Early Changes in Kidney Function Predict Long-Term Chronic Kidney Disease and Mortality in Patients After Liver Transplantation

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Background. Chronic kidney disease (CKD) is a well-known complication after liver transplantation (LT) and is associated with increased mortality. The purpose of this study was to determine risk factors of advanced CKD and mortality after LT.

Methods. Four hundred forty-five adult patients underwent LT between June 1990 and September 2007 and survived more than 1 month. Multivariate Cox regression analyses were performed for time to CKD stage 4 (glomerular filtration rate [GFR] ≤30 mL/min), time to chronic dialysis, and all-cause mortality. Several patient and disease characteristics were used as independent pre- and posttransplant variables. We specifically analyzed a drop more than or equal to 30% in the estimated GFR (eGFR) during the first year posttransplant.

Results. Diabetes mellitus pretransplant and a drop more than or equal to 30% in the eGFR between 3 and 12 months predicted CKD stage 4 (odds ratio [OR] 4.1, 95% confidence interval [CI] 1.9–5.4, $P<0.001$ and OR 16.1, 95% CI 5.9–44.5, $P<0.0001$, respectively), the need for chronic dialysis (OR 3.8, 95% CI 1.1–13.2, $P=0.03$ and OR 14.6, 95% CI 3.0–71.4, $P<0.001$, respectively), and all-cause mortality (OR 1.9, 95% CI 1.2–2.9, $P=0.004$ and OR 2.6, 95% CI 1.6–4.4, $P<0.001$, respectively), more than 1 year after LT.

Conclusions. Diabetes mellitus pretransplant and a drop more than or equal to 30% in the eGFR within the first year are strong predictors of advanced CKD, chronic dialysis, and death more than 1 year after LT. These easily determined clinical variables define a population at risk for CKD who should be targeted for renal protection strategies.

Keywords: Liver transplantation, Glomerular filtration rate, Chronic kidney disease, Chronic dialysis, Survival, Mortality.

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Chronic kidney disease (CKD) is a critical complication after liver transplantation (LT). The risk of developing CKD has been reported to be close to 25% at 10 years after LT (*1*, *2*). We have previously reported that LT patients with end-stage kidney disease requiring chronic dialysis are at an increased risk of death compared with those without end-stage kidney disease and with matched dialysis controls (*3*). This phenomenon is also seen in renal and heart transplant recipients (*4*, *5*).

The cause of CKD after LT is multifactorial, including calcineurin inhibitor (CNI) nephrotoxicity, advanced age, diabetes mellitus, IgA nephropathy, hepatitis C-related membranoproliferative glomerulonephritis, hepatitis B virus-related membranous glomerulonephritis, hepatorenal syndrome, pretransplant renal insufficiency, and postoperative acute kidney injury (*6*–*9*). CNI nephrotoxicity was initially reported as high as 73.3% (*6*). However, more recently, kidney biopsies obtained from LT recipients with CKD showed glomerular changes (consistent with diabetic nephropathy and hypertensive changes) in 42% of the patients and evidence of CNI toxicity in only 16% of the patients (*8*).

In clinical practice, it would be ideal to identify simple clinical characteristics of the population at risk of progression to CKD at an early stage. The purpose of this study was therefore to determine early potentially modifiable clinical risk factors of advanced CKD and mortality after LT.

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RESULTS

A summary of patients' baseline and posttransplant information is shown in Table 1. All these variables were considered in the multivariate Cox regression analyses.

Continuous veno-venous hemofiltration was required in 11 patients preoperatively and during the first 3 weeks postoperatively in 39 who survived more than 1 month after LT. We observed 31 patients with new-onset diabetes mellitus at 3 months and 14 patients between 3 and 12 months posttransplant.

Mean (±SD) time to first estimated glomerular filtration rate (eGFR) less than 30 mL/min was 3.19±2.61 years. Thirty-seven of 392 patients surviving more than 1 year had an eGFR that decreased below 30 mL/min. Twelve of the 427 patients surviving more than 3 months after LT needed chronic dialysis. The cumulative incidences of chronic dialysis in patients with a drop of less than 30% and in those with a drop of more than or equal to 30% in the eGFR between 3 and 12 months after LT were 0% and 0% at 1 year, 0.5% and 7.1% at 5 years, and 4.2% and 7.1% at 10 years, respectively.

Fifty-three patients in the study population died between 1 and 12 months posttransplant. The causes of death were infections (n=13), recurrent disease (n=9), malignancy (n=7), cardiac (n=7), graft failure (n=6), portal vein thrombosis (n=3), multiorgan failure (n=3), hepatic artery thrombosis (n=2), and acute renal failure, cerebrovascular accident, and other (n=1 each).

One hundred nine patients died after the first year. There were eight patients with missing data who were excluded for the analysis of renal function. The causes of death after 1 year posttransplant included recurrence of hepatitis C virus (n=20), malignancies (n=20), cardiovascular (n=12), infections (n=8), recurrence of alcoholic cirrhosis (n=6), other causes (n=19), and unknown causes (n=24). Cox regression results are summarized in Tables 2 and 3.

Univariate Analysis

Predictors of CKD stage 4 (eGFR <30 mL/min) more than 1 year posttransplant included age, positive serology for hepatitis C virus, diabetes mellitus pretransplant, transplant after 1996, eGFR before LT, eGFR at 1, 3, and 12 months, eGFR drop more than or equal to 30% between 3 months and 1 year, systolic blood pressure at 1 year, total bilirubin and alkaline phosphatase at 1 month, and alkaline phosphatase at 1 year (Table 2).

Predictors of chronic dialysis more than 1 year posttransplant included eGFR before LT, eGFR at 1 and 3 months and at 1 year posttransplant, diabetes mellitus pretransplant, and total bilirubin at 1 month and 1 year posttransplant (Table 2).

Predictors of all-cause mortality more than 1 year posttransplant included age, male gender, diabetes mellitus pretransplant, positive serology for hepatitis C virus, cumulative cyclosporine A (CsA) dose during the first 3 months posttransplant, systolic blood pressure at 1 year, total bilirubin at 1 month and 1 year, alkaline phosphatase at 1 year, and eGFR drop more than or equal to 30% between 1 or 3 months and 1 year posttransplant (Table 2).

At 1 year, there were 44 of 363 (12.1%) patients at risk as defined by a drop in of eGFR more than or equal to 30%. In addition, there were 98 of 363 (27%) patients with pretransplant diabetes mellitus, of whom 11 patients also experienced a drop in the eGFR more than or equal to 30% at 1 year posttransplant. Finally, 131 patients (36%) had either of the

TABLE 1. Demographic, clinical, and biochemical variables

Variable	n=445
Female gender, n (%)	137 (31)
Age (yr)	55.2±11.1
Hepatitis C virus, n (%)	152 (34)
Diabetes mellitus pretransplant	123 (28)
Weight (kg)	
Pretransplant (n=445)	75.2±16.4
1 mo (n=437)	72.6±18.4
3 mo (n=416)	73.4±18.2
12 mo (n=382)	77.8±18.6
eGFR (mL/min)	
Pretransplant (n=363)	70.4±32.4
1 mo (n=431)	70.1±27.9
3 mo (n=410)	67.1±24.4
12 mo (n=378)	64.5±24.7
CsA dose (mg/kg)	
Total over 3 mo (n=204)	398.2±203.7
CsA dose (mg/kg/d)	
1 mo (n=181)	5.59±3.33
3 mo (n=179)	4.79±2.74
12 mo (n=153)	3.70±2.36
CsA trough levels (ng/mL)	
1 mo (n=64)	214.2±115.6
3 mo (n=57)	178.8±95.1
12 mo (n=44)	170.7±138.6
CsA C2 levels (ng/mL)	
1 mo (n=40)	756.4±265.7
3 mo (n=30)	802.1±339.2
12 mo (n=28)	615.5±215.2
Tacrolimus dose (mg/kg)	
Total over 3 mo (n=226)	7.84±5.38
Tacrolimus dose (mg/kg/d)	
1 mo (n=201)	0.11±0.07
3 mo (n=199)	0.11±0.09
12 mo (n=183)	0.07±0.05
Tacrolimus trough levels (ng/mL)	
1 mo (n=230)	8.10±4.25
3 mo (n=212)	8.19±3.86
12 mo (n=187)	7.09±3.00
SBP (mm Hg) at 12 mo (n=140)	127.9±19.9
DBP (mm Hg) at 12 mo (n=140)	74.2±13.5
Hypertension pretransplant, n (%)	76 (17%)
ACEi and/or ARB use, (n [%]) 3 mo 12 mo	38 (8.5%) 58 (13%)

Data are expressed as mean±SD or frequency (percentage) as appropriate.
Scr, serum creatinine; eGFR, estimated glomerular filtration rate; CsA, cyclosporine; C2, CsA levels 2 hr post-AM dose; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE 2. Univariate Cox regression analyses

Variables	eGFR ≤30 mL/min at >1 yr (n=34/288)[a] OR (95% CI)	Chronic dialysis at >1 yr (n=11/356)[a] OR (95% CI)	All-cause mortality at >1 yr (n=98/360)[a] OR (95% CI)
Age (per 10 yr)	1.79 (1.23–2.60); $P=0.002$	1.64 (0.87–3.10); $P=0.12$	1.39 (1.15–1.69); $P<0.001$
Gender (male)	0.67 (0.35–1.28); $P=0.23$	1.69 (0.46–6.26); $P=0.43$	1.73 (1.11–2.70); $P=0.02$
Hypertension pretransplant	1.31 (0.55–3.15); $P=0.54$	1.49 (0.33–6.85); $P=0.61$	1.05 (0.61–1.82); $P=0.86$
MELD–NOCA (per scale unit)	1.02 (0.98–1.05); $P=0.37$	1.01 (0.95–1.07); $P=0.73$	0.98 (0.96–1.00); $P=0.10$
Hepatitis C virus	2.84 (1.49–5.44); $P=0.002$	2.58 (0.83–8.04); $P=0.10$	1.49 (1.01–2.20); $P=0.04$
Calendar year of transplant (per 10 yr)	0.57 (0.23–1.42); $P=0.22$	0.18 (0.03–1.19); $P=0.08$	0.95 (0.54–1.65); $P=0.85$
Transplant after 1996	0.37 (0.19–0.73); $P=0.004$	0.17 (0.04–0.80); $P=0.03$	1.01 (0.67–1.53); $P=0.97$
Initiated on Tacrolimus	0.91 (0.47–1.76); $P=0.79$	0.28 (0.06–1.30); $P=0.10$	1.09 (0.74–1.63); $P=0.65$
Initiated on CsA	1.09 (0.57–2.11); $P=0.79$	3.59 (0.77–16.8); $P=0.10$	0.91 (0.62–1.36); $P=0.65$
MMF treatment	0.62 (0.30–1.29); $P=0.20$	0.44 (0.09–2.08); $P=0.30$	0.98 (0.65–1.49); $P=0.94$
Aza treatment	1.54 (0.78–3.03); $P=0.21$	1.89 (0.50–7.21); $P=0.35$	0.83 (0.56–1.23); $P=0.35$
Scr pretransplant (per 10 μmol/L)	1.01 (1.00–1.03); $P=0.14$	1.02 (0.99–1.04); $P=0.20$	1.00 (0.97–1.02); $P=0.76$
eGFR pretransplant (per 10 mL/min)	0.83 (0.73–0.95); $P=0.01$	0.94 (0.76–1.17); $P=0.58$	0.98 (0.91–1.05); $P=0.57$
eGFR at 1 mo (per 10 mL/min)	0.71 (0.60–0.84); $P<0.001$	0.70 (0.53–0.93); $P=0.01$	0.98 (0.91–1.06); $P=0.64$
eGFR at 3 mo (per 10 mL/min)	0.67 (0.55–0.82); $P<0.001$	0.55 (0.39–0.79); $P=0.001$	1.00 (0.92–1.09); $P=0.99$
eGFR at 1 yr (per 10 mL/min)	0.40 (0.30–0.53); $P<0.001$	0.43 (0.29–0.66); $P<0.001$	0.97 (0.89–1.05); $P=0.45$
CVVH pretransplant	1.11 (0.15–8.10); $P=0.92$	3.78 (0.49–29.3); $P=0.20$	1.22 (0.39–3.86); $P=0.73$
CVVH <3 wk posttransplant	1.91 (0.68–5.40); $P=0.22$	3.47 (0.75–16.0); $P=0.11$	1.37 (0.69–2.72); $P=0.36$
CsA dose (10 mg/kg total over first 3 mo)	0.98 (0.95–1.00); $P=0.10$	0.98 (0.94–1.02); $P=0.27$	0.98 (0.97–1.00); $P=0.04$
Tacrolimus dose (mg/kg) total over first 3 mo	1.02 (0.92–1.13); $P=0.71$	1.10 (0.93–1.31); $P=0.25$	0.96 (0.90–1.02); $P=0.18$
Diabetes mellitus pretransplant	2.46 (1.27–4.76); $P=0.01$	4.64 (1.45–14.9); $P=0.01$	1.80 (1.19–2.71); $P=0.01$
New onset diabetes mellitus at 3 mo	0.32 (0.04–2.34); $P=0.26$	0.00 (0–∞); $P=0.35$	1.54 (0.82–2.88); $P=0.18$
New onset diabetes mellitus at 1 yr	2.36 (0.73–7.71); $P=0.15$	0.00 (0–∞); $P=0.46$	0.71 (0.22–2.23); $P=0.56$
ACEi and/or ARB posttransplant	1.39 (0.58–3.36); $P=0.46$	0.98 (0.12–7.82); $P=0.99$	1.05 (0.57–1.93); $P=0.88$
SBP 1 yr posttransplant (per 10 mm Hg)[b]	1.45 (1.07–1.97); $P=0.02$	1.22 (0.72–2.06); $P=0.47$	1.46 (1.21–1.76); $P<0.001$
DBP 1 yr posttransplant (per 10 mm Hg)[b]	1.50 (0.92–2.43); $P=0.11$	0.97 (0.43–2.20); $P=0.94$	1.18 (0.87–1.61); $P=0.28$
Total bilirubin at 1 mo	2.48 (1.73–3.56); $P<0.001$	2.53 (1.19–5.39); $P=0.02$	1.74 (1.17–2.58); $P=0.01$
Total bilirubin at 3 mo	1.33 (0.88–2.01); $P=0.17$	0.34 (0.01–18.0); $P=0.59$	1.17 (0.87–1.58); $P=0.29$
Total bilirubin at 1 yr	1.40 (0.74–2.66); $P=0.30$	2.30 (1.21–4.38); $P=0.01$	1.79 (1.34–2.40); $P<0.001$
Alkaline phosphatase at 1 mo	1.19 (1.05–1.35); $P=0.01$	1.12 (0.88–1.42); $P=0.37$	0.97 (0.86–1.09); $P=0.59$
Alkaline phosphatase at 3 mo	1.10 (0.99–1.22); $P=0.09$	1.10 (0.89–1.36); $P=0.38$	1.06 (0.98–1.14); $P=0.13$
Alkaline phosphatase at 1 yr	1.20 (1.09–1.33); $P<0.001$	1.15 (0.90–1.46); $P=0.26$	1.24 (1.17–1.32); $P<0.001$
eGFR $drop_{1-3}$ ≥30%	1.45 (0.61–3.42); $P=0.40$	1.85 (0.40–8.46); $P=0.43$	1.43 (0.81–2.52); $P=0.21$
eGFR $drop_{1-12}$ ≥30%	2.01 (0.98–4.10); $P=0.06$	2.87 (0.91–9.04); $P=0.07$	1.96 (1.29–2.97); $P=0.002$
eGFR $drop_{3-12}$ ≥30%	3.52 (1.65–7.52); $P=0.001$	3.15 (0.85–11.7); $P=0.09$	2.60 (1.62–4.18); $P<0.001$

[a] Patients with non-missing data.

[b] SBP and DBP were available for only a minority of the patients, so these were not part of the multivariate analysis.

OR, odds ratio; CI, confidence interval; MELD NOCA, Model for end-stage liver disease (no cancer); Scr, serum creatinine; eGFR, estimated glomerular filtration rate; CsA, cyclosporine; MMF, mycophenolate mofetil; Aza, azathioprine; CVVH, continuous veno-venous hemofiltration; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR $drop_{1-3}$ and eGFR $drop_{1-12}$ denotes the decline in eGFR between 1 and 3 mo and between 1 and 12 mo posttransplant, respectively.

risk factors outlined earlier. The use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers did not result in protection of the progression of CKD or reduction of mortality (Table 2).

Multivariate Analysis

The strongest predictor of CKD stage 4 was the eGFR drop of more than or equal to 30% between 3 months and 1 year posttransplant (odds ratio [OR] 16.1, confidence interval [CI] 5.9–44.5, $P<0.001$), followed by diabetes mellitus pretransplant (OR 4.1, CI 1.9–5.4, $P<0.001$), positive serology for hepatitis C virus (OR 4.0, CI 2.0–8.2, $P<0.001$), new-onset diabetes mellitus within the first year posttransplant (OR 5.4, CI 1.5–20.2, $P=0.01$), and total bilirubin at 1 month (OR 3.2, CI 1.9–5.4, $P<0.001$) (Table 3, Fig. 1A).

The strongest predictor of chronic dialysis was the eGFR drop of more than or equal to 30% between 3 months and 1 year posttransplant (OR 14.6, CI 3.0–71.4, $P<0.001$), followed by diabetes mellitus pretransplant (OR 3.8, CI 1.1–13.2, $P=0.003$) (Table 3, Fig. 1B).

TABLE 3. Multivariate Cox regression analyses

Variables	eGFR ≤30 mL/min at >1 yr (n=34/288)[a] OR (95% CI)	Chronic dialysis at >1 yr (n=11/356)[a] OR (95% CI)	All-cause mortality at >1 yr (n=98/360)[a] OR (95% CI)
Diabetes mellitus pretransplant	4.1 (1.9–5.4); $P<0.001$	3.8 (1.1–13.2); $P=0.03$	1.9 (1.2–2.9); $P=0.004$
Hepatitis C virus	4.0 (2.0–8.2); $P<0.001$	—; $P>0.10$	1.9 (1.2–2.8); $P=0.004$
New onset diabetes at 1 yr	5.4 (1.5–20.2); $P=0.01$	—; $P>0.10$	—; $P>0.10$
eGFR at 3 mo	0.63 (0.51–0.78); $P<0.001$	0.51 (0.34–0.77); $P=0.001$	—; $P>0.10$
Alkaline phosphatase (IU/L) at 1 mo	—; $P>0.10$	—; $P>0.10$	0.84 (0.72–0.97); $P=0.02$
Alkaline phosphatase (IU/L) at 1 yr	—; $P>0.10$	—; $P>0.10$	1.2 (1.1–1.3); $P<0.001$
Total bilirubin (μmol/L) at 1 mo	3.2 (1.9–5.4); $P<0.001$	—; $P>0.10$	—; $P>0.10$
Total bilirubin (μmol/L) at 1 yr	—; $P>0.10$	—; $P>0.10$	1.6 (1.1–2.2); $P<0.007$
eGFR $drop_{3-12}$ ≥30%	16.1 (5.9–44.5); $P<0.001$	14.6 (3.0–71.4); $P<0.001$	2.6 (1.6–4.4); $P<0.001$

[a] Patients with non-missing data.

OR, adjusted odd ratio, controlling for other covariates with ORs given; CI, confidence interval; eGFR, estimated glomerular filtration rate; eGFR $drop_{3-12}$ denotes the decline in eGFR between 3- and 12-mo posttransplant.

The strongest predictor of all-cause mortality was the eGFR drop of more than or equal to 30% between 3 months and 1 year posttransplant (OR 2.6, CI 1.6–4.4, $P<0.001$), followed by diabetes mellitus pretransplant (OR 1.9, CI 1.2–2.9, $P=0.004$), positive serology for hepatitis C virus (OR 1.9, CI 1.2–2.8, $P=0.004$), total bilirubin at 1 year (OR 1.6, CI 1.1–2.2, $P<0.007$), and alkaline phosphatase at 1 year (OR 1.2, CI 1.1–1.3, $P<0.001$) (Table 3, Fig. 1C).

DISCUSSION

Given its ominous significance, it is important to determine potentially modifiable risk factors in LT recipients at risk of developing CKD. The most relevant finding of this study is that a decline of more than or equal to 30% in the eGFR between 3 months and 1 year is a significant predictor of CKD stage 4, the need for chronic dialysis, and death more than 1 year after LT. We previously described that a drop in the eGFR during the first year in heart transplant recipients predicted similar outcomes. This finding adds external validity to our results (*10*).

Previous studies in LT patients have reported that predictors of advanced CKD included hepatitis C virus, hepatorenal syndrome, the use of CsA, the development of postoperative acute renal failure, female gender, hypertension, diabetes mellitus, and increased serum creatinine at 1, 3, and 12 months after LT, but few of these are potentially correctable (*1*, *6*, *7*, *11*). Increased mortality was described in LT recipients with hepatorenal syndrome (*11*), in those with postoperative acute renal failure (*12*, *13*), and in patients developing end-stage kidney disease (*3*, *13*, *14*). Cholestatic markers and hepatitis C virus have also been reported to be predictors of poor LT outcomes (*15*, *16*).

The most clinically important finding of our study is the identification of patients with deterioration in eGFR of more than or equal to 30% between 3 months and 1 year postoperatively, as those patients are at greatest risk for negative outcomes, namely CKD and mortality. Although further analysis is required to see whether the worsening renal dysfunction is reversible, this finding identifies a target population where renal protective strategies may be aggressively entertained. Although the causes of CKD may be multifactorial, several clinical maneuvers to decrease exacerbating causes for this specific group of patients may be attempted.

We also found that hepatitis C virus, diabetes mellitus at baseline, and total bilirubin at 1 month are predictors of advanced kidney disease. Alkaline phosphatase at 1 month and at 1 year, and hepatitis C virus also predicted all-cause mortality more than 1 year after LT. Although the model for end-stage liver disease score is useful to predict mortality in the 3 months after LT (*17*), in our study it did not predict the subsequent development of advanced CKD, the need for chronic dialysis, or mortality more than 1 year after LT.

The initial work by Myers et al. (*18*) in heart transplant recipients showed that patients on CsA may develop tubulointerstitial injury and focal glomerulosclerosis that may progress to an irreversible state. Fisher et al. (*14*) showed that serum creatinine at 3 months, CsA trough levels at 1 month, and the cumulative dose of CsA at 5 years were associated with the development of severe CKD in LT patients. In our study, CsA trough levels at 1 month were lower compared with the ones reported by Fisher et al. (*14*). We did not find an association between the cumulative dose of CsA or tacrolimus during the first 3 months posttransplant and the development of advanced CKD. We used the initial formulation of CsA (Sandimmune, Novartis Pharmaceuticals Canada Inc., Dorval, Canada) until 1997 and CsA microemulsion (Neoral, Novartis Pharmaceuticals Canada Inc., Dorval, Canada) thereafter. The lack of correlation between CsA trough levels and the development of CKD might be explained because CsA trough levels have a poor correlation with the area under the curve in patients receiving the initial formulation of CsA or CsA microemulsion (*10*). The relationship between tacrolimus trough levels and the development of CKD needs to be further assessed in LT recipients. In the present study, hypertensive diabetic or nondiabetic patients were treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers to reduce microalbuminuria or proteinuria. The use of these medications unfortunately did not result in protection of the progression of CKD or reduction of mortality. We observed similar results in heart transplant recipients (*10*). These results are, however, at variance with previously reported data from nontransplant patients and renal transplant patients on maintenance CNI

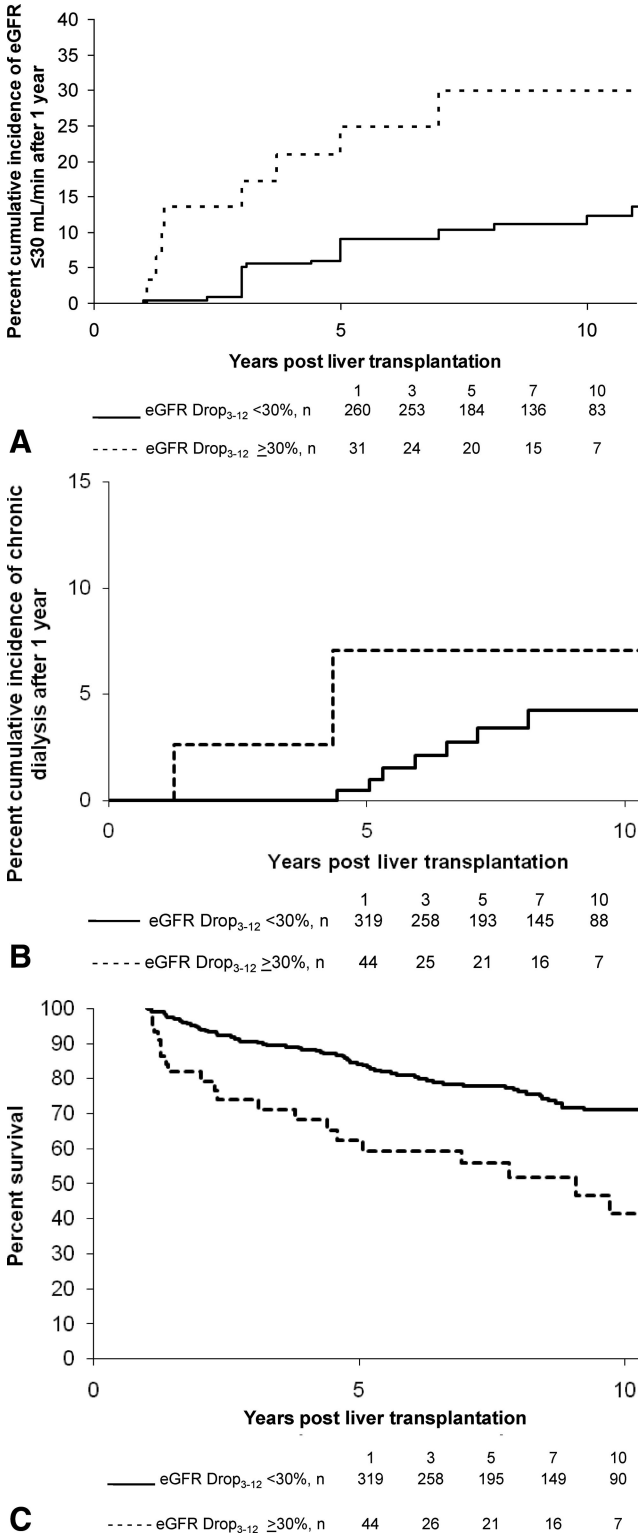

FIGURE 1. (A) Kaplan-Meier estimates of the cumulative incidence of estimated glomerular filtration rate (eGFR) ≤30 mL/min occurring 1 year after first liver transplant in patients with or without eGFR drop$_{3-12}$ ≥30%. (B) Kaplan-Meier estimates of the cumulative incidence of chronic dialysis occurring 1 year after first liver transplant in patients with or without eGFR drop$_{3-12}$ ≥30%. (C) Kaplan-Meier estimates of survival 1 year after first liver transplant in patients with or without eGFR drop$_{3-12}$ ≥30%.

(*19*). There is no clear explanation for this discrepancy, and it should be addressed in future research. We acknowledge the fact that one of the limitations of this study is the lack of consistent data regarding proteinuria or albuminuria throughout the 18-year span of the analysis. Albuminuria is a risk factor for the progression of CKD (*20*), and it should be included in future analysis in this transplant population.

In conclusion, our findings suggest that in addition to pretransplant diabetes mellitus, a decline of more than or equal to 30% in the eGFR between 3 months and 1 year is a significant predictor of advanced CKD, chronic dialysis, and death more than 1 year after LT. Our results could be useful to select patients at risk of progression to CKD after LT. This should be further explored in a prospective study implementing renal protective strategies to reduce the incidence of end-stage kidney disease and mortality in this subgroup of patients after LT.

MATERIALS AND METHODS

We included 445 patients with a first LT performed at the Royal Victoria Hospital, McGill University Health Center (Montréal, Québec, Canada), between June 1990 and September 2007 who survived more than 1 month. The information on these patients has been prospectively recorded and updated in our McGill multiorgan transplant database. Follow-up was until October 2008. Patients with combined organ transplants (n=18) and those with follow-up less than 1 month (n=44) were excluded. Fifty-eight patients received retransplants; 49 received a second, 7 patients received a third, and 2 patients received a fourth LT. Patients with retransplants were included in the study according to the date of their first LT. Of the 445 patients included in the study, 427 had a follow-up of at least 3 months and 392 had a follow-up of at least 1 year.

Immunosuppression consisted of antithymocyte globulin (ATG)-induction, 1.5 mg/kg/day for 5 to 7 days (Thymoglobulin, Genzyme Canada Inc, Mississauga, ON, Canada) in the majority of the patients, methylprednisolone 500 mg administered intravenously, intraoperatively, rapidly tapered to 5 mg/day (prednisone) by 3 months posttransplant. Until 1997, CsA (Sandimmune, Novartis Pharmaceuticals Canada Inc., Dorval, Canada) and then CsA microemulsion (Neoral, Novartis Pharmaceuticals Canada Inc., Dorval, Canada) were used. CsA was started at a dosage of 2 mg/kg/day on postoperative day 1 to 2, if the patients were clinically stable. In patients with postoperative renal dysfunction, CsA was delayed 1 to 2 weeks under ATG coverage, until serum creatinine had decreased to less than 150 μmol/L. CsA was monitored based on trough levels of 200 to 300 ng/mL during the first 3 months posttransplant, then 150 to 250 ng/mL until month 6 and 100 to 200 ng/mL thereafter.

Until 1997, azathioprine was used and thereafter replaced in our standard protocol by mycophenolate mofetil (CellCept, Hoffmann-LaRoche Ltd., Mississauga, ON, Canada). Mycophenolate mofetil was started at a dosage of 0.5 g two times per day and increased to 1.0 g two times per day at the end of the ATG-induction course. Starting in June 1997, CsA C2 levels (2-hr post-AM dose of CsA) were measured and replaced CsA trough levels for CsA dose adjustment after June 1998. CsA C2 target range was 600 to 800 ng/mL during the first 3 months posttransplant, 500 to 700 ng/mL until month 6, and 300 to 600 ng/mL thereafter (*21*). After 1997, we progressively replaced CsA as the primary CNI in de novo LT recipients with tacrolimus (Prograf, Astellas, Mississauga, ON, Canada). Tacrolimus was started at a dosage of 0.01 mg/kg/day in two divided doses, aiming for trough levels 8 to 12 ng/mL during the first 3 months posttransplant and 4 to 8 ng/mL thereafter. Lower CsA and tacrolimus doses were used in patients with postoperative renal dysfunction.

We examined the following variables: age, gender, weight, primary liver disease, history of diabetes mellitus and hypertension preoperatively, need for antihypertensive medication, need for use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, new-onset diabetes after transplant, serum creatinine, eGFR, CsA dose, and CsA trough and C2 levels.

For the purpose of this study, patients receiving oral agents or insulin were considered as diabetics. Variables that have been reassessed over time were recorded at baseline and at 1 and 3 months, and at 1, 3, 5, 7, and 10 years posttransplant.

The endpoints of this study included eGFR less than or equal to 30 mL/min, chronic dialysis, and all-cause mortality more than 1 year after LT. For the outcome analyses, dates related to initiation of chronic dialysis, death, and loss to follow-up were used. The eGFR was calculated using the Modified Diet in Renal Disease six variables formula (*22*). The pretransplant eGFR was calculated based on serum creatinine levels on the day of LT. The eGFR at 1 month posttransplant was based on an average of the three lowest serum creatinine measurements during the first postoperative month. The eGFR at 3 and 12 months was based on one value because the patients were followed up less frequently after the first month posttransplant. After the initial hospital stay, the patients were followed up at the transplant clinic twice a week during the first month, weekly during the second month, every 2 weeks during months 3 and 4, monthly until month 6, every 2 months between months 6 and 12, and every 3 months after the end of the first year posttransplant.

We evaluated the relationship between the covariates listed earlier and the three endpoints. Also, we studied the effect of changes in the eGFR within the first year posttransplantation and the same outcomes. We selected a drop in the eGFR of more than or equal to 30% because it is clinically relevant, being clearly different from expected minor fluctuations observed with repeated serum creatinine measures due to assay or other measurement-related factors (intrapatient variability). Kidney biopsies were not routinely performed.

Statistical Analysis

Univariate and multivariate Cox regression analyses were used to determine the association of the various predictors with time to first eGFR less than or equal to 30 mL/min, time to chronic dialysis, and time to all-cause mortality. Results from the multivariate model were recorded as adjusted OR, with a 95% CI and the associated *P* value (Gehan-Wilcoxon test).

Kaplan-Meier curves were constructed to depict univariate associations. Statistical analyses including descriptive statistics and Cox regression were performed with SAS (version 9.01, SAS Institute, Cary, NC).

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REFERENCES

1. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; 349: 931.
2. Yalavarthy R, Edelstein CL, Teitelbaum I. Acute renal failure and chronic kidney disease following liver transplantation. *Hemodial Int Suppl* 2007; 3: S7.
3. Al Riyami D, Alam A, Badovinac K, et al. Decreased survival in liver transplant patients requiring chronic dialysis: A Canadian experience. *Transplantation* 2008; 85: 1277.
4. Knoll G, Muirhead N, Trpeski L, et al. Patient survival following renal transplant failure in Canada. *Am J Transplant* 2005; 5: 1719.
5. Alam A, Badovinac K, Ivis F, et al. The outcome of heart transplant recipients following the development of end-stage renal disease: Analysis of the Canadian Organ Replacement Register (CORR). *Am J Transplant* 2007; 7: 461.
6. Gonwa TA, Mai ML, Melton LB, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: Risk of development and treatment. *Transplantation* 2001; 72: 1934.
7. Paramesh AS, Roayaie S, Doan Y, et al. Post-liver transplant acute renal failure: Factors predicting development of end-stage renal disease. *Clin Transplant* 2004; 18: 94.
8. Kim JY, Akalin E, Dikman S, et al. The variable pathology of kidney disease after liver transplantation. *Transplantation* 2010; 89: 215.
9. Moreau R, Durand F. Renal insufficiency: Management prior to transplantation. *Liver Transplantation* 2010; suppl S2: S72.
10. Cantarovich M, Hirsh A, Alam A, et al. The clinical impact of an early decline in kidney function in patients following heart transplantation. *Am J Transplant* 2009; 9: 348.
11. Gonwa TA, Klintmalm GB, Levy M, et al. Impact of pretransplant renal function on survival after liver transplantation. *Transplantation* 1995; 59: 361.
12. Gonwa TA, Mai ML, Melton LB, et al. Renal replacement therapy and orthotopic liver transplantation: The role of continuous veno-venous hemodialysis. *Transplantation* 2001; 71: 1424.
13. Fraley DS, Burr R, Bernardini J, et al. Impact of acute renal failure on mortality in end-stage liver disease with or without transplantation. *Kidney Int* 1998; 54: 518.
14. Fisher NC, Nightingale PG, Gunson BK, et al. Chronic renal failure following liver transplantation: A retrospective analysis. *Transplantation* 1998; 66: 59.
15. Ben-Ari Z, Weiss-Schmilovitz H, Sulkes J, et al. Serum cholestasis markers as predictors of early outcome after liver transplantation. *Clin Transplant* 2004; 18: 130.
16. Ghobrial RM, Steadman R, Gornbein, et al. A 10-year experience of liver transplantation for hepatitis C. Analysis of factors determining outcome in over 500 patients. *Ann Surg* 2001; 234: 384.
17. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; 124: 91.
18. Myers BD, Ross J, Newton L, et al. Cyclosporine-associated chronic nephropathy. *N Engl J Med* 1984; 311: 699.
19. Lin J, Valeri A, Markowitz G, et al. Angiotensin converting enzyme inhibition in chronic allograft nephropathy. *Transplantation* 2002; 73: 783.
20. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA* 2011; 305: 1553.
21. Cantarovich M, Barkun J, Tchervenkov JI, et al. Comparison of Neoral dose monitoring with cyclosporine trough levels versus 2-hour post-dose levels in stable liver transplant patients. *Transplantation* 1998; 66: 1621.
22. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461.