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# Incidence of Chronic Kidney Disease after Liver Transplantation in a Chinese Cohort

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## Abstract

**Background:** Kidney dysfunction frequently occurred after Orthotopic Liver Transplantation (OLT). Chronic Renal Disease (CKD) is a complicated problem and is associated with increased mortality. The aim of this study is to find the risk factors for the incidence of CKD at 1 year after OLT in China.

**Methods:** From January 2017 to December 2017, we retrospectively assessed 292 recipients in our single center. Chronic renal failure was defined as estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73 $m^2$ for 3 months, regardless of the presence or absence of structural kidney damage. Cox proportional hazard model was used to identify the factors to the incidence of CKD after liver transplantations. Kaplan-Meier plots with log-rank test were presented to evaluate patient survival time in those with and without CKD.

**Results:** With a median follow-up of 17.4 months, 55 patients developed CKD after liver transplantations, representing18.8% of the cohort. The cox-regression model showed that recipients age (OR=1.093, P<0.01), Acute Kidney Injury (AKI) (OR=1.496, P<0.01) and baseline eGFR (OR=1.939, P<0.01) were significantly associated with the development of post-transplant CKD at 1 year. Recipient survival at 1 year was significantly worse in recipients with CKD compared to those without CKD (P<0.01).

**Conclusion:** Our findings suggested that age, AKI and baseline eGFR was associated with the incidence of CKD 1 year after OLT in a Chinese cohort. Recipients with CKD were associated with worse survival.

**Keywords: Liver transplantation; Chronic kidney disease; Risk factor; Survival**

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## Abbreviations

AKI: Acute Kidney Injury; CKD: Chronic Kidney Disease; CNI: Calcineurin-Inhibitor; DM: Diabetes Mellitus; eGFR: Estimated Glomerular Filtration Rate; HCV: Hepatitis C Virus; KDIGO: Kidney Disease of Improving Global Outcomes; MELD: Model of End-Stage Liver Disease; OLT: Orthotopic Liver Transplantation; RRT: Renal Replacement Therapy; SCR: Serum Creatinine

## Introduction

Kidney dysfunction frequently occurs after Orthotopic Liver Transplantation (OLT). Acute Kidney Injury (AKI) has a strong impact on patient survival. Multiple studies have shown that in-hospital and 1-year mortality are significantly higher in patients with AKI [1-5]. The aetiology of post-OLT AKI is thought to be multifactorial and includes hemodynamic instability leading to renal ischemia, blood loss, bacterial infections, liver dysfunction, hypoalbuminemia and chronic renal disease [6-8]. Despite the high incidence of AKI after liver transplantations, most of the OLT recipients recover from the postoperative AKI. However, a proportion of patients develop Chronic Kidney Disease (CKD). CKD is associated with higher mortality rates and increased costs, where further analysis of causes and underlying mechanisms is essential. Some studies reported that pretransplantation elevated Serum Creatinine (sCr), Hepatitis C Virus (HCV) infection, Diabetes Mellitus (DM), hypertension, and Calcineurin-Inhibitor (CNI) nephrotoxicity had impact on the development of CKD [9-13]. However, the data from China is limited. Based on the resources from our center, we try to find out the causes for the development of CKD in our country.

## Methods

### Patients

All adult patients who underwent orthotopic liver transplantation from January 2017 to

December 2017 at our center were included in this study and their medical records were retrospectively assessed. Recipients surviving more than three months after transplantations were included and minimal follow-up was one year. Patients were evaluated before transplantation as well as during the first week and 1, 3, 6, 9 and 12 months after transplantation. Recipients that did not have two Estimated Glomerular Filtration Rate (eGFR) measurements at least three months apart, were excluded. The other exclusion criteria included retransplantation, multi-organ transplantation, Renal Replacement Therapy (RRT) prior to liver transplantation and loss of follow-up. This study was approved by the ethics committee of Shanghai Ren Ji Hospital affiliated to Shanghai Jiao Tong University.

### Acute kidney injury and chronic kidney disease

AKI was defined according to the Kidney Disease of Improving Global Outcomes (KDIGO) criteria [14]: either an increase in Scr by ≥ 26.5 μmol/L within 48 h or an increase in creatinine to ≥ 1.5 times baseline within the first 7 postoperative days. AKI was classified into 3 stages: stage 1, increase ≥ 26.5 μmol/L or increase of 1.5-1.9 -fold from baseline; stage 2, increase of 2-2.9 -fold; stage 3, increase >3 -fold or increase in serum creatinine to ≥ 354 μmol/L or initiation of RRT. Chronic renal failure was defined as a GFR <60 mL/min/1.73m$^2$ for 3 months, regardless of the presence or absence of structural kidney damage. eGFR was calculated according to the CKI-EPI equation [15].

### Immunosuppression

Immunosuppression therapy was based on calcineurin inhibitor, cyclosporine or tacrolimus, during the initial hospitalization for transplantation. When renal function was impaired, we delayed introduction of the CNI.

### Statistical analysis

SPSS 18.0 software for windows was used to analyze the data. To compare categorical variables, the Chi-square test or the Fisher's exact test were used. Student's *t* test was used to compare parametric variables. A Cox proportional hazard model was used to identify the factors to the incidence of CKD after liver transplantations. Kaplan-Meier plots with log-rank test were presented to evaluate patient survival time in those with and without CKD. P<0.05 was considered statistically significant in all reported P values.

## Results

A total of 311 conducted orthotopic liver transplantations during 2017 in our center. Of these, one patient experienced retransplantation, two patients lost connection and sixteen patients died within the first three months. Overall, a total of 292 recipients were included in our study with a median follow-up of 17.4 months (IQR 14.6-21.1 months). We identified 93 (31.8%) recipients developed AKI within the first week after liver transplantations, including 70 who developed stage I, 17 who developed stage II and 6 who developed stage III. 55 patients developed CKD after liver transplantations, representing 18.8% of the cohort. The base-line characteristics of the OLT recipients were summarized in Table 1. As shown, neither sex, BMI, pretransplantation hypertension, pretransplantation DM, use of neither CNI, nor primary liver disease was associated with the development of CKD after liver transplantations. The univariable analysis demonstrated that the risk factors for the development of CKD at 1 year were age (P<0.01), model of end-stage liver disease (MELD) score (P<0.01), AKI (P=0.01) and baseline eGFR (P<0.01). We examined age, MELD score, AKI and Baseline eGFR as possible risk factors for post-transplant CKD. The multivariable cox-regression model (Table 2) showed that recipients age (OR=1.093, P<0.01), AKI (OR=1.496, P<0.01) and baseline eGFR (OR=1.939, P<0.01) were significantly associated with the development of post-transplant CKD at 1 year. Recipient survival at 1 year was significantly worse in recipients with CKD compared to recipients without CKD (log-rank P=0.02) (Figure 1).

**Table 1:** Baseline characteristics of OLT recipients.

| | CKD (n=55) | Non-CKD (n=237) | P value |
|---|---|---|---|
| Male, n (%) | 47 (85.4) | 186 (78.5) | 0.27 |
| Median age, years (IQR) | 57.0 (50.0-64.0) | 49.0 (42.0-55.0) | <0.01 |
| Median BMI, kg/m$^2$ (IQR) | 23.9 (22.5-25.7) | 23.3 (21.0-25.6) | 0.2 |
| Median MELD score (IQR) | 21.7 (18.5-28.3) | 19.9 (16.2-24.2) | <0.01 |
| HBP, n (%) | 12 (21.8) | 40 (16.9) | 0.41 |
| DM, n (%) | 14 (25.5) | 40 (16.9) | 0.14 |
| CNI, n (%) | | | 0.05 |
| Tacrolimus | 32 (58.2) | 170 (71.7) | |
| Cyclosporine | 23 (41.8) | 67 (28.3) | |
| AKI, n (%) | | | 0.01 |
| Non | 28 (50.9) | 171 (72.2) | |
| Grade I | 19 (34.5) | 51 (21.5) | |
| Grade II | 5 (9.1) | 12 (5.1) | |
| Grade III | 3 (5.5) | 3 (1.3) | |
| Baseline eGFR, n (%) | | | <0.01 |
| >90 mL/min/1.73 m$^2$ | 32 (58.2) | 207 (87.3) | |
| 60-90 mL/min/1.73 m$^2$ | 15 (27.3) | 26 (11.0) | |
| 30-60 mL/min/1.73 m$^2$ | 7 (12.7) | 4 (1.7) | |
| 30-60 mL/min/1.73 m$^2$ | 1 (1.8) | 0 | |
| Primary liver disease, n (%) | | | 0.77 |
| Hepatitis B | 21 (37.3) | 69 (29.2) | |
| Hepatocellular carcinoma | 24 (42.4) | 112 (47.6) | |
| Primary biliary cirrhosis | 3 (5.1) | 23 (9.9) | |
| Alcoholic liver disease | 1 (5.1) | 7 (2.1) | |
| Hepatitis C | 1 (1.7) | 4 (1.7) | |
| Other | 5 (8.5) | 22 (9.4) | |

**Table 2:** Cox proportional hazard model examining the risk factors for CKD 1 year after liver transplantation.

| Risk factor | Odds ratio | 95% CI | P-value |
|---|---|---|---|
| Age | 1.093 | 1.061-1.125 | <0.01 |
| AKI | 1.496 | 1.110-2.016 | <0.01 |
| Baseline eGFR | 1.939 | 1.376-2.732 | <0.01 |

## Discussion

Chronic kidney disease is a common complication after orthotopic liver transplantation, affecting 14% to 21% recipients after transplantation within 36 months [9,16]. In this study, we tried to find the risk factors associated with the development of CKD after liver transplantations in China. 292 recipients were included in our study with a median follow-up of 17.4 months. In our cohort, 18.8% of recipients occurred CKD within 1 year after liver transplantations. The cox-regression showed that recipients age (OR=1.093, P<0.01), AKI (OR=1.496, P<0.01) and baseline eGFR (OR=1.939, P<0.01)

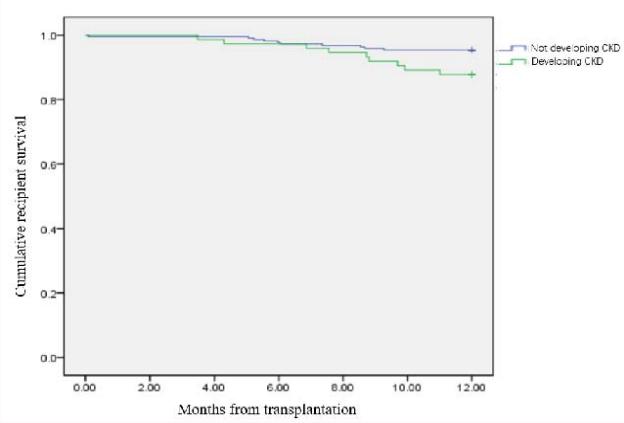


**Figure 1:** Kaplan–Meier plot showed that recipient survival for patients who developed CKD (green line) was significantly worse compared with those who did not develop CKD (blue line) (log-rank P=0.02).

were significantly associated with the development of CKD at 1 year. Several studies have shown that older recipients were more likely to suffer from CKD [9,17,18]. AKI is a frequent post-operative complication after liver transplantation. AKI may possibly result in irreversible renal injury, which leads to chronic kidney disease. In our study, AKI (OR=1.496, P<0.01) was significantly associated with the development of CKD. Trinh [19] demonstrated that AKI was associated with a twofold increase in developing CKD. Ojo also reported that postoperative acute renal failure was associated with an increase by a factor of more than two in the risk of chronic renal failure among patients with liver transplants. Another risk factor associated with CKD was baseline eGFR. Greater reductions in the pretransplantation glomerular filtration rate were also associated with progressive increases in the risk of chronic renal failure. This highlights the importance of proper long-term follow-up in these recipients. Hypertension and diabetes are known risk factors for development of renal disease. In our study, we didn't find these relationships. Burra found pretransplantation hypertension was a neared significant predictor (P=0.08) of GFR at1 year. Paramesh just showed that a history of diabetes prior to OLT had a significant increased incidence of CKD. It is conceivable that the exposure periods to hypertension and diabetes before liver transplantations may cause these different results. As regard to the use of CNI, we suggested that the risk of chronic renal failure had a trend towards higher proportion of cyclosporine-based immunosuppressive regimens, but not to be statistically significant (P=0.05). Ojo demonstrated that the risk of chronic renal failure was higher among recipients of liver transplants who were treated with cyclosporine than among those who were treated with tacrolimus. Trompeter [20] found that mean glomerular filtration rate was significantly higher in the tacrolimus group (62+/-20 ml/min per 1.73 $m^2$, n=84) than in the cyclosporine group (56+/-21 ml/min per 1.73 $m^2$, n=74, P=0.03) at 1 year. Paramesh also showed that cyclosporine immunosuppression had a significantly higher incidence of end-stage renal disease than tacrolimus in their patients. Hepatitis C virus (HCV) liver disease patients have been reported to have a higher risk of developing renal disease by several studies [10,21,22]. In China, Hepatitis B virus is the major cause of liver disease. In our study, we didn't find the association between HBV infection and the development of CKD. In terms of risk of death, patient survival at 1 year was significantly worse in recipients with CKD compared to recipients without CKD. Ojo demonstrated that in a comparison with transplant recipients who did not have chronic renal failure, chronic renal failure was associated with an elevated risk of death after transplantation (relative risk, 4.55; 95% CI, 4.38 to 4.74; P<0.001). There were also some limitations for this study. First, it was a single-center study, which limited analysis of data from other hospitals. Second, the sample size was relatively small. Through the development of our liver transplantation center, we could include more eligible recipients. Furthermore, the median follow-up of recipients was 17.4 months. Further studies may therefore analyze the long-term kidney function more than ten years after liver transplantation. To conclude, our study showed that age, AKI and baseline eGFR were associated with higher incidence of CKD after liver transplantations at 1 year. This emphasized the importance to prevent and manage AKI in OLT recipients, such as monitoring fluid status, avoiding nephrotoxic medications and early treatment of infectious diseases. What's more, the evaluation of pre-OLT renal function should always be considered in the follow-up of liver transplant recipients.

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