Kidney Transplantation at a Southern Brazilian University Hospital: A 35-Year Practice Review

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ABSTRACT

Background. The Nephrology Unit at São Lucas Hospital, a University Hospital in Southern Brazil, has recently reached 35 years since its first kidney transplant. Few centers in the area have made a longitudinal analysis of processes, problems, grafts, and patient survival changes along this time.

Methods. A single-center, retrospective study was performed. Data were separated into different eras, based on the nature of immunosuppression used: pre-cyclosporine (1978–1986), cyclosporine (1987–1997), mycophenolate introduction (1998–2002), new immunosuppressant drugs (2003–2007), and the current period (2008–2013).

Results. Between April 27, 1978, and April 30, 2013, 1231 transplants were performed. Significant differences were detected among different eras. The number of transplants has been progressively increasing, to include significantly older recipients (and donors), at a longer waiting list time, receiving organs that underwent longer cold ischemia time ($P < .001$). Yet, fewer acute rejection episodes and lower incidence of myocardial infarction and post-transplant diabetes mellitus ($P < .001$) were detected. In the present era, patient survival at 1, 3, and 5 years is 98.3%, 94.6%, and 90.5% respectively, for living donors, and 92.4%, 87.2%, and 80.7% for deceased donors, respectively. Living donor graft survival is 92.2%, 88.7%, and 82.4%, respectively, whereas deceased donor survival is 80.4%, 71.1%, and 63.7%, respectively.

Conclusions. This retrospective analysis has significant historical value. It assembles and depicts a long follow-up period of a transplant series at a single Brazilian center. Throughout the eras, organ and patient survival increased, with fewer rejection episodes or complications, yet with overall decreased graft function.

ALONG its evolution, kidney transplantation has presented physicians with different challenges in regard to changes in recipient and donor profiles, highly significant co-morbidities, unpredicted infectious and metabolic complications, as well as new immunosuppressive drug–combined use. Large kidney transplant series reports, from different centers, have been previously presented [1–6]. However, such records may have introduced a selection bias: not all centers report their information, and those who have better results and are usually more organized tend to report more consistently. To exemplify, the Brazilian Transplant Registry (ABTO) [7] only collects information from 53% of all the Brazilian kidney transplant centers. Very few individual centers report or compare their longitudinal experiences and results. Therefore, this study, by recording the transplant practice emergence and its development in a single teaching institution, may have historic and scientific justification.

METHODS

The study population comprised all patients undergoing a kidney transplant, from April 27, 1978, to April 30, 2013, at the hospital.

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Table 1. Patient Characteristics According to Different Transplant Eras

	Total n = 1231	Pre-CyA n = 62	CyA n = 286	MMF n = 209	NIA n = 280	Current n = 394	*P*
Age, years, mean ± SD	39.9 ± 16.1	33.2 ± 13.3	36.5 ± 13.8	38.3 ± 15.4	38.6 ± 16.8	45.3 ± 16.3	<.001[†]
Stratified age, n (%)							
<18 Years	138 (11.2)	7 (11.3)	37 (12.9)	27 (12.9)	42 (15)	25 (6.3)	<.001[*]
19–59 Years	954 (77.5)	53 (85.5)	238 (83.2)	171 (81.8)	209 (74.6)	283 (71.8)	
60–69 Years	116 (9.4)	2 (3.2)	11 (3.8)	10 (4.8)	26 (9.3)	67 (17.0)	
>70 Years	23 (1.9)	0 (0)	0 (0)	1 (0.5)	3 (1.1)	19 (4.8)	
Male, n (%)	687 (55.8)	42 (67.7)	161 (56.3)	128 (61.2)	133 (47.5)	223 (56.6)	.14[*]
Deceased, n (%)	943 (76.6)	32 (51.6)	214 (74.8)	155 (74,2)	212 (75,7)	330 (83.8)	<.001[*]
Pre-Tx HD, media (IR)	22 (10–47)			20.5 (10–42)	26 (8.3–55)	27 (12–52)	<.001[‡]
Donor age, years, mean ± SD	38 ± 15.6	29.5 ± 12.4	31.7 ± 12.8	34.1 ± 13.5	38.4 ± 15.5	42.1 ± 16.3	<.001[†]
ECD, n (%)	131 (17.7)			10 (8.6)	29 (11.6)	92 (24.7)	<.001[†]
Ischemic time, hours, mean ± SD	18 (3–24)			16.3 (1.7–23)	18.2 (12.1–22)	23 (15.7–28.9)	<.001[‡]
DGF, n (%)	461 (46.5)	8 (26.7)	48 (39.7)	83 (48.8)	120 (43.3)	202 (51.3)	.006[*]
Ureteral catheter, n (%)	451 (36.6)	0 (0)	2 (0.7)	43 (20.6)	157 (56.1)	249 (63.2)	<.001[*]
Lymphocele, n (%)	140 (13.5)	2 (9.1)	43 (26.9)	30 (16)	38 (13.8)	27 (6.9)	<.001[*]
Hematoma, n (%)	210 (20.6)	4 (17.4)	23 (16.1)	48 (26.5)	60 (21.5)	75 (19)	.91[*]
Urinary fistula, n (%)	53 (5.2)	3 (13)	15 (10.3)	9 (4.9)	15 (5.4)	11 (2.8)	<.001[*]
Ureter stenosis, n (%)	70 (6.8)	1 (4.8)	14 (9.5)	16 (8.6)	21 (7.5)	18 (4.6)	.04[*]
Acute rejection, n (%)	351 (28.7)	12 (19.4)	112 (39.2)	68 (32.5)	85 (30.4)	74 (18.8)	<.001[*]
CMV disease, n (%)	227 (22)	0	32 (22.1)	52 (26.9)	71 (25.4)	72 (18.3)	.46[*]
BKVN, n (%)	19 (1.9)	0	0	0	6 (2.1)	13 (3.3)	.002[*]
Herpes virus, n (%)	187 (15.2)	6 (9.7)	33 (11.5)	52 (24.9)	60 (21.4)	36 (9.1)	.42[*]
Fungal infection, n (%)	122 (12)	2 (10)	25 (17.5)	25 (13.7)	32 (11.4)	38 (9.6)	.02[*]
Pyelonephritis, n (%)	415 (40.5)	6 (28.6)	52 (36.9)	79 (41.4)	135 (48.4)	143 (36.4)	.99[*]
Pneumonia, n (%)	222 (22)	4 (20)	36 (26.1)	54 (29.8)	68 (24.4)	60 (15.3)	.001[*]
Meningitis, n (%)	29 (2.9)	2 (10)	8 (6)	9 (4.8)	6 (2.1)	4 (1)	<.001[*]
Tuberculosis, n (%)	51 (5)	4 (21.1)	19 (13.6)	5 (2.7)	15 (5.4)	8 (2)	<.001[*]
Myocardial infarct, n (%)	42 (4.1)	1 (5)	15 (10.1)	8 (4.4)	9 (3.2)	9 (2.3)	<.001[*]
Stroke, n (%)	41 (4)	2 (9.5)	4 (2.8)	16 (8.6)	12 (4.3)	7 (1.8)	.02[*]
NODM, n (%)	131 (12.6)	3 (13)	27 (17.8)	31 (16.2)	41 (14.8)	29 (7.4)	<.001[*]
Neoplasia, n (%)	107 (10.2)	9 (31)	38 (24.5)	18 (9.6)	24 (8.6)	18 (4.6)	<.001[*]

Abbreviations: CyA, cyclosporine; MMF, mycophenolate; NIA, new immunosuppressive agents; SD, standard deviation; IR, interquartile range; HD, hemodialysis; Tx, transplant; ECD, expanded-criteria donors; NODT, new-onset diabetes mellitus.
[*]Mantel-Haenszel χ^2.
[†]ANOVA.
[‡]Kruskal-Wallis test.

Patient data were recorded at transplantation, and follow-up was maintained until graft loss, death, or loss to follow-up. Additionally, a retrospective review of all medical records was performed to check for flaws and to add information to recorded data.

Demographic characteristics of donors and recipients and surgical data were collected; the evolution of the renal function was assessed, as well as the occurrence of early and late complications, for a minimum of 1 year. Patients were allocated to different eras, depending on the initial immunosuppression design used. The first period, or "pre-cyclosporine" (pre-CyA), going from 1978 to 1986, used high corticosteroid doses associated with azathioprine. The second period, "cyclosporine" (CyA), encompassing 1987 to 1997, used a triple-immunosuppression regime: cyclosporine, azathioprine, and prednisone. The sequence period, "mycophenolate" (MMF), extending from 1998 to 2002, witnessed azathioprine being substituted by mycophenolate in a triple-therapy regimen that used either tacrolimus or cyclosporine. The age of "new immunosuppressive agents" (NIA), extending from 2003 to 2007, corresponds to a period of many different schemes, using mycophenolate acid precursors associated with either calcineurin inhibitors or m-Tor inhibitors, with or without steroids. Finally, the "current era" (CE), covers the last 5 years, in which thymoglobulin has been prescribed to 86% of transplanted patients; it corresponds to a more complex period, with older recipients and the extensive use of expanded-criteria donors.

Continuous variables with normal distribution are expressed as mean and standard deviation (SD); variables with skewed distribution are presented as median and interquartile range. Kolmogorov-Smirnov and Shapiro-Wilks tests were performed to ascertain distribution normality. The Student *t* test or Mann-Whitney *U* test was used to verify differences between 2 groups of continuous variables. Categorical variables were presented as frequency or percentage. The χ^2 test was used to compare 2 groups of categorical variables. To compare 2 or more groups of variables, analysis of variance (ANOVA) was used for continuous normally distributed variables and the Kruskal-Wallis test was used for continuous skewed variables. In survival analysis, Kaplan-Maier survival curves were used, and the differences between them were assessed through the bilateral log-rank test. Multivariate analysis of the last 10 years of transplant, using Poisson regression with robust variance, was used to quantify risk factors for graft and patient survival (as outcomes) and their relationship with the predictor

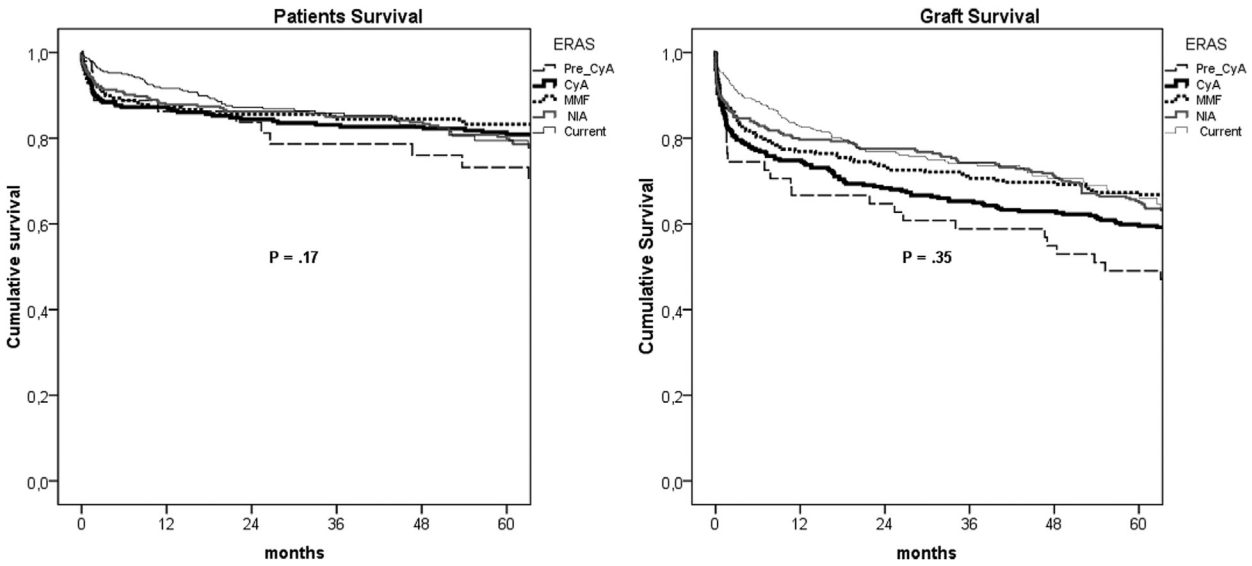

Fig 1. Patient and graft survival by eras, along the follow-up period.

variables (age, sex, living or deceased donor, extended-criteria donors, delayed graft function [DGF], acute rejection, ischemia time, and pyelonephritis within 30 days of transplant). Data were logged on a computer spreadsheet (Microsoft Excel for Mac 2011 version 14.0.0 Redmond, Wash, USA); a Statistical Package for Social Sciences (SPSS for Macintosh, version 22, IBM Corp, Armonk, NY, USA) statistical package was used in all statistical computations. A value of $P < .05$ was considered statistically significant.

RESULTS

During the examined time interval, 1231 transplants were performed. A majority of the recipients were male (55.8%) and Hispanic (86.9%), mostly receiving organs from deceased donors (76.6%), at a mean age of 39.9 ± 16.1 years. The youngest transplanted patient was a 16-month-old infant and the oldest was a 74-year-old man. The recipient was under the age of 18 years in 138 (11.2%) transplants; in 116 (9.4%) between 60 and 69 years; and in 1.9% above 70 years. The deceased transplant donors' main cause of death was trauma (40.9%), ischemic or hemorrhagic stroke (32.9%), subarachnoid hemorrhage (15.6%), anoxic encephalopathy (4%), brain tumor (3.5%), and others (3.1%). From all kidney transplants performed in the period, 615 (50%) underwent graft loss. Otherwise, the leading cause of graft loss was death with graft function, followed by chronic nephropathy, primary loss, acute rejection, and infection. There were 286 (23.2%) deaths, the main causes being infectious diseases (52.1%) and cardiac disease (15.7%). Patient survival rates at 1, 3, and 5 years were 89.6%, 86%, and 82.8%, respectively, and graft survival rates were 78.4%, 70.3%, and 63.4%, respectively. Patient survival rates for kidneys from living donors were 95.5%, 93.3%, and 91% for 1, 3, and 5 years, respectively, and overall graft survival rates were 85.5%, 78.2%, and 72.6% for 1, 3, and 5 years, respectively. For deceased donor organs, patient and graft survival rates were 85% and 76.2% at 1 year, 85% and 71.2% at 3 years, and 80.3% and 60.4%, at 5 years, respectively.

When the different eras were compared (Table 1), it was evident that the patient mean age significantly and progressively increased throughout the eras ($P < .001$). In the current era, 19 of the 23 transplants were done with recipients older than 70 years, and the percentage of deceased donors has reached 87.6%, also significantly ($P < .001$) different along the eras. Donor mean age has also significantly ($P < .001$) increased to 42.1 ± 16.3 years. Of course, surgical technique has also undergone significant changes throughout the eras. Cold ischemia time has progressively increased ($P < .001$), particularly during the last 3 eras. The percentage of DGF has also progressively increased, currently encompassing a majority (51.3%; $P = .006$) of transplanted organs. Acute rejection episodes now occur in 18.8% of the transplants and has decreased progressively and significantly ($P < .001$), with a clear trend of being progressively lower throughout the eras. In the pre-CyA period, its incidence was 19.4%, but it was possibly underestimated. In CyA, MMF, and NIS eras, rejection incidence progressively decreased, going from 39.2% to 32.5% and 30.4%, respectively. With regard to complications, development of lymphocele was significantly ($P < .001$) less frequent in the early eras, except in the pre-CyA period. Incidence of urinary fistulas decreased from 13% to 2.8% ($P < .001$), possibly related to the significantly more frequent (63.2%; $P < .001$) use of surgically placed temporary ureteral catheters. The incidence of viral infectious complications (cytomegalovirus [CMV] and herpes virus) was not different throughout the eras ($P = .46$ and

.42), but there appears to be a tendency to decreasing over the last 3 eras—currently 18.3% and 9.1%, respectively. The occurrence of bacterial pneumonia and fungal infections was higher in the first 2 eras, yet gradually decreasing in the last 3, with current incidence at 9.6%. Tuberculosis occurrence decreased from 21.1% to 2% and meningitis from 10% to 1% ($P < .001$) along the eras. Polyomavirus nephropathy (BKVN) has made its appearance only in the last 2 eras, with an incidence of 2.1% and 3.3%, consistent with previous reports (between 1.1% and 8.0%) [8,9]. Acute myocardial infarction, stroke, and new-onset diabetes mellitus incidence has decreased in recent eras, being currently at 2.3%, 1.8%, and 7.4%, respectively. Neoplasia has also significantly decreased over time, from 31% to 4.6% ($P < .001$).

Survival analysis showed no significant difference on patient and graft survival among the different eras (Fig 1). Graft survival at 5 years was lower in pre-CyA (49%) and CyA (59.5%), compared with MMF (66.8%), NIA (65%), and CE (67.1%), yet with no statistical significance ($P = .35$).

Multivariate analysis of the past 10 years (n = 674) disclosed age (odds ratio [OR], 1.005; 95% confidence interval [CI], 1.003–1.007, $P < .001$), pyelonephritis within 30 days (OR, 1.096; 95% CI, 1.010–1.190, $P = .028$), and DGF (OR, 1.074; 95% CI, 1.012–1.139, $P = .018$) as risk factors for patient survival. For graft survival, DGF (OR, 1.768; 95% CI, 1.369–2.284, $P < .001$) and acute rejection (OR, 1.356; 95% CI, 1.032–1.782, $P = .029$) were identified as risk factors.

DISCUSSION

A Brazilian poet once said: "Time does not stop; only nostalgia makes things stop in time." We live in the present, yet we are shadowed by the past. To review one's own history may improve one's present day and point the course to a more rewarding future. This study is, in some ways, a halt in time to relive, in a nostalgic sense, a history of kidney transplantation written over a 35-year period by a particular group of physicians in a singular hospital. It includes a significant number of patients with a long follow-up period, subject to data measurement bias and exposure to different factors, at different times. Large previously published series have mostly been multicenter surveys or data records from transplant societies, an exception to the São Paulo University Kidney and Hypertension Hospital, currently the world's largest kidney transplant center, which can review large series of transplanted patients in a very short time.

CONCLUSIONS

This study presents a significant number of patients with a long follow-up period, subject to data measurement bias and exposure to different factors, at different time points. Review of these data re-assures the learning curve and improvement of medical practice over time.

This is was a retrospective study covering a 35-year experience on kidney transplantation at Hospital São Lucas. Graft survival and long-term kidney function were different along these eras. There was worse kidney function in the past eras, but with significantly better survival. The number of early and late complications was different along the eras, with a tendency to decrease over the years. It is risky to compare this study with others in the literature because of differences in sample characteristics and especially by the type of data search.

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