Ten-year kidney transplant survival of cyclosporine- or tacrolimus-treated patients in Brazil

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Abstract
Background: Cyclosporine and tacrolimus are well established immunosuppressants; however little know about long term survival rates. Aim: Compare 10-year graft survival and associated factors among kidney transplant patients within the Brazilian Public Health system (SUS) prescribed either medicine. Methods: Analyze a national cohort of kidney transplant recipients within SUS. Graft loss defined by death or dialysis for more than three months. Kaplan-Meier method used to estimate cumulative probabilities of survival. Cox proportional hazards model used to evaluate factors associated with progression to graft loss. Results: 13,811 patients were included, 5,887 used cyclosporine and 7,924 tacrolimus. A higher risk of graft loss was associated with tacrolimus, a deceased donor, additional years of age, median period of dialysis greater than 47 months, diagnosis of diabetes as the primary cause of chronic kidney disease and transplantation between 2005 and 2009. Conclusions: Among other factors, tacrolimus-based regimens were associated with worse graft survival.

Introduction

Chronic kidney disease (CKD) is characterized by slow, progressive, and irreversible loss of kidney function. The main causes include high blood pressure and diabetes mellitus. The number of patients with CKD worldwide has increased in recent decades, reaching epidemic proportions. The survival of patients with end-stage renal failure depends on the use of renal replacement therapy (RRT)[(1-3)].

For patients with no contraindications, kidney transplantation is the best alternative among existing RRT options because it offers higher survival and better quality of life than dialysis, in addition to being more cost effective[(4-6)]. Clinical outcomes of kidney transplantation have improved over the years, e.g. in the United States in 1998, one-year graft survival was 89.7%

with live-donor grafts and 76.0% with deceased-donor grafts; in 2014, these rates reached 94.3% and 88.7%, respectively[7, 8].

In 2012, Brazil ranked 31st in the number of living donor kidney transplantations per million inhabitants and 25th considering deceased donors among 71 countries. However in Latin America, Brazil occupied the 1st and 3rd places for transplantations with living and deceased donor grafts, respectively[13].

The Unified Health System in Brazil (Sistema Único de Saúde, SUS) provides more than 95% of all transplantations performed in Brazil and, in accordance with the concept of comprehensive care, ensures access to immunosuppressants for transplant patients without co-payment[14]. SUS also provides more than 84% of all dialysis performed in Brazil. According to the Clinical Protocol and Therapeutic Guidelines of the Brazilian Ministry of Health, maintenance immunosuppression among kidney transplant patients consists of a triple-drug regimen, typically containing a corticosteroid, a calcineurin inhibitor (cyclosporine or tacrolimus), and an antiproliferative agent (azathioprine, mycophenolate mofetil, or sodium mycophenolate)[15]. Alternatively, either of the latter two drug classes can be replaced with mTOR inhibitors (sirolimus or everolimus), depending on the clinical characteristics of the patient[15, 16]. Azathioprine and cyclosporine have been provided by SUS since 1982, tacrolimus and mycophenolate since 1990, sirolimus in 1999, and everolimus in 2008.he national transplantation program in Brazil, which provides medical procedures and post-transplantation medicines[16], is seen as successful with survival rates of SUS kidney transplant recipients similar to rates seen in developed countries[17].

Calcineurin inhibitors are considered the hallmark immunosuppression. Despite their similar mechanisms of action, cyclosporine and tacrolimus have different pharmacokinetic profiles, which can translate into different benefits and side effects[18, 19]. Both drugs are associated with long-term nephrotoxicity, but tacrolimus is associated with a higher incidence of post-transplant diabetes mellitus; whereas cyclosporine is associated with hyperlipidemia and hypertension[15, 20, 21].

Different approaches have been adopted to compare tacrolimus and cyclosporine. With regard to efficacy, a recent systematic review that included 26 randomized controlled trials involving 6,054 patients reported a lower risk of acute rejection with tacrolimus; however, this did not translate into differences in one- to five-year graft survival between groups[19]. Another systematic review that compared the effects of these two drugs as primary therapy for kidney transplant recipients found no difference between the two treatments after a five-year follow-up[22].

Graft loss is mainly due to death with a functioning graft (predominantly caused by cardiovascular events), glomerular disease (which may be recurrent), fibrosis/atrophy, acute rejection, and medical or surgical conditions, including recurrence of the disease that led to CKD[23]. The occurrence of acute rejection during the first year after transplantation has been associated with worse long-term survival[24]. However, Meier-Kriesche et al[25] evaluated 62,103 kidney transplants and concluded that long-term (six-year period) graft survival and patient survival were not affected by decreased acute rejection rates. As a result, the authors criticized the use of acute rejection rates as the primary outcome in clinical trials. In view of this, short term studies comparing tacrolimus and cyclosporine could be of limited benefit to provide guidance on their long term effectiveness and cost-effectiveness. Our initial study[26] with five years follow-up showed a clinical benefit for cyclosporine versus tacrolimus, with differences also seen in their relative cost-effectiveness with a paired analysis and five years follow-up [27].

However, we wanted to look further at the Brazilian cohort, especially given the heterogeneity of the population in Brazil and concerns with shorter term studies, to provide further guidance to Ministry of Health personnel as well as physicians treating patients following kidney transplantation. Consequently, the objective of this study is to evaluate up to 10-year graft survival of SUS kidney transplant patients who used either cyclosporine or tacrolimus.

Methods

This non-concurrent open cohort study included patients who underwent kidney transplantation from living or deceased donors among all Brazilian transplantation centers. This cohort was developed by deterministic-probabilistic linkage of the following SUS administrative databases: Hospital Information System (SIH); Ambulatory Information System (SIA), and Mortality Information System (SIM)[26, 28-31].

Patients who underwent kidney transplantation and received immunosuppressive regimens containing either cyclosporine or tacrolimus between January 1, 2000, and December 31, 2009, were included in the study. This entry period was established to ensure a minimum follow-up of 12 months. The entry date was the date of transplantation registered in SIH.

The event used for survival analysis was graft loss. This was defined as death or having had another kidney transplant or the need for dialysis for more than three months without concomitant use of immunosuppressive drugs. Patients were excluded if deaths occurred within six months of transplantation as this could be related to the surgical procedure rather than lack of effectiveness of immunosuppressive medicines in line with our previous study[26]. The event date was defined as the date of death, the date of re-transplantation or the last date of immunosuppressive treatment, whichever occurs first. We censored patients lost to follow-up as the date of the last recorded immunosuppressive treatment supply. Right censoring was established on 12/31/2010, i.e. the date of the event (death or return on dialysis) and the date of final entry (censoring right). In Brazil, mortality notification is mandatory, and continuous immunosuppressive treatment is dispensed to SUS patients on a monthly basis. Re-transplantation was identified in the same way as the entry event (SIH) and dialysis is recorded in the same way as immunosuppressant therapy.

We present descriptive statistics of all the study variables, i.e. frequency distribution for categorical variables and central tendency and variability for continuous variables. The variables included: (a) the region where the transplant was performed, (b) calendar year of transplantation categorised as 2000 to 2004 and 2005 to 2009, (c) gender, (d) age at the time of transplantation, (e) primary diagnosis of kidney disease, (f) treatment regimen (tacrolimus- or cyclosporine-based), (g) type of transplant received (living or deceased donor), and (h) period of dialysis prior to kidney transplantation. Student's t-test was used to assess differences between the means of two groups, e.g. between the treatment regimens, and the chi-square test was used to evaluate differences in frequencies.

We analyzed the factors that influenced graft survival using univariate analysis for each descriptive variable and evaluated their association with graft loss. The Kaplan-Meier method was used to estimate the cumulative probability of survival. The different survival curves were compared using the log-rank test. A value of $p<0.20$ was considered for inclusion of the variable in the multivariate model. The hazard ratio (HR) for progression to the event was calculated by univariate and multivariate analyses considering a 95% confidence interval (95% CI) and using the Cox proportional hazards model.

Additionally, we performed a subgroup analysis according to donor type and treatment regimen (living donor/cyclosporine vs. living donor/tacrolimus and deceased donor/cyclosporine vs. deceased donor/tacrolimus) and an analysis considering only the return to dialysis as the event (death-censored graft loss analysis), focusing on the immunosuppressant agents tacrolimus and cyclosporine. We also performed supplementary analysis including all patients incorporating those who died within six months of transplantation as well as the use of either azathioprine or mycophenolate in addition to either cyclosporine or tacrolimus (Appendix).

The statistical analysis was performed using "R" version 3.1.1 (R Foundation for Statistical Computing) and SPSS version 17 (SPSS Inc., Chicago, USA) considering a significance level of 5%.

The study was approved by the Research Ethics Committee of the Universidade Federal de Minas Gerais (UFMG) (Approval number: 16334413.9.0000.5149).

Results

From among 17,731 identified patients, the following were excluded: 1,181 for being younger than 18 years at the date of surgery, 322 for having underwent more than one transplantation during the study period, 2,044 for having switched calcineurin inhibitor (cyclosporine or tacrolimus) during the follow-up period, and 695 for having died within the first six months from the date of transplantation.

Of the 13,811 patients included in the study, 5,887 (43%) used cyclosporine-based regimens and 7,924 (57%) used tacrolimus-based regimens. The majority of transplants were performed in Southeastern (62.5%) and Southern (20.9%) Brazil (Table 1). The number of patients entering the cohort on cyclosporine-based treatments decreased from 931 in 2000 to 244 in 2009, whereas the number of those on tacrolimus treatment increased from 107 in 2000 to 1,683 in 2009. Between 2000 and 2004, more patients were prescribed immunosuppression with cyclosporine-based regimens (68.0%) than with tacrolimus-based regimens (32.0%), and between 2005 and 2009 the opposite was observed, i.e. more patients were prescribed tacrolimus-based regimens (77.8%) than cyclosporine-based regimens (22.2%).

Table 1. Demographic characteristics of study population. Brazil: 2000-2010 (N=13.811)

Characteristic	Total (n= 13.811)		Cyclosporine-based regimens (n= 5.887)		Tacrolimus-based regimens (n= 7.924)		
	n	%	n	%	n	%	*P*
Geographic origin[a]							<0,001
Southeast	7.865	62.5	3.013	54.3	4.852	69	
South	2.625	20.9	1.509	27.2	1.116	15.9	
Northeast	1.352	10.7	636	11.5	716	10.2	
Midwest	595	4.7	312	5.6	283	4.0	
North	145	1.2	79	1.4	66	0.9	
Year of transplantation							
2000 a 2004	6.165	44.6	4.192	68.0	1.973	32.0	<0,001
2005 a 2009	7.646	55.4	1.695	22.2	5.951	77.8	
Recipient sex							<0,001
Female	8.316	60.2	3.815	64.8	4.501	56.8	
Male	5.495	39.8	2.072	35.2	3.423	43.2	
Age group (years)							<0,001
18 - 29	2.838	20.6	1.155	19.6	1.683	21.2	
30 - 39	3.485	25.2	1.603	27.2	1.882	23.8	
40 - 49	3.640	26.4	1.563	26.6	2.077	26.2	
50 - 64	3.499	25.3	1.425	24.2	2.074	26.2	
≥ 65	349	2.5	141	2.4	208	2.6	
Primary cause of Chronic Kidney Disease							<0,001
Nephritis[b]	2.740	19.8	1.304	47.6	1.436	52.4	
Hypertension / Cardiovascular Disease	2.453	17.8	1.167	47.6	1.286	52.4	
Organ failure or rejection	737	5.3	332	45.0	405	55.0	
Diabetes Mellitus	648	4.7	279	43.1	369	56.9	
Kidney cystic disease/ Neoplasms / Tumors	278	2.0	123	44.2	155	55.8	
Uropathies	188	1.4	83	42.8	111	57.2	
Undetermined / Other causes	6.761	49.0	2.599	38.4	4.162	61.6	
Donor type							<0,001
Living	7.527	54.5	3.570	47.4	3.597	52.6	
Deceased	6.284	45.5	2.317	36.9	3.967	63.1	
Time on dialysis prior to transplantation (months)[a, c]							<0,001

≤ 47	5.801	49.9	3.331	62.4	2.470	39.4	
> 47	5.817	50.1	2.011	37.6	3.806	60.6	
Events							<0,001
Censoring[d]	11.699	84.7	4.846	82.3	6.853	86.5	
Graft loss	2.212	15.3	1.041	17.7	1.071	13.5	
Death	967	7.0	512	8.7	455	5.7	
Dialysis for more than 3 months	823	6.0	445	7.6	378	4.8	
Re-transplant	322	2.3	84	1.4	238	3.0	

P-value refers to the comparison between groups (Pearson Chi^2 test). In post hoc test of Geographic region, the following comparisons showed significant statistic difference: Southeast vs. Northeast; South vs. Northeast; and South vs. Midwest. For Age group the following comparisons showed statistic difference: (18 - 29) vs. (30 - 39); and (30 - 39) vs. (50 - 64). Primary cause of Chronic Kidney Disease showed significant statistic difference when comparing Undetermined / Other causes with the other categories.

[a] Refers to individuals with valid data.

[b] Glomerulonephritis / Interstitial nephritis / pyelonephritis.

[c] Median time= 47 months.

[d] Loss to follow-up or right censoring.

The majority of the patients were women (60.6%), and the median age was 41 years. The main causes of CKD were glomerulonephritis, nephritis, and pyelonephritis (19.8%), with secondary causes of hypertension/cardiovascular diseases (17.8%). A considerable number of patients (49.2%) had an indeterminate diagnosis, which limited the etiological analysis. The most common type of transplant was from a living donor (54.5%), and the mean pre-transplant dialysis period was 47 months. During follow-up, there were 2,212 (15.3%) graft losses (7.0% deaths, 2.3% re-transplants and 6.0% returning to dialysis for more than three months) and 11,699 (84.7%) censorings occurred (Table 1).

There were more women in the cyclosporine group than in the tacrolimus group (64.8% vs. 56.8%; $p<0.001$). The distribution of patients among the age groups was significantly different; however, the mean patient age in the cyclosporine and tacrolimus groups was not significantly different (41.16±12.06 and 41.42±12.57 years, respectively; $p=0.231$). Among patients who received deceased-donor grafts, tacrolimus was used more frequently (63.1%) than cyclosporine (36.9%) ($p<0.001$) (Table 1). Mycophenolate (mofetil or sodium) was the most commonly used anti-proliferative agent in both groups (Table 2).

Table 2. Immunosuppressive drug combinations used by the patients in the cohort. Brazil: 2000-2010 (N= 13,811)

Cyclosporine-Based Immunosuppressive Regimens		Tacrolimus-Based Immunosuppressive Regimens	
Regimen	**n**	**Regimen**	**n**
Cyclosporine (monotherapy)	539	Tacrolimus (monotherapy)	216
Cyclosporine + azathioprine	1322	Tacrolimus + azathioprine	939
+ mycophenolate	577	+ mycophenolate	587
+ mycophenolate/sirolimus	143	+ mycophenolate/sirolimus	132
+ mycophenolate/sirolimus/everolimus	2	+ mycophenolate/sirolimus/everolimus	0
+ mycophenolate/everolimus	6	+ mycophenolate/everolimus	27
+ sirolimus	94	+ sirolimus	39
+ sirolimus/everolimus	1	+ sirolimus/everolimus	3
+ everolimus	4	+ everolimus	7
Cyclosporine + mycophenolate	2595	Tacrolimus + mycophenolate	4795
+ sirolimus	433	+ sirolimus	907
+ sirolimus/everolimus	8	+ sirolimus/everolimus	19
+ everolimus	38	+ everolimus	121
Cyclosporine + sirolimus	83	Tacrolimus + sirolimus	119
+everolimus	0	+ everolimus	0
Cyclosporine + everolimus	42	Tacrolimus + everolimus	13
Total	5887	Total	7924

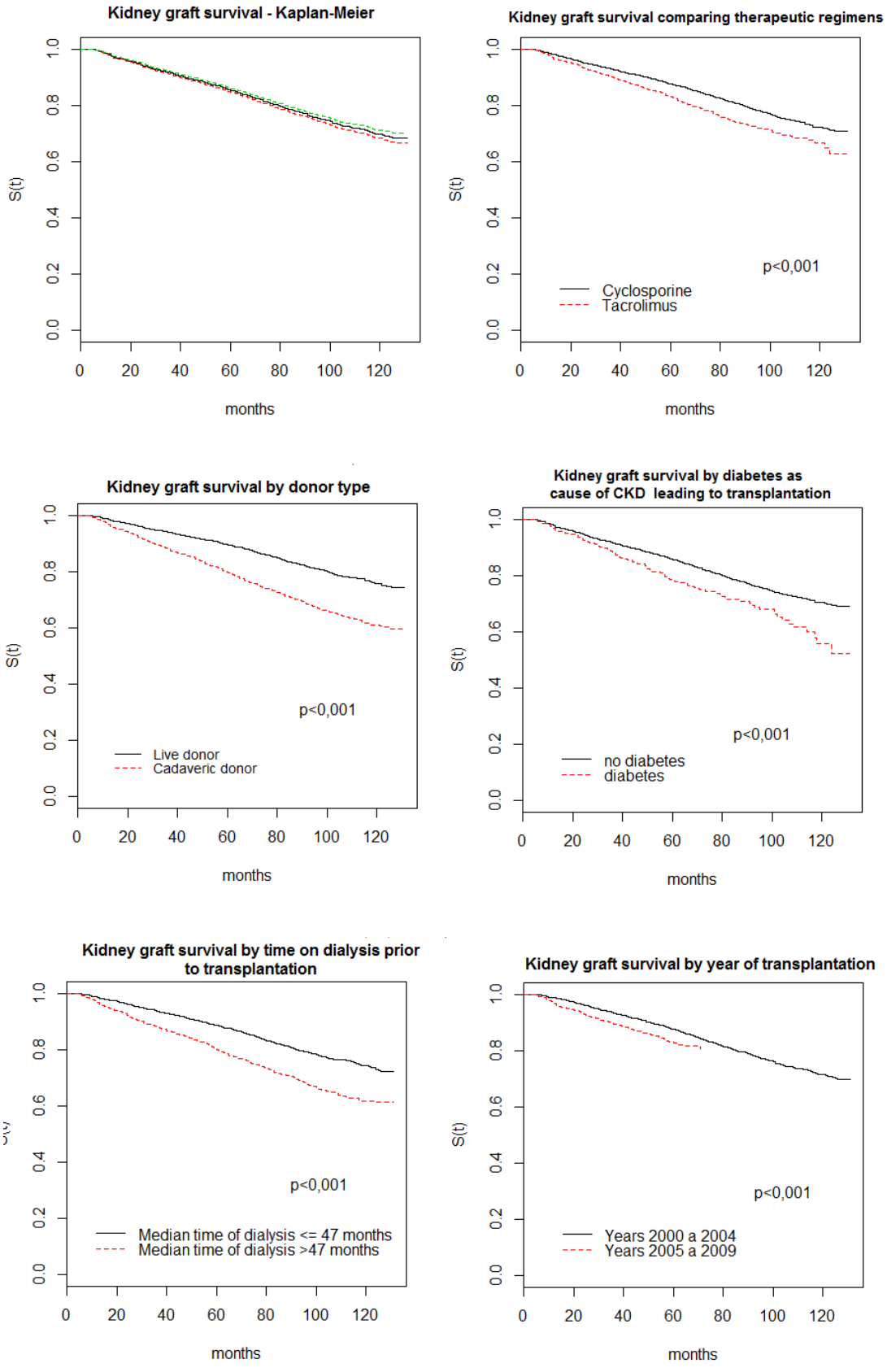
The univariate analysis indicated a higher risk of graft loss among patients treated with tacrolimus (HR=1.369; 95% CI 1.253–1.495) and among male patients (HR=1.107; 1.007–1.218). The risk of graft loss increased for each additional year of age of the recipient (HR=1.015; 1.011–1.023) and was higher among those who underwent pre-transplantation dialysis for more than 47 months (HR=1.741; 1.591–1.906) and among those who received transplants between 2005-2009 (HR= 1.465; 1.323–1.624). The patients who received a deceased-donor organ also had a higher risk of graft loss (HR=1.926; 1.767–2.101) and, similarly, those patients with diabetes as the primary cause of CKD (HR=1.494; 1.242–1.796). (Table 3). A graphic representation of survival according to the explanatory variables is shown in Figure 1.

Table 3. Hazard ratio for graft loss by demographic and clinical characteristics of the study population. Brazil: 2000-2010 (N=13,811)

Variable	Total	Graft loss						HR (95% CI)	*P*
		Total		Death		Dialysis for more than 3 months/re-transplant			
	n	n	%	n	%	n	%		
Sex									
Female	8.316	1,253	15.6	607	48,4	646	51.6	0.991 (0.9089–1.081)	0.845
Male	5.495	859	15.1	360	41.9	499	58.1	1.0	
Age at transplantation (additional year)	13,811							1.015 (1.011–1.023)	<0.001
Primary cause of Chronic Kidney Disease									
Diabetes Mellitus	648	129	19.9	80	62.0	49	38.0	1.494 (1.242–1.796)	<0.001
Hypertension / Cardiovascular Disease	2.453	432	17.6	199	46.1	233	53,9	1.114 (0.994–1.249)	0.064
Nephritis[a]	2.740	488	17.8	188	38.5	300	61,5	1.053 (0.943–1.176)	0.356
Organ failure or rejection	737	73	9,91	41	56.2	32	43.8	0.679 (0.535 –0.810)	<0.001
Uropathies	194	27	13.9	8	29.6	19	70,4	0.919 (0.627–1.347)	0.665
Kidney cystic disease/ Neoplasms / Tumors	278	45	16.2	24	53.3	21	46.7	1.062 (0.788–1.433)	0.689
Undetermined / Other causes	6.761	918	13.6	427	46.5	491	53.5	0.959 (0.873–1.053)	0.380
Calcineurin inhibitor									
Tacrolimus	7.924	1.071	13.5	455	42.5	616	57.5	1.369 (1.253–1.495)	<0.001
Cyclosporine	5.887	1.041	17.7	512	49.2	529	50.8	1.0	
Donor type									
Deceased	6.284	1.188	18.9	556	46.8	632	53.2	1.926 (1.767–2.101)	<0.001
Living	7.527	924	12.3	411	44.5	513	55.5	1.0	
Time on dialysis prior to transplantation (months)									
> 47	5.817	1008	17,3	459	45.5	549	54.5	1.741 (1.591–1.906)	<0.001
≤ 47	5.801	944	16.3	435	46.1	509	53.9	1.0	
Year of transplantation									
Year 2005 a 2009	7.646	793	10.4	397	50.1	396	49.9	1.465 (1.323 – 1.624)	<0.001
Year 2000 a 2004	6.165	1.319	21.4	570	43.2	749	56.8	1.0	

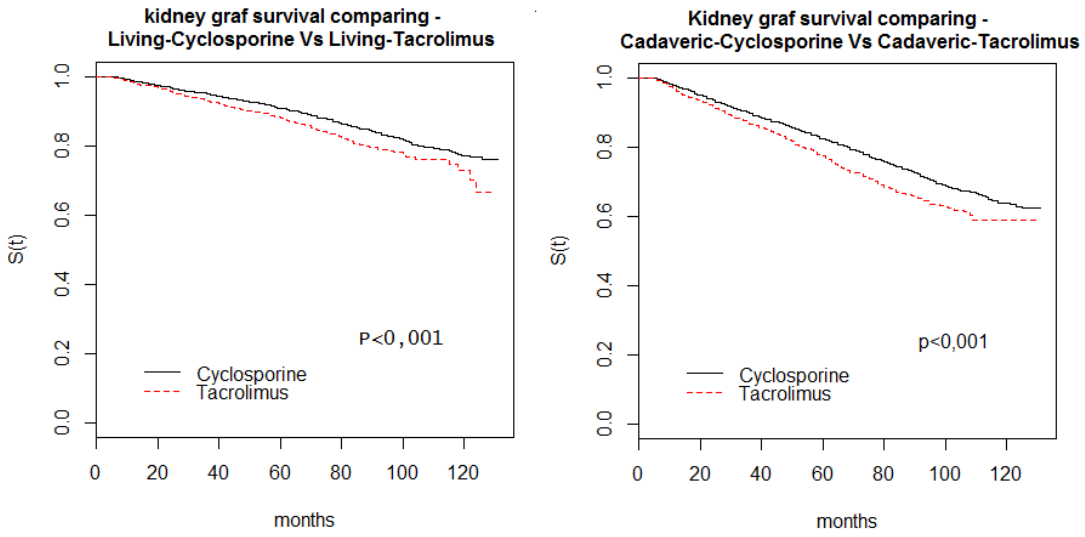
[a] Glomerulonephritis / Interstitial nephritis / pyelonephritis.

Figure 1. Kaplan-Meier graft survival estimates for 10 years after renal transplantation according to calcineurin inhibitor, time on dialysis prior to transplantation, and CKD primary diagnosis.



The Kaplan-Meier curves for the subgroup analysis of living or deceased donors among the cyclosporine and tacrolimus groups are shown in Figure 2. This analysis revealed a significant difference in favor of cyclosporine in both groups. To evaluate the impact of death on graft survival, we performed a death-censored graft loss analysis. Even in this scenario, tacrolimus failed to demonstrate a therapeutic advantage (log rank test p<0.001.

Figure 2. Kaplan-Meier curves of tacrolimus and cyclosporine comparisons by living or deceased donor for 10 years after renal transplantation.



The overall 10-year graft survival was 69.5% (95% CI 68.0–71.1). Graft survival among patients treated with cyclosporine or tacrolimus was 71.9% (71.5–75.0) and 64.8% (60.1–70.0), respectively. The overall graft survival per drug group per follow-up year is shown in Table 4.

Table 4. Annual graft survival rates of the study population according to the calcineurin inhibitor used. Brazil: 2000-2010 (N=13,811).

Follow-up year	Relative risk (95%CI)		
	Total	Cyclosporine-based regimens	Tacrolimus-based regimens
1st	0.976 (0.973 - 0.978)	0.982 (0.978 - 0.985)	0.971 (0.968 - 0.975)
2nd	0.944 (0.940 - 0.948)	0.954 (0.949 - 0.960)	0.936 (0.931- 0.942)
3rd	0.913 (0.908 - 0.918)	0.929 (0.922 - 0.936)	0.899 (0.892 - 0.907)
4th	0.885 (0.879 - 0.891)	0.904 (0.896 - 0.912)	0.867 (0.857 - 0.876)
5th	0.853 (0.846 - 0.860)	0.875 (0.866 - 0.884)	0.830 (0.819 - 0.842)
6th	0.819 (0.810 - 0.827)	0.844 (0.834 - 0.855)	0.788 (0.774 - 0.802)
7th	0.783 (0.774 - 0.793)	0.812 (0.800 - 0.824)	0.745 (0.728 - 0.762)
8th	0.752 (0.741 - 0.763)	0.778 (0.765 - 0.791)	0.715 (0.696 - 0.735)
9th	0.723 (0.710 - 0.735)	0.748 (0.733 - 0.763)	0.691 (0.668 - 0.714)
10th	0.695 (0.680 - 0.711)	0.719 (0.701 - 0.737)	0.648 (0.601 - 0.700)

The multivariate analysis revealed that the following variables were associated with a higher risk of graft loss: use of tacrolimus (HR=1.194; 95% CI 1.082–1.318), deceased donor transplantation (HR=1.604; 1.455–1.769), additional year of age of the recipient (HR=1.008; 1.004–1.012), median period of pre-transplantation dialysis greater than 47 months (HR=1.351;

1.224–1.491), diagnosis of diabetes as the primary cause of CKD (HR=1.333; 1.109–1.604) and transplantation year between 2005 and 2009 (HR= 1.266; 1.128–1.422) (Table 5).

Table 5. Hazard ratio for graft loss: Cox logistic regression of 10-year follow-up. Brazil: 2000-2010 (N=13,811).

Variable	HR (95%CI)	*P*
Calcineurin inhibitor (tacrolimus-based regimens)	1.194 (1.082–1.318)	<0.001
Donor type (deceased)	1.604 (1.455–1.769)	< 0.001
Age (additional year)	1.008 (1.004–1.012)	<0.001
Time on dialysis prior to transplantation (>47 months)	1.351 (1.224–1.491)	<0.001
Primary cause of Chronic Kidney Disease (Diabetes Mellitus)	1.333 (1.109–1.604)	0.002
Year of transplantation (2005 a 2009)	1.266 (1.128–1422)	<0.001

Discussion

With this study, we aimed to evaluate the long-term effectiveness of maintenance immunosuppression in kidney transplantation at the national level. Consequently, we conducted a deterministic-probabilistic linkage of SUS administrative databases and extracted a cohort of transplanted patients. The 10-year graft survival of 69.5% was influenced by both clinical and demographic characteristics.

Our results revealed an increase in the number of transplantations in Brazil and indicated a worst graft survival for patients undergoing transplantation between 2005 to 2009, although there were no major changes in the guidelines and procedures between 2000 and 2009 in Brazil[15,16]. Our results also indicated a higher concentration in more developed regions of the country, as previously reported by others[17]. Glomerulonephritis, nephritis, and pyelonephritis, along with hypertension and diabetes mellitus, were the leading causes of CKD, which is similar to our previous study as well as other published studies[26, 10, 32].

Our cohort also showed that 4.7% of patients had “diabetes” registered as their primary cause of CKD. The International Diabetes Federation reported a prevalence of diabetes of 6.4% in Brazil in 2010, the last year of our cohort study[33]. A former study of the SUS databases in Brazil revealed a prevalence of 16% among patients in dialysis [34] .This is important as diabetes is associated with poorer outcomes[35]. This difference between patients in our study and undergoing dialysis may be explained by the fact that some patients with diabetes, who are undergoing dialysis, will present with a clinical status that precludes transplantation as an option. However, future studies are needed to more accurately determine the reason for the lower transplantation rate among patients with diabetes in Brazil.

Among the demographic variables, age influenced graft survival, considered here as death, re-transplantation or a return to dialysis. Gender did not influence graft survival in our study. However recent studies have suggested men have a higher risk of graft loss compared with women in the long term[11,36-38].

The distribution of transplants according to age group in Brazil between 2000 and 2010 corresponds with the profile of the patients waiting on the kidney transplant list [39]. This distribution includes fewer older patients (≥65 years), who are less likely to be on the waiting list and who spend more time on dialysis before entering the list[39]. Consequently, only 2.6% of the transplantations were performed in older people. Although older age has been identified as a risk factor for graft loss in this and other studies[26, 37, 40], some authors have questioned this assumption and have reported that the survival rates of patients aged <50 years were similar to those of patients aged >50 years[12, 41]. As a result, we believe age should not necessarily be a discriminatory factor against receiving a transplant.

Among the clinical variables, a median period of dialysis greater than 47 months, a diagnosis of diabetes mellitus as the primary cause of CKD, donor type, and the specific calcineurin inhibitor affected graft survival in our study. This is in agreement with other studies that found a longer dialysis period and a diagnosis of diabetes are predictors of poor prognosis in kidney transplantation[40, 42]. A further study demonstrated that patients with diabetes exhibited an increased risk of post-transplantation cardiovascular events, all-cause death, and death from cardiovascular causes compared with those without diabetes[35]. Consequently, additional care is needed with these patients.

In our cohort, the use of tacrolimus increased over time coincided with an increase in the number of deceased donor transplants. More graft loss events occurred with cyclosporine; however, the time until the event (the survival time) were worse for tacrolimus compared with cyclosporine (Figures 1 and 2). In addition, the Kaplan-Meier curves in the subgroup analysis of living or deceased donors within the tacrolimus and cyclosporine groups showed that tacrolimus failed to demonstrate a therapeutic advantage, regardless of donor type (Figure 2). Additionally, in the death-censored graft loss analysis, tacrolimus did not present an advantage over cyclosporine.

Furthermore, the final multivariate model, which was adjusted for other variables, including donor type, showed poorer graft survival rates in patients treated with tacrolimus compared with those treated with cyclosporine after a 10-year follow-up (survival rates of 64.8% and 71.9%, respectively). This is in agreement with the study by Bunnapradist et al.[43] involving 7,079 patients treated with tacrolimus or cyclosporine, both in combination with mycophenolate, which showed a higher risk of treatment failure with tacrolimus (HR=1.28; 95% CI 1.09-1.49). In our study, the residual analysis indicated a good fit based on the procedure proposed by Schoenfeld, with a mean value close to zero and no violation of the homoscedasticity assumption.

Studies from different countries have evaluated the outcomes of kidney transplantation using tacrolimus or cyclosporine according to donor type and other variables. In the United States, the two-year survival rate of 7,079 living donor graft recipients was 94.3% among patients treated with cyclosporine and 92.2% among those treated with tacrolimus[43]. Considering only deceased donor graft recipients, a study conducted in the United States with more than 50,000 patients reported that the five-year graft survival was similar between patients who received cyclosporine- or tacrolimus-based regimens[44]. Similar results were obtained in a previous study in the United States using a paired analysis of deceased donor transplants with a five-year follow-up[45] and in a Saudi Arabian study with a two-year follow-up[46].

Overall our findings with this longer-term follow-up of patients, combined with the findings from other countries involving longer-term follow-up, indicate that the rationale for the preferred use of tacrolimus in kidney transplant patients is not supported by the clinical data. Consequently, other factors associated with this practice should be investigated especially if they lead to higher costs and worse outcomes for patients. In the meantime, SUS should consider prescribing restrictions for tacrolimus versus cyclosporine to improve patient outcomes following transplantation as well as save resources, with tacrolimus currently costing up to three times for SUS patients in Brazil than cyclosporine.

The major limitation of this study is that it involves the use of administrative databases. As a result, information was not available on several factors that influence short- and long-term graft survival, including acute rejection rates, immunological compatibility, ischemia time, serum creatinine levels and graft function, as well as the specific causes of graft loss. In addition, blood levels of immunosuppressants were not available. However the Clinical Protocol and Therapeutic Guidelines of the Brazilian Ministry of Health recommend drug level monitoring, and SUS pays for these procedures. Another limitation involves the comparison of tacrolimus and cyclosporine independently of adjuvant medicines as the Clinical Protocol and Therapeutic Guidelines of the Brazilian Ministry of Health recommends a triple-drug regimen as maintenance immunosuppressive treatment.

Furthermore, data from administrative records might have been incomplete or contain inconsistencies inherent with the retrospective nature of the study. Despite these limitations, we

believe our findings are valid as these were obtained using a long-term nationwide observational study involving more than 13,000 patients. In addition, this reflects the real world situation in Brazil.

In conclusion, our study showed that among other factors, the use of tacrolimus-based regimens was associated with worse graft survival. As a result, as mentioned, SUS should potentially consider prescribing restrictions for tacrolimus in Brazil especially given the cost differential with cyclosporine.

Acknowledgements and conflicts of interest

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Key issues

- Chronic kidney disease (CKD) is characterized by slow, progressive, and irreversible loss of kidney function. For patients with no contraindications transplantation is the renal replacement therapy of choice for patients with end-stage renal failure.

- Immunosuppression regimens supplied by Unified Health System (Sistema Único de Saúde, SUS), which provides more than 95% of all kidney transplants in Brazil, consists of a triple-drug regimen, typically containing a corticosteroid, a calcineurin inhibitor (cyclosporine or tacrolimus), and an antiproliferative agent. Calcineurin inhibitors have been considered the hallmark immunosuppression. However in Brazil, tacrolimus costs three times more than cyclosporine.

- The overall 10-year graft survival in our study was 69.5% (95% CI 68.0–71.1) with graft survival among patients treated with cyclosporine- or tacrolimus-based regimens was 71.9% (70.1–73.7) and 64.8% (60.1–70.0), respectively. The use of tacrolimus-based regimens increased the risk of graft loss, defined as death or return to dialysis, in comparison with the use of cyclosporine-based regimens in 10 years of follow-up (HR=1.194; 95% CI 1.082–1.318).

- Analysis per donor type (living or deceased) revealed no advantage of the use of tacrolimus in both groups.

- The rationale for the preferred use of tacrolimus in Brazil and other countries is not supported by the literature or our findings. Future research should look at the factors associated with this practice especially since if thisleads to higher costs and worse outcomes for patients

References

1. Levin A, Stevens PE, Bilous RW. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013; 3: 1.
2. Sesso RC, Lopes AA, Thomé FS, et al. Brazilian Chronic Dialysis Survey 2013 - trend analysis between 2011 and 2013. J Bras Nefrol 2014; 36 (4): 476.

3. Romão Junior JE. Doença renal crônica: definição epidemiologia e classificação. J. bras. nefrol 2004; 26 (3, supl. 1): 1.
4. Opelz G, Döhler B. Effect of human leukocyte antigen compatibility on kidney graft survival: comparative analysis of two decades. Transplantation 2007; 84 (2): 137.
5. Machnicki G, Seriai L, Schnitzler MA. Economics of transplantation: a review of the literature. Transplantation reviews 2006; 20 (2): 61.
6. Alvares J, Cesar CC, Acurcio FA, et al. Quality of life of patients in renal replacement therapy in Brazil: comparison of treatment modalities. Qual Life Res 2012; 21 (6): 983.
7. Hariharan S, Johnson CP, Bresnahan BA, et al. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med 2000; 342 (9): 605.
8. Port FK, Dykstra DM, Merion RM, Wolfe RA. Trends and results for organ donation and transplantation in the United States, 2004. Am J Transplant 2005; 5 (4 Pt 2): 843.
9. Tasaki M, Saito K, Nakagawa Y, et al. 20-year analysis of kidney transplantation: a single center in Japan. Transplant Proc 2014; 46 (2): 437.
10. Soylu H, Oruc M, Demirkol OK, et al. Survival of renal transplant patients: data from a tertiary care center in Turkey. Transplant Proc 2015; 47 (2): 348.
11. Chen PD, Tsai MK, Lee CY, et al. Gender differences in renal transplant graft survival. J Formos Med Assoc 2013; 112 (12): 783.
12. Kostakis ID, Moris DN, Barlas A, et al. Impact of donor and recipient age difference on long-term allograft survival after living donor renal transplantation: analysis of 478 cases. Clin Transplant 2013; 27 (6): 838.
13. Gómez MP, Pérez B, Manyalich M. International Registry in Organ Donation and Transplantation--2013. Transplant Proc 2014; 46 (4): 1044.
14. Medina-Pestana JO, Vaz ML, Park SI, et al. Organ transplantation in Brazil in the year 2002. Transplant Proc 2004; 36 (4): 799.
15. BRASIL. Portaria nº 221 de 01 de abril de 2002. Aprova a Diretrizes Clínicas e Protocolos Terapêuticos de Medicamentos Excepcionais e de Alto Custo no SUS. Transplantes Renais. In: Saúde Md, ed. Diário Oficial da União, 2002.
16. BRASIL. Portaria nº 666, de 17 de julho de 2012. Aprova a Diretrizes Clínicas e Protocolos Terapêuticos de Medicamentos Excepcionais e de Alto Custo no SUS. Transplantes Renais. In: Saúde Md, ed. Diário Oficial da União, 2012.
17. Medina-Pestana JO, Galante NZ, Tedesco-Silva H, et al. Kidney transplantation in Brazil and its geographic disparity. J Bras Nefrol 2011; 33 (4): 472.

18. Garcia SC, Lopes LdS, Schott KL, et al. Cyclosporine A and tacrolimus: a review. Jornal Brasileiro de Patologia e Medicina Laboratorial 2004; 40 (6): 393.
19. Liu JY, You RX, Guo M, et al. Tacrolimus Versus Cyclosporine as Primary Immunosuppressant After Renal Transplantation: A Meta-Analysis and Economics Evaluation. Am J Ther 2014.
20. Azzi JR, Sayegh MH, Mallat SG. Calcineurin inhibitors: 40 years later, can't live without. J Immunol 2013; 191 (12): 5785.
21. Almeida CC, Silveira MR, de Araújo VE, et al. Safety of immunosuppressive drugs used as maintenance therapy in kidney transplantation: a systematic review and meta-analysis. Pharmaceuticals (Basel) 2013; 6 (10): 1170.
22. Webster AC, Woodroffe RC, Taylor RS, et al. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. BMJ 2005; 331 (7520): 810.
23. El-Zoghby ZM, Stegall MD, Lager DJ, et al. Identifying specific causes of kidney allograft loss. Am J Transplant 2009; 9 (3): 527.
24. Pirsch JD, Miller J, Deierhoi MH, et al. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. FK506 Kidney Transplant Study Group. Transplantation 1997; 63 (7): 977.
25. Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 2004; 4 (3): 378.
26. Guerra AA, Cesar CC, Cherchiglia ML, et al. Cyclosporine versus tacrolimus in immunosuppressive maintenance regimens in renal transplants in Brazil: survival analysis from 2000 to 2004. Ann Pharmacother 2010; 44 (1): 192.
27. Guerra Júnior AA, Silva GD, Andrade EI, et al. Cyclosporine versus tacrolimus: cost-effectiveness analysis for renal transplantation in Brazil. Rev Saude Publica 2015; 49: 1.
28. Coeli CM, Camargo Jr KRd. Avaliação de diferentes estratégias de blocagem no relacionamento probabilístico de registros. Rev Bras Epidemiol 2002; 5 (2): 185.
29. Cherchiglia ML, Guerra Júnior AA, Andrade EIG, et al. A construção da base de dados nacional em terapia renal substitutiva (TRS) centrada no indivíduo: aplicação do método de linkage determinístico-probabilístico. Revista Brasileira de Estudos de População 2007; 24 (1): 163.
30. Guerra Junior AA, Acúrcio FA, Andrade EI, et al. [Cyclosporine versus tacrolimus in kidney transplants in Brazil: a cost comparison]. Cad Saude Publica 2010; 26 (1): 163.

31. Acúrcio FA, Brandão CMR, Guerra Júnior AA, et al. Perfil demográfico e epidemiológico dos usuários de medicamentos de alto custo no Sistema Único de Saúde; Perfil demográfico y epidemiológico de los usuarios de medicamentos de costo elevado en el Sistema Único de Salud. Rev. bras. estud. popul 2009; 26 (2): 263.
32. Harada KM, Mandia-Sampaio EL, de Sandes-Freitas TV, et al. Risk factors associated with graft loss and patient survival after kidney transplantation. Transplant Proc 2009; 41 (9): 3667.
33. International Diabetes Federation. IDF Diabetes Atlas: Fourth edition. 2009
34. Cherchiglia ML, Machado EL, Szuster DAC, et al. Perfil epidemiológico dos pacientes em terapia renal substitutiva no Brasil, 2000-2004. Ver Saúde Pública 2010; 44 (4): 639.
35. Cosio FG, Hickson LJ, Griffin MD, et al. Patient survival and cardiovascular risk after kidney transplantation: the challenge of diabetes. Am J Transplant 2008; 8 (3): 593.
36. Zhou JY, Cheng J, Huang HF, et al. The effect of donor-recipient gender mismatch on short- and long-term graft survival in kidney transplantation: a systematic review and meta-analysis. Clin Transplant 2013; 27 (5): 764.
37. Traynor C, Jenkinson A, Williams Y, et al. Twenty-year survivors of kidney transplantation. Am J Transplant 2012; 12 (12): 3289.
38. Santiago EVA, Silveira MR, Araújo VE, et al. Gender in the allocation of organs in kidney transplants: meta-analysis. Rev Saúde Pública 2015; 49
39. Machado EL, Cherchiglia ML, Acúrcio FeA. [Profile and clinical outcome of patients in waiting list for kidney transplantation, Belo Horizonte (MG, Brazil), 2000-2005]. Cien Saude Colet 2011; 16 (3): 1981.
40. Hariharan S, McBride MA, Cherikh WS, et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int 2002; 62 (1): 311.
41. Rodelo JR, Nieto-Ríos JF, Serna-Higuita LM, et al. Survival of renal transplantation patients older than 60 years: a single-center experience. Transplant Proc 2013; 45 (4): 1402.
42. Gill JS, Tonelli M, Johnson N, et al. The impact of waiting time and comorbid conditions on the survival benefit of kidney transplantation. Kidney Int 2005; 68 (5): 2345.
43. Bunnapradist S, Daswani A, Takemoto SK. Graft survival following living-donor renal transplantation: a comparison of tacrolimus and cyclosporine microemulsion with mycophenolate mofetil and steroids. Transplantation 2003; 76 (1): 10.
44. Opelz G, Döhler B, Study CT. Influence of immunosuppressive regimens on graft survival and secondary outcomes after kidney transplantation. Transplantation 2009; 87 (6): 795.

45. Kaplan B, Schold JD, Meier-Kriesche HU. Long-term graft survival with neoral and tacrolimus: a paired kidney analysis. J Am Soc Nephrol 2003; 14 (11): 2980.

46. Alghamdi S, Nabi Z, Skolnik E, et al. Cyclosporine versus tacrolimus maintenance therapy in renal transplant. Exp Clin Transplant 2011; 9 (3): 170.