

Prevalence and Risk Factors of Chronic Kidney Disease After Liver Transplantation: Outcomes in The Main Transplant Center of Peru

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1. Abstract

1.1. Background: Chronic kidney disease is one of the most significant complications after liver transplant.

1.2. Materials and Methods: We included in this study 151 of 206 patients transplanted from March 2000 to March 2016 in the Liver Transplant Service at the Guillermo Almenara National Hospital (EsSalud) Lima-Peru, and had been alive with follow up for at least 3 months after liver transplantation: 98 males (64.9%), 53 females (35.1%); mean age, 49.9 years; age range, 18-77 years. Updated data were collected regarding age, sex, body mass index, underlying liver disease, graft type, immunosuppressive treatment, MELD score, last serum creatinine levels in the outpatient clinic follow up, and glomerular filtration rate (GFR) at 1,3,5,10 and > 10 years after liver transplant. GFR was calculate for 2 methods: CKD-EPI and MDRD4. Data were analyzed with SPSS software version 25.0.

1.3. Results: The mean follow-up was 60.1 months (range, 3-192 months). The main indications for liver transplantation were: Metabolic associated fatty liver disease (MAFLD: 25.8 %, n = 39), autoimmune hepatitis: 24.5% (n = 37), Primary Biliary Cholangitis (PBC: 12.6 %, n = 19), alcohol cirrhosis: 12.6 % (n = 19) and hepatitis C cirrhosis: 9.3% (n = 14). The MELD score at the time to transplant were MELD score <19: 50.3%, 20-29:41.7%, 30-40: 7.9%. Cumulative prevalence for each stage of CKD was Stage 3:16.5%, Stage 4: 3.3% and Stage 5: 0.6%. Sex, type of immunosuppressive treatment,

underlying liver disease and MELD score were not predictors of renal dysfunction.

1.4. Conclusions: Chronic kidney disease may be a significant problem for patients after liver transplant, and early detection of renal dysfunction in patients after liver transplant is very important. In our experience chronic kidney disease after liver transplantation has a low impact in our patients in the short, medium and long time.

2. Introduction

Kidney dysfunction is a common complication before and after liver transplantation. In the pre- and post-transplant stage there are several causes that can originate kidney dysfunction including acute kidney injury (AKI) [1], history of chronic kidney disease secondary to high blood pressure, diabetes mellitus and other glomerulopathies associated especially with chronic alcoholic liver disease and Chronic Hepatitis B and C: membranoproliferative glomerulonephritis, membranous, extra capillary, focal and segmental, mesangial IgA [2-5]. In this sense, the burden of chronic kidney disease (CKD) is increasing in cirrhotic patients and has a deleterious effect on the results in the post-transplant stage [6]. Likewise, the prevalence of CKD in patients with cirrhosis at the time of transplantation in some reports reach 18%, with the risk of death also increasing by 16% after liver transplantation [6].

The improvement in survival after liver transplantation has been the result of the optimization of immunosuppression protocols as

well as the reduction of corticosteroids and calcineurin inhibitors: tacrolimus and cyclosporine, drugs most frequently used in organ transplants, the same that present a wide range of adverse effects, especially nephrotoxicity [2, 3, 4].

Ojo et al., reported that the risk of developing chronic renal failure five years after non-renal organ transplantation is 7 to 21%, depending on the type of organ transplanted [5-7], in this same study transplant recipients Non renal solid organs with chronic kidney disease had a 4.55-fold mortality risk compared to patients with normal kidney function.

In liver transplant recipients, post-transplant kidney dysfunction may be reversible if it is diagnosed and identified early. The calcineurin inhibitors (CNI): cyclosporine and tacrolimus are contributory factors of kidney damage [8-10] due to nephrotoxicity, involving in its pathogenesis, the reduction of glomerular blood flow and interstitial fibrosis [11-13]. However, current immunosuppression regimens with reduced doses, delayed initiation or free from calcineurin inhibitors are known to be associated with an improvement in renal function [14].

According to the current definition proposed by Kidney Disease Improving Global Outcomes (KDIGO), the diagnostic criteria for CKD are the so-called markers of kidney damage or a reduction in GFR below 60 ml / min / 1.73m². The duration greater than 3 months of any of these alterations can be verified prospectively or interfered with from previous records [15]. However, glomerular filtration rates may vary according to the definition used and the different methodologies for calculating them, since most of the formulas were not initially applied in the transplanted population.

In cirrhotic patients especially with ascites and kidney dysfunction is common overestimation and wide overlap in confidence intervals/precision of GRF by 10-20 ml/min/1.73 m². In a meta-analysis, CKD-Epi-SCr-CysC formula it was concluded may be acceptable to estimate kidney function across the spectrum of GRF in this population [16].

In the study by Wagner et al., the formulas based on CrS and CysC were evaluated for the calculation of the glomerular filtration rate in liver transplant recipients, using inulin clearance and using as reference: MDRD 4, Cockcroft-Gault and CKD-EPI; resulting in formulas based on Cystatin C. They were found to be superior to those based on serum creatinine in the identification of patients with a GFR rate <60 ml / min / 1.73 m² [17]. However, this test is not used as a routine examination in the laboratory of hospital centers due to its high cost and the equipment it requires.

To date, most studies have focused on the development of End-Stage Renal Disease (ESRD) defined with a glomerular filtration rate (GFR) <30 ml / min 1.73 m², but only a few studies have evaluated the spectrum Complete Chronic Kidney Disease in Liver Transplant Recipients. Ojo et al., reported a prevalence of CKD of 16% at 5 years in post liver transplant patients; CKD was defined as a GFR

<30 ml / min / 1.73 m². O'Riordan et al, conducted a study in 230 LT recipients, using the KDOQI criteria, finding at 10 years, 2.26% developed stage V CKD, 6.11% stage 4, 56.77 stage 3 [10]. Gonwa et al reported an incidence of ESRD of up to 18% at 10 years' post-liver transplantation. [18] (Table 1)., shows comparative studies in CKD after liver transplantation.

A recent publication from a high-volume transplant center showed the findings of the effect of organ donor type and the development of post-transplant kidney dysfunction, finding that liver recipients who deceased heart donors experienced high rates of post-transplant renal dysfunction compared to beating-heart donors or related living donors, suggesting that other risk factors for the development of severe renal injury such as a high MELD score, massive transfusion or donors >= 60 years should be avoided [19].

The objective of this study was to show the clinical characteristics, prevalence and stratification of chronic kidney disease in patients receiving liver transplantation in our center, follow up in the outpatient clinic in the short, medium and long term; in order to make an early diagnosis, to prevent renal deterioration and consequently reduce the increased risk of morbidity and mortality in this group of patients.

Table 1: Comparative studies of CKD (Stage 4 & 5) post Liver Transplantation.

Autor and year	Patients No	GRF < 30 Ml/min/1.73 m2
Ojo, 2002	36,849	18% / 5 y
Cohen, 2002	191	20.4% / 3 y
O'Riordan, 2006	230	6.5% / 10 y
Aberg, 2008	396	7.4% / 5y
Sharma, 2009	221	22% / 5 y
Burra, 2009	233	2,7 / 5 y
Karie-Guigues,2009	1508	5% / 5 y
Ramachandran, 2010	130	8% / 5 y
HNGAI, 2021	151	3,3% / 15 y

3. Material and Methods

A retrospective, cross-sectional study was conducted reviewing the medical records of liver transplant patients from the Guillermo Almenara Essalud hospital, from March 2000 to March 2016, alive at the time of the study. The universe and the inclusion and exclusion criteria are shown in (Figure 1).

An Excel database was created for all patients in the waiting list and continued after transplantation. The data was kept confidential and analyzed with IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA) Variables: Sex, etiology, MELD, comorbidity (HTN, DM, coronary disease), Creatinine clearance determined by CKD-EPI and GFR by MDR4.

Likewise, data on the use of pre-transplant induction therapy, type of immunosuppression received, on the other hand, complications

were recorded after transplantation: acute rejection, chronic rejection and the presence of CMV disease. The determination of renal function was calculated by 2 methods: Glomerular filtration rate (the creatinine value taken for the study was the last current value of the control of the patient in the outpatient clinic from January 01, 2016 to March 30, 2016):

- CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration equation) Ann Intern Med 2009; 150: 60: 604-612. $GFR = 141 * \min(\text{Scr} / k, 1) \text{ to } * \max(\text{Scr} / k, 1) - 1209 * 0993 \text{ Age} * 1018 \text{ (female)} * 1159 \text{ (black)}$
- MDRD4: National Kidney foundation: $K / DOQI \text{ (Clini-}$

cal practice guidelines for chronic kidney disease evaluation, classification and stratification). Am J Kidney Dis 200239 Suppl 1): S1.

For the purposes of the present study, kidney function in the liver transplant patients studied was evaluated according to the glomerular filtration rate, divided into 3 groups of chronic kidney disease (CKD) [15]:

- A. Stage 3 (Mild to Moderate): eGFR, 30-59 ml / minute / 1.73 m²,
- B. Stage 4 (Severe): eGFR, 15-29 ml / minute / 1.73 m² and
- C. Stage 5 (Renal failure): eGFR, <15 ml / minute / 1.73 m²

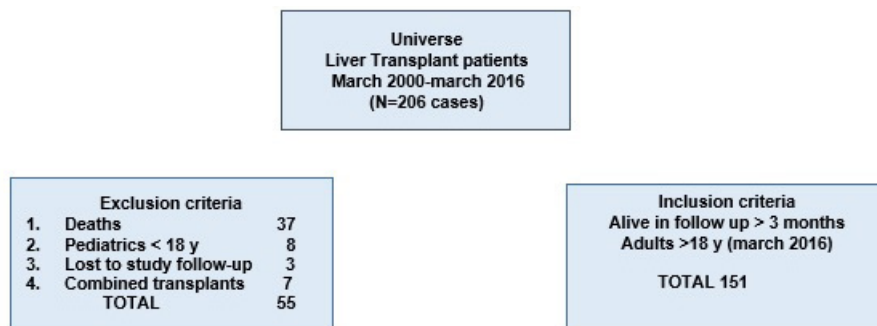


Figure 1: Inclusion and exclusion criteria

4. Results and Discussion

Of the 206 liver transplant patients in the study period, 151 cases that met criteria were included: 98 men (64.9%) and 53 women (35.1%); average age 49.9 years, ranges 18-77 years. The mean follow-up time of the patients was 60.1 months (range, 3-192 months). The main indications for liver transplantation were: Metabolic associated fatty liver disease (MAFLD: 25.8 %, n = 39), autoimmune hepatitis (AIH): 24.5% (n = 37), Primary Biliary Cholangitis (PBC): 12.6 %, n = 19), alcoholic cirrhosis: 12.6 % (n = 19) and hepatitis C (HCV) cirrhosis: 9.3% (n = 14). 50% of the patients had MELD score < 20 at the time to transplantation. (Table 2), shows the pre-transplant characteristics.

Table 2: Clinical and demographics characteristics (n = 151).

Age (years), media (SD)	44.8 (+14.9)
18 – 44 , n (%)	45 (29.8)
45 – 60 , n (%)	59 (39.1)
> 60 , n (%)	47 (31.1)
Sex: Male (%) / Female (%)	98 (64.9) / 53 (35.1)
MELD, media (SD)	18.7 (+6)
10 – 19 , n (%)	76 (50.3)
20 – 29 , n (%)	63 (41.7)
30 – 40 , n (%)	12 (7.9)
BMI (kg/m²)	25.1 (5.9)
Etiology, n (%)	
<i>Cirrhosis</i>	
<i>NASH</i>	39 (25.8)
<i>AIH</i>	37 (24.5)
<i>PBC</i>	19 (12.6)
<i>Alcohol</i>	19 (12.6)
<i>HCV</i>	14 (9.3)
<i>Hepatocellular Carcinoma</i>	20 (13.2)
<i>Acute Liver Failure</i>	---
<i>Other</i>	23 (15.2)
Comorbidities, n (%)	
<i>Hypertension</i>	16 (10.6)
<i>Diabetes Mellitus</i>	14 (9.3)
<i>Coronary disease</i>	1 (0.6)

In 150/151 patients (99.3%) received complete grafts from cadaveric donors. 1 graft (0.7%) was from a related living donor. According to our immunosuppression protocol, our patients received a double scheme based on tacrolimus 138 patients (91.4%) and corticosteroids, with increasing doses of tacrolimus, starting with the lowest dose of 0.05 to 0.1 mg / kg / day, with a level target serum tacrolimus in the first 6 months after transplantation of 8-10 ng / ml, month 6 to 12: 8ng / ml and > 1 year after transplantation around 5 ng / ml. The alternative scheme used by our center is the triple scheme based on cyclosporine in 8 patients (5.3%) + mycophenolate and corticosteroids; with increasing doses of cyclosporine, starting with the lowest dose of 8 - 10 mg / kg / day with a target serum C2 level of 800-1000 ng / ml until month 6th, 800 ng / ml from month 7 to 12 and 600 ng / ml > 1 years after transplantation. A very small number of patients, 3 patients (3.3%) used mTOR as a base regimen (2 everolimus, 1 sirolimus). Only in the case of previous renal dysfunction or pre-transplantation AKI and/or persistent encephalopathy, was the protocol of delaying the initiation of calcineurin inhibitor applied after 5-7 days' post transplantation using monoclonal antibodies (Basiliximab 20 mg days 0 and 5) or polyclonal antibodies (thymoglobulin x 2 doses). (Table 2), shows the characteristics of immunosuppression and the post-transplant characteristics.

The calcineurin inhibitor was switched to everolimus in 3 patients due to identified neoplasia. Of the patients with post-transplant kidney dysfunction, none required chronic hemodialysis. In the present study, no case of kidney after liver transplantation was found in our case series.

The post-transplant chronic kidney disease found in our cases was

CKD Stage 3: 16.5% and CKD Stage 4: 3.3% and CKD Stage 5: 0.6%, see (Table 3). There was no correlation with a history of diabetes, hypertension or cardiovascular disease.

Table 3: Factors related to renal dysfunction in Liver Transplantation.

Induction therapy,	n (%)
<i>Basiliximab</i>	48 (31.8)
<i>Thymoglobulin</i>	5 (3.3)
<i>None</i>	98 (64.9)
Immunosuppression, n (%)	
<i>Tacrolimus</i>	138 (91.4)
<i>Cyclosporine</i>	8 (5.3)
<i>mTOR</i>	5 (3.3)
Complications, n (%)	
<i>Cellular rejection</i>	18 (11.9)
<i>Chronic rejection</i>	8 (5.2)
<i>Infection CMV</i>	5 (3.3)
Renal dysfunction in LTx n (%)	
<i>AKI</i>	17 (11.3)
<i>Dialysis Post-Liver Transplantation</i>	11 (7.3)
<i>No Dialysis</i>	140 (92.7)
<i>Chronic dialysis</i>	0

Although immunosuppressive therapy with calcineurin inhibitors after liver transplantation has markedly improved patient and graft survival rates, there are nephrotoxic effects of these drugs that have been reported in previous studies [8, 9]. This renal dysfunction occurs despite adequate perioperative management and is related to cardiovascular risk factors and infectious complications [10]. Likewise, chronic kidney dysfunction is associated with increased morbidity and mortality [11], however, in our experience we did not find this association (Table 4).

Table 4: CKD Stage and time of Liver Transplantation

CKD STAGE (GRF) mL/kg/min	TIME OF TRANSPLANTATION					No	%
	< 1 y	1-3 y	3-5 y	5-10 y	10-15y		
3 (30-59)	4	9	3	0	4	20	13.2
4 (15-29)	0	0	1	1	2	4	2.6
5 (< 15)	0	0	0	1	0	1	0.6
CrCl < 60	4	9	4	2	6	25	16.5
CrCl < 30	0	0	1	2	2	5	3.3

Calcineurin inhibitors cause nephrotoxicity through various mechanisms including interference with intrarenal blood flow [12], increased expression of certain cyclosporine-binding proteins in kidney cells [12], transforming growth factor beta, and increased cell turnover of the extracellular matrix [13, 20].

A retrospective study of 834 liver transplant recipients with survival greater than 6 months, reported a decrease in kidney function post-transplantation and an increased incidence (18%) of severe renal dysfunction [21]. As has been reported in other studies, there is a gradual decrease in kidney function after liver transplantation [22-25].

Our study shows a prevalence of stage 4 CKD (Clcreat <30 ml / min 1.73 m²) of 3.3%, which is lower than that reported by Ojo et al [7] and several other similar published studies, see (Table 1). In others <https://jgastrohepto.org/>

reports kidney failure was associated with diabetes mellitus and hepatorenal syndrome. It has also been reported that the risk of chronic kidney dysfunction is more associated with the use of cyclosporine [13] than with tacrolimus. In contrast, in our study, more than 90% of liver transplants are on the tacrolimus-based regimen.

In a study, no other factor was correlated with decreased kidney function, including initial disease, nephrotoxic drugs, high blood pressure, or rejection episodes. Independent risk factors for chronic kidney failure including calcineurin inhibitors, advanced age, low glomerular filtration rate, female gender, diabetes mellitus, arterial hypertension, and hepatitis C infection [3, 10].

In the present study, chronic kidney disease was not marked by these factors since the presence of diabetes, hypertension and hepatitis C were present in less than 10% of our patients. Likewise, 70% of the patients in our series were less than 60 years old. On the other hand, it is shown that our cellular and ductopenic rejection rates are low compared to other series [10, 14], this could be due to the use of doses and blood levels of calcineurin inhibitors at lower limit therapeutic ranges, which somehow it would explain less collateral effects on kidney function in the medium and long term in our transplant patients; Likewise, we found low rates of cytomegalovirus (CMV) infections in our experience, which was only 3.3%, using universal prophylaxis with valganciclovir in the first 90 days post transplantation.

Since post-transplantation CKD is significantly associated with a higher frequency of cardiovascular events, mortality, and liver graft dysfunction, it is important to make an early recognition of kidney dysfunction and implement changes to improve long-term results. In this sense, renal dysfunction should be recognized and treated as early as 3 months after transplantation.

For all the aforementioned, we can conclude that post-transplant CKD in our experience has a low prevalence in our patients in the short, medium and long term; probably due to the low frequency of cardiovascular risk comorbidity in the pre-transplantation phase, as well as the rational use and management of the on-demand immunosuppression scheme in our patients with individualized use and with low therapeutic levels of CNI, especially tacrolimus.

It is important to point out that our study has limitations: firstly, since we do not have cystatin C dosing regularly in our center, we determined chronic kidney disease from stage III, using 2 formulas, which turned out to be almost identical in its results to classify chronic kidney disease and secondly because, being a retrospective study, it did not allow us to collect other important data such as the presence of hematuria and proteinuria prospectively in our patients.

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