Transplant International

ORIGINAL ARTICLE

# Post-liver transplantation chronic kidney disease is associated with increased cardiovascular disease risk and poor survival

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## SUMMARY

Chronic kidney disease (CKD) is common following liver transplantation (LT). We aimed to investigate the frequency, risk factors, and impact of CKD on cardiovascular disease (CVD), graft, and patient survival. We analyzed 752 patients who received LT at the University of Alberta. Development of CKD was defined as eGFR <60 ml/min for greater than 3 months, intrinsic renal disease or presence of end-stage renal disease requiring renal replacement therapy. 240 patients were female (32%), and mean age at LT was 53 ± 11 years. CKD was diagnosed in 448 (60%) patients. On multivariable analysis, age (OR 1.3; $P = 0.01$), female sex (OR 3.3; $P < 0.001$), baseline eGFR (OR 0.83; $P < 0.001$), MELD (OR 1.03; $P = 0.01$), de novo metabolic syndrome (OR 2.3; $P = 0.001$), and acute kidney injury (OR 3.5; $P < 0.001$) were associated with CKD. A higher tacrolimus concentration to dose ratio was protective for CKD (OR 0.69; $P < 0.001$). CKD was associated with post-transplant CVD (26% vs. 16% $P < 0.001$), reduced graft (HR 1.4; $P = 0.02$), and patient survival (HR 1.3; $P = 0.03$). CKD is a frequent complication following LT and is associated with an increased risk of CVD and reduced graft and patient survival.

*Transplant International* 2021; 34: 2824–2833

**Key words**
cardiovascular disease, cirrhosis, liver transplantation, metabolic syndrome, renal failure

Received: 13 March 2021; Revision requested: 25 October 2021; Accepted: 1 November 2021; Published online: 23 November 2021

## Introduction

Liver transplantation (LT) is frequently complicated by chronic kidney disease (CKD), which is associated with increased morbidity and mortality [1]. Indeed, of all the patients undergoing solid organ transplantation, those with LT have the second highest risk of developing CKD [2]. CKD has been reported in up to 45% of patients following LT [3]. The reported prevalence is highly variable depending on how CKD is defined and the total duration of follow up. Some of the previous studies used serum creatinine to define CKD, whereas others have used an estimated glomerular filtration rate (eGFR) or measured glomerular filtration rate to define renal impairment [3].

CKD is a known risk factor for cardiovascular disease (CVD) in the general population. Stage 2 CKD has more than a 2.5-fold increased risk of cardiovascular death [4]. In a recent study, decline in eGFR post-LT was associated with higher CVD mortality. In this study, those with a rapid decline had the highest odds of CVD related mortality [5]. The true impact of CKD remains unknown as most studies looked at advanced stages (3b or worse) of CKD and were from the pre-MELD era.




doi:10.1111/tri.14154

Numerous factors contribute to the development of CKD following LT; these include the presence of comorbidities such as diabetes, hypertension, HCV-related renal disease, the use of antibiotics, peritransplant acute kidney injury (AKI) related to hemodynamic insults, and the presence of hepatorenal syndrome. Postoperative use of antibiotics and immunosuppression, such as calcineurin inhibitors (CNI), is an additional risk factor for development of CKD post-LT [1].

In this study, we investigated the frequencies of development of CKD post-LT based on criteria developed by the Kidney Disease: Improving Global Outcomes (KDIGO) at various time points [6]. We also wanted to identify risk factors and assess the impact of CKD on CVD, patient, and graft survival.

## Methods

### Study population

The study population comprised 752 consecutive adult patients with end-stage liver disease who received a LT at the University of Alberta over the period of 2001 to 2015. Patients who had retransplants, individuals with combined liver and kidney transplant, and individuals with pre-existing CKD were excluded. Patients with pre-existing CVD (CAD, atrial fibrillation) and AKI (HRS) were included. The study period was stopped in 2015 to allow for longer follow up of patients. This study was approved by the Institutional Review Board of the University of Alberta Hospital (approval number: Pro00083247). The requirement for informed consent was waived due to the retrospective nature of the study.

### Clinical and laboratory assessments

Data obtained from the Organ Transplant Tracking Record (OTTR) database included sex, age, BMI, serum creatinine, and total bilirubin. The presence of comorbidities, including diabetes, hypertension, history of alcohol use and smoking, and pretransplant diagnosis of CVD, was recorded. All patients underwent extensive cardiac workup at the time of liver transplant assessment. In patients with pre-existing CVD, investigations did not show significant coronary artery disease that would affect transplant surgery. These patients were optimized using medical management. In patients with evidence of pre-existing CAD cardiology consultation with percutaneous coronary intervention was recommended prior to LT. CVD was defined by need for hospitalization or death from coronary artery disease (CAD), myocardial infarction, angina, arrhythmia (atrial fibrillation), heart failure, cardiac arrest, or cerebrovascular disease (transient ischemic attack, stroke).

Post-LT immunosuppression used, subsequent creatinine levels, and a new diagnosis of diabetes, hypertension, dyslipidemia, or CVD were also recorded. Higher tacrolimus concentration is associated with toxicity, but even individuals with lower concentrations experience nephrotoxicity suggesting the involvement of other factors [7]. Recent studies have shown each patient's tacrolimus metabolism rate, calculated as the ratio of tacrolimus trough level (ng/ml) to the corresponding daily dose (mg) (C/D ratio), is associated with renal dysfunction and its severity [8]. A low C/D ratio ($<1.8$ ng/ml $\times$ 1/mg) is seen in fast metabolizers and is associated with renal dysfunction in comparison to slow metabolizers [7, 9]. Indeed, higher C/D ratio is associated with higher C2 tacrolimus levels in patients despite having comparable trough levels [8]. Similarly, patients with comparable AUC for tacrolimus can have different drug peak levels based on the metabolism [8]. Thus, we used the C/D ratio as opposed to trough concentration in this study. The four-variable Modification of Diet in Renal Disease (MDRD) equation was used to calculate eGFR, as reported elsewhere [10].

AKI was defined as at least a 50% increase in serum creatinine level relative to the reference value at 7 days following LT [6]. CKD was defined as eGFR $<60$ ml/min for greater than 3 months (according to the KDIGO criteria [6]), evidence of intrinsic renal disease (e.g. proteinuria, evidence of medical renal disease on US), or presence of end-stage renal disease requiring renal replacement therapy post-LT. The reference creatinine used to calculate the eGFR was the closest value available pre-LT (within the week). The Model for End-Stage Liver Disease score (MELD) was calculated as reported elsewhere [11].

### Statistical analysis

The Fisher exact probability test was used to compare categorical variables, and the unpaired *t*-test was used to compare differences in the means of continuous variables. Graft loss was defined as either death or retransplantation, and survival was defined from the date of the LT to the date of last follow-up (censored), or date of death (uncensored). Cumulative probabilities of graft loss and overall survival were calculated using the Kaplan-Meier method, and they were compared using the Log-Rank test. We used the Cox proportional hazards model to study the association between CKD and CVD, graft and patient survival. Data are presented as the absolute and relative

frequencies, and means ± standard deviation in tables and text. Statistical analyses were performed using SPSS (version 26.0, SPSS, Chicago, IL, USA) with a p-value less than 0.05 considered being statistically significant.

## Results

### Characteristics of study population

The main demographic, clinical, and biochemical characteristics of patients are summarized in Table 1 (Tables S1, S2). The study population consisted of 240 females (32%), majority were Caucasian (641; 85%), and the mean age at LT was 53 ± 11 years. Cirrhosis etiology included autoimmune liver disease (24%), HCV cirrhosis (22%), alcohol-related cirrhosis (16%), NASH cirrhosis (7%), HBV cirrhosis (5%), and other etiology (10%). Hepatocellular carcinoma was an indication for transplant in 218 (29%) patients.

The mean BMI was 26 ± 6 kg/m$^2$ at the time of LT. Pre-LT diabetes was present in 171 patients (23%), hypertension in 161 (21%), and dyslipidemia in 52 (7%). Smoking history was reported in 432 (57%), and history of alcohol use in 334 patients (44%). Mean

**Table 1.** Patient characteristics based on the presence or absence of CKD.

| Characteristics | *N* = 752 | CKD (*n* = 448) | No CKD (*n* = 304) | *P*-value |
|---|---|---|---|---|
| Age, years | 53 ± 11 | 54 ± 9 | 50 ± 12 | **<0.001** |
| Female (%) | 240 (32) | 172 (38) | 68 (22) | **<0.001** |
| Caucasian (%) | 641 (85) | 385 (86) | 256 (85) | 0.82 |
| Baseline eGFR (ml/min) | 84 ± 41 | 73 ± 38 | 101 ± 38 | **<0.001** |
| Baseline total bilirubin (umol/L) | 146 ± 223 | 163 ± 239 | 119 ± 195 | **0.01** |
| MELD | 18 ± 10 | 20 ± 10 | 16 ± 9 | **<0.001** |
| Hypertension (%) | 161 (21) | 104 (23) | 57 (19) | 0.17 |
| Diabetes (%) | 171 (23) | 118 (26) | 53 (18) | **0.01** |
| Dyslipidemia (%) | 52 (7) | 36 (8) | 16 (5) | 0.19 |
| Pre-LT cardiovascular disease | 104 (14) | 67 (15) | 37 (12) | 0.33 |
| BMI (kg/m$^2$) | 26 ± 6 | 27 ± 6 | 26 ± 6 | 0.49 |
| BMI ≥ 25 kg/m$^2$ | 373 (55) | 228 (57) | 145 (53) | 0.48 |
| BMI < 25 kg/m$^2$ | 301 (45) | 175 (43) | 126 (47) | 0.48 |
| History of smoking (%) | 432 (57) | 266 (66) | 166 (62) | 0.28 |
| History of alcohol use (%) | 334 (44) | 200 (48) | 134 (48) | 0.94 |
| **Etiology of cirrhosis (%)** | | | | |
| Alcohol-related cirrhosis | 123 (16) | 78 (17) | 45 (15) | 0.34 |
| Autoimmune liver disease | 183 (24) | 109 (24) | 74 (24) | >0.99 |
| Hepatitis B cirrhosis | 36 (5) | 16 (4) | 20 (7) | 0.08 |
| Hepatitis C cirrhosis | 166 (22) | 88 (20) | 78 (26) | 0.06 |
| NASH cirrhosis | 53 (7) | 42 (9) | 11 (4) | **<0.01** |
| Other etiology | 73 (10) | 42 (9) | 31 (10) | 0.71 |
| Hepatocellular carcinoma | 218 (29) | 117 (26) | 101 (33) | **0.04** |
| **Post-LT course** | | | | |
| Tacrolimus C/D ratio at 3 months | 1.5 ± 1.4 | 1.3 ± 0.94 | 1.8 ± 1.8 | **<0.001** |
| Tacrolimus level at 3 months | 7.9 ± 3.5 | 7.3 ± 3.6 | 8.6 ± 3.3 | **<0.001** |
| Tacrolimus level at 1 year | 7.0 ± 2.9 | 6.8 ± 2.8 | 7.3 ± 3.0 | 0.16 |
| AKI in the first 7 days | 117 (16) | 82 (19) | 35 (12) | **0.01** |
| Rejection episodes | 304 (40) | 188 (42) | 116 (38) | 0.33 |
| BMI at 1 year (kg/m$^2$) | 27 ± 5 | 27 ± 5 | 27 ± 5 | 0.41 |
| BMI at last FU (kg/m$^2$) | 27 ± 6 | 28 ± 6 | 27 ± 6 | 0.11 |
| New diagnosis of hypertension (%) | 351 (47) | 223 (50) | 128 (42) | **0.04** |
| New diagnosis of diabetes (%) | 152 (20) | 91 (20) | 61 (20) | >0.99 |
| New diagnosis of dyslipidemia (%) | 285 (38) | 184 (41) | 101 (33) | **0.03** |
| De novo metabolic syndrome | 192 (26) | 135 (30) | 57 (19) | **<0.01** |
| New diagnosis of cardiovascular disease | 160 (21) | 117 (26) | 43 (16) | **<0.001** |

All significant values are in bold.

BMI, body mass index; C/D ratio is calculated as Tacrolimus concentration divided by daily dose in mg; AKI, acute kidney injury; FU, follow-up.



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MELD was 18 ± 10 and mean eGFR was 84 ± 41 ml/min. Hepatorenal syndrome was present in 114 patients (15%).

### Immunosuppression regimens

Our center is *corticosteroid free*, and the standard immunosuppression during the study period was induction with basiliximab (on days 0 and 4), tacrolimus, and mycophenolate mophetil (the latter two started on day 1). We aim for tacrolimus target of 8–10 in the first 6 months followed by a target of 5-8 for the first year. After LT, most of the patients were on tacrolimus (709; 94%) and a minority on cyclosporine (49; 6%). We use immediate release tacrolimus formulation in the first year following transplant. Some patients (195; 25%) were switched to extended release formulation 1 year or more following transplant at the discretion of the treating physician. Mycophenolate mofetil was used in a majority of patients (667; 85%). A small proportion of patients (114; 15%) were on low-dose sirolimus and low-dose tacrolimus. In this group, we aim for a tacrolimus target of 3–5 and sirolimus target of 6–8. During the course of follow-up, patients with either CNI neurotoxicity or nephrotoxicity were switched to sirolimus. Patients with hepatocellular carcinoma were also switched to sirolimus at 4 weeks or more following LT, per our protocol. Our target for sirolimus is 7-10 during the first year post-LT. During the follow-up, 338 (45%) patients needed to be switched to sirolimus.

### Comorbidities post-transplant

Over the course of follow up, a new diagnosis of diabetes was made in 152 (20%) patients regardless of the presence of CKD (Table 1). New onset hypertension was diagnosed in 351 (47%) patients with more individuals in the CKD group having the diagnosis (223 (50%) vs. 128 (42%); $P = 0.04$). Similarly, dyslipidemia was diagnosed in 285 (38%) patients, with more individuals in the CKD group being diagnosed (184 (41%) vs. 101 (33%); $P = 0.03$). A new diagnosis of metabolic syndrome was made in 192 patients (26%), with higher rates in those with CKD (135 (30%) vs. 57 (19%); $P < 0.01$). Of note, as the number of components of metabolic syndrome increased, there was a higher prevalence of CKD (Fig. 1). CVD was diagnosed in 160 (21%) patients with a significantly higher number of individuals in the CKD group receiving this diagnosis (117 (26%) vs. 43 (14%); $P < 0.001$). There was an association between CKD and CVD, independent of age or sex. Those with stage 3a (OR 2.4 [1.01, 5.76]; $P < 0.05$) or stage 3b (OR 3.7 [1.4, 10.0]; $P < 0.01$) CKD had the highest risk of CVD in comparison to individuals with eGFR > 90 ml/min. In patients with CKD at 6 months, mean time to CVD was shorter (3.0 ± 0.5 *vs.* 4.7 ± 0.5 years, $P = 0.08$) in comparison to those without CKD, but this difference was not significant (Fig. 2). In individuals with CKD at 6 months post-LT, hazard ratio was adjusted for age, and sex was 1.4 (95% CI 0.6 – 2.9, $P = 0.42$). Similarly, no significant difference was seen with regard to onset of CVD in patients with or without CKD during follow up (3.5 ± 0.4 vs. 4.3 ± 0.6 years, $P = 0.49$).

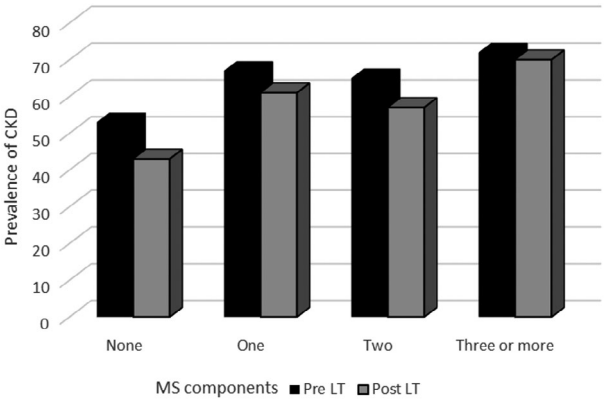


**Figure 1** There is a significant rise in the prevalence of CKD both pre- and post-LT ($P = 0.01$ and $P < 0.001$, respectively) with increasing components of metabolic syndrome (MS). The bars represent percentage of patients in each category.

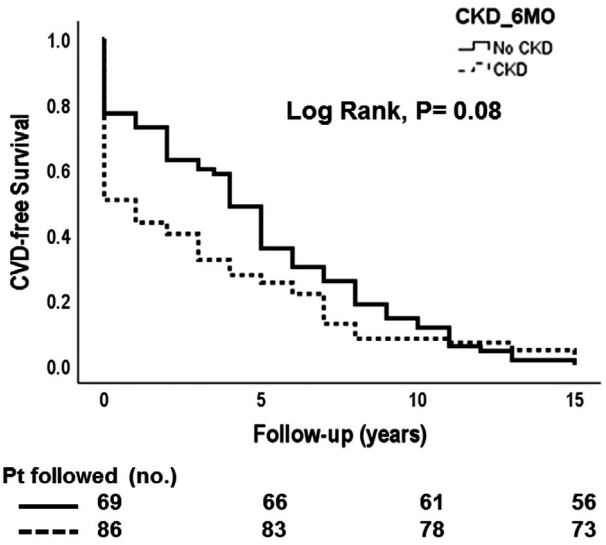


**Figure 2** CVD-free survival in patients with and without CKD at 6 months post-LT.

In a subgroup analysis, we divided groups based on BMI. The relationship between CKD and CVD remained in the group with BMI ≥ 25. Individuals with stage 3a CKD had no association with CVD (HR 2.8 [0.81–9.5]; $P = 0.10$), but those with stage 3b CKD had an increased risk of CVD (HR 5.7 [1.5–21.4]; $P = 0.01$). There was no association between CKD and CVD in patients with normal BMI. If we further broke down the groups by sex there was no association found between CKD and CVD in either the normal or ≥ 25 BMI group. This could be due to low numbers and lack of power to detect differences.

### Renal dysfunction post-liver transplant

During a mean follow-up of 7 ± 5 years (range, 0 - 19 years), there was a significant drop in eGFR at 6 months from 84 ± 41 ml/min to 67 ± 25 ml/min (mean change 17 ± 34 ml/min; $P < 0.001$) (Table 2). A large number of patients transitioned from CKD stage 1 to stage 2 or 3. AKI was diagnosed in 117 (16%) patients following LT. Of these individuals, 82 (70%) went on to develop CKD. The patients with AKI were similar to their counterpart with normal renal function with regard to age (53 ± 10 years vs. 53 ± 11 years; $P = 0.81$), sex (28% vs. 33% females; $P = 0.42$), pre-LT MELD (19 ± 10 vs. 18 ± 9; $P = 0.19$), and post-LT immunosuppression use (94% vs. 95% on tacrolimus and 15% vs. 15% on sirolimus; $P = 0.81$, and $P = 1.0$, respectively). The AKI group was overweight (BMI 29 ± 6 kg/m$^2$ vs. 27 ± 6 kg/m$^2$; $P = 0.03$) and had a lower baseline creatinine (69 ± 21 ml/min vs. 98 ± 54 ml/min; $P < 0.001$) in comparison to those without AKI. More than half of the patients met criteria for CKD over the course of follow up (448; 60%). A large number of patients (327; 44%) met the criteria for CKD at 6 months. For those who had follow-up creatinine, a significant number met criteria for CKD at 1- (247; 43%), 3- (239; 50%), and 5-years (170; 51%) post-LT.

Subgroup analysis was done to assess the impact of nephroprotective immunosuppression. Patients (155 (21%)) who were switched to sirolimus by 3 months post-transplant and had no tacrolimus for the first year were analyzed. In the first 6 months, CKD was higher in this group (83 (56%) vs. 244 (42%); $P < 0.01$). This is not surprising as many patients were switched due to renal impairment. At 3 months following transplant, those in the CNI group had much higher rates of acute kidney injury (136 (25%) vs. 16 (13%); $P < 0.01$) dictating change in immunosuppression. Of note, no

**Table 2.** Renal trends over the course of follow up and association with graft loss and mortality.

| Time | Mean eGFR | Percentage with CKD Stage | | | | | Adjusted HR for mortality* in patients with CKD | *P* | Adjusted HR for graft loss* in patients with CKD | *P* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3a | 3b | ≥ 4 | | | | |
| Pre-LT | 84 ± 41 | 266 (35) | 238 (32) | 113 (15) | 55 (7) | 80 (11) | | | | |
| 7 days post-LT | 82 ± 43 | 259 (34) | 209 (28) | 103 (14) | 80 (11) | 96 (13) | | | | |
| 6 months post-LT† | 67 ± 25 | 82 (11) | 272 (36) | 182 (24) | 77 (10) | 17 (2) | 1.6 [1.2, 2.1] | **0.001** | 1.6 [1.3, 2.1] | **<0.001** |
| 1 year post-LT† | 65 ± 22 | 69 (9) | 267 (36) | 163 (22) | 80 (11) | 20 (3) | 1.2 [0.89, 1.7] | 0.20 | 1.1 [0.81, 1.5] | 0.49 |
| 3 years post-LT† | 62 ± 22 | 47 (6) | 203 (27) | 145 (20) | 74 (10) | 28 (4) | 1.7 [1.1, 2.5] | **0.02** | 1.6 [1.1, 2.4] | **0.02** |
| 5 years post-LT† | 61 ± 24 | 39 (5) | 143 (20) | 117 (16) | 53 (7) | 26 (4) | 2.4 [1.3, 4.2] | **<0.01** | 2.6 [1.5, 4.3] | **<0.001** |

All significant values are in bold.

*Adjusted for age, sex and pre-LT MELD

†No data available for: 16% patients at 6 mo postLT; 20% at 1-yr postLT; 34% at 3-yrs postLT; 50% at 5-years postLT.

difference was seen between the groups with regard to CKD at 1- (44 (45%) vs. 203 (43%); $P = 0.74$), 3- (43 (55%) vs. 196 (49%); $P = 0.39$), and 5-years (31 (61%) vs. 139 (50%); $P = 0.17$).

### Risk factors for CKD post-liver transplant

Individuals with CKD were older, more likely to be female, had lower baseline eGFR and higher MELD score (Table 1). The two groups were similar with regard to race (85% Caucasian). Patients with CKD were more likely to have a diagnosis of NASH cirrhosis (42 (9%) vs. 11 (4%); $P < 0.01$) and pre-LT diabetes (118 (26%) vs. 53 (18%); $P = 0.01$). There was no difference in BMI, pre-LT hypertension, and dyslipidemia in the two groups. Individuals with HCC were less likely to have CKD (117 (26%) vs. 101 (33%); $P = 0.04$). Patients with CKD had a low tacrolimus C/D ratio ($1.3 \pm 0.94$ vs. $1.8 \pm 1.8$; $P < 0.001$) and were more likely to have AKI (82 (19%) vs 35 (12%); $P = 0.01$). On multivariable analysis, independent risk factors for CKD included age (per decade) (OR 1.3 [1.1, 1.6]; $P = 0.01$), female sex (OR 3.3 [2.1, 5.3]; $P < 0.001$), baseline eGFR (per 10 ml/min) (OR 0.83 [0.77, 0.88]; $P < 0.001$), MELD score (OR 1.03 [1.0, 1.1]); $P = 0.01$), de novo metabolic syndrome (OR 2.3 [1.4, 3.8]; $P = 0.001$), and AKI (OR 3.5 [1.7, 7.1]; $P < 0.001$). A higher tacrolimus C/D ratio was protective for CKD (OR 0.69 [0.56, 0.84]; $P < 0.001$) (Table 3).

Subgroup analysis was done to assess the impact of BMI. The results of the multivariable analysis were similar in the group with BMI $\geq 25$ with the exception of age no longer being an independent risk factor for CKD (Table 3). If we analyzed this group by sex, neither age nor MELD were associated with CKD in male patients. In female patients, age, MELD, de novo metabolic syndrome, and AKI were no longer associated with CKD. In patients with normal BMI, age, MELD, and de novo metabolic syndrome were no longer associated with CKD (Table 3). When we analyzed this group by sex, in female patients only baseline eGFR and tacrolimus C/D ratio remained associated with risk for CKD. In male patients, only baseline eGFR and AKI remained associated with risk of CKD.

### CKD impact on graft and patient survival

Overall graft survival was reduced in those with CKD ($11 \pm 0.4$ vs. $13 \pm 0.4$ years, $P < 0.01$) (Fig. 3). This association was present at 6 months, and 3- and 5-years following LT; graft survival was reduced in patients with CKD at 6 months ($11 \pm 0.5$ vs. $13 \pm 0.4$ years, $P < 0.001$) (Fig. 4). Hazard ratio for graft survival was

**Table 3.** Characteristics associated with CKD following liver transplantation in multivariable analysis.

| | Characteristic | OR | 95% CI | *P* |
|---|---|---|---|---|
| All patients | Age (per decade) | 1.3 | 1.1–1.6 | 0.01 |
| | Female (F vs. M) | 3.3 | 2.1–5.3 | <0.001 |
| | Baseline eGFR (per 10 ml/min) | 0.83 | 0.77–0.88 | <0.001 |
| | MELD (per point) | 1.03 | 1.0–1.1 | 0.01 |
| | Tacrolimus C/D ratio at 3 months | 0.69 | 0.56–0.84 | <0.001 |
| | AKI in the first 7 days | 3.5 | 1.7–7.1 | <0.001 |
| | De novo metabolic syndrome | 2.3 | 1.4–3.8 | 0.001 |
| BMI ≥ 25 | Age (per decade) | 1.3 | 0.93–1.9 | 0.12 |
| | Female (F vs. M) | 3.7 | 1.8–7.9 | 0.001 |
| | Baseline eGFR (per 10 ml/min) | 0.75 | 0.66–0.84 | <0.001 |
| | MELD (per point) | 1.04 | 1.0–1.1 | 0.04 |
| | Tacrolimus C/D ratio at 3 months | 0.66 | 0.48–0.91 | 0.01 |
| | AKI in the first 7 days | 3.8 | 1.5–9.5 | 0.01 |
| | De novo metabolic syndrome | 2.3 | 1.2–4.3 | 0.02 |
| Normal BMI | Age (per decade) | 1.3 | 0.91–1.7 | 0.17 |
| | Female (F vs. M) | 3.8 | 1.9–7.7 | <0.001 |
| | Baseline eGFR (per 10 mL/min) | 0.81 | 0.73–0.90 | <0.001 |
| | MELD (per point) | 1.03 | 0.99–1.1 | 0.15 |
| | Tacrolimus C/D ratio at 3 months | 0.76 | 0.57–0.99 | <0.05 |
| | AKI in the first 7 days | 12.0 | 2.8–63.5 | <0.01 |
| | De novo metabolic syndrome | 1.6 | 0.56–4.4 | 0.39 |

C/D ratio is calculated as Tacrolimus concentration divided by daily dose in mg; AKI, acute kidney injury.

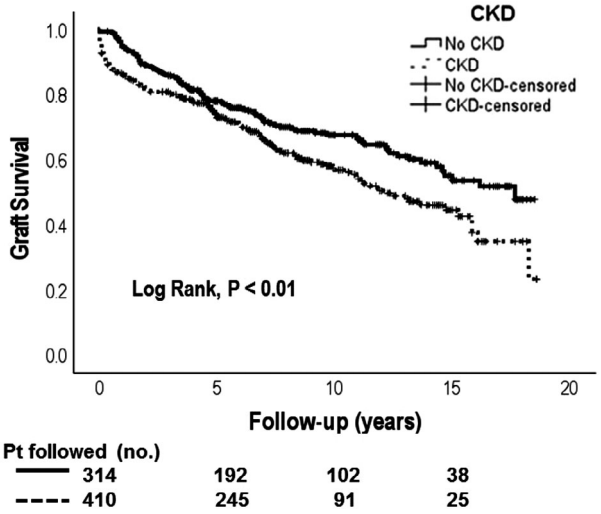


**Figure 3** Overall graft survival in patients with and without CKD.

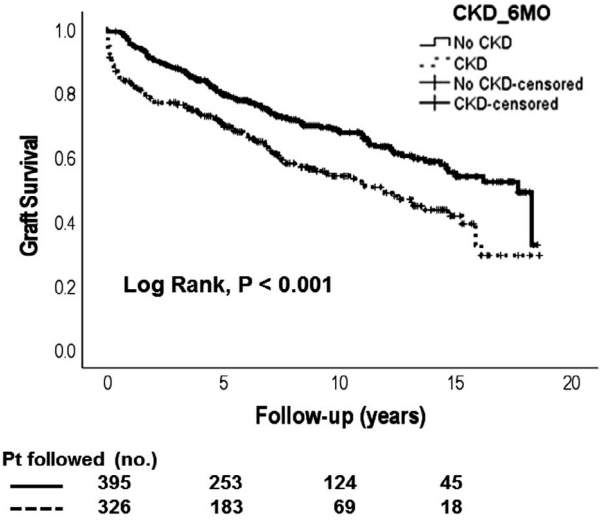


**Figure 4** Graft survival in patients with and without CKD at 6 months post-LT.

1.4 (95% CI 1.1–1.7, $P = 0.02$). In individuals with CKD at 6 months post-LT, hazard ratio adjusted for age, sex, and MELD was 1.6 (95% CI 1.3–2.1, $P < 0.001$) (Table 4).

Patient survival was significantly reduced in patients with CKD following LT (12 ± 0.4 vs. 13 ± 0.4 years, $P = 0.02$) (Fig. 5). This association was present at 6 months, and 3- and 5-years following LT; patient survival was significantly reduced in patients with CKD at 6 months (11 ± 0.5 vs. 14 ± 0.4 years, $P < 0.001$) (Fig. 6). Hazard ratio for patient survival was 1.3 (95% CI 1.02–1.70, $P = 0.03$). In patients with CKD at 6 months, hazard ratio for mortality, adjusted for age, sex, and MELD, was 1.6 (95% CI 1.2–2.1, $P = 0.001$) (Table 4).

Malignancy (25%), sepsis (21%), cardiovascular disease (18%), and graft abnormality (disease recurrence or rejection) (15%) accounted for a majority of deaths. Fifteen percent of deaths were due to other causes including renal failure and accidental death. The cause of death was unknown in 16 cases (6%). Not surprisingly, those with CKD were more likely to die from complications of renal failure (7 (2%) vs. 1 (0%); $P = 0.03$), CVD (30 (9%) vs. 16 (4%); $P = 0.01$) and sepsis (33 (10%) vs. 18 (5%); $P = 0.01$). There was no difference between the groups with regard to death related to malignancy (22 (7%) vs. 41 (10%); $P = 0.1$) or graft abnormality (disease recurrence/graft rejection) (14 (4%) vs. 19 (5%); $P = 0.9$).

## Discussion

This study provides several insights regarding the course of CKD following LT and its risk factors. First, there was a significant drop in eGFR at 6 months following

**Table 4.** Patient characteristics associated with graft and patient survival after liver transplantation.

| | Univariate | | | Multivariable | | |
|---|---|---|---|---|---|---|
| Characteristics | HR | 95% CI | *P* | HR | 95% CI | *P* |
| **Graft survival analysis** | | | | | | |
| Age (per decade) | 1.26 | 1.11–1.42 | **<0.001** | 1.23 | 1.07–1.40 | **<0.01** |
| Female (F vs. M) | 0.89 | 0.69–1.15 | 0.37 | 0.81 | 0.62–1.06 | 0.13 |
| MELD | 1.00 | 0.99–1.02 | 0.68 | 1.00 | 0.99–1.01 | 0.80 |
| CKD at 6 months | 1.66 | 1.31–2.11 | **<0.001** | 1.62 | 1.25–2.09 | **<0.001** |
| **Overall survival analysis** | | | | | | |
| Age (per decade) | 1.34 | 1.17–1.53 | **<0.001** | 1.33 | 1.15–1.54 | **<0.001** |
| Female (F vs. M) | 0.84 | 0.64–1.09 | 0.19 | 0.77 | 0.58–1.02 | 0.07 |
| MELD | 1.00 | 0.99–1.02 | 0.67 | 1.00 | 0.99–1.01 | 0.91 |
| CKD at 6 months | 1.65 | 1.28–2.12 | **<0.001** | 1.58 | 1.21–2.06 | **0.001** |

All significant values are in bold.



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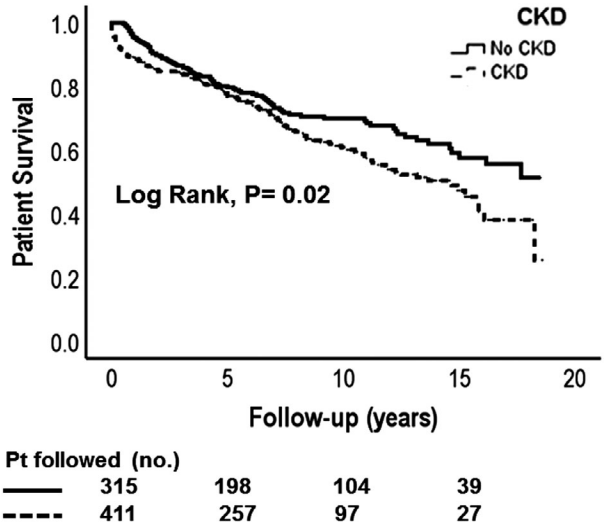


**Figure 5** Patient survival in those with or without CKD over the course of follow up.

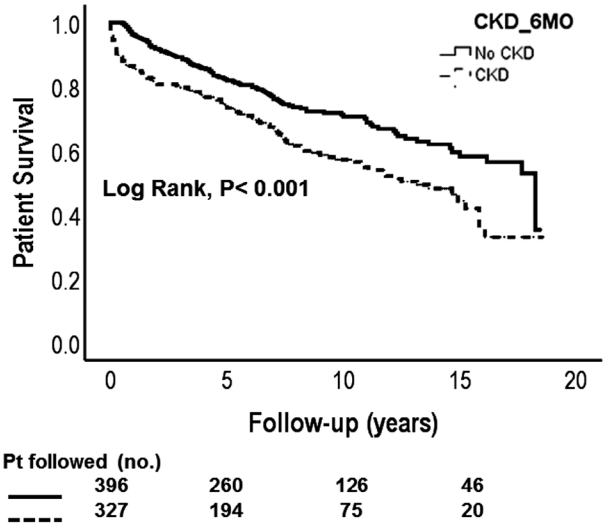


**Figure 6** Patient survival in those with or without CKD at 6 months post-LT.

LT, which was associated with both reduced graft (1.6; $P < 0.001$) and patient survival (HR 1.6; $P = 0.001$). There was a continued drop in eGFR over time, which stabilized at 5 years post-transplant. Reduced graft survival at 6 months may reflect episodes of rejection (patients with rejection are treated with higher levels of CNI, which may lead to increased CKD). However, our study shows no difference between the groups with regard to rejection episodes. Another possibility is that individuals with CKD have hyperhomocysteinemia, which leads to vascular and cellular injury, resulting in ischemic injury to the graft [12]. Second, the tacrolimus C/D ratio at three months was an independent risk factor for CKD. Each unit increase in the ratio reduced the risk for CKD by 31%. Third, we have identified potentially modifiable risk factors associated with CKD, including AKI following LT, de novo metabolic syndrome, and its components (hypertension or dyslipidemia). Finally, we show post-LT CKD is a risk factor for CVD. This is likely due to shared risk factors, including metabolic syndrome. The more severe the stage of CKD the higher the risk for CVD; a shift from stage 3a to 3b almost doubles the risk of CVD (OR 2.4 and 3.7, respectively).

The overall frequency of CKD post-LT was 60% in this study. A high proportion of patients met the criteria for CKD at 6 months (44%). This is consistent with other studies showing increased incidence of CKD in the first 6 months [3,13]. This highlights the importance of paying careful attention to renal function in the first few months and allowing for early intervention. In our institution, we delay use of tacrolimus in all patients with renal impairment (eGFR <60 ml/min). We use CNI-free immunosuppression in patients requiring hemodialysis prior to LT or in patients with worsening renal function post-LT (eGFR <60 ml/min). We know the longer an individual has CKD the less likely intervention is to reverse it [14,15]. Of note, we show eGFR continues to drop throughout follow-up with continued reduction in the proportion of patients with stage 1 CKD (35% pre-LT to 5% at 5-years post-LT). This highlights the need to use ongoing interventions for preservation of renal function in *all patients* and not just those with low eGFR pre-LT.

Congruent with previous studies, we show age, female sex, baseline eGFR, and MELD score to be associated with CKD [3,5]. Although creatinine is part of the MELD score, we believe MELD is truly an independent risk factor for CKD. The MELD reflects severity of liver disease and alterations in hemodynamics and vasoactive hormones, which make patients susceptible to renal injury. Our data are consistent with this and show patients with HCC, who have normal liver function, were less likely to have CKD. Baseline total bilirubin was also significantly higher in patients with CKD. The potentially modifiable risk factors identified in this study include AKI post-LT, the tacrolimus C/D ratio and post-LT metabolic syndrome and its components. Numerous studies have assessed ways in which to minimize CNI exposure to preserve renal function [16–18]. The predominant measures have been either minimizing CNI in the early post-transplant period or in the first few months or using CNI-free regimens. Unfortunately,

most centers do not adjust immunosuppression regimens in those with eGFR > 60 ml/min. Indeed, changes to immunosuppression regimens are in response to worsening renal function. Uniformly delaying tacrolimus to 72h following LT may help reduce the number of patients with AKI following LT. Being cognizant of tacrolimus C/D ratio and decline in renal function may further guide physicians to minimize CNI or potentially switch to CNI-free regimens at an early period. It makes sense that management of post-LT hypertension or dyslipidemia would prevent onset of CKD, but well designed, multicenter studies are needed for confirmation.

Limitations of this study are its retrospective nature and the single center patient population, which may not be representative of other centers. We estimated GFR using the MDRD-4 formula, which has been shown to overestimate renal function and underestimate mortality [3]. This biases our results to the null and so CKD may have an even larger impact than is shown in this study. Of all the equations estimating renal function, one study showed the MDRD-4 formula was the most accurate in estimating GFR in patients following solid organ transplantation [19]. A major strength of this study is the long-term follow-up, which is much shorter in most other studies. This long-term follow up allowed for a more accurate measurement of important clinical outcomes.

In conclusion, our study shows CKD is a frequent complication after LT. Renal function deteriorates rapidly following transplant with a high proportion having CKD at 6 months. CKD is associated with increased risk of CVD and poor graft and patient survival. Uniform minimization of CNI with potential use of tacrolimus C/D ratio as a guide may lead to improved outcomes. Further studies assessing impact of intervention on CVD, graft, and patient survival after LT are needed.

## Authorship

RAB: conception, design, data collection, statistical analysis, interpretation, drafting the manuscript, and critical revision. JC: data collection and revision of the manuscript. MM, NP, VGB and NK: assisted with the compilation and revision of the manuscript. AJM: statistical analysis, interpretation and revision of the manuscript. All authors approve of the final manuscript. RAB is the guarantor of the article.

## Funding

Rahima A. Bhanji is a recipient of the GILDR Hepatology award from the University of Alberta.

## Conflict of interest

The authors have declared no conflicts of interest.

## Acknowledgments

Presented in part at the International Liver Congress, the Annual Meeting of the European Association for the study of the Liver. April 12, 2014; London, UK. The authors thank Anuj Narang and Glenda Meeberg (Data Coordinator, Liver Transplant Program, and Alberta Health Services) for their statistical support.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** Characteristics of female patients based on presence or absence of CKD.

**Table S2** Characteristics of male patients based on presence or absence of CKD.

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