Early predictors of renal dysfunction in cirrhotic patients after liver transplantation

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Summary

Background. *Assessment of renal function 12 months after liver transplantation (LT) predicts chronic renal failure on long-term follow up.* ***Objective.*** *To evaluate pre- and post-LT factors associated with development of renal dysfunction (RD) in cirrhotic patients.* ***Methods.*** *Between June 2005 and June 2010, 104 cirrhotic patients were selected from 268 consecutively transplanted adult patients. RD was defined as a calculated glomerular filtration rate (cGFR) < 50 ml/min/1.73m² by modification of diet in renal disease (MDRD), 12 months after LT.* ***Results.*** *Baseline pre-LT creatinine was 1.0 ± 0.7 mg/dL and cGFR was 64 ± 32.8 mL/min. At 12 month follow up, creatinine was 1.3 ± 0.6 mg/dL and cGFR was 47 ± 18 mL/min. The prevalence of RD was 55%. Variables related to RD on univariate analysis were age (P = 0.007), pre-LT GFR (P = 0.012) and 7th day post-LT GFR (P = 0.003). Risk factors associated with RD on multivariate stepwise regression analysis were patient age [Odds ratio (OR) 1.04 (95% confidence interval (CI) 0.99-1.09, P = 0.06)] and 7ᵗʰ day post-LT GFR [OR 0.97 (95% CI 0.96-0.99, P = 0.013)]. ROC curve analysis for 7ᵗʰ day post-LT GFR was 0.71 (95% CI 0.61-0.81).* ***Conclusion.*** *The 7ᵗʰ day post-LT GFR in cirrhotic patients may be a useful clinical tool to identify which patients might benefit from earlier nephroprotective immunosuppression.*

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Predictores tempranos de disfunción renal en pacientes cirróticos luego del trasplante hepático
Resumen

Introduction. *La evaluación de la función renal al año post-trasplante hepático (TH) predice el desarrollo de injuria renal crónica y progresiva a largo plazo.* ***Objetivo.*** *Evaluar variables predictoras pre- y post-TH de desarrollo de disfunción renal (DR) en pacientes cirróticos luego del TH.* ***Métodos.*** *Entre junio de 2005 y junio de 2010, 104 pacientes cirróticos fueron incluidos de un total 268 pacientes adultos trasplantados de hígado. La DR se definió cuando la tasa de filtrado glomerular (TFG) era de <50 ml/min/1,73m² calculada con la fórmula MDRD (modification of diet in renal disease), a 12 meses post-TH. Se evaluaron las odds ratios (OR) en función del desarrollo de DR.* ***Resultados.*** *La creatinina sérica y la TFG basal pre-trasplante fueron de 1,0 ± 0,7 mg/dl y 64 ± 32,8 ml/min. A los 12 meses post-TH, la creatinina fue de 1,3 ± 0.6 mg/dl y la TFG de 47 ± 18 ml/min. La prevalencia de DR fue de 55%. Las variables relacionadas con el desarrollo de DR en el análisis univariado de regresión logística fueron la edad del paciente (P = 0,007), la TFG pre-TH (P = 0,012) y la TFG post-TH al día 7 (P = 0,003). En el análisis multivariado las variables que permanecieron relacionadas con el desarrollo de DR fueron la edad [OR 1,04 (intervalo de confianza del*

95% (IC 95%) 0,99-1,09, P = 0,06)] y la TFG al día 7 post-TH [OR 0,97 (IC 95% 0,96-0,99, P = 0,013)]. La curva ROC de la TFG al día 7 post-TH para la predicción de DR fue de 0,71 (IC 95% 0,61-0,81). **Conclusiones.** *La TFG al día 7 post-TH en pacientes cirróticos podría ser de utilidad en la identificación de aquellos pacientes candidatos a inmunosupresión nefroprotectora.*

Palabras claves. *Cirrosis, falla renal, trasplante hepático, inmunosupresión.*

Abreviaturas
ACR: acute cellular rejection.
CNI: calcineurin inhibitors.
CsA: cyclosporine.
DM: diabetes mellitus (DM).
ESKD: end stage kidney disease.
GFR: glomerular filtration rate.
HCV: hepatitis C virus.
LT: liver transplantation.
MDRD: modification of diet in renal disease.
MELD: model for end stage liver disease.
MELD Na: MELD sodium.
MMF: mophetil or sodium mycophenolate.
OR: odds ratio.
RD: renal dysfunction.
ROC: receiving operator curves.
RRT: renal replacement therapy.
Tac: tacrolimus.

Calcineurin inhibitors (CNI), tacrolimus (Tac) and cyclosporine (CsA), remain the cornerstone of maintenance immunosuppression in liver transplantation (LT).[1, 2] However, these drugs have many side effects, predominantly acute and chronic kidney injury.[3, 4] Actuarial incidence of end stage kidney disease (ESKD) or glomerular filtration rate (GFR) lower than 30 ml/minute/1.73 m^2 is close to 20% after 5 to 10 years following liver transplantation, carrying greater morbidity and mortality.[5, 6-9] Cirrhotic patients may be at higher risk of developing ESKD after transplantation due to hemodynamic changes secondary to portal hypertension.

The ability to identify which patients will experience progressive renal failure after liver transplantation in order to avoid over-immunosuppression is a real clinical challenge. Several published studies have shown that late CNI-associated nephrotoxicity can be predicted by pre-transplant serum creatinine and renal function assessment in the 3rd and 12th month after LT.[10-12] Patients with more

advanced renal impairment or renal dysfunction (RD) (GFR lower than 50 ml/minute 12 months post-LT) evidence the main improvement in GFR over time with nephroprotective immunosuppression strategies.[13, 25-26] In this sense, we think that early predictors of RD (immediate post-LT period) are needed to identify which patients will have more benefit with nephroprotective strategies. The aim of this study was to identify early predictors of RD assessed 12 months after LT in patients transplanted for cirrhosis.

Patients and methods

We performed a retrospective single centre analysis of 268 adult patients who consecutively underwent liver transplantation at the Hospital Italiano de Buenos Aires, Argentina, between June 1st 2005 and June 30th 2010. Patients included in the study were only adult cirrhotic patients who received a first liver transplant with a deceased brain donor and who were alive 12 months after transplantation. Patient information was taken from medical records and from a prospectively maintained database. All patients included for the analysis had at least one year of clinical and laboratory follow-up. Laboratory values closest to the time of transplantation, data from donors (age, sex, weight, height, laboratory values) and from cold and warm ischemic times were included for the analysis. Immediate pre-transplant scores were calculated: Child Pugh, model for end stage liver disease (MELD) and MELD sodium (MELD Na).[27, 28]

Since 1988, more than 1,000 liver transplants were carried out and 50-70 liver transplants per year are performed at the Hospital Italiano de Buenos Aires. The usual immunosuppression protocol is methylprednisolone 1g in the operating room and 500 mg during the first 24 to 48 hours after transplantation. Tacrolimus or cyclosporine with or without mycophenolate (MMF) are associated with steroid tapering. A subgroup of patients with renal impairment before LT underwent induction with basiliximab to delay the start of CNI. During the first 3 to 6 months Tac target blood through levels were 8 to 10 ng/mL and CsA 250 to 300 ng/mL, declining gradually between 6 to 8 ng/mL and 200 to 250 ng/mL during the subsequent months, respectively. The decision to choose one or other CNI (Tac or CsA), basiliximab induction or MMF is taken by a team of transplant hepatologists and liver surgeons in a case-by-case basis.

Our primary outcome was RD 12 months following liver transplantation defined as calculated GFR (cGFR) lower than 50 mL/minute/1.73 m^2. Modification of diet c GFR in renal disease (MDRD) equation was calculated.[29] Pre and post-LT renal function was categorized ac-

cording to the RIFLE Criteria by GFR-MDRD:[30] group 1: cGFR higher or equal to 90 mL/min, group 2: cGFR from 89 to 60 mL/min, group 3: cGFR from 59 to 30 mL/min and group 4: cGFR lower than 30 mL/min or renal replacement therapy (RRT). Although RIFLE criteria are not standardized for cirrhotic patients, we considered these criteria in order to compare more precisely any changes between pre- and post-LT settings and compare our findings with other already published. Our Institution Ethics Committee approved this retrospective study and it was in accordance with the Helsinki Declaration of 1975 and Declaration of Istanbul

Statistical Analysis

Dichotomous variables are expressed as frequencies and continuous variables as mean (± SD) for a normal distribution. Univariate analysis using logistic regression was performed in order to identify significant variables related to the primary outcome. All univariate variables with P values ≤ 0.10 were considered for multivariate analysis. Multivariate logistic regression models were generated by stepwise backward elimination (Wald test), using a P value > 0.05 to remove variables not significantly associated with the outcome. Risk estimate statistics for development of RD were made with odds ratios and their respective 95% confidence intervals (95% CI). Only variables with $P < 0.05$, which were clinically relevant or presented a confounding effect on the event, were retained in the model to provide the predictive power of the model. To establish the model's goodness of fit a Hosmer-Lemeshow test was carried out, and the discrimination power of the model was assessed with receiving operator curves (ROC) and c-statistics was calculated. Collected data was included in a database and analysed by *Stat View for Windows, Abacus Concepts (STATA version10.1).*

Results

From a total of 268 consecutively transplanted adult patients, a cohort of 104 cirrhotic transplanted patients was included for the analysis. Ten patients with combined liver-kidney transplantation, 26 with acute liver failure and 24 with re-transplantation were excluded. Thirty seven patients lost of follow-up and 15 deceased before the first year after transplantation were also excluded (Figure 1). The Table 1 describes the general characteristics of the entire cohort. Mean patient age was 54.5 ± 10.5 years and 12 patients (12.5%) of the study cohort had pre-LT DM.

Prevalence of RD was 54.8% (57 patients). Only 7 patients (6.7%) had ESKD, whereas 99 (96.1%) had at least mild renal dysfunction (cGFR lower than 90 mL/min).

Regarding the subgroup of patients with RD, 6 patients had a renal biopsy performed during follow up. Evidence of chronic renal toxicity associated with CNI was present in 50% of these patients. RD developed in 6 of 12 patients (50%) with a pre transplant MELD score higher than 30.

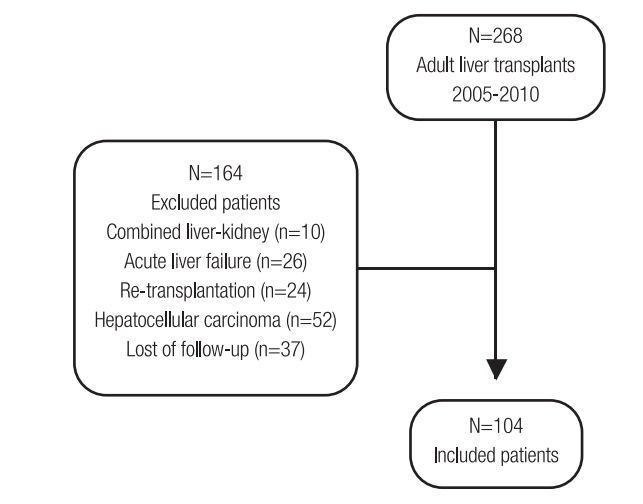**Figure 1.** *Inclusion and exclusion criteria flow chart.*

Table 1. *Patients' baseline characteristics (n=104).*

Age (mean years + SD)*	54.5±10.5
Male Gender [n (%)]	63 (60.6)
Hepatitis C virus positive	19 (18.3)
[n (%)]	12 (12.5)
Diabetes mellitus [n (%)]*	21 ± 7.0
MELD	25 ± 7.7
MELD sodium	70 (67.3)
Child Pugh C [n (%)]	45 (43.3) / 58
Tac/CsA [n (%)]	(56.3)
Basiliximab induction [n (%)]	20 (19.2)
ACR [n (%)]	37 (35.6)
RRT [n (%)]†	1 (1.0)

MELD: model for end stage liver disease, Tac: tacrolimus, CsA: cyclosporine, ACR: acute cellular rejection, RRT: renal replacement therapy.
* Pre-liver transplantation variables. † Post-liver transplantation variables.

Comparative analysis of changes on cGFR between pre- and post-LT time points

According to RIFLE criteria, 58 patients (55.8%) had a pre-LT cGFR higher or equal to 60 mL/min (groups 1-2), while 46 (44.2%) had less than 60 mL/min (groups 3-4). Twenty patients had a pre-LT serum creatinine higher or equal to 1.5 mg/dL (19.2%), 1 patient had type 1 hepatorenal syndrome, and 1 patient required pre-LT RRT.

On the 7th day following transplantation, 59 patients (66.3%) were on RIFLE criteria groups 1-2 (cGFR higher than 59 mL/min) and 35 (33.7%) had less than 60 mL/min. There was a median 6.8 mL/min improvement on cGFR between pre-LT and that transplant time point. Median detriments of cGFR from 7th day to 1st, 3rd and 12th months after-LT were 12.4, 13.7 and 23.3 mL/min, respectively. At 12 months following transplantation, 79 patients (76%) were in groups 3-4 of RIFLE criteria. Patients with lower pre-LT cGFR (groups 3 and 4) showed a higher proportion of stability or improvement in their renal function, while 58 patients (55.8%) in groups 1 and 2 worsened their kidney function (Table 2).

Risk variables associated with development of RD

Among variables included in the univariate logistic regression analysis, patient age *(P = 0.007)*, MELD Na *(P = 0.08)*, pre-LT serum sodium lower than 126 mEq/L *(P = 0.09)*, pre-LT cGFR *(P = 0.012)*, 7th day cGFR *(P = 0.003)* and 1st month post-LT cGFR (P = 0.08) were associated with RD. Presence of DM, MELD score, hepatitis C virus (HCV) postive status, monoclonal antibody induction and presence of acute cellular rejection were not associated with RD. Furthermore, neither surgical times nor donor age had influence on the development of the primary outcome (Table 3).

Independent risk variables associated with RD on multivariate logistic regression analysis were patients'age [OR 1.88 (95% CI 0.99-1.09, P = 0.06)] and 7th day cGFR [OR 0.97 (95% CI 0.96-0.99, P=0.001)] (Table 4). ROC curve analysis for 7th day cGFR was 0.71 (95% CI 0.61-0.81) with the best cut-off set on 7th day cGFR lower than 65 mL/min (Figure 2).

Table 2. *Comparative analysis of pre and post-LT calculated glomerular filtration rate (GFR-MDRD) regarding RIFLE Criteria (28) at different time points among the entire cohort.*

Time / Variable	Creatinine mg/dl	cGFR ml/min	RIFLE 1 n (%)	RIFLE 2 n (%)	RIFLE 3 n (%)	RIFLE 4 n (%)
Pre-LT	1.0±0.7	64±32.8	21 (20.2)	37 (35.6)	41 (39.4)	5 (4.8)
7th day†	1.0±0.8	71±33.4	26 (25.0)	43 (41.3)	32 (30.8)	3 (2.9)
1st month†	1.2±0.5	58±34.5	14 (13.5)	36 (34.6)	45 (43.3)	9 (8.7)
3rd month†	1.2±0.4	57±25.5	8 (7.7)	32 (30.8)	62 (59.6)	2 (1.9)
12th month†	1.3±0.6	47±18.8	4 (3.8)	21 (20.2)	72 (69.2)	7 (6.8)

Normal values: creatinine 0.6-1.1 mg/dL. † Post-liver transplantation variables.
RIFLE criteria: group 1 GFR MDRD ≥ 90 mL/min, group 2 GFR MDRD 89-60 mL/min, group 3 GFR MDRD 59-30 mL/min and group 4 GFR MDRD < 30 mL/min.

Table 4. *Multivariate logistic regression analysis of variables in cirrhotic patients with/without renal dysfunction at 12th month after liver transplantation.*

Variable	OR	95% CI	P
Age (years)*	1.88	0.99-1.09	0.06
Pre-LT GFR-MDRD mL/min*	0.99	0.97-1.01	0.25
GFR 7thday (mL/min) †	0.97	0.96-0.99	0.013
GFR 1st month (mL/min)†	1.01	0.99-1.02	0.28

OR: odds ratio, 95% CI: 95% confidence interval, LT: liver transplantation, GFR: glomerular filtration rate, MDRD: modification of diet in renal disease.
* Pre-LT variables. † Post-LT variables.

Table 3. *Univariate logistic regression analysis of variables in cirrhotic patients with/without renal dysfunction 12 months after liver transplantation.*

Variable	NO RD n=47 (45.2%)	RD n=57 (54.8%)	P
Age (years) [median (interquartile range)]*	49.5 (21-70)	58 (38-70)	0.007
Male gender [n (%)]	25 (53.2)	38 (66.6)	0.16
MELD [median (interquartile range)]	22 (10-40)	21 (6-40)	0.34
MELD sodium [median (interquartile range)]	26.5 (9-40)	23 (6-46)	0.088
Diabetes mellitus [n (%)]*	3 (6.4)	10 (17.5)	0.1
Serum sodium <126 mEq/L [n (%)]*	6 (12.8)	2 (3.5)	0.09
Hepatitis C virus positive [n (%)]	22 (21.3)	9 (15.8)	0.47
Donor age >40 years [n (%)]	23 (48.9)	31 (54.4)	0.58
Pre-LT creatinine (mg/dL) [median (interquartile range)]*	1.0 (0.40-7.40)	1.10 (0.60-3.0)	0.38
Pre-LT GFR-MDRD (ml/min) [median (interquartile range)]*	77 (7-217)	58 (17-137)	0.012
Basiliximab induction [n (%)]	9 (19.1)	11 (19.3)	0.98
ACR [n (%)]	19 (40.4)	18 (31.6)	0.34
Retransplantation [n (%)]	2 (4.3)	1 (1.8)	0.46
GFR 7thday (mL/min) [median (interquartile range)]†	81.5 (33.2-209.9)	62.6 (21.2-115.4)	0.003
GFR 1st month (mL/min) [median (interquartile range)]†	67.9 (16-196.3)	56.1 (18.5-215.2)	0.082

RD: renal dysfunction, MELD: model for end stage liver disease, LT: liver transplantation, GFR: glomerular filtration rate, MDRD: modification of diet in renal disease, ACR: acute cellular rejection.
* Pre-LT variables. † Post-LT variables.
Normal values: serum sodium 135-145 mEq/L, creatinine 0.6-1.1 mg/dL.

Figure 2. *ROC curve analyzing development of renal dysfunction and calculated glomerular filtration rate at 7th day following liver transplantation.*
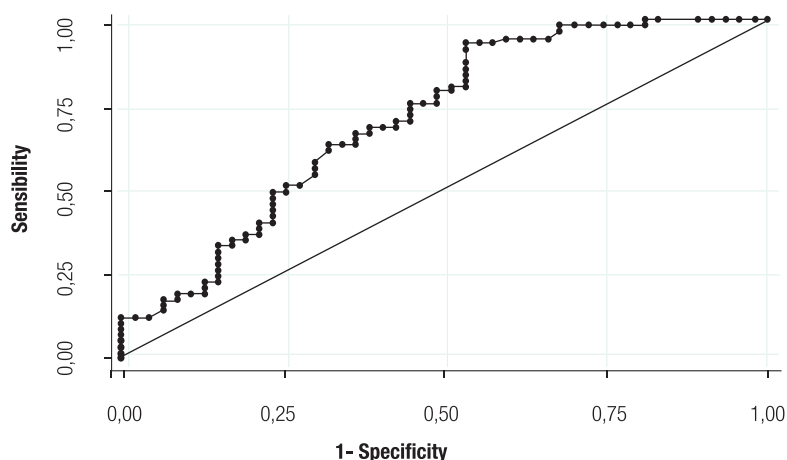
Area under ROC curve= 0.7094

Note: Receiver operating characteristic (ROC) curve for development of renal dysfunction ranked on the basis of pre-transplant and glomerulr filtration rate (GFR) at 7th day following LT. The c-statistic was 0.71 (95% CI 0.61–0.81). Best cut-off of sensibility and specificity for GFR 7th day is < 65 mL/min.

Discussion

Our data shows that 7th day cGFR is an accurate early predictor of induced CNI chronic kidney injury following LT in cirrhotic patients. Our study is one of the few studies that evaluate early predictors of renal dysfunction in cirrhotic transplanted patients followed up shortly after liver transplantation. We found that the majority of these patients have a progressive decline in the cGFR following LT.

Consistent with previously published data,[5-9, 11, 14, 32-34] we found that pre-LT risk factors for renal impairment were age, MELD Na, severe hyponatremia, pre-LT cGFR and cGFR at 7th day and 1st after transplantation. Our multivariate analysis revealed that the only post-LT factor associated with RD was the 7th day cGFR.

Known risk predictors for the development of ESKD are age, pre-LT GFR, length pre-LT kidney failure, need for RRT before transplantation, HCV seropositive status, history of pre-transplant DM and acute kidney injury (AKI) after LT.[5, 11, 33, 34] Pre-LT renal failure and renal impairment at 3 and 12 months following liver transplantation identify those patients with higher risk of developing ESKD on long-term follow-up.[5, 10, 12]

Although our outcome was set at 12 months, our data are reassuring, showing that at that time point the majority of patients develop at least mild renal dysfunction (cGFRlower than 90 mL/min) and 55% had advanced

renal impairment (cGFR lower than 50 mL/min). Most of the patients with pre-LT RIFLE criteria from groups 1 and 2 worsened their GFR one year after LT. This finding could be due in part to a higher CNI target blood level exposure maintained during the first year after LT in the first group, when comparing pre-LT RIFLE groups 1-2 and 3-4. However, we did not compare blood CNI blood-through levels between patients with or without RD. On the other hand, an increase from baseline GFR was noted on the 7th day following LT. This could be due to an improvement of the hemodynamic effects of portal hypertension on renal function in cirrhotic patients after transplantation. Exposure to CNI following transplantation between the 7th day and the 12th month could explain the observed cGFR detriment thereafter.

RD was set at 12th month post-LT cGFR lower than 50 mL/min and was chosen as our primary end point for two reasons: first, assessment of GFR 1 year after LT correlates well with renal function at 3 years;[26] and second, nephroprotective immunosuppression strategies must be implemented in these patients in order to avoid progressive renal injury following liver transplantation.[11, 31] An earlier implementation of these strategies is crucial in order to avoid CNI's irreversible kidney damage, such as interstitial fibrosis, and glomerular or arteriolar sclerosis.[31] There are three traditional nephroprotective strategies following LT: delaying the introduction of CNI with

monoclonal antibody induction (basiliximab), reducing later-on the exposure of CNI with the addition of myco-phenolate acid (MMF) or switching to mTOR inhibitors (sirolimus or everolimus).[31]

We recognize some limitations of our study. First, it is a retrospective cohort analysis and further follow up was not analysed. Second, our results would only have to be taken into account for cirrhotic patients and not all liver transplant patients. Finally, we took into consideration a short-term follow up.

This study adds to our current understanding of renal dysfunction after liver transplantation by identifying a group of cirrhotic patients who are at higher risk for the development of kidney failure in short-term follow up. Following these early predictors of RD, nephroprotective strategies could be implemented earlier in order to minimize the long-term CNI's nephrotoxicity. We therefore propose the use of 7th day cGFR as a useful clinical tool to identify patients at higher risk of chronic renal injury after CNIs exposure.

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