Incidence of chronic kidney disease and risk factors for patients who underwent liver transplantation at Fundación Santa Fe University Hospital from 2004 to 2008

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Abstract

Background: Chronic Renal Failure (CRF) frequently develops in patients who undergo transplantation of solid organs such as livers, hearts, lungs, and small intestines. CRF increases morbidity and mortality rates, increases costs and results in deterioration in the quality of patients' lives.

The development of CRF is a common complication in post-liver transplant patients. It is defined as a glomerular filtration rate between 29 and 60 ml/min/1.73 m^2 of body surface area during post-surgical procedures.

Multiple factors contribute to the risk of developing CRF in this group of patients. The most important among these factors are renal function prior to transplantation as measured by MDRD formula (Modification of Diet in Renal Disease), acute perioperative renal failure, and immune-suppressors such as calcineurin inhibitors.

During the first six months after transplantation renal function deteriorates rapidly, but declines slowly thereafter. It is important to determine our incidence of chronic renal failure, the degree of severity according to the classification and the risk factors in patients who underwent liver transplantation. The aim of this study is to determine the incidence of chronic renal disease and the risk factors affecting post-liver transplant patients in the Fundación Santa Fe de Bogota University Hospital from January 2004 to November 2008.

Materials and methods: This was a descriptive and retrospective study of a population of patients who had undergone liver transplantation in the Fundación Santa Fe de Bogota University Hospital between January 1, 2004 and November 11, 2008. These patients presented normal renal functions as measured by the MDRD formula. We excluded patients with previous renal insufficiency and combined liver-kidney transplantation patients.

Results: 79 patients were included in the study. 27 (34.2% CI 95% 23.9 – 45.7) had developed Stage 2 MDRD renal failure by the 6th month of surveillance. 6 of the 27 patients (22.2%) presented cirrhosis resulting from NASH. 5 of the 27 (18.5%) presented hepatitis C.

The 27 patients who developed chronic renal failure by the 6th month of surveillance presented an average MDRD score of 89.4 ml/min/m^2/SC prior to transplantation.

Chronic renal failure following transplantation is an increasingly common complication, associated with risk factors prior to and following transplantation. These factors include arterial hypertension, diabetes mellitus, hepatitis C and immunosuppression.

Conclusions: Patients with pre-transplantation diagnoses of cirrhosis resulting from NASH or of hepatitis have a tendency to develop chronic renal failure. Immunosuppression immediately after transplantation influences the development of chronic renal failure. In our study we observed high percentages of cyclosporine A in patients who developed chronic renal failure. New studies are needed to determine the association between these risk factors and the development of chronic renal failure.

Key words

Chronic kidney disease (CKD), MDRD, calcineurin inhibitors.

INTRODUCTION

As the number of liver transplant patients around the world and here in our country increases, the numbers of complications associated with these transplantations has also been increasing.

Chronic Kidney Disease (CKD) frequently develops after transplantation of solid organs such as the liver, heart, lungs, and small intestine. CKD is associated with increased rates of both morbidity and mortality as well as increased costs of patient care and decreased patient quality of life.

The development of CKD is a common complication among patients who have undergone liver transplants. CKD is defined by a glomerular filtration rate between 29 ml/min/1.73m^2 of body surface area and 60 ml/min/1.73m^2 of body surface area (1).

Multiple factors contribute to the risk of developing CRF in this group of patients. The most important among these factors are renal function prior to transplantation (as measured by the MDRD formula), demographic characteristics of the recipient, comorbidities, acute perioperative renal failure, and the use of immune-suppressors such as calcineurin inhibitors to prevent rejection of the transplanted organ.

During the first six months after transplantation renal function deteriorates most rapidly, but declines slowly thereafter. It has been demonstrated that those patients who suffer deteriorating renal function during the first six months after transplantation have higher risks of developing CKD. Consequently these patients have shorter life expectancies following transplantation (2).

There have been no studies done in our environment of either the most common risk factors involved in the development of CKD or of its incidence. Nevertheless, it is well known from the international literature that there are clear measures which can be taken to diminish these risks and the progression of CKD among these patients. For this reason is it important for us to uncover the risk factors involved and the incidence of this disease in our midst so that we can take the necessary measures to decrease this incidence of this entity.

EPIDEMIOLOGY

Prevalence

The prevalence of Chronic Kidney Disease (CKD) among patients who have had solid organ transplants (except for kidneys) varies from 10% to 90%. This wide range is explained by the absence of one single criterion for defining CKD and by the fact that diagnosis of CKD is determined by equations which depend on levels of creatinine. These levels overestimate kidney functioning due to the kidney's small muscle mass, so that the kidney has lower yields of creatinine as a consequence.

Studies of the prevalence of CKD in this population have used the MDRD formula and have defined CKD as glomerular filtration rates of less than 30ml/min/m^2 of body surface.

Incidence

In 2003 Ojo's study published in the New England Journal of Medicine pointed out that the incidence of CKD depends on the organ that is been transplanted and on time elapsed after transplantation. The highest incidence was found for small intestine transplants followed by orthotopic-hepatic transplants. The largest number of cases occurred six to 36 months after organ transplantation (6).

In the study of O´Riordan published in 2006, the incidence of CKD following transplantation of solid organs other than kidneys was 53.72% for Stage 2 and 56.77% for Stage 3 according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guide (1).

In an analysis performed by the Scientific Registry of Transplant Recipients (SRTR), 1.815 out of 36,849 patients with hepatic transplants developed CKD in the subsequent five years, and 4% of the survivors needed permanent dialysis three years after transplantation (1).

RISK FACTORS FOR THE DEVELOPMENT OF CHRONIC KIDNEY DISEASE FOLLOWING TRANSPLANTATION OF A SOLID ORGAN OTHER THAN A KIDNEY

The most important determining factors for development of CKD among solid organ (other than kidneys) transplant patients are:

1. Renal function prior to transplantation
2. Comorbidity and demographic factors
3. Perioperative renal damage
4. Polyomavirus (PVD) infection
5. Calcineurin inhibitors

1. Renal function prior to transplantation

This is a very important risk factor for development of CKD disease subsequent to transplantation of a solid organ other than a kidney.

Renal functioning of patients on transplant waiting lists is generally overestimated due to the close relation of its determination to serum creatinine levels. Renal functioning of these patients is often compromised by poor effective circulating volume as occurs among patients suffering from cirrhosis or hepatorenal syndrome (HRS).

In the study by Ojo published on September 2003 approximately 49.2% of pre-transplant patients had renal functions in Stages 2 and 4. The patients on the waiting list for liver transplantation had impaired renal function, and 53.7% were in stages 2 and 4. In other words their molecular rates of glomerular filtration were between 29 and 60 mil/min/m^2.

These patients had poor capacities for recovering normal renal functioning following any kidney damage. Consequently a large percentage of them are certain to develop renal disease following the transplantation (Figure 1) (1).

2. Comorbidity and demographic factors

Similarly, comorbidities and demographic factors influence the development of CKD following transplantation of a solid organ other than a kidney.

Many studies have shown that age at the time of transplantation and feminine sex confer greater risks for development of CKD. Comorbidities which are common among liver transplantation waiting list patients increase the risk of developing a chronic renal disorder or disease in stages subsequent to transplantation.

Hepatitis C Viral Infection

HCV infections are an important reason for hepatic transplants. Nearly 41% of hepatic transplants are subsequent to liver cirrhosis caused by HCV. It has been accepted as an important risk factor for CKD following hepatic transplants. This increased risk is due to increased incidence of glomerulonephritis. 80% of these cases are due to deposits of immune complexes and to membrane proliferation followed by nephropathy caused by mesangial IgA deposits.

Ojo (2003) reported that approximately 21.4% of hepatic transplant patients had antibodies for HCV, and that these patients had a relative risk of developing CKD of 1.15 (95% CI 1.08 to 1.26) (6).

Arterial Hypertension and Diabetes Mellitus

Arterial hypertension and diabetes Mellitus are comorbidities which are frequently found in hepatic transplant waiting list patients. They are important factors in the development of CKD among these patients.

The study conducted by O' Riordan in 2006 found that 6.52% of patients with orthotopic liver transplants suffered from arterial hypertension prior to transplantation and that 10.87% suffered from diabetes mellitus prior to transplantation. These patients had high risks of developing CKD. The pre-transplantation risk for patients with diabetes mellitus was 2.27 (95% CI 1.01-5.12) (3).

Age, Race and Sex

Ojo's (2003) study of demographic factors looked at patients' ages, race and sex. As age increases, the relative risks of developing CKD increase. White and black patients had higher relative risks of developing CKD than did other racial groups.

O' Riordan's (2006) study reported a higher risk for the development of CKD among women than among men (OR 7.84, 95% CI 2.04-30.08).

Nephrotoxicity Caused by Calcineurin Inhibitors

Since their introduction in 1980, immunosuppresors such as cyclosporine have revolutionized the field of organ transplants. Immunosuppression regimes based on the use of cyclosporine have improved patient survival rates following solid organ transplants.

Today cyclosporine and tacrolimus have become key pieces for handling patients who have solid organ transplants. Both cyclosporine and tacrolimus inhibit the enzyme calcineurin (PPP3-CA) which plays an important role in activation of T lymphocytes.

Inhibitors of calcineurin cause vasoconstriction which predisposes patients to renal damage and can lead to CKD.

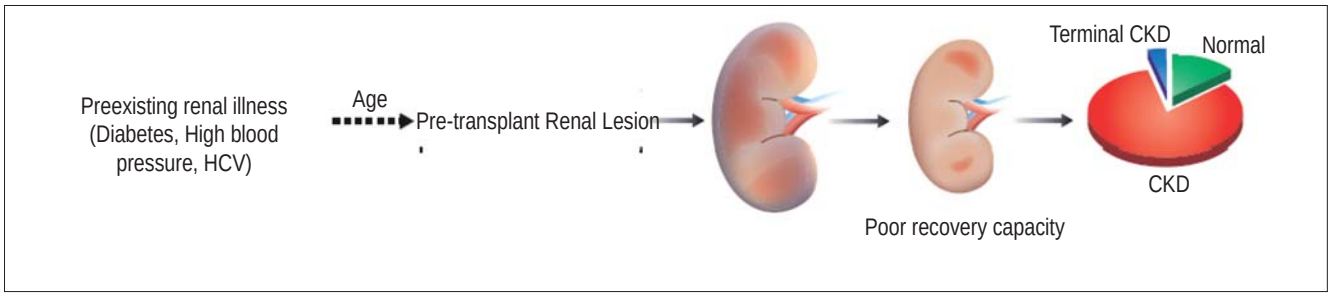

Figure 1. Relation between pre-transplant risk factors and development CKD.

Although, cyclosporine's role in this process has been better studied, tacrolimus functions in the same way.

Alterations of secondary renal functioning caused by calcineurin inhibitors are primarily observed during the first six months following transplantation.

Its nephrotoxicity is time dependent and almost irreversible when medication is suspended.

The effects of this group of medications on the kidneys are divided into acute and chronic effects. The acute effect occurs because these medications produce reversible vasoconstriction of the glomerular afferent and efferent arterioles. Vasoconstriction reaches a maximum point immediately after peak concentration is reached. The effect is mediated by inhibition of nitric oxide production caused by increased levels of angiotensin II and thromboxane as well as by increased endothelin activity.

The chronic nephrotoxicity of these medications is typically characterized by an absence of symptoms, normal urinary sediment, proteinuria in a range which is not nephrotic, and a gradual and progressive reduction of renal functioning.

In these cases histopathology shows fibrosis with rays and nodular arteriolar hyalinosis as well as belated tubular atrophy, glomerulosclerosis, and arteriosclerosis.

This group of medicines may directly or indirectly cause nephrotoxicity. Calcineurin inhibitors directly increase products of oxidative stress which produces swelling and endothelial dysfunction. They increase fibrogenic activity of cytokines such as transforming growth factor beta (TGF-β), matrix metalloproteinase (MMP)-9 and platelet derived growth factor (PDGF). In addition to these mechanisms transcription and expression of Angiotensin II also increases.

Calcineurin inhibitors, especially cyclosporine, are indirectly associated with higher sodium retention and hypertension and with high blood cholesterol levels. Tacrolimus is also indirectly associated with higher rates of diabetes mellitus.

Ojo (2003) reported higher risks of CKD following liver transplantation among those patients who received Calcineurin inhibitors. This risk increased more with cyclosporine than with tacrolimus (RR 1.25, 95% CI 1.17-1.30 vs. 1.00 respectively) (6).

O´Riordan (2006) reported that progression to CKD is not associated with cyclosporine levels and that tacrolimus was linked to lower risks of developing CKD among post liver transplant patients (3).

PERIOPERATIVE RENAL DAMAGE

Secondary renal lesions commonly develop in early postoperatory stages as a result of diminished effective intravascular volume due to hypovolemia or persistent hepatorenal syndrome.

Patients who develop renal damage soon after transplant rarely recover complete renal functioning or overcome CKD.

As mentioned earlier, use of calcineurin inhibitors and HCV infections increase the risk of early renal damage. Acute post-transplant renal failure, defined as either a 50% decrease of the glomerular filtration rate or a necessity for dialysis upon initial hospitalization, is a clear risk factor for development of CKD.

In Ojo´s study (2003), 7.6% of the studied patients developed perioperative acute renal failure which was associated with twice the risk of developing CKD (RR 2.13, 95: IC 1.99-2.27) (6).

S. Lu's 2006 study reported that duration of surgery and post-liver-transplant volume of transfused blood are risk factors in the development of acute renal failure. The development of acute renal failure among post hepatic transplant patients increases mortality rates in the immediate period following surgery (OR 10.239, P<0.001) (7).

DIAGNOSIS OF CKD FOLLOWING TRANSPLANTATION OF SOLID ORGANS OTHER THAN KIDNEYS

We recommend the use of the MDRD formula for calculating the rate of glomerular filtration even though this formula can underestimate renal functioning and result in false diagnoses of CKD. Ideally, glomerular filtration rates should be measured by means of iothalamate clearance, but this technique is not available.

Studies of post hepatic transplant patients using MDRD formula to calculate the glomerular filtration rate and to diagnose CKD have had precise and reliable results.

CKD TREATMENT FOLLOWING LIVER TRANSPLANTATIONS AND RECOMMENDATIONS FOR MAINTAINING RESIDUAL RENAL FUNCTION

Treatment is based on the same standards principles used for the general population with CKD which are in turn based on the National Kidney Foundation Disease Outcomes Quality Initiative (NKF KDOQI)™ guidelines.

Among recommendations for maintenance of residual renal functioning among CKD patients following hepatic transplants is use of angiotensin II receptor antagonists which have demonstrated broad capacity for diminishing levels of TGF-β which, as previously mentioned, mediates fibrosis caused by calcineurin inhibitors.

Another important recommendation is to decrease the dosage of cyclosporine and tacrolimus by using mycophenolate mofetil or sirolimus. This measure has positive

effects on renal functioning, blood pressure, glycemia and blood cholesterol levels.

The objective is to minimize the dosage of calcineurin inhibitor by adding and then increasing the dosage of mycophenolate mofetil or sirolimus.

Some studies have shown significant improvements in glomerular filtration rates by converting from calcineurin inhibitors to sirolimus after three months or after one year.

Christopher J.E. Watson (2007) demonstrated that the use of sirolimus achieved significantly better glomerular filtration rates than did the use of calcineurin inhibitors at the end of three months treatment (7.7ml/min/1.73m^2 body surface area, 95% CI 3.5-11.9) and after a year of treatment (6.1ml/min/1.73 m^2 body surface area, 95% CI 0.9-11.4). The difference was statistically significant after three months (P=0.02) but the one year difference was not statistically significant (P=0.07) (5).

MATERIALS AND METHODS

Type of Study

This study was observational, descriptive and retrospective.

Target Population

All patients who underwent hepatic transplantation at the Hospital Universitario Fundación Santa Fe de Bogotá from January 1, 2004 to November 11, 2008, and who had normal renal functioning as calculated by MDRD prior to liver transplantation, were included in this study. Patients with insufficient renal function prior to transplantation and those who underwent both kidney and liver transplantation were excluded.

INFORMATION COLLECTION TECHNIQUE

A questionnaire including pre-transplant and post-transplant data was designed. Pre-transplant variables asked about included age, gender, basic hepatic illness, Child-Pugh score, MELD score, cytomegalovirus serology, and MDRD. Post-transplant variables asked about included MDRD, serology for HCV, post-transplant renal damage, immunosuppression, blood pressure and diabetes mellitus.

After requesting and receiving patients' clinical histories from the medical records department, the histories of all patients who had undergone liver transplants at the Hospital Universitario Fundación Santa Fe de Bogotá between January1, 2004 and November 11, 2008 were reviewed. Both the paper files and records in the *Servicios Integrados de Salud* SISIPS system were used to conduct systematic research of all study variables using the data collection instrument designed for this purpose. Afterwards all data was entered into an Excel worksheet for later analysis.

STATISTICAL ANALYSIS

Stata Version 9 was used for all statistical analyses. The incidence of CKD six months after organ transplantation was calculated for all patients included in the study to determine if there were any relations among the different variables in the study and the development of CKD. Calculations of relative risk and 95% confidence intervals were also performed.

ETHICAL ISSUES

Patients' clinical histories were accessed only after authorization had been received from the Medical Records Department and the Hepatology and Hepatic Transplant group which was responsible for these patients. The study complied with all ethical standards and procedures required by the Hospital Universitario Fundación Santa Fe de Bogotá and with the standards established by Helsinki Declaration.

RESULTS

1. Post-hepatic transplant CKD six months after liver transplantation. Seventy nine patients who had undergone liver transplantation between 2004 and 2008, and who had not developed renal failure at the moment when surgery was performed, were included in the study. Twenty seven (34.2%) developed CKD in the following six months (95% CI 23.9-45.7) (See Table 1).
2. Age at the moment of transplantation and development of CKD within the first six months following hepatic transplant. The average age of patients who developed CKD within the first six months following hepatic transplant was 59 years. The average age of patients who did not develop CKD within the first six months following hepatic transplant was 49.8 years. (See Table 2)
3. Gender and CKD following hepatic transplant. Seventeen (63%) of the 27 patients who developed CKD in the sixth month period following transplantation were men. (See Table 2)
4. Child-Pugh Scores at the end of the first six months following hepatic transplant
5. At the end of the first six months following hepatic transplant twelve of the twenty seven patients who developed CKD had Child-Pugh Scores of B, eight had Child-Pugh Scores of C, and seven had Child-Pugh Scores of A. (See Table 2)
6. Basic hepatic illnesses and development of CKD in the first sixth months of monitoring following trans-

plantation. Six of the 27 patients who developed CKD (22.2%) were diagnosed with liver cirrhosis due to NASH between the first and sixth month following transplantation. Five (18.5%) were diagnosed with HCV. (See Table 2)

7. Acute Renal Failure and development of CKD in the first six months following hepatic transplant. Six of the 27 patients who developed CKD in the first six months following hepatic transplant (22.2%) developed Acute Renal Failure. (Table 2)
8. Pre-transplant MDRD and development of CKD in the first six months following hepatic transplant. The average pre-transplant MDRD of the 27 patients who developed CKD in the first six months following hepatic transplant was 89.4 ml/min/m^2 of body area. (See Table 3). The 52 patients who did not develop CKD in the first six months following hepatic transplant had an average MDRD of 113.5 ml/min/m^2. (See Table 3)
9. Immunosuppression in the period immediately following transplantation and development of CKD in the first six months following hepatic transplant. Twenty six of the 27 patients (96.3%) who developed CKD in the first six months following hepatic transplant were treated with Cyclosporin A while only one (3.7%) was treated with tacrolimus (See Table 4). Eleven of the 52 patients (21.2%) who did not develop CKD in the first six months following hepatic transplant were treated with tacrolimus immediately following surgery.

Table 1. MDRD sixth months after liver transplantation.

	Average	N
Renal failure	54,6	27
No renal failure	83,8	52

DISCUSSION

It is important to highlight that a large percentage of patients who underwent liver transplants suffered deteriorating glomerular filtration rates as calculated by the MDRD test. The incidence of CKD was 34.2% in the first six months following liver transplantation. Most of those patients had been classified as Stage 2 or 3 according to the KDOQI classification. This finding closely correlates to those observed in studies like that of O´Riordan in 2006.

O´Riordan's study also showed that elderly patients are more likely to develop CKD. In our study people over 58 years of age were also more likely to develop CKD in the first six months following liver transplantation. The average was very similar to those found in the studies of Ojo et al. and of O´Riordan.

Tabla 2. General data for all patients with and without reference to development of CKD following transplantation in a follow up period of six months.

		Average			
Age	Renal failure	59,1			
	No renal failure	49,8			
		Renal failure		No renal failure	
		N	%	N	%
Gender	Male	17	63,0	28	53,8
Child Pugh score	A	7	25,9	8	15,4
	B	12	44,4	30	57,7
	C	8	29,6	14	26,9
	Total	27	100	52	100,0
Basic disease	Primary biliary cirrhosis	3	11,1	6	11,5
	Autoinmune hepatitis	3	11,1	7	13,5
	Hepatitis C	5	18,5	5	9,6
	Cryptogenic cirrhosis	3	11,1	5	9,6
	Alcoholic cirrhosis	4	14,8	8	15,4
	NASH	6	22,2	4	7,7
	Acute hepatic failure	0	0,0	1	1,9
	Hepatocellular carcinoma	1	3,7	1	1,9
	Hemochromatosis	1	3,7	1	1,9
	Autoinmune hepatitis	0	0,0	4	7,7
	Biliary atresia	0	0,0	3	5,8
	Other	1	3,7	7	13,5
	Total	27	100	52	100
Pre-Transplant High Blood Pressure	Yes	12	44,4	7	13,5
Pre-Transplant Diabetes	Yes	13	48,1	11	21,2
Pre-Transplant HCV	Yes	6	22,2	5	9,6
Pre-Transplant Hepatitis B	Yes	1	3,7	0	0,0
Pre-Transplant Cytomegalovirus	Yes	0	0,0	1	1,9
Post-transplant CKD	Yes	6	22,2	8	15,4

A large portion of the patients who developed CKD in the first six months following liver transplantation had Child-Pugh scores of B and C which indicate the most severe stages of the illness.

The patients with NASH and/or HCV had the highest incidences of post-transplantation CKD.

Table 3. MDRD prior to transplantation and development of CKD within first six months following transplant .

	Average	N
Renal failure	89,4	27
No renal failure	113,5	52

Table 4. Calcineurin Inhibitors and CKD.

	Renal failure		No renal failure	
	N	%	N	%
Cyclosporine	26	96,3%	42	80,8%
Tacrolimus	1	3,7%	11	21,2%

Our study, in contrast to that of Ojo, found that NASH was a risk factor for development of CKD following hepatic transplants. As in Ojo's study, our study found that HCV led to a high incidence of CKD.

In our study we also observed that patients with high blood pressure and diabetes mellitus prior to transplantation had higher incidences of renal failure following hepatic transplantation. This coincides with the findings of Dr Ojos´s study.

The MDRD test prior to transplantation is an important indicator of post-transplant renal failure. We observed that patients who developed CKD following liver transplantation had average MDRD scores of 89ml/min/m^2 prior to surgery while those who did not develop CKD had pre-surgery average MDRD scores over 100ml/min/m^2. These results are very similar to Ojo´s results in which patients with pre-surgery MDRD scores lower than 89ml/min/m^2 had greater risks of developing CKD following transplantation.

We also observed that cyclosporin A was used for almost all of the patients who developed CKD following transplantation. This coincides well with the findings of both Dr O´Riordan and Dr Ojo. Ojo´s study found that use of cyclosporine and tacrolimus was associated with high risks of development of CKD.

CONCLUSIONS

Post-transplantation CKD, a complication which is becoming increasingly more common, is associated with pre-transplant and post-transplant risk factors including high blood pressure, diabetes mellitus, HCV and immunosuppression.

We can also say that there is a tendency for patients with pre-transplant cirrhosis due to NASH to develop CKD following transplants.

Immunosuppression in the immediate post-transplant period has a huge influence on development of CKD. In our work we observed that cyclosporine A was used to treat a very large percentage of those patients who later developed CKD.

Based on this study we can say that better measures must be taken to prevent and control the development of this complication among these patients.

New studies to determine the association among those risk factors and the development of CKD are now needed.

REFERENCES

1. Colm Magee, Manuel Pascual, M.D. The Growing Problem of Chronic Renal Failure after Transplantation of a Nonrenal Organ. N Engl J Med 2003; 349(10): 994-996.
2. DY Kim, C Lim, R Parasuraman, M Raoufi, A Yoshida, J Arenas, et al. Renal Disease Burden Following Liver Transplantation. Transplantation Proceedings 2006; 38: 3663-3665.
3. Aisling O'Riordan, Vincent Wong, Aiden McCormick, John E Hegarty, Alan J Watson1. Chronic kidney disease post-liver transplantation. Nephrol Dial Transplant 2006; 21: 2630-2636.
4. Roy D Bloom, Peter P Reese. Chronic Kidney Disease after Nonrenal Solid-Organ Transplantation. J Am Soc Nephrol 2007; 18: 3031-3041.
5. Christopher JE Watson, Alexander ES Gimson, Graeme J Alexander, Michael ED Allison, Paul Gibbs, Jane C Smith, et al. A Randomized Controlled Trial of Late Conversion from Calcineurin Inhibitor (CNI)-Based to Sirolimus-Based Immunosuppression in Liver Transplant Recipients with Impaired Renal Function. Liver Transpl 2007; 13: 1694-1702.
6. Akinlolu O Ojo, Philip J Held, Friedrich K Port, Robert A Wolfe, Alan B Leichtman, Eric W Young, et al. Chronic Renal Failure after Transplantation of a Nonrenal Organ. N Engl J Med 2003; 349: 931-40.
7. Y Wey, L Zhang, H Lin, J Li, B Li, L Yan, S Lu, et al. Factor Related to Post-liver Transplantation Acute Renal Failure. Transplantation Proceedings 2006; 38: 2982-2984.