidney Disease Outcome Quality Initiative of the National Kidney Foundation on chronic kidney disease does not consider serum creatinine alone as a sufficient criterion for staging chronic kidney disease.[10] In our study as well as Ojo et al.'s study, the estimated GFR was calculated with the MDRD equation, which accounts for weight, race, gender, and body surface area[6,11] and is more accurate than measured creatinine clearance from 24-hour urine collections or estimation using the Cockcroft and Gault formula.[12]

In Ojo et al.'s study,[7] age, pre-LT GFR, pre-LT hypertension and diabetes, and the use of cyclosporine were predictors of post-LT CRF. In our study, GFR at the time of LT was the only independent predictor of post-LT CRF. Even among candidates with higher MELD scores (≥20) at LT, those with lower estimated GFR at LT had a higher incidence of post-LT CRF. Age was a significant covariate in the univariate analysis; however, it lost significance in the multivariate model. The use of CNI-sparing strategies (delay in the introduction of a CNI in the immediate postoperative period) in patients with tenuous renal function at LT was not predictive of post-LT CRF either. Several other studies have also reported a higher incidence of post-LT CRF among patients with a low GFR or high serum creatinine at the time of LT.[3,7-9,13] Most of the previous studies defined renal insufficiency on the basis of serum creatinine.[8,9,13] However, serum creatinine is influenced by gender, age, ethnicity, and muscle mass. Many patients with cirrhosis have muscle wasting; therefore, serum creatinine may grossly overestimate their renal function.

One study found that the duration of pre-LT renal failure was predictive of 6- and 12-month serum creatinine post-LT.[8] This study included 69 patients with baseline serum creatinine ≥ 1.5 mg/dL. Thirteen of these patients underwent combined liver and kidney transplantation. The authors found that pre-LT dialysis of >3.6 weeks predicted serum creatinine of ≥1.5 mg/dL at 12 months post-LT. Our definition of pre-LT renal dysfunction was different from that of Campbell et al.'s study.[8] Although our study failed to show any association between the duration of pre-LT renal dysfunction and post-LT CRF, the duration of pre-LT RRT was shorter for patients who recovered their renal function after LT in comparison with those who did not.

Several studies have reported that CRF per se is associated with an increase in mortality.[14,15] Ojo and colleagues[7] confirmed that post-LT CRF after nonrenal organ transplantation was associated with higher mortality. Our study validated their results and showed that a decrease in post-LT GFR over time was associated with a significant decrease in post-LT survival (hazard ratio = 2.9 for GFR < 30 mL/minute versus GFR = 30-60 mL/minute; hazard ratio = 3.2 for GFR < 30 mL/minute versus GFR ≥ 60 mL/minute). Although creatinine is one of the components of the MELD score,[1] MELD was not associated with post-LT CRF or post-LT mortality. Even though some of the earlier studies found that a high MELD score at LT correlated with lower 1- to 2-year post-LT survival,[16-18] the predictive ability of MELD for post-LT mortality is poor.

The main limitations of our study include its retrospective design, the small number of patients from a single center, and the lack of comparison to a similar cohort transplanted in the pre-MELD era. An additional limitation is the use of an indirect method for determining GFR. Although iothalamate clearance or a 24-hour urine collection for creatinine clearance are the gold standards for measuring GFR, these methods are time-consuming and cumbersome, especially in end-stage liver disease patients. Moreover, the MDRD equation measures the estimated GFR more accurately than the Cockcroft-Gault formula.[12] Despite these limitations, this is the first study that has evaluated the incidence and predictors of post-LT CRF in the MELD era.

In conclusion, our study shows that post-LT CRF is common in the MELD era with an incidence of 22% at 5 years. Although this incidence is not substantially different from that of prior reports in the pre-MELD era, additional studies involving larger numbers of patients with a longer follow-up are warranted to confirm or refute our observations. Given the higher incidence of post-LT CRF among patients with MELD ≥ 20 at the time of transplant and the fact that the mean MELD score at the time of LT is over 20 in the United States,[19] these results may have a substantial impact on future outcomes with LT. Finally, because post-LT CRF is strongly associated with patient survival, strategies to reduce the frequency and severity of pre-LT, peri-LT, and post-LT renal failure are needed to improve the clinical outcomes with LT in the MELD era. Specifically, prospective studies of pretransplant medical therapies such as renal vasodilators and post-LT immunosuppression regimens with CNI minimization and mechanistic studies of the risk factors and pathogenesis of post-LT CRF are warranted.

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