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ORIGINAL ARTICLE

# Infectious complications as the leading cause of death after kidney transplantation: analysis of more than 10,000 transplants from a single center

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**Abstract**
*Aim* To identify specific causes of graft failure in a large sample of kidney transplant patients from a middle-income, developing country.
*Methods* Retrospective cohort study analyzing all consecutive single kidney transplants (KTs) performed at a single center in Brazil between January 1st 1998 and December 31st 2013. The database closing date was December 31st 2014.
*Results* Out of 10,400 KTs, there were 1191 (11.45%) deaths with a functioning graft, 40 cases (0.38%) of primary non-function (PNF) and 1417 cases (13.62%) of graft loss excluding death and PNF as the cause. Infectious complications (404 cases, 34% of all deaths) were the major cause of death. Most deaths due to infection occurred within the first year after transplantation (157 deaths, 38.86%). Immunologic mechanisms, comprising acute rejection and immune-mediated interstitial fibrosis/tubular atrophy (IF/TA), were responsible for 52% of all cases of graft failure not involving recipient death. Half of the losses by acute rejection occurred late after transplantation.
*Conclusion* Contrary to what is observed in developed countries, infectious complications are the main challenge with kidney transplantation in Brazil. Non-adherence to treatment also appears to contribute significantly to long-term kidney graft loss. Strategies for improvement should focus on better compliance and a greater safety profile of immunosuppressive treatment.

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**Keywords** Kidney transplantation · Patient survival · Graft loss · Infectious diseases · Acute rejection

## Introduction

Kidney transplantation is the best treatment option for patients with end-stage renal disease (ESRD). It is well known that patient and graft survival are influenced by several variables related to inherent recipient, donor and transplant characteristics [1–3]. The local health system as well as the environment also influence these demographic characteristics and the associated outcomes [4, 5]. Even in countries with a public healthcare universal cover that provides for free laboratory tests, appointments and medication, the long-term adherence to prescribed therapies is poor, due to other factors such as socio-economic, educational and cultural aspects. The local environment also plays an important role since endemic and opportunistic diseases may complicate the post-transplant course. Even if patients at risk at the time of transplantation are identified and proper prophylactic measures are implemented, most patients will return to their local environment, increasing the risk of repeated exposure to local pathogens.

Despite improvements in short- and medium-term outcomes, long-term survival has made only moderate progress over the years [6]. In developed countries, this lack of improvement is explained by premature graft loss due to patient cardiovascular death, chronic allo-immunity leading to interstitial fibrosis/tubular atrophy (IF/TA), and glomerular pathologies [7, 8]. On the other hand, in developing countries, the available data are scarce. Because of the poor socioeconomic and nutritional features of the population on the waiting list for kidney transplantation and the presence of a high number of nationally endemic infections, it

is possible that long-term results are different compared to those found in high-income countries. Thus, the aim of this study was to analyze the specific causes of graft failure and recipient death at a single center from a developing country.

## Methods

### Study design and sample

This was a single-center, retrospective cohort study that analyzed data from all first kidney transplants performed between January 1st 1998 and December 31st 2013 in Sao Paulo, Brazil. Multi-organ transplants were excluded from this analysis. The study design was reviewed and approved by the local Ethics Committee. All patients were followed until the last medical visit or until graft loss or death, whichever occurred first. The database closing date was December 31st 2014. All data were collected through review of medical records, and all graft losses and deaths were adjudicated.

### Definitions

Graft loss was defined as a permanent absence of renal function due to the recipient's death or irreversible graft injury requiring chronic dialysis and/or re-transplantation. The timing of graft loss was considered as the start of the renal replacement therapy; graft nephrectomy; re-transplant; or the patient's death. Death-censored graft failure was classified in accordance with El-Zoghby et al. [7], except for technical issues, which were defined as graft surgical removal due to nonimmune arterial or venous thrombosis, lymphocele, or urinary fistula in the initial days after transplantation. Primary non-function (PNF) was defined as the permanent absence of graft function, starting immediately after transplantation, the preceding causes excluded. Specific causes of death were described as the underlying cause stated in the patient's death certificate. Non-adherence was expressed as a well-documented physician remark in the patient's file.

### Statistical analysis

Continuous variables were expressed as the mean and standard deviation, and categorical variables as frequency and percentage. For numerical variables analysis, we used Student's t-test. To compare proportions, we used the Chi square test. Survival curves were obtained using the Kaplan–Meier method, and comparisons were carried out by Log-rank test (Mantel–Cox). Statistical analyses were performed by SPSS program v. 18.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 6.00 for Mac OSX (GraphPad Software, La Jolla, California, USA, http://www.graphpad.com). Statistical significance was assumed at $p < 0.05$.

## Results

From January 1st 1998 to December 31st 2013, 10,837 transplants were performed. Of these, 437 were simultaneous multi-organ transplants and were thus excluded from analysis. Of the 10,400 kidney transplant recipients, most subjects were middle-aged Caucasian men with unknown ESRD etiology. Living donor transplants were more prevalent than deceased donor transplants. Diabetic nephropathy was the 5th most common etiology of ESRD in this group. Detailed demographic characteristics are presented in Table 1.

**Table 1** Demographic characteristics of the study population

| Characteristics | | Valid |
|---|---|---|
| Age, years | 40.8 ± 14 (2–80) | 10,289 |
| Male, n (%) | 6296 (61%) | 10,400 |
| Race, n (%) | | 10,052 |
| Caucasian | 6161 (61%) | |
| Mixed | 1381 (14%) | |
| Black | 2304 (23%) | |
| Other | 206 (2%) | |
| CKD etiology, n (%) | | 10,060 |
| Diabetes mellitus | 930 (9%) | |
| Hypertension | 1042 (10%) | |
| Polycystic kidney disease | 733 (7%) | |
| Glomerular disease | 2428 (25%) | |
| Unknown | 3674 (37%) | |
| Miscellanea | 1253 (12%) | |
| RRT, n (%) | | 10,080 |
| Hemodialysis | 8424 (83.5%) | |
| RRT duration, months | 37.1 ± 38.4 (0–360) | 9595 |
| Deceased donor, n (%) | 4996 (48%) | 10,400 |
| Donor age, years | 40.3 ± 17.1 (0–80) | 10,013 |
| Cold ischemia duration, hours | 22.8 ± 7.4 (5–49) | 1335 |
| Donor's death type | | 4565 |
| Cerebrovascular | 2491 (55%) | |
| Trauma | 1693 (37%) | |
| CNS tumor | 69 (2%) | |
| Other | 312 (6%) | |
| Induction therapy | | 10,082 |
| None | 6911 (69%) | |
| Anti-lymphocyte antibody | 1241 (12%) | |
| Anti-interleukin 2 antibody | 1930 (19%) | |

*CKD* chronic kidney disease, *RRT* renal replacement therapy, *CNS* central nervous system

During a mean follow-up of 71.4 ± 51.5 months (median 61.4 months, range 0–203.5), 2648 (25.46%) grafts were lost: 1191 (45%) due to death with a functioning allograft, 40 (1.51%) due to PNF and 1417 (53.51%) due to graft loss excluding death. The overall survival results are depicted in Fig. 1. For living donor transplants, patient survival was 94.2% at 5 years, 89.6% at 10 years and 82.8% at 15 years; death-censored graft survival was 92.9% at 5 years, 85.1% at 10 years, and 76.4% at 15 years. For deceased donor transplants, patient survival was 84.9% at 5 years, 74.2% at 10 years and 63.1% at 15 years; death-censored graft survival was 83.8% at 5 years, 74% at 10 years and 59.4% at 15 years. A comparison of these findings with data from the current international literature is reported in Table 2.

### Graft loss due to recipient's death

Death with a functioning allograft was the most common cause of graft loss, representing 1191 out of 2648 losses (45%), and 11.45% of the total number of transplants

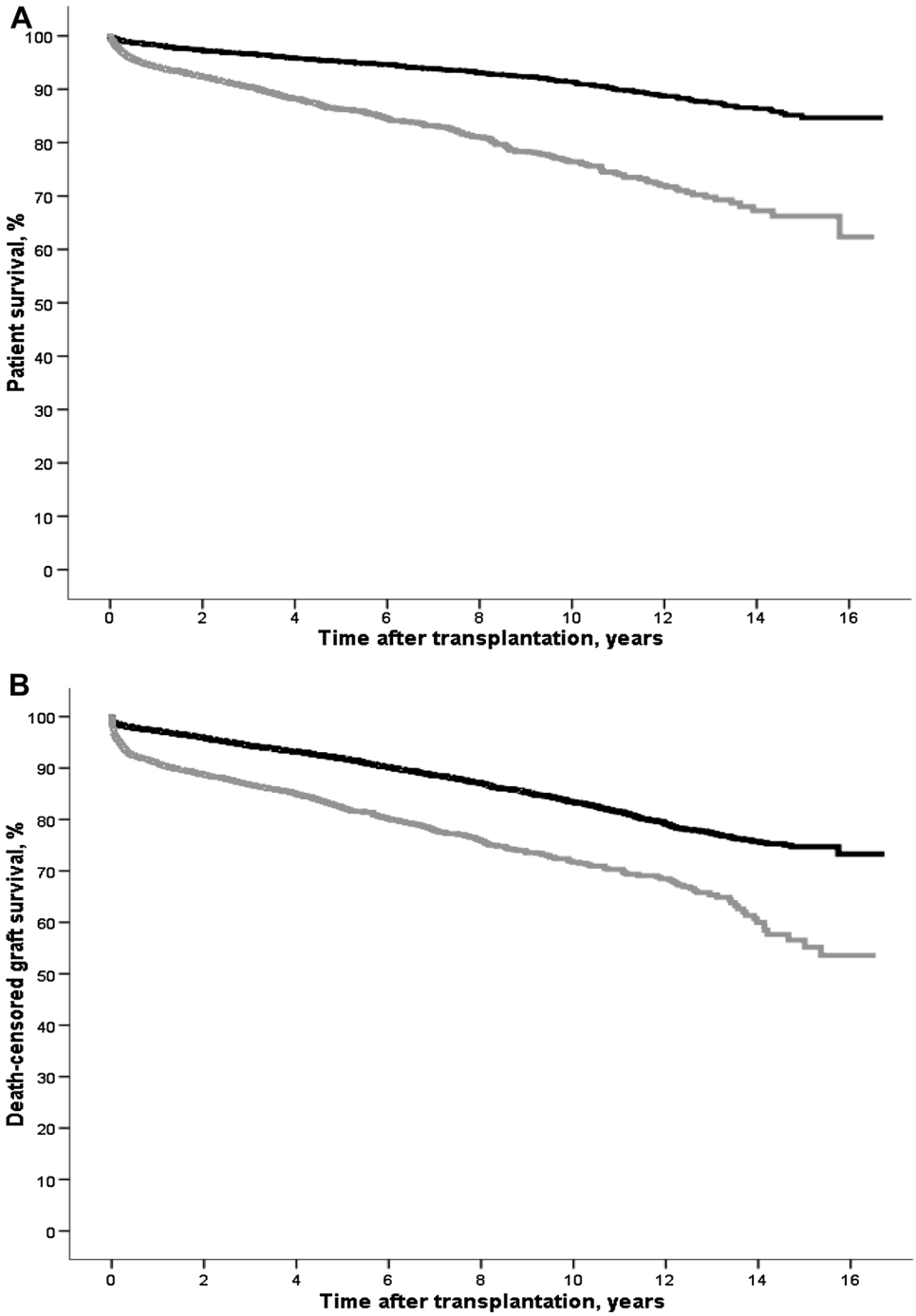


**Fig. 1** **a** Patient survival according to donor type. **b** Death-censored graft survival according to donor type (*grey* deceased donor, *black* living donor)

**Table 2** Unadjusted international comparison regarding overall graft and patient survival after first kidney transplantation: results from the Brazilian center versus North American, Australia and New Zealand and European data

| | Brazilian center | ERA-EDTA[a] | US[a] | ANZ[a] |
|---|---|---|---|---|
| Graft survival—living donor, % | | | | |
| 1 year | 93.5 | 95.8 | 97.2 | 98 |
| 5 years | 84.7 | 86.9 | 84.6 | 90 |
| 10 years | 73.5 | NA | NA | NA |
| Graft survival—deceased donor, % | | | | |
| 1 year | 87.3 | 90.7 | 93.7 | 95 |
| 5 years | 73.1 | 77.8 | 72.4 | 81 |
| 10 years | 57.7 | NA | NA | NA |
| Patient survival—living donor, % | | | | |
| 1 year | 98 | 98.6 | 98.7 | 99 |
| 5 years | 94.2 | 94.3 | 93.1 | 95 |
| 10 years | 89.6 | NA | NA | NA |
| Patient survival—deceased donor, % | | | | |
| 1 year | 93.5 | 96 | 97 | 98 |
| 5 years | 84.9 | 87.1 | 86.1 | 90 |
| 10 years | 74.2 | NA | NA | NA |

*ERA-EDTA* European Renal Association-European Dialysis and Transplant Association 2013 Annual Report, *US* United States, *ANZ* Australia and New Zealand, *NA* non-available

[a]Extracted from reference [5]

during follow-up. The causes of death are illustrated in Table 3. Death with a functioning graft was more prevalent among deceased than living donor recipients (14.3 and 8.7%, respectively, $p < 0.0001$). Figure 2a shows the impact of the most frequent causes of death on patient survival

**Table 3** Unadjusted international comparison regarding causes of recipients' death and allograft loss: Brazilian center versus North American data

| | Brazilian center (%) | United States (%)[a] |
|---|---|---|
| Causes of recipient death | | |
| Infection | 34 | 15.2 |
| Cardiovascular | 21 | 28.2 |
| Neoplasia | 11 | 13.8 |
| Other | 16.2 | 11.6 |
| Unknown | 17.8 | 31.2 |
| Causes of graft loss | | |
| Acute rejection | 18.6 | 11.8 |
| Glomerular disease | 12.2 | 36.6 |
| Fibrosis/atrophy (IF/TA) | 43.3 | 30.7 |
| Other and technical issues | 21.8 | 16.3 |
| Unknown | 4.1 | 4.6 |

[a]Extracted from reference [7]

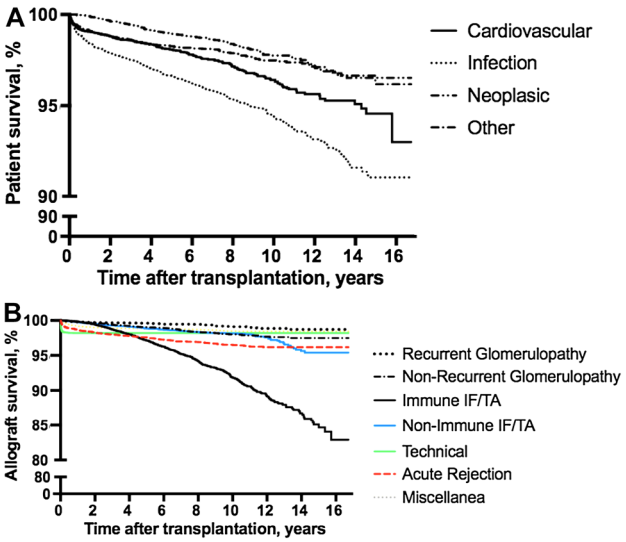


**Fig. 2** **a** Actuarial patient survival according to the main causes of death. **b** Actuarial death-censored allograft survival according to the main causes of graft loss

over time. Infectious complications were the major factors responsible for these occurrences, 404 (34%) events overall. Most deaths due to infection occurred within the first year after transplantation (157 deaths, 38.86%), but such complications were present throughout the study period. Cardiovascular events were the second most prevalent cause of death (250 out of 1191 cases, 21%) and had a greater impact later after transplant. Neoplasia was responsible for 132 (11%) deaths, and it reached its highest rate (15.8%) after 5 years from transplantation. Other etiologies such as pancreatic, hepatic, metabolic and external factors were responsible for 193 (16.2%) deaths. In 212 (17.8%) cases, the data available were insufficient to deduce the cause of death. Table 3 compares the main causes of death found in the present study with the data presented in the classical American report by El-Zoghby et al. [7].

## Graft loss excluding death

The causes of graft loss, excluding recipient death, are also illustrated in Table 3. PNF was responsible for 40 (1.5%) out of 2648 losses representing 0.38% of total transplants. There were 1417 cases of graft loss excluding death and PNF, representing 53.5% of all losses and 13.62% of all transplants. The influence of the causes of death-censored graft loss over time is depicted in Fig. 2b. Losses due to acute rejection occurred earlier than those associated with IF/TA and glomerular disease. Graft failure risk due to IF/TA increased progressively after transplantation.

Acute rejection was responsible for 264 (18.6%) out of 1417 cases representing 2.53% of all transplants. Poor

patient adherence to the immunosuppressive regimen was well documented in 60 cases of late graft failure (>1 year) due to acute rejection. There were only four cases related to hyperacute rejection and 6 to acute antibody-mediated rejection in this cohort. Glomerular diseases were responsible for 173 (12.2%) cases of death-censored loss, representing 1.66% of all transplants. Recurrent disease was responsible for 56 (4%) out of 1417 lost grafts. The other 117 (8.2%) cases could not be classified as recurrent and were presumed to be "de novo".

IF/TA was recognized as the cause of graft failure in 614 (43.3%) cases of death-censored graft loss, representing 5.9% of total transplants. Most cases (473 losses, 77%) could be attributed to immunological phenomena such as recurrent acute cellular rejection and chronic antibody-mediated rejection episodes. Poor patient adherence to the immunosuppressive regimen was well documented in 18 cases. In 141 cases, there were no immunological components identified, and these cases were attributed to polyomavirus nephropathy, recurrent urinary tract infections, severe donor lesions and urinary obstruction.

Other medical and surgical conditions were responsible for 120 cases (8.4% out of 1417 lost grafts, 1.15% of total transplants). Among them were 30 cases of thrombotic microangiopathy, 23 cases of acute pyelonephritis, 18 cases of abandonment of immunosuppression due to the patient's subjacent condition, 9 cases of late idiopathic graft thrombosis, 6 cases of severe graft artery stenosis, 6 of graft biopsy complications, 6 of primary oxalosis, 5 cases of severe sepsis, 4 cases of primary graft neoplasms, 3 cases of graft tuberculosis, 3 of mechanical trauma, 2 cases of graft fungal infection, 2 of severe congestive heart failure, 1 case of cortical necrosis, 1 of diabetic nephropathy and 1 of renal infarction due to embolism and subsequent occlusion of the graft artery.

## Discussion

The present study describes the long-term results of kidney transplantation, with a focus on the causes of graft loss and recipient death in a large cohort of recipients from a middle-income country.

First of all, overall graft and recipient survival rates were at least comparable to those reported by other well-established transplant programs from developed countries [9, 10]. Some of the explanations for these results may reside in distinct government healthcare policies and striking differences in patients' individual sociodemographic characteristics. Contrary to the Brazilian health care system, which provides universal access to health services and medications, current U.S. Medicare coverage for immunosuppressive drugs abruptly ceases at 3 years after kidney transplantation for all Medicare patients [4, 11]. Although poverty has a strong negative impact on health outcomes [12], income-related disparities between patients from both countries seem to be eliminated from extended coverage programs, resembling what Woodward et al. demonstrated before [13].

Death with a functioning allograft was the single leading event responsible for graft loss, representing 45% of all grafts lost. Although cardiovascular and neoplastic occurrences were pivotal causes of death among transplant subjects in the American and Australian reports [9, 10], the most common underlying cause of death in our study was infectious complications. It is of note that infection also determined some death-censored graft losses. At least two reasons could explain these findings. Firstly, patients in the present study were relatively younger and had a smaller proportion of ESRD due to diabetic nephropathy than the American and Australian cohorts. These are two well-known risk factors related to cardiovascular death among transplanted subjects [5, 14]. Secondly, and perhaps more important, there is a high prevalence of several infectious diseases in Brazil such as tuberculosis, systemic protozoal infections, toxoplasmosis, and cryptococcosis, including among kidney transplant recipients [15–17], and a higher mortality rate from infection in Caribbean and Latin American countries compared to developed countries [18]. Although overimmunosuppression is a well-known risk factor associated with infection in transplanted patients, the majority of subjects in this study did not receive any type of induction therapy and were receiving either cyclosporine or azathioprine.

Higher initial and maintenance doses of steroids are another risk factor related to death by infection among transplanted patients. However, even in the recent era, in which faster tapering of lower initial steroid doses is practiced, death by infectious disease prevailed over cardiovascular causes, regardless of the time since transplantation.

Chronic immunological damage has been demonstrated to have an additive and independent impact on graft outcome [8]. Immunologic mechanisms, comprising acute rejection and immune-mediated IF/TA, were responsible for more than half of the graft failure cases excluding recipient death, findings similar to those observed in the classical American study [7]. The risk of graft loss due to acute rejection remained significant over time since half of the losses by this mechanism occurred late after transplantation. The importance of late acute rejections worsening transplantation outcomes has been well-recognized [19, 20]. Poor adherence to the immunosuppressant regimen is an important risk factor for late immunologic graft loss [21]. The well documented 78 cases clearly underestimate the perceived number of graft losses due to poor adherence. In the present study, only a few cases of graft loss could

not be attributed to a specific cause, supporting the abandonment of previous concepts such as "chronic allograft nephropathy" to explain a graft's deteriorating process [7].

The main strengths of this study are the large sample size, the clinical and histopathologic evaluation of the cases and the long observation time. Limitations include its retrospective nature and the unavailability of data on donor-specific antibodies in all cases, which may underestimate the impact of the humoral arm of the chronic renal allograft loss.

## Conclusion

Unlike what is observed in developed countries, this large Brazilian cohort demonstrated that infectious diseases are one of the main challenges regarding kidney transplantation. In addition, non-adherence to treatment may have played an important role in long-term graft loss, excluding death, as suggested by a high frequency of late acute rejection episodes. This study provides data for future analysis and for the development of strategies to improve the care of transplant patients and suggests that these strategies should focus on better compliance, an improved safety profile of the immunosuppressive regimens, the improvement of health and primary care services, and a targeted use of prophylaxis aiming to prevent or provide early diagnosis and treatment of endemic diseases.

#### Compliance with ethical standards

**Conflict of interest** FCRF: no conflict of interests to declare. MPC: travel grants for Novartis, Alexion, Pfizer, Libbs. Eventual speaker for: Novartis, Alexion, Pfizer, Libbs, Sanofi. MIP: travel grants from Libbs. HP: travel grants from Novartis. CRF: no conflict of interests to declare. HTS: clinical investigation fundings from Novartis, Pfizer, Sanofi, Roche. JOMP: travel grants for Novartis.

**Ethical standards and informed consent statements** All procedures performed in the present study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Due to the retrospective nature of this study, formal consent was not required.

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