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Sixteen years of kidney transplant: an open cohort in brazil's Unified Health System

Dezesseis anos de transplante renal: uma coorte aberta no Sistema Único de Saúde do Brasil

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ABSTRACT

Objective: To analyze the graft survival of kidney transplant patients in Brazil between 2000 and 2015. **Methods**: Open historical cohort of kidney transplant patients through the SUS, constructed through deterministic-probabilistic matching of administrative databases. The cumulative probability of survival was estimated using Kaplan-Meier and the difference between the curves compared using the Log-Rank Test. Potential factors associated with graft loss were evaluated by univariate and multivariate analyses. The Cox model was used to calculate the Hazard-Ratio considering the 95% confidence interval. **Results**: 44,795 patients were included. The majority were male (60.1%) with a median age of 42 years. The analysis demonstrated renal graft survival rates of 91.2%, 77.0%, 57.5% and 42.1% for one, five, ten and 15 years respectively. Multivariate analysis demonstrated that a higher risk of graft loss was associated with transplantation with deceased donor organs, additional years of age, patients who declared themselves black, longer median period of dialysis prior to transplantation (>38 months), diagnosis primary treatment of diabetes mellitus and arterial hypertension and immunosuppressive regimen containing mycophenolate. **Conclusion**: This nationwide retrospective analysis presents epidemiological data of relevance to public health regarding the survival rate and risk factors associated with graft loss in kidney transplant patients in the SUS. The results provide of the scenery of kidney transplantation in the country, demonstrating efficiency and progressive improvements that are potentially useful for managers in reevaluating clinical guidelines.

Keywords: kidney transplant, SUS, survival, immunosuppressants, cohort.

RESUMO

Objetivo: Analisar a sobrevida do enxerto dos pacientes transplantados renais no Brasil entre 2000 e 2015. **Métodos:** Coorte histórica aberta, de pacientes transplantados renais pelo SUS, construída por meio de pareamento determinístico-probabilístico de bases de dados administrativos do SUS. A probabilidade acumulada de sobrevivência foi estimada por Kaplan-Meier e a diferença entre as curvas comparada pelo Teste de Log-Rank. Potenciais fatores associados à perda do enxerto foram avaliados por análises uni e multivariada. O modelo de Cox foi utilizado para calcular o Hazard-Ratio, considerando o intervalo de confiança 95%. **Resultados:** Foram incluídos 44.795 pacientes. A maioria do sexo masculino (60,1%) com idade mediana de 42 anos. A análise demonstrou taxas de sobrevivência do enxerto renal de 91,2%, 77,0%, 57,5% e 42,1% para um, cinco, dez e 15 anos, respectivamente. A análise multivariada demonstrou um risco maior de perda do enxerto associado ao transplante com órgãos de doador falecido, aos anos adicionais de idade, aos pacientes que se declararam de cor preta, à maior período mediano de diálise anterior ao transplante (>38 meses), ao diagnóstico primário de diabetes mellitus e hipertensão arterial e ao regime imunossupressor contendo micofenolato. **Conclusão:** Esta análise retrospectiva de âmbito nacional apresenta dados epidemiológicos de relevância para a saúde pública acerca da taxa de sobrevivência e dos fatores de risco associados à perda do enxerto de pacientes transplantados renais no SUS. Os resultados possibilitam um panorama do transplante de rim no país, demonstrando efetividade e melhorias progressivas potencialmente úteis para os gestores na reavaliação de diretrizes clínicas.

Palavras-chave: transplante renal, SUS, sobrevivência, sobrevida, imunossupressores, coorte.

Introduction

Chronic kidney disease (CKD) has a high global prevalence[1] and is characterized by the slow, progressive, and irreversible loss of kidney function. The survival of patients with advanced renal failure depends on the use of renal replacement therapy (RRT).[2,3,4] Kidney transplantation is considered the best option for most of these patients, as it allows for a better quality of life and, in some cases, increases life expectancy, in addition to being more cost-effective than dialysis.[5,6,7] With these evident benefits, its importance in the global scenario is increasing.[8]

The results obtained after kidney transplantation have significantly improved in recent years, with enhanced procedural performance and advancements in immunosuppressive treatments.[8,9] This has resulted in a demand for better funding and availability of this transplantation, with incentives and investments in this área.[10]

Studies conducted in Brazil suggest that the one-year graft survival rate is 97.6%, the five-year rate is 85.3%, and the ten-year rate is 69.5%[11], being higher in some healthcare units[12]. These results are relevant considering the recent annual growth in the number of kidney transplants in the country, increasing from 1,811 transplants in 1995 to 6,302 in 2019[12,13]. Brazil is the fourth largest country in the world in terms of the absolute number of kidney transplants performed annually. However, it ranks 32nd in the number of transplants adjusted for population size[13]. Furthermore, the number of patients on the waiting list exceeds 50% of the total kidney transplants performed in the country,[13,14] raising concerns that the annual number of kidney transplants has stabilized in recent years due to the unavailability of kidneys from deceased donors[15]. Consequently, there is potential for growth in the annual number of kidney transplants, especially since the national organ transplant program is considered the largest public transplant program in the world, presenting graft survival rates similar to those observed in developed countries.[10,11,15]

Immunosuppressive regimens in the maintenance of kidney transplantation generally utilize a combination of two or three agents from different therapeutic classes to prevent rejection and maintain graft functionality.[2,16] In Brazil, the Clinical Protocol and Therapeutic Guidelines of the Ministry of Health follow global practices and recommend a triple regimen for maintenance immunosuppression, consisting of a corticosteroid, a calcineurin inhibitor (CNI), either cyclosporine or tacrolimus, and a proliferation inhibitor, either azathioprine or mycophenolate. Alternatively, any of the last two classes can be replaced by sirolimus or everolimus [mammalian target of rapamycin (mTOR)], depending on the clinical characteristics of the patient.[11,17]

In this context, an evaluation of the long-term outcomes of patients who underwent kidney transplantation is of utmost importance, especially due to the heterogeneity of the Brazilian population, the increasing recognition of chronic rejection as a significant cause of graft loss, and the scarcity of organs for kidney transplantation. Thus, the objective of this study was to analyze kidney graft survival and the factors associated with its loss through a cohort with 16 years of follow-up of patients who underwent kidney transplantation in the Brazilian Unified Health System (SUS) nationwide.

Methods

This open historical cohort included patients who underwent kidney transplantation at transplant centers in Brazil. The cohort was developed through deterministic-probabilistic matching of the administrative databases of the Brazilian Unified Health System (SUS): Hospital Information System (SIH/SUS), System of High Complexity Procedures (SIA/SUS), and the Mortality Information System (SIM).[18-21]

All adult patients aged 18 years or older who underwent kidney transplantation (from either living or deceased donors) through SUS were included.

The event evaluated was graft loss, defined as death, the need for dialysis for more than three months without the concomitant use of immunosuppressive medication, or re-transplantation. The occurrence of the event was defined as the date of registration of death, re-transplantation, or return to dialysis, whichever occurred first. Informative

censoring was characterized as the date of the last record regarding immunosuppression, and for right censoring, the date of study follow-up termination (December 31, 2015). Thus, each patient was followed for at least one year.

Descriptive statistical analyses were performed for all variables used in the study, that is, frequency distribution for categorical variables and measures of central tendency for continuous variables. The explanatory variables analyzed were: (a) region where the transplantation was performed, (b) calendar year of transplantation categorized into eras: 2000 to 2004, 2005 to 2009, and 2010 to 2014, (c) sex, (d) age at the time of transplantation, (e) skin color declared by the patient, (f) primary diagnosis of kidney disease, (g) therapeutic immunosuppression regimen, (h) type of transplant received (living or deceased donor), and (i) period of dialysis before kidney transplantation. For the therapeutic regimen variable, intention to treat (ITT) was considered, with all regimens containing corticosteroids. The Student's t-test was used to assess the difference in means between groups, and the chi-square test was used to assess differences in frequencies.

The Kaplan-Meier estimator was used to determine the cumulative probability of graft survival. The difference between the curves was compared using the Log-Rank test. Potential associations between the explanatory variables and the event were evaluated through univariate and multivariate analyses, with a p-value < 0.20 being considered for inclusion in the multivariate model. The semiparametric proportional hazards model, the Cox model, was used to calculate the Hazard Ratio (HR), considering the 95% confidence interval (CI) and Schoenfeld residual analysis.

Additionally, a stratified analysis by donor type was performed, since kidney transplantation with living donors has shown better outcomes[23-25], which may affect, for example, the choice of the immunosuppressive regimen.

All statistical analyses were performed using the "R" software, version 3.6.0, from the R Foundation for Statistical Computing, and a significance level of 5% was considered.

This study was approved by the Research Ethics Committee of UFMG (Opinion No. CAAE - 44121315.2.0000.5149).

Results

A total of 44,795 adult kidney transplant patients were identified between the years 2000 and 2014, with 26,689 (59.6%) transplants performed using organs from deceased donors and 18,106 (40.4%) from living donors. The majority of patients were male (60.1%) with a median age of 42 years (Table 1).

The majority of transplants occurred in the Southeast Region (56.7%), followed by the South Region (22.1%). The main etiology of chronic kidney failure was hypertension/cardiovascular diseases (29.1%). The second and third causes were nephritis/pielonephritis (6.3%) and diabetes mellitus (2.7%), respectively. Many patients had an undetermined diagnosis (59.8%), complicating the etiological identification (Table 1).

Most patients were identified as having undergone dialysis prior to transplantation, with a median duration of dialysis of 38 months. During the follow-up, there were 10,807 (24.1%) graft losses, with 15.6% due to death, 6.9% due to dialysis for more than three months, and 1.6% due to re-transplantation. It was observed that 9,921 (22.0%) individuals in the cohort did not use medications through SUS. It is expected that among the individuals without medication records are not only those who acquire immunosuppressants through the supplementary health system or personal resources but also those who died during or shortly after the transplantation. It was also noted that among the 9,921 individuals, 20.1% died within the first three months after kidney transplantation. The other characteristics of the study population are presented in Table 1.

There was an increase in the number of kidney transplants performed during the period, with an observed shift in the type of donor from living to deceased starting in 2007. A significant increase in the number of transplants from deceased donors was noted in the more recent period of the cohort (Table 1).

Table 1. Characteristics of the kidney transplant population, by donor type. Brazil: 2000-2015 (N=44,795)

Characteristic	Total Cohort					
	Total		Living Donor		Deceased Donor	
	44.795	**100**	**18.106**	**40,4**	**26.689**	**59,6**
Region of transplantation	N	%	N	%	N	%
Southeast	25,396	56.7	11,025	60.9	14,371	53.8
South	9,914	22.1	3,598	19.9	6,316	23.7
Northeast	6,572	14.7	2,138	11.8	4,434	16.6
Central-West	2,227	5.0	1,036	5.7	1,191	4.5
Year of transplantation (era)						
2000-2003	8,902	19.9	5,129	28.3	3,773	14.1
2004-2007	8,626	19.3	4,444	24.5	4,182	15.7
2008-2011	14,164	31.6	5,251	29.0	8,913	33.4
2012-2014	13,103	29.3	3,282	18.1	9,821	36.8
Patient's sex[a]						
Male	27,054	60.4	11,022	60.9	16,032	60.1
Female	17,741	39.6	7,084	39.1	10,657	39.9
Skin color						
Yellow	695	5.5	204	4.6	491	6.0
White	6,773	53.5	2,477	56.1	4,296	52.1
Indigenous	5	0.04	1	0.02	4	0.05
Brown	4,053	32.0	1,426	32.3	2,627	31.9
Black	1,134	9.0	307	7.0	827	10.0
Age range (years)						
18-25	4,333	9.7	2,691	14.9	1,642	5.1
26-35	9,48	21.2	5,063	28.0	4,417	16.5
36-45	10,956	24.5	4,865	26.9	6,091	22.8
46-55	11,297	25.2	3,662	20.2	7,635	28.6
56-65	7,165	16.0	1,614	8.9	5,551	20.8
≥ 65	1,564	3.5	211	1.2	1,353	5.1
Primary cause of CKD						
Nephritis[b]	2,804	6.3	1,229	6.8	1,575	5.9
Hypertension/Cardiovascular Diseases	13,042	29.1	5,205	28.7	7,837	28.5
Diabetes Mellitus	1,19	2.7	411	2.3	779	2.9
Neoplasms/Tumors	730	1.6	224	1.2	506	1.9
Uropathies	237	0.5	90	0.5	147	0.6
Indeterminate/Other causes	26,792					
Time of dialysis prior to transplantation (months)						
≤ 38	19,349	49.5	9,917	63.0	13,903	59.6
> 38	19,72	50.5	5,817	37.0	9,432	40.4
Events						
Censoring*	33,938	75.9	14,324	79.1	19,664	73.7
Graft loss	10,807	24.1	3,782	20.9	7,025	26.3
Death	6,973	15.6	2,331	12.9	4,642	17.4
Dialysis (>3 months)	3,112	6.9	1,092	6.0	2,02	7.6
Re-transplantation	772	1.6	359	2.0	363	1.4
Patients identified without the use of immuno-suppressive drugs in SUS	9,921	22.0	3,125	17.3	6,796	25.4

*Percentage refers to the total number of individuals with valid data.
b Glomerulonephritis/Interstitial Nephritis/Pyelonephritis.
*Loss of follow-up or right-censoring.

Comparing the groups of patients who received kidneys from living and deceased donors, it was observed that the distribution of patients considering age groups showed statistically significant differences. Among patients over 65 years old, the majority (86.5%) received transplants from deceased donors. The median age of the deceased donor group was higher than that of the living donor group (46 years vs. 37 years; $p < 0.001$). The median duration of dialysis prior to transplantation was greater in the deceased donor group, 47.0% vs. 27.0% (Table 1).

Survival Analysis

The analysis demonstrated kidney graft survival rates of 91.2%, 77.0%, 57.5%, and 42.1% at one, five, ten, and fifteen years, respectively. The median survival of kidney transplants in the country during this period was achieved at 12 years. Patients who received organs from living donors had a graft survival of 50.9% (95% CI: 49.1% to 52.6%), while patients who received organs from deceased donors had a survival rate of 31.8% (95% CI: 29.7% to 34.3%) over 15 years of follow-up. The median survival of kidney transplants from living donors was 15.6 years, while the median for deceased donor patients was 9.9 years (Table 2).

Potential Factors Associated with Kidney Graft Loss

The univariate analysis demonstrated an increased risk of graft loss for each additional year of the recipient's age (HR = 1.02; 95% CI: 1.01 to 1.03), for patients who underwent pre-transplant dialysis for more than 38 months (HR = 1.59; 95% CI: 1.30 to 1.95), for patients who received organs from deceased donors (HR = 1.88; 95% CI: 1.46 to 2.16), for those patients with diabetes (HR = 1.36; 95% CI: 1.25 to 1.48) and hypertension/cardiovascular diseases (HR = 1.09; 95% CI: 1.04 to 1.12) as the primary cause of CKD, and for patients who identified as black (HR = 1.54; 95% CI: 1.39 to 1.71). The graphical representation of the survival rates concerning the mentioned variables is shown in Figure 1.

Use of Immunosuppressive Medications

Among the patients who underwent transplantation, 37,303 (79.0%) used medications through SUS. The majority (50.8%) of the patients used tacrolimus + mycophenolate, 11.3% used cyclosporine + mycophenolate, 9.9% used cyclosporine + azathioprine, 9.7% used tacrolimus + azathioprine, 11.4% used monotherapy, and 6.9% used other regimens (Table 3).

The probabilities of graft survival for the most frequent therapeutic regimens during the follow-up of this cohort are presented in Figure 2. The difference in survival probability among these regimens was statistically significant ($p < 0.0001$). Regimens based on azathioprine (cyclosporine + azathioprine and tacrolimus + azathioprine) achieved the best survival probabilities (Figure 2).

Table 2. Survival Rate According to Donor Type. (Brazil: 2000-2015)

Follow-up Year	Survival Rate		
	Total adult population	Living Donor	Deceased Donor
1st	91.2 (90.9 – 91.4)	98.3 (98.1 – 98.5)	95.9 (95.7 – 96.2)
2nd	77.0 (76.6 – 77.5)	84.2 (83.6 – 84.8)	71.3 (70.6 – 72.0)
10th	57.5 (56.7 – 58.3)	66.8 (65.8 – 67.8)	48.2 (47.0 – 49.4)
15th	42.1 (40.8 – 43.4)	50.9 (49.1 – 52.6)	31.8 (29.7 – 34.0)

CI = Confidence Interval

Figura 1. Renal graft survival at 15 years of follow-up by the Kaplan-Meier method.

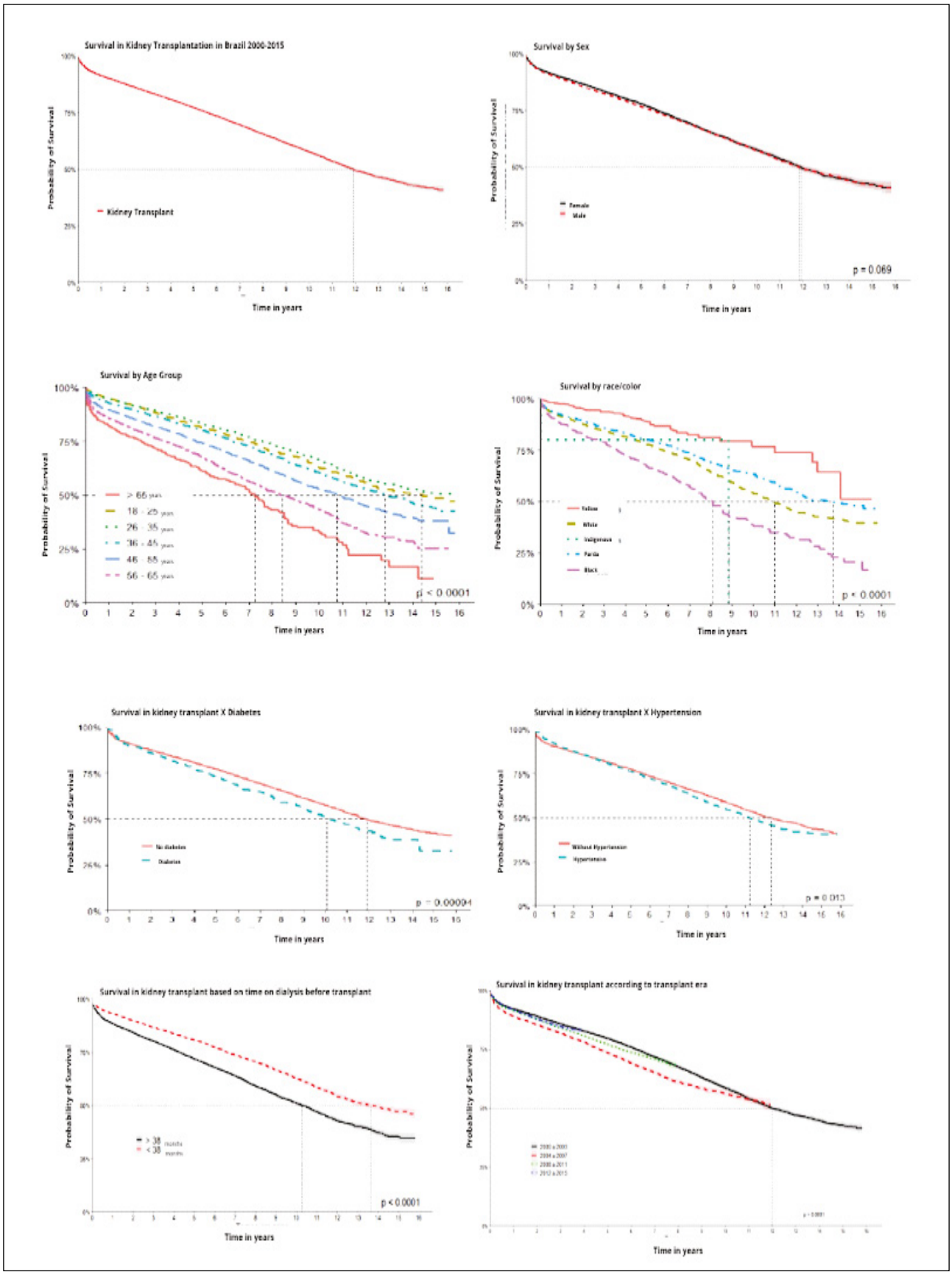
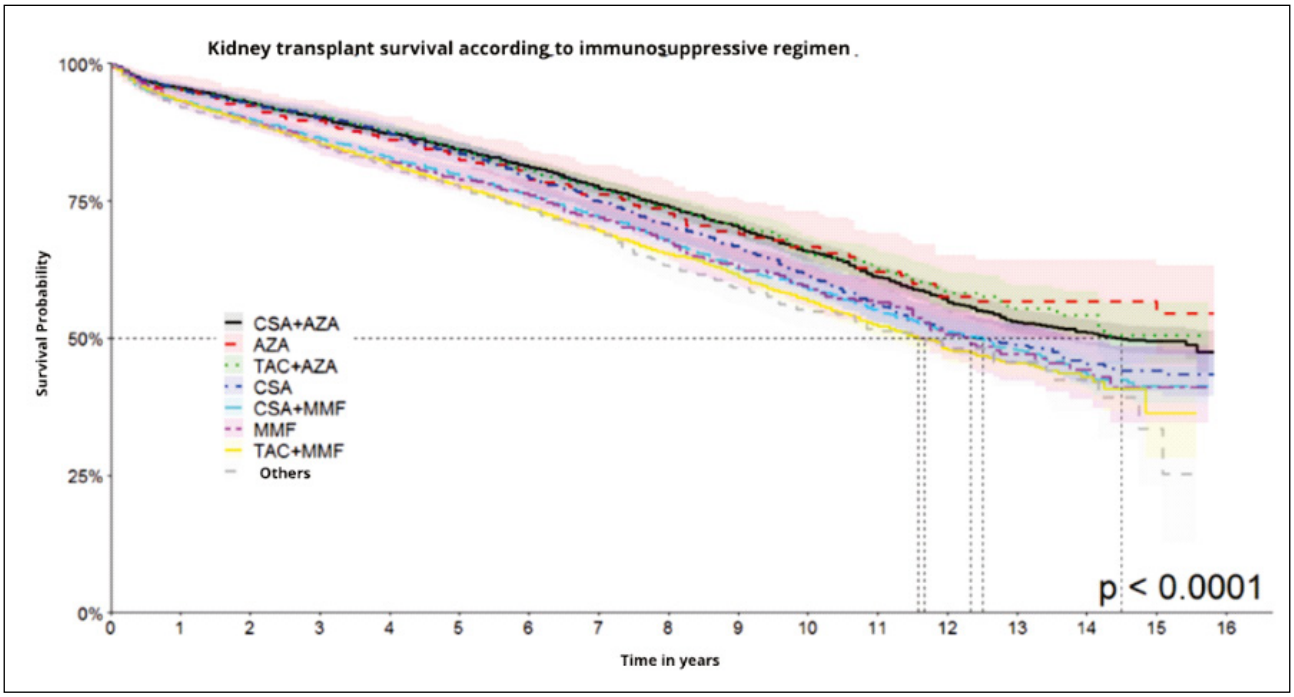


Table 3. Use of maintenance immunosuppressive medications in SUS. Brazil: 2000 to 2015 (N:37,303)

Therapeutic Regimen	Patients under treatment		
	n	%	Cumulative %
Tacrolimus + Mycophenolate	18,933	50.8	50.8
Cyclosporine + Mycophenolate	4,205	11.3	62.0
Cyclosporine + Azathioprine	3,685	9.9	71.9
Tacrolimus + Azathioprine	3,63	9.7	81.6
Mycophenolate	1,606	4.3	85.9
Cyclosporine	1,299	3.5	89.4
Tacrolimus	1,06	2.8	92.3
Azathioprine	296	0.8	93.1
Other regimens	2,589	6.9	100.0
Sirolimus + Mycophenolate	723	1.94	1.94
Tacrolimus + Everolimus	478	1.30	3.24
Everolimus + Mycophenolate	206	0.80	4.04
Sirolimus + Tacrolimus	228	0.61	4.65
Everolimus + Mycophenolate + Tacrolimus	164	0.44	5.09
Sirolimus	146	0.40	5.49
Sirolimus + Mycophenolate + Tacrolimus	118	0.32	5.81
Azathioprine + Mycophenolate + Tacrolimus	96	0.26	6.09
Azathioprine + Cyclosporine + Mycophenolate	60	0.16	6.23
Cyclosporine + Sirolimus	53	0.14	6.37
Others	227	0.53	6.90
Total	37,303	100	100

Figure 2. Probability of graft survival according to the therapeutic regimen



Multivariate Analysis

The multivariate analysis revealed that the variables of deceased donor status, an additional year of patient age, median dialysis time prior to transplantation exceeding 38 months, diagnosis of diabetes mellitus, and hypertension as the primary cause of chronic kidney disease (CKD) were associated with a higher risk of graft loss. Patients who utilized therapeutic regimens with mycophenolate exhibited an increased risk of graft loss, while regimens with azathioprine demonstrated graft protection. The analysis considering the type of donor followed the same trend as the overall analysis, with the variable of sex showing an association with the event (Table 4). The analysis of residuals indicated that the multivariate models exhibited good fit, with a mean close to zero and no violation of the homoscedasticity assumption.

Discussion

This nationwide cohort demonstrated an increase in the number of kidney transplants performed over the years since the implementation of the Brazilian Unified Health System (SUS), accompanied by changes in the donor profile and the use of immunosuppressive medications. The median survival of kidney transplants during this period was achieved at 12 years. The survival rate was higher among patients who received kidneys from living donors compared to those who received organs from deceased donors. In addition to the type of donor, clinical and demographic characteristics, as well as the type of therapeutic regimen, influenced graft survival, with the best results obtained from regimens containing azathioprine.

The profile of patients and transplant characteristics in this study is similar to those of previously published articles in Brazil.[18,19,10] There was an observed trend of increasing proportions of transplants from deceased donors compared to studies focusing on earlier periods.[10,18] Over the years, there has also been a significant increase in the use of tacrolimus at the expense of cyclosporine, as well as mycophenolate at the expense of azathioprine, mainly among patients who received kidneys from deceased donors. Previously published articles reported graft survival rates similar to those of this study.[25,26,27] In Turkey, the five-year survival rate was 85%;[25] in Taiwan, it was 84.7%;[25] and the ten-year survival rate was

Table 4. Multivariate Cox Analysis - Hazard Ratio for graft loss: Cox regression, Brazil: 2000–2015

Characteristics	Total		Living Donor		Deceased Donor	
	Hazard Ratio (CI 95%)	p-value	Hazard Ratio (CI 95%)	p-value	Hazard Ratio (CI 95%)	p-value
Type of transplant (deceased donor)	1.648 (1.550 - 1.730)	< 0.001	-	-	-	-
Median time of dialysis prior to transplantation (>38 months)	1.196 (1.142 - 1.268)	< 0.001	1.173 (1.065 - 1.251)	< 0.001	1.180 (1.178 - 1.356)	< 0.001
Age (additional year)	1.014 (1.011 - 1.015)	< 0.001	1.010 (1.008 - 1.013)	< 0.001	1.095 (1.008 - 1.011)	< 0.001
Sex (male)	1.022 (0.979 - 1.068)	0.314	0.912 (0.848 - 0.978)	0.0106	1.094 (1.035 - 1.156)	< 0.001
Primary diagnosis of CKD:						
Diabetes mellitus	1.257 (1.089 - 1.336)	< 0.001	1.356 (1.160 – 1.583)	< 0.001	1.207 (1.081 - 1.347)	< 0.001
Arterial hypertension/cardiovascular diseases	1.162 (1.140 - 1.259)	< 0.001	1.150 (1.071 - 1.234)	0.001	1.174 (1.112 - 1.240)	< 0.001
Entry therapeutic regimen:						
CSA + AZA	1.0		1.0		1.0	
TAC + MMF	1.151 (1.073 - 1.233)	< 0.001	1.387 (1.254 - 1.533)	< 0.001	0.976 (0.885- 1.076)	< 0.001
CSA + MMF	1.041 (0.964 - 1.136)	0.233	1.210 (1.077 - 1.359)	< 0.001	0.914 (0.818-1.021)	0.636
TAC + AZA	0.876 (0.794 - 0.968)	0.001	1.007 (0.871 – 1.164)	0.920	0.747 (0.651- 0.856)	< 0.001
CSA (monotherapy)	1.064 (0.956 - 1.362)	0.253	1.160 (1.001 – 1.344)	0.049	0.942 (0.806-1.102)	0.460
MMF (monotherapy)	1.187 (1.105 - 1.339)	< 0.003	1.132 (0.944 – 1.358)	0.179	1.156 (0.993 - 1.347)	< 0.061
TAC (monotherapy)	1.132 (1.162 - 1521)	< 0.001	1.238 (0.985 – 1.555)	0.066	1.269 (1.069 - 1.507)	< 0.006

CI: confidence interval
CSA: cyclosporine; TAC: tacrolimus; MMF: mycophenolate; AZA: azathioprine

77.7% in Greece.[26] Lower rates were reported in Iran (62.1%), Europe (56%), and three populations in the United States (46% for whites, 48% for Hispanics, and 34% for African Americans).[28] In Brazil, five-year graft survival varied between 46.5% and 93.1%, depending on the type of donor and the time when the transplant was performed,[10,19] and ten-year graft survival was 69.5%.[18] At 15 years, the projected survival was 57% for living donors and 32.7% for deceased donors in patients transplanted at a specialized center[22], values similar to those found in this study.

The analysis of factors associated with graft survival in the subgroups of living and deceased donors was similar to the overall analysis, with specificities regarding sex, causes of CKD, and immunosuppressive regimens. Recent studies have discussed the role of sex in kidney transplant outcomes, and there seems to be consensus that men present a higher risk of long-term graft loss compared to women.[26,29,30] However, these results are influenced by the type of donor and the sex matching between donor/recipient, with male survival potentially being greater than female survival when matching is performed.[29]

Older age has been associated with worse survival regardless of the type of donor (living or deceased) in this and previous studies.[18-19,30-31] These results may be related to age-related immunological changes[32], a higher occurrence of acute rejection, and a distinct HLA profile among older individuals[33], as well as a greater occurrence of other complications.[34]

Among the clinical variables, longer duration of dialysis prior to transplantation negatively influenced graft survival,[18-19,31] especially among deceased donors, in this and other studies.[22,35-36] Primary diagnoses of CKD, including hypertension and diabetes, were also associated with an increased risk of graft loss. Previous studies have reported that patients with diabetes have a lower likelihood of being transplanted and obtaining a kidney from a living donor,[36] as well as worse post-transplant outcomes.[18,19] Miscegenation is a demographic characteristic of the Brazilian population,[48] and its documentation has become mandatory in the information systems of SUS.[41] Patients who self-identified as black presented a higher risk of graft loss, and this finding is similar to a study[40] that evaluated factors associated with kidney graft loss in Brazil. The results suggest that additional efforts should be directed toward the development and implementation of policies/guidelines for monitoring specific groups, such as recipients of black ethnicity, as previously noted.[10]

This study indicated a higher concentration of transplants in more developed regions of the country, as reported in previous studies.[11,18] However, no relationship was found between graft survival rates and the macroregion where the transplant was performed, suggesting a better alignment in the quality of specialized kidney transplant healthcare services across the national territory, in accordance with the principle of decentralization of SUS. Additionally, the timing of the transplant did not translate into differences in clinical outcomes when assessed collectively, although this association has been described in international studies,[9,31] and national studies with shorter follow-up periods.[11,18] It is likely that factors related to the transplant technique, the type of immunosuppressive regimen, and access to medications have a greater impact in the early years post-transplant. Moreover, it is reasonable to assume that few changes have occurred in these factors in recent years, reducing the association between the timing effect and graft survival.

Regarding the results related to therapeutic regimens, it was observed that regimens combined with azathioprine showed a reduction in the risk of graft loss, while regimens combined with mycophenolate presented worse outcomes. The use of the tacrolimus + mycophenolate regimen notably increased over the years and, consequently, became the most frequent combination.This was also observed in a study involving over 50,000 patients in the United States.[7] However, the multivariate analysis found in this study showed that patients treated with this regimen exhibited a higher risk of graft loss in the overall analysis (HR = 1.15) and in the living donor group (HR = 1.38) compared to the cyclosporine + azathioprine regimen. These findings were similar to those found in other studies,[24,41] which also reported a higher risk of graft loss in the group of patients treated with tacrolimus + mycophenolate. The results of the present study suggest that immunosuppressive regimens combined with azathioprine should be encouraged, as they showed better long-term outcomes.

The Brazilian kidney transplant immunosuppression protocol[18] recommends the use of a triple immunosuppressive regimen. However, it was observed that 10.2% of the study population used regimens with only one immunosuppressant (monotherapy), indicating that the protocol recommendation was not followed for this population. Furthermore, the use of these medications in monotherapy, except for azathioprine, was associated with worse clinical outcomes.[43]

Based on the findings of this study, it is suggested that the decision regarding the use of the immunosuppressive regimen, in addition to considering effectiveness in preventing acute rejection, should also analyze safety and long-term outcomes. This is particularly important given the increasing recognition of chronic rejection as a significant cause of graft loss, the heterogeneity of the Brazilian population, and the high number of people waiting for a kidney transplant in the country. To deepen the evidence obtained, it is suggested that the long-term outcomes of these immunosuppressive regimens be evaluated through a matched analysis between groups, aiming to reduce baseline differences between patients and more robustly establish the effectiveness of immunosuppressive regimens.

Limitations

This study has limitations related to its design and the source of information. Additionally, clinical information that potentially affects graft survival, such as rates of acute rejection, immunological compatibility, ischemia times, and graft function in the first year after transplantation, were not available in our database. A notable strength is the large number of patients included (which encompassed nearly the entire population of the country undergoing kidney transplantation), representing the entire adult population that underwent kidney transplantation through SUS at the national level.

Conclusion

The median survival of kidney transplants was achieved at 12 years. The survival rate was higher among patients who received kidneys from living donors compared to those who received organs from deceased donors. In addition to the type of donor, clinical and demographic characteristics, as well as the type of therapeutic regimen, influenced graft survival. The results obtained provide an overview of kidney transplantation in the country, demonstrating effectiveness and progressive improvements, which may be useful for managers in the reassessment of guidelines and clinical protocols.

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