Port J Nephrol Hypert 2010; 24(1): 45-50
Advance Access publication 10 November 2009

Impact of renal dysfunction on liver transplantation: a retrospective study in 708 orthotopic liver transplant recipients

Ana Carina Ferreira, Fernando Nolasco, Sandra Sampaio, Alexandre Baptista, Pedro Pessegueiro, Estela Monteiro, Eduardo Barroso

Transplantation Unit, Hospital de Curry Cabral. Lisbon, Portugal.

Received for publication: 29/08/2009
Accepted in revised form: 21/10/2009

ABSTRACT

Renal dysfunction often complicates the course of orthotopic liver transplant recipients and is associated with increased morbid-mortality.

The aims of this study were to determine the incidence of chronic renal disease and its impact on patient survival.

Clinical data included age, gender and weight, aetiology of hepatic failure, presence of diabetes, hypertension, hepatitis B and C infection, renal dysfunction pretransplant and immunosuppression. Laboratory data included serum creatinine at days 1, 7, 21, month 6, 12 and yearly. The glomerular filtration rate was determined by Cockcroft-Gault equation. We studied retrospectively from September 1992 to March 2007 708 orthotopic liver transplant recipients. Mean age 44±12.6 years, 64% males, 17% diabetic, 18.8% hypertensive, 19.9% with hepatitis C and 3.8% hepatitis B. Renal dysfunction pretransplant was known in 21.6%. Mean follow-up was 3.6 years. Mean transplant survival 75% at 12 months. 154 patients died. Univariate and multivariate analyses were performed and a $p<0.05$ was considered significant.

Acute kidney injury occurred in 33.2%. Chronic kidney disease stage 3 was observed in 34.3%, stage 4 in 6.2% and stage 5 in 5.1%. At the time of this study, 46.4% were on Cyclosporine A, 44.7% on tacrolimus and 8.9% on sirolimus.

Using multivariate analysis, renal dysfunction was correlated with renal dysfunction pre-orthotopic liver transplant ($p<0.001$), acute kidney injury ($p<0.001$), haemodialysis development ($p<0.001$), and inversely correlated with the use of mycophenolate mophetil ($p<0.001$); mortality was positively correlated with renal dysfunction pretransplant ($p=0.03$), chronic kidney disease stage 4 ($p=0.001$), chronic kidney disease stage 5 ($p<0.001$) and inversely correlated with the use of tacrolimus ($p=0.006$).

In conclusion orthotopic liver transplant recipients are disposed to renal complications that have a negative impact on survival of these patients.

Key-Words:
Chronic kidney disease (CKD); mortality; orthotopic liver transplantation (OLT).

INTRODUCTION

Orthotopic liver transplantation (OLT) has become the treatment of choice for advanced liver disease. Improved outcomes among solid organ transplant

recipients have contributed to the growth in the absolute number of patients with chronic kidney disease (CKD) in this group[1], and this complication significantly compromises patients' outcome[2-4]. The commonly suggested causes for CKD after liver transplantation include advanced age, hepatitis C virus, hypertension, diabetes mellitus, IgA nephropathy, calcineurin inhibitors' nephrotoxicity, interstitial nephritis, pre-existing renal insufficiency and early postoperative acute kidney injury (AKI)[4-9]. CKD has been reported to occur in 4-80% of OLT recipients[5], depending on criteria used to define CKD and duration of follow-up. Ojo *et al.*[2] demonstrated that after 5 years posttransplantation 18% of these patients developed CKD stage 4, according to K/DIGO definition. More recently, O'Riordan *et al.*[4] reported 6% CKD in stage 4, but 56.7% in stage 3 and 2.3% in stage 5 at 10 years posttransplantation follow-up. We know that CKD is a well defined risk for increased morbidity and mortality and dialysis patients have an exceptionally high mortality rate. Likewise, post liver transplant kidney disease is an important cause of morbidity and mortality after OLT[1,3,4,7]. For preventing decline in renal function, the use of effective alternative immunosuppressive agents without renal toxicity has been proposed, such as azathioprine, sirolimus or mycophenolate mophetil (MMF)[10]. Of note, all these studies do not involve a large number of OLT recipients, ranging from 14-569 patients.

Portugal has been recently considered a leader in terms of absolute number of OLT performed. In our unit, 708 OLT recipients were followed September 1992 to March 2007. The aim of this retrospective study was to determine the incidence of chronic renal dysfunction after OLT, and to determine whether this complication affects the outcome of OLT patients.

PATIENTS AND METHODS

We retrospectively studied 708 OLT recipients transplanted in our unit between September 1992 and March 2007 using the piggy back technique with partial cava clamping. Different immunosuppressive protocols have been used since 1992. Ciclosporin, azathioprine and prednisolone were used in the majority of recipients up to 2003. Since then, 82% of the recipients have received an association of tacrolimus, MMF and prednisolone. Steroids were usually employed in a low dose (20 mg/day) during the first months, and then slowly decreased during a period of 12 months. Since 2001, sirolimus has been used in a limited number of recipients. We note that the Model for End stage Liver Disease (MELD) classification was introduced in February 2002, but in Portugal it has only been used since 2007, and therefore we did not classify recipients according to this score.

We recorded the following data: age and weight at transplantation, gender, aetiology of hepatic failure, presence of diabetes mellitus, hypertension, hepatitis B and C infection, immunosuppression (ISS) and need for acute renal replacement therapy. Serum creatinine (Scr) values and glomerular filtration rate (GFR), determined by Cockcroft-Gault equation, were evaluated at different time points: pretransplantation, days 1, 7 and 21 posttransplantation, 6 months after transplantation and afterwards yearly.

Renal dysfunction pretransplantation (RD pre) was defined by GFR ≤60ml/min or Scr ≥1.5 mg/dl. AKI posttransplantation was defined by the RIFLE criteria (a persistent decrease in renal function in the first 21 days – at least an increase of Scr x1.5 above baseline and/or decreasing GFR in 25%). CKD was defined according to the K/DIGO Clinical Practice Guidelines: CKD stage 3 if GFR 30-59 ml/min; CKD stage 4 if GFR 15-29 ml/min and CKD stage 5 if GFR <15ml/min or dialysis[11].

Univariate analysis (Spearman correlation) and multivariate analysis (linear regression, confidence interval of 95%, with forward method) were performed using the SPSS system 15.0 (SPSS Inc., Chicago, IL) and a $p<0.05$ was considered statistically significant.

RESULTS

Clinical data are summarised in Table I. The mean follow-up was 3.6±3.4 years (ranging from 1 day to 15 years), 28.8% (204/708 patients) had more than five years' follow-up and 6.5% (46/708) were followed for more than 10 years. The majority of patients were male (64%). The most common indication for OLT in our population was familial amyloidotic polyneuropathy, Portuguese type (n=217), followed by alcoholic cirrhosis (n=143) and viral hepatitis cirrhosis (n=123; 27 patients with hepatitis B virus infection and 96 with hepatitis C virus – HCV infection), primary billiar cirrhosis (n=35),

Table I

Clinical characteristic of OLT recipients

Variable	Patients (n=708)
Age (yr)	44±12.6
Male gender	453 (64%)
Female gender	255 (36%)
Diabetes	17% (106)
Arterial hypertension	18.8% (117)
Aetiology	
Familiar amyloidotic polyneuropathy	31.1% (217)
Alcoholic cirrhosis	20.5% (143)
HBV and HCV cirrhosis	18.2% (129)
Fulminate hepatitis	5.1% (36)
Primary biliar cirrhosis	5% (35)
Others	20.1% (148)
Renal dysfunction pre-OLT	133 (21.6%)
Retransplantation	11.6% (82)
Immunosuppression	
With Ciclosporin	46.4%
With Tacrolimus	44.7%
With Sirolimus	8.9%
Mean follow up time (yr)	3.6
Mean transplant survival	
12 months	75%
3 years	69%
Development of chronic kidney disease	45.6% (323)
Stage 3	34.3% (243)
Stage 4	6.2% (44)
Stage 5d	5.1% (36)
Months to CKD (≥ stage 3)	14.1±21.7
Mortality	21.8% (154)

autoimmune hepatitis (n=28), primary sclerosing cirrhosis (n=9) and Amanita Phalloides intoxication (n=9). A hepatic nodule was present in 66 patients.

Renal dysfunction prior to OLT was present in 133 patients (21.6%) and 14 of these patients had hepatorenal syndrome (HRS): eight of these 14 patients died, with a mean follow-up of three weeks; three patients recovered renal function with no need for renal replacement therapy, and three patients needed dialysis temporarily, recovering renal function within 22 days after OLT.

Acute kidney injury

AKI was registered in 33.2% (235 patients) of OLT. CKD developed in 70% of these recipients (n=164/235, r=0.3, p<0.0001) and 9% of these (n=21/235) are on haemodialysis due to terminal chronic renal failure (r=0.45, p<0.0001).

AKI was significantly more frequent in HCV infected patients (r=0.08, p=0.02) and less frequent in recipients with familial amyloidotic polyneuropathy (r=-0.1, p=0.003).

AKI was a risk factor for development of CKD in all stages in both univariate and multivariate analysis (CKD stage 3: p<0.001, 95% CI 0.2 to 0.4, stage 4: p<0.001, 95% CI 0.2 to 0.5 and stage 5: p<0.001, 95% CI 0.3 to 0.6).

Chronic kidney disease

CKD was a common complication, and 323 OLT recipients developed variable degrees of renal failure: 34.3% (n=243) developed CKD stage 3, diagnosed at a mean follow-up of 11.4±17.1 months' posttransplantation, 6.2% (n=44) had CKD stage 4 at a mean follow-up of 22.3±27.7 months, and 5.1% (n=36) attained CKD stage 5 at a mean follow-up of 14.1±26.3 months. Analysing the population with more than 5 years' follow-up (n=204), 52% (106/204) developed CKD stage 3 to 5d, and 9.8% (n=20/204) presented CKD stage 4 or 5. If we analysed the population with 10 or more years' follow-up, this number would reach 70%: stage 3 would be observed in 56.6% (n=26/46), and stage 4 or 5 in 13% (n= 6/46).

As mentioned previously, CKD was observed in 70% of patients who suffered from AKI. In addition, CKD was also present in 33.2% (157/473 recipients) patients without any preceding episodes of acute injury of the kidney, and 25.4% (n=120/473) of these patients developed a stage 3 and 7.9% (n=37/473) progressed to stage 4 or 5.

On univariate analysis, all three stages positively correlated between themselves (p<0.0001). Using Spearman's correlations, risk factors for CKD development were age (r=0.2; p<0.0001), female gender (r=0.1, p=0.006), alcoholic cirrhosis (r=0.1; p=0.01), primary billiar cirrhosis (r=0.07; p=0.04) and hypertension (r=0.1; p=0.002). Familial amyloidotic polyneuropathy was inversely correlated with development of CKD (r=-0.1; p<0.001). Each stage was also positively correlated with RD pre-OLT (stage 3: r=0.3; p<0.001; stage 4: r=0.1; p=0.001; stage 5: r=0.1; p=0.002), and AKI (stage 3: r=0.3; p<0.001; stage 4: r=0.1; p=0.01; stage 5: r=0.1; p=0.001).

Table II

Multivariate analysis for risk factors of CKD development

Dependent variable	Independent variables	95% CI	p	R^2
CKD development	Age	0.002 to 0.007	0.001	0.04
	RD prior to OLT	0.4 to 0.5	<0.001	
	Acute renal failure	0.2 to 0.3	<0.001	
	Dialysis requirement	0.2 to 0.4	<0.001	
CKD (GFR <45ml/min)	Sirolimus	0.05 to 0.31	0.008	0.004
	MMF	-0.2 to -0.07	<0.001	

Stages 4 and 5, the worst in terms of severity, were correlated with need for acute haemodialysis (stage 4: r=0.2; p<0.0001; stage 5: r=0.7; p<0.0001) and with mortality (stage 4: r=0.1; p=0.04; stage 5d: r=0.3; p<0.001).

According to multivariate analysis (Table II), risk factors for CKD development were age (p=0.001, 95% CI 0.002 to 0.007), renal dysfunction prior to OLT (p<0.001, 95% CI 0.4 to 0.5), AKI (p<0.001, 95% CI 0.2 to 0.3), and need for haemodialysis (p<0.001, 95% CI 0.2 to 0.4). Stages 4 and 5 were positively correlated with mortality (stage 4: p=0.005, 95% CI 0.02 to 0.1; stage 5: p<0.001, 95% CI 0.01 to 0.02).

Immunosuppression (ISS)

During the observation period, the majority of patients were treated with calcineurin inhibitor associated to an anti-metabolite. In terms of most recent ISS, 46.4% of patients were on Cyclosporine A (CyA) associated with azathioprine (AZA) or mycophenolate mofetil (MMF), 44.7% were on tacrolimus mostly associated with MMF and 8.9% were on sirolimus. Sirolimus was more frequently used in recipients with evidence of renal dysfunction prior to OLT (15.8% versus 7.3% without previous renal dysfunction; p=0.0013), and in recipients with evidence of AKI (p=0.001).

There was no impact on CKD development whenever calcineurine inhibitors were or not used, probably due to the fact that almost all patients were under these drugs. Correlating ISS and permanent renal dysfunction (CKD stage 4), univariate analysis showed a positive correlation between the use of AZA (r=0.13, p=0.001), CyA (r=0.12, p=0.003) and sirolimus (r=0.16; p<0.001). In contrast, the use of tacrolimus (r=-0.12; p=0.002) and MMF (r=-0.16; p<0.001) were inversely correlated with the development of CKD stage 4, suggesting a protective effect on renal dysfunction.

On multivariate analysis, sirolimus continued to show a positive correlation with the development of CKD stage 4 (p=0.008, 95% CI 0.05-0.31). CKD stage 4 was inversely correlated with use of MMF (p<0.001, 95% CI -0.2 to -0.07). In multivariate analysis the use of AZA and tacrolimus had no apparent influence.

Mortality

Mortality occurred in 154 patients and, as described above, and using Spearman correlation, was higher in patients with renal dysfunction (acute or chronic), particularly in CKD stage 5, occurring in 75% (27/36, r=0.3; p<0.0001). Others prognostic factors in terms of mortality were age (r=0.1; p=0.001), RD prior to OLT (r=0.1; p=0.001), HRS (r=0.09; p=0.01), need for acute dialysis (r=0.4; p<0.001) and ISS with AZA (r=0.1; p=0.007). The use of tacrolimus and MMF had a favourable impact (r=-0.1; p=0.006 and r=-0.9; p=0.02, respectively). Familial amyloidotic polyneuropathy was inversely correlated with mortality (r=-0.1; p=0.001).

Using linear regression, mortality was correlated with RD pre-OLT (r=0.03, 95% CI 0.006 to 0.1), CKD stage 4 (p=0.001, 95% CI 0.07 to 0.3), and stage 5 (p<0.001, 95% CI 0.5 to 0.7), and was inversely associated with tacrolimus use (p=0.006, 95% CI -01

to -0.02). We did not find any correlation between mortality and retransplantation.

DISCUSSION

Renal dysfunction proved to be a common complication in OLT patients and when present has a strong negative impact on survival. Of our 708 OLT patients, almost 50% developed CKD at the end of follow-up, defined by GFR<60 ml/min after at least six months' posttransplantation. In those patients that were followed for a 10 year period, only 30.4% of surviving recipients did not have evidence of CKD. Risk factors for all the three stages of CKD attained were presence of renal dysfunction, either pretransplantation or as acute injury posttransplantation.

According to our data, RD pre-OLT was observed in 133 patients. Reliance on Scr typically leads to an overestimation of renal function before OLT, particularly in those with malnutrition, low muscle mass and oedema[1] and consequently we cannot exclude that the number of patients with previous renal dysfunction may have been underestimated. Despite this limitation, the presence of RD pre-OLT was a risk factor for occurrence of AKI, development of CKD and for high mortality. RD pre-OLT has been shown to influence postoperative morbidity and mortality in patients undergoing OLT[12-14]. Coincident with these findings, the MELD system created the MELD score, relying on bilirubin, international normalised ratio and Scr, to allocate organs to waiting list patients. With this score, renal failure becomes a major factor in the decision for most urgent liver transplant[8]. After the introduction of MELD system no study showed an increase in post-OLT mortality[14,15] and renal function remains an independent predictor of death following OLT[14]. The MELD score was introduced only after 2007 in Portugal and as our study period goes back to 1992, we did not use this score for patient classification.

The other important risk factor for CKD development was AKI. The incidence of AKI ranges from 12 to 70%[16-18] depending on criteria used to define AKI after OLT. The aetiology of AKI is multifactorial and it may be precipitated by preoperative, intraoperative and postoperative factors[19]. AKI predisposes the patients to further complications, such as the development of CKD or high mortality[19,20]. Our study demonstrated exactly the same.

ISS regimes have a well known impact on renal disease posttransplant. Although both calcineurin inhibitors are well known nephrotoxines[6,10,23], tacrolimus has been associated with a better outcome[23,24], as we saw in our study. A similar observation was noted with MMF use. Some studies have already shown that introduction of therapy with MMF in OLT is beneficial in renal function, allowing reduction or withdrawal of calcineurin inhibitors[10,23]. Our data shows that, using multivariate analysis, the potential benefit of tacrolimus is lost and only MMF remains as renal protector. However this apparent benefit may only result from the shorter follow-up of patients treated with these two immunosuppressants. Recent reports showed that sirolimus, associated with lower levels of calcineurin inhibitors, improved renal function in OLT recipients[24-26]. Our results are not in concordance with those and we believe that this discrepancy may be related to the late introduction of sirolimus in our patients, when they already had renal dysfunction.

Patient survival was also compromised with any renal impairment. In fact, this issue is severely influenced by renal dysfunction, with a 40% survival at 5 years (Kaplan Meyer) for patients that required any kind of dialysis. Immunosuppressant therapies were also implicated in patient survival.

Our study has several limitations. First of all, it is a retrospective study and we could not obtain all desirable data. Secondly, the renal function estimate is based on Scr, which only increases markedly when the GFR has decreased to less than 50% of normal. Kniepeiss *et al.*[27] have suggested that cystatin C, a protease inhibitor, is superior to Scr or GFR as a prognostic marker in patients with RD after transplantation[27,28]. Thirdly, the recipient selection was not based on the MELD score, as stated. Finally, the number of familial amyloidotic polyneuropathy patients is very high and not comparable to the majority of liver centres. Nevertheless, our familial amyloidotic polyneuropathy patients had less AKI events ($p<0.005$), less renal dysfunction prior to OLT ($p=0.01$) and less CKD than the other patients ($p<0.0001$). We analysed the data excluding these patients and the results were similar to those presented here.

CONCLUSIONS

OLT recipients are disposed to acute and chronic renal complications. Chronic renal dysfunction appears as one of the main prognostic markers of clinical evolution in these patients.

Conflict of interest statement. None declared.

Acknowledgments

We thank Dr Dulce Carvalho, PhD, for assistance in the preparation of the manuscript.

References

1. Roy DB, Reese PP. Chronic kidney disease after nonrenal solid organ transplantation. J Am Soc Nephrol 2007;18:3031-3041
2. Ojo AO, Held PJ, Port FK, *et al.* Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931-940
3. Scmitz V, Laudi S, Moeckel F. Chronic renal dysfunction following liver transplantation. Clin Transplant 2008;22:333-340
4. O'Riordan A, Wong V, McCormick PA, Hegarty J, Watson AJ. Chronic kidney disease post-liver transplantation. Nephrol Dial Transplant 2006;21:2630-2636
5. Wilkinson A, Pham PT. Kidney dysfunction in the recipients of liver transplants. Liver Transpl 2005;11:547-551
6. Pillebout E, Nochy D, Hill G, *et al.* Renal histopathological lesions after orthotopic liver transplantation (OLT). Am J Transplant 2005;5:1120-1129
7. Moreno JM, Cuervas-Mons V, Rubio E, *et al.* Chronic renal dysfunction after liver transplantation in adult patients: prevalence, risk factors, and impact on mortality. Transplant Proc 2003;35:1907-1908
8. Davis CL. Impact of pretransplant renal failure: when is listing for kidney- liver indicated? Liver Transpl 2005;11:535-544
9. Velidedeoglu E, Bloom RD, Crawford MD, *et al.* Early kidney dysfunction post liver transplantation predicts late chronic disease. Transplantation 2004;77:553-556
10. Créput C, Blandin F, Deroure B, *et al.* Long term effects of calcineurin inhibitor conversion to mycophenolate mofetil on renal function after liver transplantation. Liver Transpl 2007;13:1004-1010
11. Levey AS, Eckardt KU, Tsukamoto Y, *et al.* Definition and classification of chronic kidney disease: a position statement from Kidney Disease Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089-2100
12. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. Hepatology 2002;35:1179-1185
13. Menon KN, Nyberg SL; Harmsen WS *et al.* MELD and other factors associated with survival after liver transplantation. Am J Transplant 2004;4:819-825
14. Gonwa TA, McBride MA, Anderson K, Mai ML, Wadei H, Ahsan N. Continued influence of preoperative renal function on outcome of orthotopic liver transplant in the US: where will MELD lead us? Am J Transplant 2006;6:2651-2659
15. Freeman RB, Weisner RH, Edwards E, *et al.* Results of the first year of the new liver allocation plan. Liver Transpl 2004;10:7-15
16. Lebron GM, Herrera ME, Seller PG, Curiel BE, Fernandez Ortega JF, Quesada GG. Risk factors for renal dysfunction in the postoperative course of liver transplant. Liver Transpl 2004;10:1379-1385
17. Chang FR, Lin CC, Wang PH, *et al.* Acute renal failure after cadaveric related liver transplantation. Transplant Proc 2004;36:2328-2320
18. Gainza FJ, Valdivieso A, Quintanilla N, *et al.* Evaluation of acute renal failure in the liver transplantation perioperative period: incidence and impact. Transplant Proc 2002;34:250-251
19. Gajate L, Martin A, Elías E, *et al.* Analysis of renal function in the immediate postoperative period after partial liver transplantation. Liver Transpl 2006;12:1371-1380
20. O'Riordan A, Wong V, McQuillan R, McCormick PA, Hegarty JE, Watson AJ. Acute renal disease, as defined by RIFLE criteria, post-liver transplantation. Am J Transplant 2006;6:1-9
21. Platz KP, Mueller AR, Blumhardt G, *et al.* Nephrotoxicity following orthotopic liver transplantation: A comparison between cyclosporine and FK506. Transplantation 1994;58:170
22. Jain A, Vekatramanan R, Eghtesad B, Gadomski M, Mohanka R, Marcos A, Fung J. Long term outcome of adding mycophenolate mofetil to tacrolimus for nephrotoxicity following liver transplantation. Transplantation 2005;80:859-864
23. Reich DJ, Clavien PA, Hodge EE. Mycophenolate mofetil for renal d4ysfunction in liver transplant recipients on cyclosporine or tacrolimus: randomized, prospective, multicenter pilot study results. Transplantation 2005;80:18-25
24. Fairbanks KD, Eustace JA, Pine D, Thuluvath PJ. Renal function improves in liver transplant recipients when switched from calcineurin inhibitor to sirolimus. Liver Transpl 2003;9:1079-1085
25. Nair S, Eason J, Loss G. Sirolimus monotherapy in nephrotoxicity due to calcineurin inhibitors in liver transplant recipients. Liver Transpl 2003;9:126-129
26. Morard I, Dumortier J, Spahr L, Hadengue A, Majno P, Morel P, Mentha G, Giostra E. Conversion to sirolimus based immunosuppression in maintenance liver transplantation patients. Liver Transpl 200;13:658-664
27. Kniepeiss D, Wirnsberger G, Iberer F, *et al.* Cystatin C and urine microscopy for early detection of renal dysfunction in patients after liver transplantation. Transplantation 2004;78:392-393
28. Gajate L, Martin A, Elías E, *et al.* Analysis of renal function in the immediate postoperative period after partial liver transplantation. Liver Transpl 2006;12:1371-1380

Correspondence to:
Dr Ana Carina Ferreira
Hospital Curry Cabral
Rua da Beneficência nº 8
1069-639 Lisboa, Portugal
karinadacostafer@hotmail.com