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Risk factors for renal dysfunction in the postoperatory course of liver transplant

ABSTRACT

Renal dysfunction (RD) is a frequent complication after liver transplantation (OLT) with an unfavourable effect on the prognosis of these patients. We intended to identify possible risk factors for RD and its impact on survival.

The relation of pre-, per- and postoperative variables possibly related to early-onset renal dysfunction (ED) (within the first 3 months), late-onset renal dysfunction (LD) (between 3 and 6 months) and chronic renal dysfunction (CRD) (beyond 6 months) was analysed.

We studied 245 liver transplants in 241 patients. RD was found in 64.1%, of which 69% recovered. LD was found in 16.7%. In the multivariate analysis baseline serum creatinine, the volume of transfused bank-Red Blood Cells peroperatively, APACHE II score at ICU admission and infection were associated with the development of RD. Overall mortality was 27.8% and for the RD group 33,5%. Only late-onset RD but not early-onset RD was related to lower survival (together with graft dysfunction and APACHE II at ICU admission).

Early-onset renal dysfunction is frequent alter OLT and is related to pre-existing dysfunction, the volume of transfused bank-RBC's during surgery, higher APACHE II score at ICU admission and infection. In general, the prognosis for ED is good in contrast with that of late-onset RD that is associated with diminished survival.

INTRODUCTION

Renal dysfunction is a frequent postoperative occurrence for liver transplant patients. It is usually acute, appearing early after transplant and a high number of patients recover from it, but in some cases (1,2) persists and results in terminal renal disease.

Serum creatinine determination is the most widely used but perhaps not the most reliable diagnostic method for assessing the renal function of patients with end stage liver disease, associated with loss of muscular mass and creatinine synthesis. In addition, hyperbilirubinemia interferes with the serum creatinine measurement hyperbilirubinemia. These facts result in underestimation of renal function. The criteria for the definition of abnormal posttransplant renal function differ markedly (3-5). Moreover, there is no agreement on the assessment method or the level of creatinine level for this definition. Subsequently, studies on transplant renal function are influenced by this lack of consensus.

Our aim is to identify the incidence, preoperative, intraoperative and postoperative risk factors related to the development and recovery of early renal dysfunction (ED), and finally, to determine whether renal dysfunction (RD) is an independent mortality factor.

MATERIALS AND METHODS

A cohort of 241 adult patients, who received a total of 250 liver transplants between March 1997 and December 2002, are the basis for this retrospective study. The indications for liver transplantation are listed in Table 1.

For analysis and follow-up purposes 5 patients with retransplant are counted as a single case, as these retransplantations resulted from primary graft failure and were therefore done immediately after the initial transplant procedure. The remaining 4 retransplantations were performed for different reasons at 6, 7, 13 and 26 months after the initial procedure and are considered to be independent episodes. The primary follow-up of these patients ended with the date of retransplantation. Therefore, the study is based on 245 cases in 241 patients.

As the follow-up continued until June 2003, all survivors have completed a minimum follow-up of 6 months and a maximum of 6 years.

Preoperative and intra-operative variables are listed in Table 2 and 3, while the postoperative variables are listed in Table 4.

Preoperative renal dysfunction was defined as serum creatinine > 1.5 mg/dl. For the diagnosis Diabetes Mellitus the need for insulin and for hypertension the need for anti-hypertensive medication are required. The intra-operative reperfusion syndrome is defined as at least a 30% fall in arterial blood pressure, lasting more than one minute, in the 5 minutes following reperfusion.

Postoperative hypotension is defined as a blood pressure requiring the need of vasoactive drugs during the ICU stay, while for the diagnosis of infection, in addition to clinical signs, positive cultures are required. The various combinations of

immunosuppressive agents are shown in Table 5 (4 patients died during surgery or shortly after ICU admission, and did not receive immunosuppressant drugs).

We considered high values to be those above our target levels: cyclosporine (baseline level: 300-400 ng/ml for the first week, 250-350 ng/ml for the first month, and from then on levels between 100-250 ng/ml. Tacrolimus: between 10-20 ng/ml in the first two weeks post-transplant and from 5-15 ng/ml in subsequent periods.

Basiliximab, which initially was used in a small number of patients with hepatitis C virus (HCV) included in a clinical trial, was used for patients with a preoperative renal dysfunction (serum creatinine levels above 1,5 mg/dL). Mycophenolate mofetil (MMF) was selected for patients with postoperative renal dysfunction in order to decrease or withdraw calcineurin inhibitors.

Postoperatively renal function was stratified as early, late or chronic. Early renal dysfunction (ED) was defined as: serum creatinine > 1.5 mg/dl within 3 months post-transplant or , in patients with pretransplant renal dysfunction, serum creatinine level > 2x that of pretransplant. ED was considered to have recovered when serum creatinine decreased to <1.5 mg/dL within six months post-transplant or < 2 mg/dL afterwards. Late-onset renal dysfunction (LD) is defined as serum creatinine > 2 mg/dL beyond 3 months posttransplantation in patients without or recovered ED. When ED did not recover after the sixth month or LD was present renal dysfunction was considered to be chronic (CRD).

Statistical analysis

Quantitative variables are described as mean ± standard deviation, except for those referring to time measurements, which are described as average (inter-quartile range). Categorical variables are described as n (%).

For quantitative variable comparison, a student-T test was performed for those following a normal distribution or presenting a number of cases over 30, and a Mann-Whitney U test for cases that did not meet these requirements.

For the univariate analysis of the categorical variables, a chi-square test (and Fischer test when this was not indicated) was carried out.

Statistical significance was defined as an α error of 95% ($p<0.05$).

For multiple comparisons and elimination of confounding variables, a multivariate analysis was performed through a step-by-step logistical regression by insertion into the model of all the variables that had shown statistical significance for an α error of 85% ($p<0.15$) in previous comparisons, and by the gradual step-by-step withdrawal of variables without significant effect on the model (for a statistical significance of 95%). The analysis results are expressed through the exponential of the regression coefficient (Odds Ratio), its confidence interval and significance level.

For the survival analysis, a Kaplan Meier test was carried out by inserting the days to termination of follow-up or death of patient as the time variable and mortality as the effect variable. Subsequently, comparisons between variables were made by means of the Log-Rank test, using $p<0.05$ as a statistical significance level. Finally, a multivariate analysis with Cox Regression Analysis was performed using the same technology described for the logistic regression analysis to determine whether early renal failure and maintained renal failure affected survival. The results of the analysis are expressed

through the exponential of the regression coefficient (Relative Risk), its confidence interval and significance level.

The statistical package SPSS 11.0 for Windows was used for performing these analyses.

RESULTS

The results of the pre-operative and peroperative variables in our series are shown in Tables 2 and 3. Within the first 6 months the frequency of patients with above target levels of cyclosporine was significantly higher than that of patients with tacrolimus ($p<0.037$) (fig 1).

ED occurred in 158 / 245 (64.1%), while LD developed in 13 (5.2%) The frequency of the pre- per- and postoperative variables in these patient groups are shown in Tables 2, 3 and 4.

Statistically significant variables associated with ED are shown in the univariate analysis (Table 6). In a multivariate analysis only pretransplant serum creatinine, the amount of transfused bank-RBC's, APACHE II score and hospital infection appeared to be independent predictors for ED (Table 7).

The use of renal replacement techniques was required for 28 of 158 (17%) patients with ED. Continuous veno-venous hemofiltration (CVVHF) was used in 26 and hemodialysis in 2 cases . Twenty of these 28 patients died (71,4%).

Of the 158 patients with ED, 109 (69%) ultimately recovered renal function, of whom 103 patients within the first year post transplant (Figure 2) .

Basiliximab was used in 17 patients and renal function recovered in 11 cases ($p<0.3$). MMF was introduced in the treatment of 51 patients, of whom 39 recovered renal function and 12 did not ($p<0.16$).

Late renal dysfunction (LD) was found in 13 patients, 10 male and 3 female, with an average age of 48.92 ±12.49 years. The mean MELD score was 14.29 ±4.89 and the mean APACHE II 16.92±4.19. In the statistical analysis none of the studies variables mentioned previously in Methods were significantly related to LD.

Along with the thirteen patients who developed LD, 21 patients who presented ED and survived for more than six months did not recover renal function, which resulted in a total of 34 (16.7%) patients presenting CRD in the long-term follow-up.

Overall mortality was 68 / 245 patients (27.8%), 4 of whom died in the operating room, 20 in the ICU, 10 in hospital and 34 after being discharged from hospital.

Mortality in the ED group was 53 /158 patients (33.5%), 34 (21.5%) during ED and 19 (12.02%) after having recovered from ED.

In the univariate analysis, APACHE II was higher in dying patients (20.83±6.03 vs 16.68±4.24, $p<0.01$). Pretransplant RD could not be significantly linked to patient survival ($p<0.6$), but the variables female gender ($p<0.01$), fibrinolysis ($p<0.01$), primary liver graph dysfunction and ED ($p<0.01$) are found to be significant. The multivariate analysis with Cox regression shows Apache II and primary liver graph dysfunction as the only independent factors related to survival. (Table 8)

In order to assess the effect of CRD on survival, the 34 patients who maintained ED or presented late-onset RD having survived more than six months were analysed. In these patients only the APACHE II score, a prolonged stay in the ICU and CRD itself are independently related to survival (Table 9).

DISCUSSION

Orthotopic liver transplant (OLT) is currently the treatment of choice for patients advanced liver disease. While initially we focussed on acceptable short term survival, currently the efforts are aimed at improving long-term prognosis. Renal dysfunction is an important problem in this scenario. However, true incidence, definition and the best diagnostic method remain unresolved.

Renal dysfunction can be defined as a decrease in glomerular filtration rate (GFR). The serum creatinine level has traditionally been considered an simple but indirect marker for GFR and in daily clinical practice has become the method of choice for detecting acute renal dysfunction (ARD) because more reliable methods are expensive and technically complicated but it is cumbersome and subjected to potential errors (6-8). Even worse, different researchers have used different serum levels to define ARD, ranging from 1.5 to 3 mgr/dl or higher, making comparison difficult (3,4,9). We have used serum creatinine above 1.5 mg/dL as diagnostic of ARD even though we are aware that we can have underestimated its real incidence (in a recent study performed on our patients we determined that, for this level, serum creatinine showed a sensibility of 60% for detecting a creatinine clearance lower than 75 mL/min) (10).

Therefore, it is not difficult to understand the differences in ARD incidence, ranging from 80% in earlier reports (11) to 50% as reported by Bilbao et al. (1). Very recently, Cabezuelo et al. reported a 12 % incidence of ARD, based on a retrospective study on 162 patients using more restrictive diagnostic criteria (creatinine > 2.5 mg/dL in the first week after OLT or the need for renal replacement treatment). (4). Our results, which are similar to those of Bilbao et al, show a high incidence of ARD (64.1%) after liver

transplantation. However, the difficulties to compare different studies demonstrate the need for consensus for the diagnosis of ARD after OLT.

Another important issue is the need to define risk factors for RD after liver transplantation, in order to apply protective strategies to minimise its occurrence. Some variables related to RD development are frequently mentioned in the literature, like the basic state of health of the patient, factors resulting from surgery and graft function after OLT (9). Although Bilbao et al (9) and Cabezuelo et al (4) found the Child-Pugh classification related to the development of ARD, we have not been able to confirm this in our study. Possibly this can be explained by difference in the way the patients were stratified, as these researchers grouped patients with Child's class B and C together, while we have opted to analyse the three groups separately.

We have found a relation between the need of transfusion of bank-RBC's and ARD, but the surgical technique (that appears to have an effect) (4) has not been included in our study because we have used the more recently described piggy-back technique in the majority (98%) of our transplants.

Our results show a clear relationship between creatinin levels before surgery and RD afterwards but, even thought established renal failure pre-existing before surgery is recognised as a risk factor (1,4,12) we have not been able to confirm this relation, perhaps due to our more restrictive approach to a diagnosis of acute on chronic renal failure (a rise of 100% of basal creatinine levels).

Although ARD is a frequent complication in OLT patients, its impact on outcome is not well defined. Velidedeoglu et al. (3) reported a 38% incidence of early renal failure, which decreased to 11% after 14 days transplant and 7% after a month, resulting in only 3% of patients with persistent renal failure at three months. In our study, recovery from

early renal failure was somewhat delayed, with a higher percentage of recovery between 3 and 6 months (25.3%) and 7% recovering renal function between 6 months and a year after OLT. These figures, however, may be an underestimate. Cohen et al (13) reported in a longer term study on 527 liver transplant patients, that using Iodothalamate clearance, 27.5% of patients had a GFR lower than 40 ml/min after 5 year follow-up. In addition, Gonwa et al reported an incidence of chronic renal failure of 1.4% at four years, which subsequently increased to 10% after 13 years of follow-up (14).

None of the studies make a difference between unrecovered early renal dysfunction and late-onset renal dysfunction, despite the fact that, theoretically, the risk factors for ARD (intraoperative and early postoperative) are not the same as for the late onset renal dysfunction (rejection, sepsis and use of nephrotoxic drugs such as calcineurin inhibitors). In the future, it could be interesting to take this differentiation into consideration. Patients in the ICU with ARD can expect a 48% mortality rate, while patients subjected to complicated surgical procedures might have an mortality rate of 70-80% (15). Specifically in liver transplantation, a relationship between ARD and mortality has been demonstrated in various publications, referring to both pre-existing and postoperative renal dysfunction.(16-18). We could not confirm these results in our series, possibly due to the low frequency of renal-hepatic syndrome (RHS) among our patients. Moreover, neither have we been able to independently link early renal dysfunction with mortality as, 35.9% of our patients with early ARD died after recovering renal function. Our data, however, similarly to the report by Gayowski et al (18), show a clear relation between the presence of maintained RD and mortality.

According to our data, early-onset renal dysfunction is a frequent complication after OLT but it seems that its prognosis is good and the possibilities for recovery fair, in contrast with that dysfunction that appears late in the postoperatory course, that is

associated with a diminished survival. There are some well known factors that predispose to the appearance of RD after OLT, as can be previous renal function, surgical related aspects or a complicated postoperatory course, but more data are needed in order to develop strategies oriented to its prevention.

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Table 1 Indication for liver transplantation

	Frequency	Percentage
HCV	103	42%
HBV	31	12,7%
Alcohol	80	32,7%
Biliary cirrhosis	9	3,7%
Acute hepatitis	10	4,1%
Others	12	4,9%

Table 2.- Preoperative data

		All patients	Early Renal Dysfunction	Late Renal Dysfunction
Population		241	158 (64.1%)	13 (5.4%)
Age (years)		51.3 ±9.8	52.3 ± 9.2	48.9 ± 12.5
Male Female		167 (69.2%) 74 (21.8%)	111 (70.2%) 47 (29.5%)	10 (76.9%) 3 (23.1%)
CHILD score	class A class B class C	26 (10.9%) 171 (71.5%) 42 (17.6%)	17 (10.5%) 109 (69.3%) 32 (20.3%)	2 (15.4%) 10 (76.9%) 1 (7.7%)
MELD score	Average <15 15-25 > 25	13.9 ± 4.9 173 (70.6%) 55 (22.4%) 17 (6.9%)	14.4 ± 5.2 106 (67.1%) 43 (27.2%) 9 (5.7%)	14.3 ± 4.9 8 (61.5%) 3 (23.1%) 2 (15.4%)
Diabetes Mellitus		47 (19.2%)	32 (20.3%)	1 (7.7%)
Hypertension		26 (10.6%)	13 (8.2%)	1 (7.7%)
Creatinine (mg/dl)		1.03 ± 0.42	1.1 ± 0.4	0.95 ± 0.38
Renal Dysfunction		2 (9%)	16 (10.1%)	2 (15.4%)
Donor age (years)		43.3 ± 17.3	43.7 ± 17.3	33.3 ± 13.1

Table 3.- Intra-operative data

		All patients	Early Renal Dysfuntion	Late Renal Dysfunction
Ischemia time (minutes)		462 ± 122	468 ± 126	455 ± 107
Fibrinolysis		49 (20%)	39 (24.7%)	1 (7.7%)
Reperfusion syndrome		58 (23.7%)	46 (29.1%)	3 (23.1%)
Portal Vein Thrombosis		21 (8.6%)	15 (9.5%)	1 (7.7%)
Blood products	Bank-RBC (ltr)	3.2 ± 3.1	3.8 ± 3.4	3.8 ± 2.3
	Auto-RBC (ltr)	2.6 ± 3.5	3.02 ± 4.1	4.2 ± 4.8
	FFP (ltr)	2.9 ± 1.9	3.2 ± 2.05	2.9 ± 1.9
	Platelets (units)	15.0 ± 14.7	16.8 ± 15.2	18.7 ± 16.1

Table 4.- Postperative data

	All patients	Early Renal Dysfunction	Late Renal Dysfunction
Apache score	17.8 ± 5.1	18.9 ± 5.2	16.9 ± 4.2
Hypotension	42 (17 %)	33 (20.9%)	1 (7.7%)
Infection	48 (20%)	37 (23.4%)	1 (7.7%)
Peak bilirubin mg/dl	10.4 ± 7.9	11.3 ± 8.7	7.2 ± 2.97
Peak AST U/dl	1423 ± 1680	1532 ± 1802	907 ± 615
Peak ALT U/dl	793 ± 820	842 ± 850	600 ± 392
Peak creatinina mg/dl	1.95 ± 1.05	2.38 ± 1.06	1.83 ± 0.98

Table 5.- Immunosuppression

	Frequency	Percentage
Cyclosporine + Steroids+ Azathioprine	112	45,7%
Cyclosporine + Steroids	49	20%
Tacrolimus +Steroids	56	22,9%
Basiliximab *(added to calcineurin inhibitors)*	24	9,8%
Mycophenolate mofetil	67	27,3%
No treatment	4	1,6%

Table 6- Variables related to early renal dysfunction. Univariate analysis

Quantitative variables	Early renal dysfunction Yes	No	p	
Age	52±9,2	49,52±10,17	0,035	
MELD	14,44±5,23	12,89±4,08	0,012	
Creatinine pretransplant (mg/dl)	1,10±0,44	0,89±0,35	0,0001	
Homologous packed eritrocytes(litres)	3,8±3,38	2,29±2,047	0,0001	
Fresh frozen plasma (litres)	3,2±2,06	2,41±1,43	0,001	
APACHE II	18,88±5,14	15,98±4,5	0,0001	
Lowest postoperative prothombin (%)	42,41±11,49	45,99±10,86	0,018	
Highest bilirrubine postoperative	11,32±8,77	8,74±5,65	0,006	
Qualitative variables	**Yes**	**No**	**p**	**OR**
Intraoperative Fibrinolysis	39 (24,7%)	10 (11,51%)	0,02	6,53
Reperfusion syndrome	46 (29,1%)	12 (13,8%)	0,007	7,76
Infection during hospitalisation	37 (23,4%)	11 (12,6%)	0,042	4,36
Postoperative hypotension	33 (20,9%)	9 (10,3%)	0,036	4,68

Table 7.- Variables related to early renal dysfunction. Regression analysis

Variable	p-value	OR	I.C. (95%)
Creatinine pretransplant	0,000	25,4	6,7-96,2
Homologous packed eritrocytes	0,008	1,3	1,1-1,5
APACHE II	0,016	1,1	1,01-1,2
Infection	0,012	2,8	1,3-6,4

Table 8.- Variables affecting to survival in early renal dysfunction patients

Variable	P value	RR	I.C. (95%)
Apache II	0,0001	1,12	1,06-1,18
Primary dysfunction	0,001	3,69	1,71-7,95

Table 9.- Variables affecting to survival in maintained renal dysfunction patients

Variable	p	RR	I.C. (95%)
Apache II	0,001	1,1	1,04-1,17
Maintained renal dysfunction	0,0001	4,1	2,34-7,21
Days in ICU	0,005	1,04	1,01-1,06