Renal transplantation in the modern immunosuppressive era in Spain: four-year results from a multicenter database focus on post-transplant cardiovascular disease

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To evaluate cardiovascular disease (CVD) after renal transplantation we established a CVD database (no-intervention) including all patients transplanted among 2000–2002 in 14 hospitals from Spain (Renal Forum Group) ($n = 2600$). They were prospective followed annually thereafter and we present herein the most important results concerning survival figures and CVD at four years. Mean recipient age was 49.7 ± 13.7 years: 16% retransplanted and 12.5% hyperimmunized. Tacrolimus, mycophenolate mofetil, and steroids was used in 63%. Acute rejection (AR) rate at 1 year was 14.8%. Graft and patient survival at 48 months were 85.6% (death censored) and 91.7% respectively. The first cause of graft loss was vascular in the first year, death with function during the 2–3 years, and chronic allograft nephropathy at the 4th year. Donor age, time on dialysis, acute tubular necrosis (ATN), AR, SCr at 6 months, the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in the first year, and systolic blood pressure at 24 months were independent risk factors for graft loss at 4th year. The first cause of death was CVD (predominantly ischemic heart disease (IHD) in the first year). Recipient age, ATN, and SCr at 6 months were independent predictors of mortality. Despite worsening of donor age, comorbidity, and advanced age of recipients, survival figures at four years are considered good in our Spanish non-selected population. Cardiovascular mortality is the most important cause of death and graft loss particularly, IHD in the first year. Therefore, to decrease post-transplant mortality a careful cardiovascular evaluation and treatment in the waiting list and a close follow-up of patients after transplantation is mandatory.

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Cardiovascular disease (CVD) is the most frequent cause of mortality in patients with chronic kidney disease.[1,2] Renal transplantation provides a better outcome than dialysis, including less frequency of CVD. Pre-emptive transplantation may also be important to prevent/decrease CVD.[1]

Cardiovascular risk factors after renal transplantation, such as arterial hypertension, hyperlipidemia, new onset of diabetes mellitus, and renal insufficiency together with acute rejection, are involved in the main cause of graft loss in the long term.[3] They are important determinants of death with a functioning graft, because CVD is an important cause of morbidity and the first cause of death in renal transplant patients. Many of these factors have also been involved in the pathogenesis of chronic allograft dysfunction.[2,3] The cardiovascular burden that is already present at the moment of

transplantation is greatly enhanced because of the chronic use of immunosuppressive drugs.

To prospectively evaluate the presence and risk factors of CVD after renal transplantation, we established a CVD database (no intervention) including all patients who were transplanted during 2000–2002 in 14 hospitals of Spain (Renal Forum Group), and they were prospectively followed annually thereafter. We present herein the most important results at 4 years concerning survival data, risk factors for patient death, and graft loss as well as cardiovascular events in the modern immunosuppressive era.

RESULTS

During 2000–2002, 2822 renal transplants were performed in 14 hospitals in Spain. We excluded from this analysis 222 double transplants: liver–kidney, pancreas–kidney, and heart–kidney. Therefore, 2600 renal transplants, including double-kidney transplantation in a single recipient (2.5%), were the subject of the study.

Donor, surgery, and recipient characteristics are shown in Table 1. Mean donor age was elevated according to the experience in Spain where a significant increase in donor age was seen in the last decade.[4] Most of them were men, and the most frequent cause of death was stroke. In these years, renal transplantation from living donors was anecdotical (0.38%). Recipient age was also high and 12.5% were hyperimmunized. HLA-DR mismatching was 0.9 ± 0.6 and HLA-A and -B, 2.6 ± 1.

Pretransplant cardiovascular data are shown in Table 2. Interestingly, in these years, only 9% of the patients who received a kidney transplant have been diagnosed with diabetes mellitus; there was a low proportion of obesity and nearly 15% had CVD. In fact, only 15% were diagnosed with pretransplant metabolic syndrome.

Table 1 | Recipient and donor baseline characteristics

	Media ± s.d. (%)
Recipient baseline characteristics	
Age (years)	49.7 ± 13.7
Male	60%
Cause of chronic renal failure	
Chronic glomerulonephritis	26.2%
Adult polycystic kidney disease	15.3%
Interstitial nephropathy	13.3%
Nephroangiosclerosis	6.9%
Diabetes	6.6%
Unknown origin	19.7%
Others	12%
Time on dialysis (months)	39.3 ± 46.7
<12 months	24%
12–24 months	28%
>24 months	48%
Type of dialysis	
Hemodialysis	81%
Peritoneal dialysis	15%
Both	2.7%
Pre-dialysis	0.9%
Hyperimmunized patients	
*PRA historical or current ⩾50%	12.5%
Prior transplants	
0	84%
1	14%
2	2.2%
3	0.2%
Incompatibilities	
HLA-DR	0.9 ± 0.6
HLA-AB	2.6 ± 1
Donor and surgery characteristics	
Age of donors (years)	46.9 ± 17
Male	63%
Causes of death	
Acute cerebrovascular accident	56%
Craneoencephalic traumatism	34.6%
Hypoxia	4.6%
Others	4.7%
Cold ischemia time (h)	19 ± 6
	Range 0–39
Type of transplant (double/simple)	2.5%/97.5%

*PRA, panel-reactive antibodies.

Immunosuppression and acute rejection

Initial immunosuppression and changes thereafter are represented in Table 3. The most frequent combination was based on tacrolimus (TAC) and mycophenolate mofetil (MMF) with or without monoclonal antibodies anti-IL2 receptor or thymoglobuline. Interestingly, 24% received antibodies as initial therapy. Patients on TAC- or cyclosporine-based immunosuppression were around 63 and 30%, respectively. At 4 years, almost 30% of patients were steroid free, the most frequent combination being TAC plus MMF, and the use of rapamycine was only 8.5%.

The most important concomitant medications were statins, increasing from 23% at 6 months to 46% at 48 months, and angiotensin-converting enzyme inhibitor or ARA, increasing from 5.4 and 9.5% at 6 months to 16 and 29% at 48 months, respectively.

It can be noted that the incidence of acute rejection in the first 6 and 12 months using steroids + TAC/CyA + MMF with or without antibodies was 14 and 14.8%, respectively. This low incidence is relevant because we included in this analysis hyperimmunized and retransplanted patients at high risk for rejection. The incidence of acute tubular necrosis (ATN) was nearly 30% according to the previous Spanish data.[4]

Graft survival

Censored-death graft survival at 4 years was 85.6% (Figure 1). Causes of graft loss are shown in Table 4. The first cause of graft loss in the first year was of vascular origin, and death with function was noted to be the leading cause of graft loss in the second and the third years, whereas chronic allograft nephropathy was the first one in the fourth post-transplant year.

Clinical evolution of renal function (Table 5) showed a mean serum creatinine (SCr) of 1.5 mg per 100 ml, with 13% of patients having proteinuria more than 1 g/day at 48 months.

Risk factors for graft loss in the fourth year are shown in Table 6. It can be noted that in the multivariate analysis

including pre- and post-transplantation variables, donor age, ATN, acute rejection, time on dialysis, the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) at 12 months (probably as expression of proteinuria), SCr at 6 months, and systolic blood pressure at 24 months were independent risk factors for graft loss.

Table 2 | Baseline cardiovascular status

BMI (kg/m^2)	
<25	5.4%
25–30	33.5%
>30	12.2%
Arterial hypertension	1950 (75%)
Diabetes mellitus	239 (9.2%)
Type I	3.5%
Type II	5.6%
Dyslipemia	553 (22.6%)
Hypercholesterolemia	9.3%
Hypertrigliceridemia	6.1%
Both	7.2%
Smoke	
Non-smoker or exsmoker >5 years	76.5%
Smoker or exsmoker <5 years	23.6%
Cardiovascular disease[a]	14.4%

BMI, body mass index.
[a]At least one from the following: acute myocardial infarction, coronary revascularization, cardiac insufficiency, acute cerebrovascular accident, intermittent claudication, amputation, or peripheric bypass.

Table 3 | Immunosuppression

	Baseline	12 months	24 months	36 months	48 months
Steroids	97.3%	93%	89%	83.2%	69.1%
Cyclosporine	32.6%	29.4%	27.7%	26.6%	21.8%
Tacrolimus	63.5%	65%	57.1%	64.3%	56.8%
MMF	87.3%	76.6%	75.7%	73%	64.5%
Sirolimus	8.1%	—	—	—	8.5%
Everolimus	0.4%	8.1%	9.1%	9.5%	—
Azatioprina	1.2%	—	—	—	2.1%
Antibody	24.3%				

MMF, mycophenolate mofetil.

Patient survival and post-transplant CVD

Patient survival at 4 years was 91.7% (Figure 2) and, as expected, CVD was the leading cause of death (Table 7). Infection and neoplasia were the second and third causes of death, respectively. It can be noted that global mortality was 7%, showing that patient death was more frequent in the first year, with the rate of death decreasing in the following years. Multivariate analysis, with pre- and post-transplantation variables, showed that patient age was the most important predictor of mortality, whereas ATN and SCr at 6 months were other independent risk factors for patient death (Table 8).

Post-transplant cardiovascular events are shown in Table 9. Interestingly, ischemic heart disease (IHD) was the most frequent complication, particularly in the first post-transplant year. It can be noted that the incidence of ischemic events clearly decreased in the following years. However, the incidence of stroke was similar in these 4 years.

DISCUSSION

In this study, we show the most important results at 4 years of renal transplantation from deceased donors in the modern immunosuppressive era in Spain. These data should be

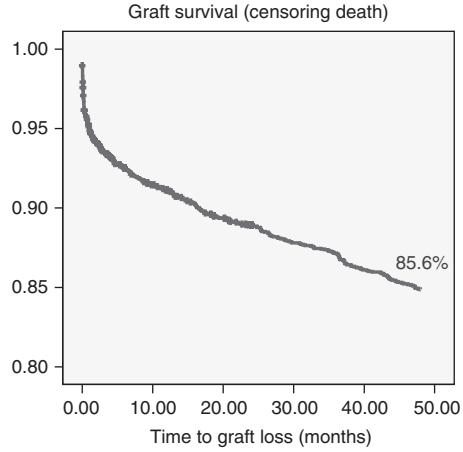

Figure 1 | Kaplan–Meier graft survival.

Table 4 | Causes of graft loss (4 years)

	First year	Second year	Third year	Fourth year
Vascular	**81 (27.6%)**	1 (1.6%)	1 (2%)	
Venous thrombosis	12.6%			
Arterial thrombosis	8.8%			
Arterial+venous thrombosis	2%			
No data	2%			
Exitus with a functioning graft	64 (21.8%)	**25 (39.7%)**	**23 (45.1%)**	**15 (25%)**
Acute rejection	53 (18.1%)	6 (9.5%)	4 (7.8%)	3 (5%)
CAN	27 (9.2%)	21 (33.3%)	14 (27.5%)	18 (30%)
Primary non-function	22 (7.5%)	—	—	—
'*de novo*' GN	—	3 (4.8%)	—	—
Recurrent GN	6 (2%)	3 (4.8%)	1 (2%)	2 (3.3%)
Others[a]	40 (13.6%)	4 (6.3%)	7 (13.7%)	22 (36.7%)
Total graft loss	**293 (11.3%)**	**64 (2.4%)**	**51 (2.3%)**	**60 (3%)**

CAN, chronic allograft nephropathy; GN, glomerulonephritis.
[a]Surgery problems, graft infection, obstructive uropathy or other recurrent disease.

Table 5 | Renal function

	6 months	First year	Second year	Third year	Fourth year
Serum creatinine (mg per 100 ml)	1.63 ± 0.78	1.63 ± 0.74 (*n*=2277)	1.57 ± 0.62 (*n*=2114)	1.7 ± 0.7 (*n*=2114)	1.5 ± 0.7 (*n*=1834)
Proteinuria (g/day)	0.4 ± 0.68	0.4 ± 0.7 (*n*=1945)	0.4 ± 0.6 (*n*=1863)	0.5 ± 1 (*n*=1489)	0.59 ± 1.1 (*n*=1272)

Table 6 | Risk factor for graft loss (4 years)

		Multivariate analysis[b]		
	Univariate analysis[a] (*P*-value)	HR	95% IC	*P*-value
Recipient aged (⩾60 vs <60 years)	<0.005	—	—	—
Donor aged (⩾60 vs <60 years)	<0.001	—	—	<0.001
Hyperimmunized	<0.001	—	—	—
Previous transplants	<0.001	—	—	—
BMI at 36 months	<0.05	—	—	—
Acute tubular necrosis	<0.001	—	—	<0.001
Cyclosporine (vs tacrolimus)	<0.05	—	—	—
Acute rejection to 12 months	<0.001	1.64	1.17–2.30	0.0039
Acute rejection accumulated	<0.001	—	—	—
Time on dialysis	<0.001	1.96	1.24–3.10	0.004
ACEI and/or ARB use at 12 months	<0.05	1.64	1.01–2.65	0.042
Serum creatinine at 6 months	<0.001	1.52	1.30–1.79	0.000
Systolic arterial hypertension at 24 months	<0.001	1.00	1.00–1.01	0.007

BMI, body mass index; HR, hazards ratio.
[a]χ^2 test.
[b]Cox-regression analysis.

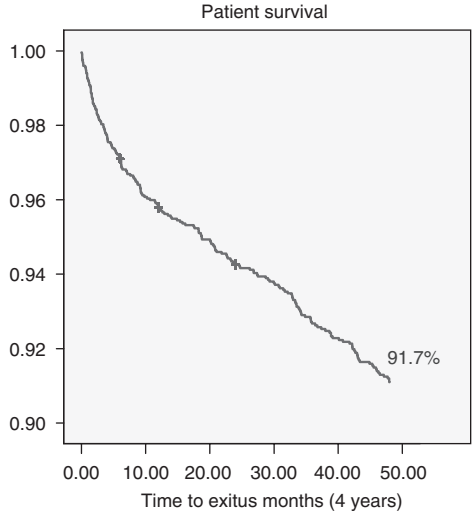

Figure 2 | Kaplan–Meier patient survival.

Table 7 | Causes of death (4 years)

	First year	Second year	Third year	Fourth year
Cardiovascular disease[a]	32 (36%)	11 (36.7%)	13 (39.4%)	7 (24.3%)
Infection	30 (33.7%)	4 (13.3%)	2 (6.1%)	5 (16.6%)
Other	15 (16.9%)	3 (10%)	3 (9.1%)	8 (26.61%)
Neoplasias	5 (5.6%)	8 (26.7%)	7 (21.2%)	3 (10%)
Unknown	4 (4.4%)	4 (13.3%)	6 (18.2%)	6 (20%)
Liver disease	2 (2.2%)	0	2 (6.1)	1 (3.3%)
Accidental	1 (1.1%)	0	0	0
Total	89	30	33	30

[a]Ischemic heart disease, sudden death, other heart causes and cerebrovascular accident.

analyzed in the context of the important modifications produced in the last years in our country: donor and recipient ages have increased; the proportion of donors dying because of head trauma has decreased; and the degree of HLA matching has worsened. In spite of these, graft survival has improved in the last decade in Spain.[4]

Graft survival that was more than 80% at 4 years can be considered good considering that all transplanted patients (even retransplants, hyperimmunized, and older than 70 years) were included in the present analysis. It can be noted that the low rate of acute rejection can contribute to these results. In this context, it is important to note that nearly 90% of patients received MMF and a calcineurin inhibitor in combination, 63% of them TAC, currently considered as the gold standard immunosuppressive regimen.[5] After the first year, the annual rate of graft attrition ranged between 2 and 3%. This finding could also be explained, at least in part, by the chronic use of MMF that reduces late allograft loss.[6]

The low rate of mortality in these 4 years can be explained in two ways: first, our population is caucasian. It includes a low rate of diabetic patients and a low proportion of patients with pretransplant CVD, and therefore it has a lower cardiovascular risk than pretransplant American[7] or North European[8] population. Second, all patients were regularly followed by a transplant physician. These aspects, demographics and health care, have been recently described to be of paramount importance to explain the differences of

Table 8 | Risk factor for patient death (4 years)

	Univariate analysis[a] (*P*-value)	Multivariate analysis[b]		
		HR	95% CI	*P*-value
Age (> vs <60 years)	<0.005	2.5	1.72–3.78	0.000
Donor age (> vs <60 years)	<0.001	—	—	—
Cause of ESRD (DM/NAS vs other)	<0.001	—	—	—
Cardiovascular disease pre-Tx	<0.001	—	—	—
Cold ischemia	<0.001	—	—	—
Cyclosporine (vs tacrolimus)	<0.05	—	—	—
Acute tubular necrosis	<0.001	1.5	1.07–2.36	0.02
Use ACEI/ARB II at 36 months	0.056	—	—	—
Acute rejection at 12 months	<0.001	—	—	—
Previous transplants	<0.001	—	—	—
Serum creatinine at 6 months	<0.05	1.3	1.11–1.53	0.001
Baseline diabetes mellitus	<0.001			
Metabolic syndrome baseline	NS	—	—	—
Time on dialysis	<0.001	—	—	—

ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; DM, diabetes mellitus; ESRD, end-stage renal disease; NAS, nephroangiosclerosis.
[a]χ^2 test.
[b]Cox-regression analysis.

Table 9 | Post-transplant cardiovascular events

Cardiovascular events (months)	Ischemic heart disease	Cerebrovascular accident	Peripheral vascular disease
6	65 (2.7%)	7 (0.3%)	6 (0.3%)
12	15 (0.7%)	8 (0.3%)	8 (0.4%)
24	19 (0.9%)	5 (0.2%)	6 (0.3%)
36	32 (1.4%)	3 (0.1%)	13 (0.6%)
48	15 (0.7%)	5 (0.24%)	10 (0.48%)

mortality between countries such as Canada (universal care coverage) vs United States (high percentage of African American and diabetics).[7,9] Therefore, demographic data and comorbidity as well as regular follow-up by an expert doctor in transplant medicine together with a universal public health-care coverage, as in Canada and Europe, seem to be decisive factors in survival of transplanted patients.

As expected, CVD was the first cause of death and IHD was the main cause of death.[10,11] Interestingly, ischemic events were more frequent in the first year and clearly decreased thereafter. The range of ischemic events after the first year was 0.7–1.4%. The question whether the control of cardiovascular risk factors and the use of statins[12] together with ACEI/ARB[13] can contribute to the control of IHD and mortality requires further evaluation. It is important to note that the good renal function and the low percentage of patients with proteinuria, as true cardiovascular risk factors,[14,15] may also contribute to these results. In fact, in the multivariate analysis, renal function was an independent risk factor for patient death. In addition, the combination TAC + MMF, which offers an acceptable cardiovascular risk profile[16] and is followed by more than 60% of patients, could also be important to explain these results.

In summary, despite worsening of donor age, comorbidity, and advanced age of recipients, survival figures at 4 years are considered good in our Spanish non-selected population. Mortality is the most important cause of death and graft loss, particularly IHD in the first year. Therefore, to decrease post-transplant mortality, a careful cardiovascular evaluation and treatment in the waiting list[17,18] and a close follow-up of patients after transplantation are mandatory.

MATERIALS AND METHODS

Population

All transplanted patients during 2000–2002 in 14 renal transplant units of Spain were included in a database (Renal Forum Database) focused on cardiovascular risk factors. This inclusion of patients was unrestricted; for instance, patients on clinical trials were also included. Therefore, this database represents the full experience of these hospitals in the first 3 years of the twenty-first century.

Database and clinical variables

The CVD database was initiated in 2000. All participating units register data concerning all the renal transplants performed in each center. Data collection is carried out every 12 months, in a database provided for that purpose, in every center. These data are transferred annually to an independent biometry unit that merges and analyzes the results from the suggestions made by a working group created within the 'Forum Renal' framework. The group 'Renal Forum' and the 'Renal Forum database' are supported by an unrestricted grant of Astellas.

Renal Forum database included donor and particularly recipient characteristics: age, original disease, time on dialysis, serology, immunological data, and pretransplant cardiovascular situation. In this way, body mass index, arterial hypertension, hyperlipidemia, diabetes, smoking, and pretransplant CVD were specifically recorded. Immunosuppressive treatment at the moment of transplantation was also recorded.

Post-transplant data included the frequency and number of acute rejections, incidence of ATN, graft survival, and causes of graft loss and patient survival as well as of mortality, renal function, and proteinuria. Cardiovascular events were also recorded, as well as modifications of immunosuppression and the presence of concomitant medications such as statins and ACEI/ARB. These data were annually collected.

Definitions

The total number of HLA mismatches was calculated as the addition of the number of mismatches in the A, B, and DR loci.

Acute tubular necrosis: This was defined as hemodialysis requirements during the first week after surgery, once accelerated or hyperacute rejection, vascular complications, and urinary tract obstruction were ruled out.

Hyperimmunized: These are patients with panel-reactive antibodies, current or historical, equal to more than 50%.

The diagnosis of acute rejection was defined according to the criteria of each center based on clinical and histological data.

Cardiovascular disease: This was defined if at least one of the following was present: angina, myocardial infarction, coronary revascularization, health failure, stroke, or intermittent claudication of peripheral bypass.

Arterial hypertension: This was defined as blood pressure greater than 140/90 mm Hg.

Metabolic syndrome: This problem was defined if more than three of the following were seen: body mass index >25, hypertrigliceridemia, hypercholesterolemia, arterial hypertension, and diabetes mellitus.

Chronic allograft nephropathy: This was defined by histological and/or clinical criteria.

Ischemic heart disease: This was defined as the presence of angina pectoris and/or a previous myocardial infarction. Angina pectoris was diagnosed from a typical history of chest pain, with a positive non-invasive test and/or coronary arteriography in the majority of cases. Myocardial infarction was diagnosed by a history of typical chest pain and a significant electrocardiographic and acute enzymatic pattern.

This study (no intervention) was approved by all the departments of Nephrology of the 14 hospitals assuring data confidentiality. A blinded code was assigned to each participating hospital to take into consideration the center effect.

Statistical methods

The objective was to analyze the 4-year follow-up information of the patients after the kidney transplantation, specifically:

(1) Descriptive analysis of the variables of interest in the 4 years: absolute and relative frequencies of the qualitative variables, and measures of association and dispersion (average, medium standard deviation, minimum, and maximum) of the quantitative ones.
(2) Study of the graft and patient survival: number of losses and exitus, causes of graft loss and patient death, curves of Kaplan–Meier.
(3) Measuring whether there was a statistically significant relationship between patient characteristics and groups defined for the 48-month study. Using the corresponding tests for independent data: In the case of quantitative variables, *t*-test (if there is normality) or Mann–Whitney (when we did not prune to assume normality in the data). In the case of qualitative variables, χ^2 test.
(4) Multivariate analysis that allows the identification of risk factors related to graft loss and patient death. Cox regression model to calculate the rate of graft loss and death as a function of time (until you see the event of interest) and forecast variables.

DISCLOSURE

Domingo del Castillo has received lecture fees from Novartis. Jose M Morales has received consulting fees from Astellas, Novartis, Wyeth, and Roche. Jose M Morales has also received lecture fees from Astellas, Novartis, and Wyeth. The remaining authors declare no financial interests.

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