Risk factors for development of chronic kidney disease in liver transplant patients – a prospective single center evaluation.

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Background: The survival rate of liver transplant (LT) patients is increasing, resulting in a higher incidence of transplant complications, including chronic kidney disease (CKD). The aim of our study was to identify the clinical signs, associated diseases and laboratory parameters implicated in the development of CKD in liver transplant patients.

Methods: We performed a prospective cohort study of all patients transplanted at a tertiary care transplant center from 2008 - 2011. Exclusion criteria were multi-organ transplant recipients (2 patients) and patients who died within 3 months post-transplantation (1 patient). The outcome of interest was the incidence of CKD stage 3-5 defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 sixty months after LT. Variables considered to be potential confounders included age, sex, BMI, MELD score, Child Pugh score, baseline eGFR, presence or absence of pre-transplant nephropathy, acute kidney injury (AKI) in the early post-transplant period, renal replacement therapy (RRT) in the early post-transplant period, presence or absence of pre-transplant hepatitis B, hepatitis C, arterial hypertension, diabetes mellitus, infection in the early post-transplant period and acute cellular rejection over 24 months period.
We have monitored the blood count of red cells and platelets, INR, as well as serum glucose, urea, creatinine, Na, K, AST, ALT, GMT, ALP, bilirubin, albumin, CRP and tacrolimus levels before LT and in regular intervals for 24 months after LT.
AKI and CKD were defined using the revised definition by the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines. Kidney function was assessed by calculating eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
Baseline demographics and clinical characteristics were described using the mean (sd) for continuous variables and n (%) for categorical variables. Comparisons were tested using the chi-square or Fisher's exact test for categorical variables and Student's t test for normally distributed variables or Mann-Whitney test for non-normally distributed variables. The risk of CKD stage 3-5 was examined using multiple step logistic regression model with a backward elimination. Variables considered to be potential confounders were gender, age, presence or absence of CKD, serum urea, eGFR and tacrolimus blood level. P<0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics 24.

Results: A total of 41 liver transplant patients were included in our cohort. All were followed-up for sixty months after LT. We identified 11 patients with CKD, representing 26.8% of the cohort. Baseline recipient characteristics and clinical variables are presented in table 1. Etiology of the primary liver disease is presented in table 2. Figure 1 shows the mean eGFR (ml/min./1,73m^2) in the non-CKD and CKD group of patients before LT and in regular intervals for 24 months after LT. After fitting a logistic regression model with a backward elimination, decrease in eGFR 3 to 24 months after LT remained significantly associated with the development of CKD sixty months after LT (figure 2).

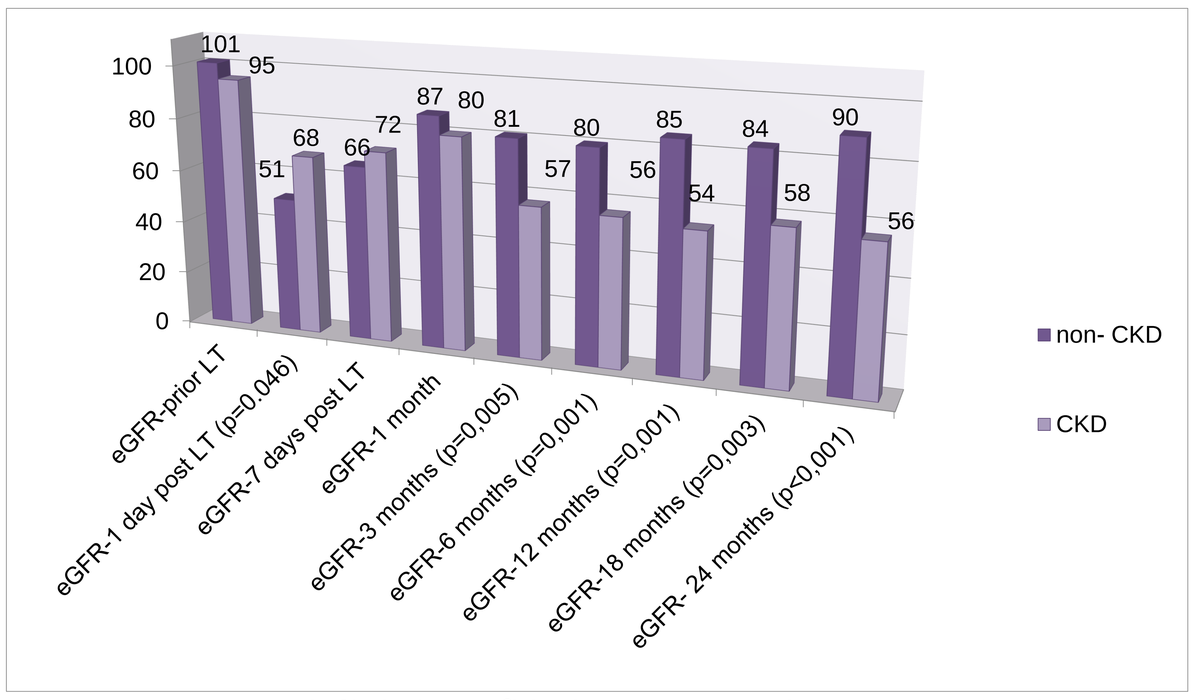

Figure 1. Mean eGFR (ml/min./1,73m²) in the non-CKD and CKD group of patients

Figure 2. OR with 95% Confidence Interval from Multiple Logistic Regression (6th step)

Table 1 Variable	Non – CKD n (%)	CKD n (%)	P value
Male/	16(53.3%)	4 (36,4%)	0.484
Female	14(46.7%)	7 (63,6%)	
Age (years)	44 ± 12.2	46 ± 16,2	0.402
BMI (kg/m^2)	23.9 ± 4.6	22.5± 3,6	0.347
MELD	16.7 ± 5.4	15,6 ± 4,6	0.460
Child Pugh A	1 (3.3%)	1 (9.1%)	
Child Pugh B	16(53.3%)	6 (54.5%)	0.03
Child Pugh C	12 (40%)	1 (9.1%)	
Acute liver failure	1 (3.3%)	3 (27.3%)	
Smokers	6 (20 %)	2 (18.2 %)	1.000
Hepatitis B	1 (3.3 %)	2 (18.2 %)	0.170
Hepatitis C	3 (10 %)	2 (18.2 %)	0.598
Arterial hypertension	8 (26.7 %)	2 (18.2 %)	0.429
Diabetes mellitus	8 (26.7 %)	1 (9.1 %)	0.814
Kidney disease prior LT	4 (13.3 %)	1 (9.1%)	1.000
eGFR prior LT			
>90 ml/min/1.73m^2	27(90.0%)	10 (90.9%)	0.810
60- 89 ml/min/1.73m^2	1 (3.3%)	1 (9.1%)	
30- 59 ml/min/1.73m^2	2 (6.7%)		
Early AKI after LT			
AKI 1 st.	3 (10.0%)	3 (27.3%)	0.05
AKI 2 st.	9 (30.0%)	0	
AKI 3 st.	10(33.3%)	2 (18.2%)	
RRT	8 (26.7 %)	2 (18.2 %)	0.700
Red cell transfusion during LT	15(50.0%)	2 (18.2 %)	0.085
Early reoperation after LT	6 (20.0 %)	2 (18.2 %)	1.000
Early infection after LT	13(43.3%)	3 (27.3 %)	0.478
Acute cellular rejection	12(40%)	4 (36.4 %)	1.000

Table 2 Primary liver disease	Non-CKD (n)	CKD (n)
Hepatitis B (HBV)	1	1
Hepatitis C (HCV)	1	1
Hepatocellular carcinoma (HCC)	1	
HBV+HCC		1
HCV+HCC	1	1
Primary sclerosing cholangitis (PSC)	6	3
Autoimmune hepatitis (AH)	3	2
Alcohol liver disease	8	
Wilson's disease	4	1
AH + PSC	1	
HCC + Primary biliary cirrhosis	1	
Amanita phalloides intoxication		1
Unknown	2	

Discussion: The formation of CKD in LT patients is associated with increased mortality and morbidity (2). The development of CKD occurs despite advances in immunosuppressive and perioperative management of patients as well as in the prevention of cardiovascular risk factors and infectious complications (3). Because of the multifactorial nature of CKD in the post-transplant period, the ability to accurately identify patients at risk and the development of preventative strategies remain unsolved issues (6). Comparison of studies about the incidence of CKD in patients after LT is challenging because of inconsistent classification of CKD and different methods of reporting GFR. We have used the KDIGO 2012 CKD definition and the CKD-EPI-creatinine equation to calculate eGFR. We expected that decreased GFR and/or presence of nephropathy before LT would be a risk factor for CKD, but it was not confirmed in our study. The incidence of early AKI after LT in our study was 65.9%. In the past, multiple definitions have been used to define AKI, therefore making comparison and interpretation of results difficult. We used the KDIGO definition. The relation between AKI after LT and the development of CKD is unclear. While there are studies that suggest that AKI is a risk factor for CKD (1, 2, 4) there are others that did not find any association between AKI and CKD after LT (5). In our study the rate of early AKI after LT was higher in the non-CKD group. Age, female gender, diabetes, arterial hypertension and hepatitis C have been identified previously as risk factors that influence the development of CKD (2). We did not confirm any of this variables in our study. The development of CKD neither depended on the Child Pugh score. It was related to acute liver failure as the reason for LT. We have assessed the impact of immunossuppressive therapy on the development of CKD. All patients in our cohort were given a single dose of daclizumab (1 mg/kg) and methylprednisolone 500 mg during the anhepatic phase of LT. From the first day after LT they were treated with corticosteroids, tacrolimus and MMF. There was not a statistically significant difference in the mean tacrolimus blood levels between the CKD and non-CKD patients in the 24 months after LT. We found that a decrease in eGFR three months after LT was a risk factor for developing CKD sixty months after LT. We suggest that this subset of patients would benefit most from a referral to a nephrologist and a close monitoring of CNI dose or conversion to non-nephrotoxic immunossuppressives such as mTor inhibitors. One of the strengths of our study is the long period of follow-up. Surprisingly, none of our patients had an eGFR < 30ml/min/1.73m^2 sixty months after LT. Being a single-center analysis with a small cohort is one of the limitations of our study, another is that we used an eGFR which can overestimate the true GFR in cirrhosis patient.

Conclusion: Decreased GFR three months after liver transplant and liver transplant for acute liver failure were risk factors for the development of chronic kidney disease sixty months after liver transplant. We did not confirm any other clinical signs, laboratory findings or associated diseases to be a risk factor for developing CKD after LT. We recommend to devise strategies to prevent or reduce the incidence of AKI and CKD in liver transplantation.

Citations:
1. Hilmi, I. A., Damian, D., Al-Khafaji, A. et al. ; Acute kidney injury following orthotopic liver transplantation: incidence, risk factors, and effects on patient and graft outcomes. *Br J Anaesth* 2015; 114 (6): 919-926. doi: 10.1093/bja/aeu556
2. Ojo, A.O., Held, P.J., Port, F.K., et al.: Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med, 2003; 349:931-940. doi:10.1056/NEJMoa021744
3. O'Riordan, A., Wong, V., McCormick, P. A. et al; Chronic kidney disease post-liver transplantation. *Nephrol Dial Transplant* 2006; 21 (9): 2630-2636. doi: 10.1093/ndt/gfl247
4. Trinh E, Alam A, Tchervenkov J*, and* Cantarovich M. Impact of acute kidney injury following liver transplantation on long-term outcomes. Clin Transplant. 2017;31*: :* e12863. doi: 10.1111/ctr.12863
5. Umbro, I., Tinti, F., Piselli, P. et al.: Occurrence of chronic renal failure in liver transplantation: monitoring of pre- and posttransplantation renal function. Transplant Proc. 2012; 44(7):1956-9. doi: 10.1016/j.transproceed.2012.06.012.
6. Weismüller, T. J., Lerch, C., Evangelidou, E., et al. ; A pocket guide to identify patients at risk for chronic kidney disease after liver transplantation. Transpl Int. 2015; 28: 519–528. doi:10.1111/tri.1252

DOI: 10.3252/pso.eu.54ERA.2017