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Cox regression analysis of compositional covariates related to death of the kidney transplant-recipient in northeastern Brazil: modeling of covariates associated with renal allograft failure

Análise de regressão de Cox de covariáveis composicionais relacionadas à morte do receptor de transplante renal no Nordeste do Brasil: modelagem de covariáveis associadas à falha do aloenxerto renal

Análisis de regresión de Cox de covariables composicionales relacionadas con la muerte del receptor de trasplante de riñón en el noreste de Brasil: modelado de covariables asociadas con falla del aloinjerto renal

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Abstract

Introduction: Kidney transplant (KT) has the highest survival rate amongst kidney replacement therapies (KRT). Objective: Analyze the incidence density of all-cause mortality in chronic kidney disease transplant-recipients and to identify covariables associated with higher risk of death. Methodology: Cohort study using medical records of 605 KT patients with seven years follow-up (2011-2018). Records with insufficient data or from patients with incomplete treatment were excluded. The variables analyzed were demographic, clinical and laboratory data, duration of KRT, type of donor, immunological compatibility, panel-reactive HLA-antibody, infections, and use of hypothermic perfusion machine (HPPM). Hazard ratio (HR) and incidence density of all-cause deaths were estimated. Results: 15 of 553 KT-recipients died during the follow-up. The survival in the first year post-KT was 98.0% and in the fifth year was 93.2%. The incidence density of deaths is 10/1,000 person-years. Variables pre- and post-KT related with higher death risk were allograft pyelonephritis ≥6-months and delayed graft function >4 weeks. Survival among KT-recipients with loss >5 mL/min/1.73m^2/year in the estimated glomerular filtration rate (eGFR) were lower than the others (88% vs. 97%). Covariates associated with mortality post-transplant included pre-KT obesity, HPPM, allograft pyelonephritis, and new-onset diabetes after transplantation. Conclusion: The mortality post-KT is low in these population. Cox's modelling demonstrated that the decline in eGFR >5 mL/min/1.73m2/year, allograft pyelonephritis ≥6-months, pre-KT obesity, fasting blood glucose ≥126 mg/dL presented worst probability of survival. Rapid decline in eGFR reduces substantially the survival probability in these population.

Keywords: Kidney transplantation; Progression of kidney function; Survival analysis; Cox regression model.

Resumo

Introdução: O transplante renal (TR) apresenta maior taxa de sobrevivência entre as terapias de substituição renal (TRS). Objetivo: Analisar a mortalidade por todas as causas em receptores de TR e identificar covariáveis associadas a maior risco de morte. Metodologia: Estudo de coorte utilizando prontuários de 605 transplantados com seguimento de sete anos (2011-2018). Foram excluídos registros com dados insuficientes ou pacientes com tratamento incompleto. As variáveis analisadas foram dados demográficos, clínicos, laboratoriais, tempo de TRS, tipo de doador, compatibilidade imunológica, reatividade contra painel, infecções e uso de máquina de perfusão hipotérmica (MPH). Foram calculadas razão de risco (HR) e densidade de incidência de todas as causas de morte. Resultados: 15 dos 553 tranplantados morreram durante o seguimento. Sobrevida no primeiro ano pós-TR foi 98,0% e no quinto ano 93,2%. Densidade de incidência de mortes foi 10/1.000 pessoas-ano. Covariáveis pré e pós-TR relacionadas com maior risco de morte foram pielonefrite do aloenxerto ≥6 meses e função retardada do enxerto >4 semanas. Sobrevivência entre TR com perda >5mL/min/1,73m^2/ano na taxa de filtração glomerular estimada (TFGe) foi menor que nos outros (88% vs. 97%). Covariáveis associadas à mortalidade pós-transplante incluíram obesidade pré-TR, MPH, pielonefrite do aloenxerto e diabetes de início recente pós-TR. Conclusão: Mortalidade pós-TR foi baixa nessa população. A modelagem de Cox demonstrou que declínio da TFGe >5mL/min/1,73m^2/ano, pielonefrite do aloenxerto ≥6 meses, obesidade pré-TR, glicemia de jejum ≥126mg/dL apresentou pior probabilidade de sobrevivência. Declínio rápido na TFGe reduz a sobrevivência nessa população.

Palavras-chave: Transplante renal; Progressão da função renal; Análise de sobrevivência; Modelo de regressão de Cox.

Resumen

Introducción: Trasplante de riñón (TR) tiene supervivencia más alta entre las terapias de reemplazo renal (TRR). Objetivo: Analizar la mortalidad por todas las causas en los receptores de RT e identificar las covariables asociadas con un mayor riesgo de muerte. Metodología: Estudio de cohorte utilizando historias clínicas de 605 trasplantado con siete años de seguimiento (2011-2018). Se excluyeron los registros con datos insuficientes o de pacientes con tratamiento incompleto. Fueron analizados datos demográficos, clínicos y de

laboratorio, duración de TRR, tipo de donante, compatibilidad inmunológica, panel reactivo de anticuerpos, infecciones y uso de máquina de perfusión hipotérmica (MPH). Se estimaron la razón de riesgo (HR) y la densidad de incidencia de las muertes por todas las causas. Resultados: 15 de los 553 receptores de TR murieron durante el seguimiento. Supervivencia en el primer año post-TR fue 98,0% y en el quinto año 93,2%. Densidad de incidencia de las muertes fue 10/1.000 personas-año. Covariables relacionadas con mayor riesgo de muerte fueron pielonefritis del aloinjerto ≥6 meses y función retardada del injerto >4 semanas. Supervivencia entre los receptores de TR con pérdida >5mL/min/1,73m^2/año en la tasa de filtración glomerular estimada (TFGe) fue menor que en los demás (88% vs. 97%). Covariables asociadas con la mortalidad postrasplante incluyeron obesidad pre-TR, MPH, pielonefritis del aloinjerto y diabetes de nueva aparición después del trasplante. Conclusión: La mortalidad post-TR es baja. Modelo de Cox demostró que TFGe >5ml/min/1,73m^2/año, pielonefritis del aloinjerto ≥6 meses, obesidad pre-TR, glucemia en ayunas ≥126mg/dL presentaron la peor probabilidad de supervivencia. Disminución rápida de la TFGe reduce la probabilidad de supervivencia en esta población.

Palabras clave: Trasplante de riñón; Progresión de la función renal; Análisis de supervivencia; Modelo de regresión de Cox.

1. Introduction

Kidney transplantation (KT) is the kidney replacement therapy (KRT) with the longest survival rate amongst all the therapeutic options available. The survival of chronic kidney disease transplant recipients (CKD-T) has been increasing in recent decades, possibly due to advances in immunopharmacology and improved care (Wekerle et al., 2017), together with reduction of infections, early identification of acute T-cell mediated rejections (aTCMR) or acute antibody-mediated rejection (aABMR) (Ashby et al., 2017).

Despite improved graft and patient survival in the first year after KT due to more appropriate clinical control and diagnosis, together with improved treatment of bacterial and viral infections, and rejection, each subsequent year increases the risk of the recipient returning to KRT or evolving to death even with a functioning graft. Long-term CKD-T survival may involve processes linked to malignancy, infections related to immunosuppression, infarction and stroke (Van Loon et al., 2020). The analysis of survival rates and the components of mortality-associated covariates are crucial in the planning and evaluation of CKD-T care (Djamali et al., 2006).

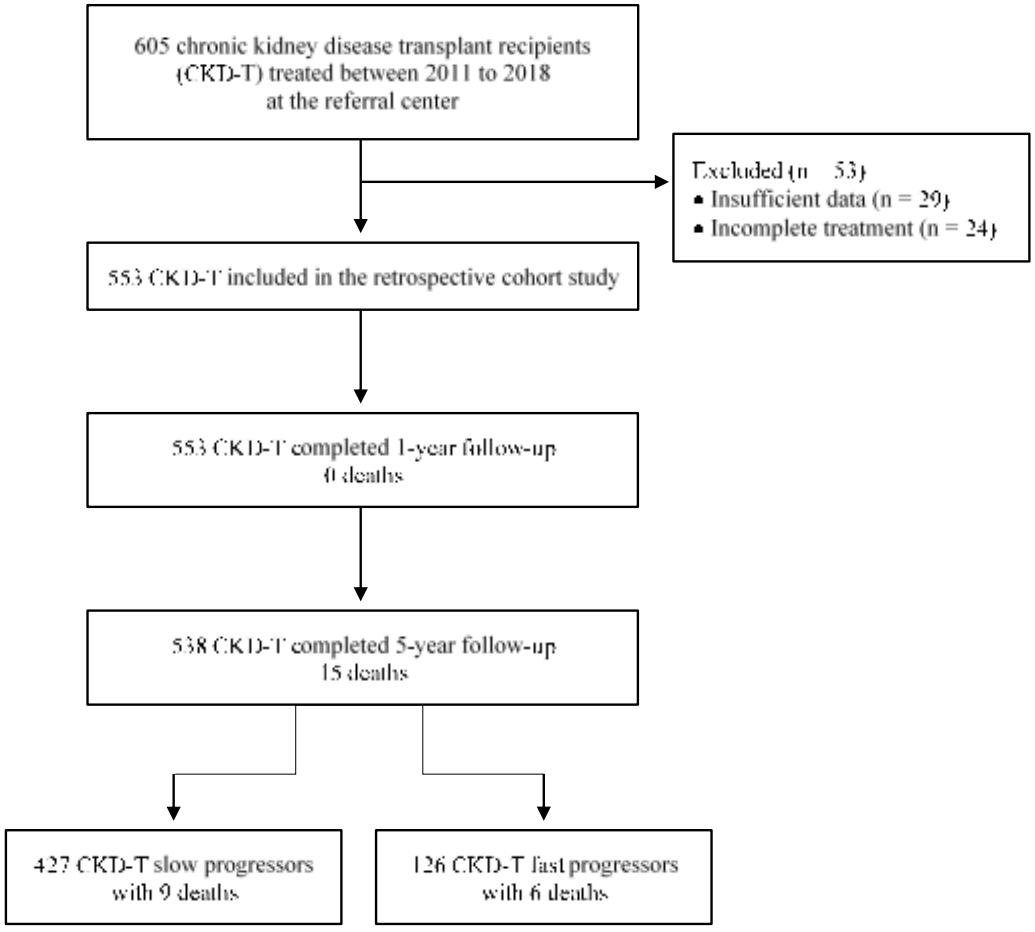
Therefore, the primary purpose of this study is to analyze the cumulative incidence of all-cause mortality in CKD-T from a reference center in Brazil. The research also aims to model a Cox regression capable of determining the composition of pre- and post-KT covariates which are associated with the mortality post-transplant.

2. Methodology

2.1 Study design and database selection

This is a retrospective cohort study (Sampieri, Collado & Lucio, 2013) involving the follow-up of CKD-T outpatients from January 2011 to January 2018, accompanied in the post-kidney transplant follow-up clinic at the Real Hospital Português de Beneficência em Pernambuco (RHP/PE), Recife, Pernambuco, Brazil. Subjects with insufficient data and dropouts from the treatment were excluded (Figure 1).

Figure 1. Flow chart of a retrospective cohort study survival analysis.



Source: Authors.

The study was approved by the Human Research Ethics Committee of Universidade de Pernambuco, Recife, Brazil (Ethics approval number: 2.520.459 in 01/03/2018) and supported by the ethics committee from the RHP/PE, Recife, Brazil (CAAE: 8258.7418.6.0000.5192).

The study complied with the Helsinki Declaration (1964) and agrees with the Resolutions 466/2012 and 510/2016 of the Brazilian National Health Council. Consent to participate was not necessary because only medical records were used without any contact with individual participants.

2.2 Analysis of covariables

CKD-T were categorized into fast progressors (CKD-T-fast) and slow progressors (CKD-T-slow). Donor type was classified as such: living donor (LV), standard deceased donor (SDD) and expanded criteria donor (ECD). The other variables were:

a) Demographic: sex, skin color and age, elderly (CKD-T ≥ 60 years old (Orlandi et al., 2015)

b) Immunological: antibody reactivity panel (PRA), mismatch in the human leucocyte antigen (HLA) system, and aTCMR or aABMR post-KT.

c) Pre-KT: obesity, systemic arterial hypertension (SAH), diabetes mellitus (DM), chronic kidney disease (CKD) etiology and KRT time until KT (ΔT-KRT&KT).

d) Post-KT: rate of decline in renal function.

e) Infectious: BK-polyomavirus (BKPyV) nephropathy, cytomegalovirus (CMV) nephritis and allograft bacterial pyelonephritis (ICU).

f) Laboratory: serum levels of hemoglobin, hematocrit, phosphorus, calcium, albumin, creatinine (Cr) and fasting blood glycose (FBG) dosed at six months and twelve months post-KT.

2.3 Immunosuppressive protocol at the RHP/PE (IP-IMS/RHP-PE)

All CKD-T underwent the IP-IMS/RHP-PE immunosuppressive protocol. This protocol used 15 mg/kg of methylprednisolone (MP) up to two hours before induction with maximum dose of one gram.

Maintenance was performed with combinations of prednisone, calcineurin inhibitor (CNI) cyclosporine (CyA) or tacrolimus (TAC); and azathioprine (AZA) or sodium mycophenolate (MPS) or mTOR sirolimus (SRL) or everolimus (EVR) inhibitors. Until 2012,

the second induction drug used was the α-chain blocker of interleukin-2 receptors (IL-2R) and was later replaced by human rabbit anti-thymocyte immunoglobulin (Thymo). Between 2012 and 2015, induction was performed with MP and IL-2R blocker, and maintenance with CyA or TAC + AZA + PRED for non-sensitized recipients (PRA = 0%) and CyA or TAC + MPS + PRED for recipients-sensitized (PRA > 0%). Between 2015 and 2018, induction was performed using MPS + Thymo (3mg/kg) for non-sensitized recipients and for maintenance the EVR or SRL + TAC + PRED combination was used.

Recipients-sensitized patients were induced using Thymo (6mg/kg), administered at doses of (2mg/kg) on days zero, three and six post-KT. The IP-IMS/RHP-PE maintenance was administered using TAC + MPS + PRED. PRED was administered throughout maintenance at doses of 0.5 mg/kg with maximum dose of 30 mg/day (Van Loon et al., 2020; Wekerle et al., 2017).

Individuals aged > 60 years, or 50-59 years who met at least two of the following criteria were characterized as ECD: a) brain death due to stroke; b) previous SAH; c) Cr ≥1,5 mg/dL (Ariza-Heredia et al., 2014). ECD were allocated to patients aged > 50 years with PRA = 0%.

Hypothermic machine perfusion preservation (HMPP) was indicated for: a) ECD kidney transplant-recipient; b) SDD with presumed ischemia time > 24h; c) SDD with previous cardiac arrest; SDD with donor final serum Cr ≥1,8 mg/dL (159.12 µmol/L). The kidneys meeting the criteria were installed in the HMPP, under dynamic preservation, upon arrival at the RHP/PE, after a period of static preservation since capture. The length of stay in the HMPP depended on the logistics of the donation-transplant process, with a minimum of six hours.

New-onset diabetes after transplantation (NODAT) had to meet the following criteria: DM symptoms added to casual blood glucose concentrations ≥ 200 mg/dL (11.1 mmol/L); FBG with two values ≥ 126 mg/dL (≥ 6.99 mmol/L) and 8 hours of fasting; oral glucose tolerance test after two hours with blood glucose ≥ 200 mg/dL (11.10 mmol/L) and glycated haemoglobin (HbA1c) ≥ 6.5% (0.07 ratio of total haemoglobin) (Davidson & Wilkinson, 2004; Port et al., 2002).

The post-KT estimate glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey et al., 2009).

CKD-T-fast were defined as CKD-T with an average annual eGFR loss >5 mL/min/1.73m2/year according to KDIGO 2012 (Levin et al., 2013). Kidney transplant

patients were named CKD-T (Stevens & Levin, 2013).

2.4 Diagnosis and management of cytomegalovirus disease (CMV)

Polymerase chain reaction (PCR) was used for the diagnosis of CMV. For the management of CMV, either prophylaxis with oral ganciclovir/valganciclovir, according to availability, or preemptive treatment with intravenous ganciclovir was employed, using PCR for diagnosis of CMV biweekly, resulting in a number of copies > 2,000/mL, collected from 15 days post-KT.

The protocol was carried out for three months in CKD-T with negative serology with positive donors, and in recipients who received induction with Thymo (6mg/kg) or maintenance with MPS. CKD-T using TAC + EVR or SRL + PRED did not undergo the preemptive strategy.

The same conduct was also carried out for three months, in all patients who were treated for rejection or were converted from MPA to SRL or EVL 10. All CKD-T showing signs or symptoms compatible with CMV syndrome, with laboratory confirmation, were diagnosed with CMV disease. In some cases, a histopathological study was necessary to diagnose invasive CMV disease or in the tissue (CMV nephritis). As a cure criterion, negative PCR for CMV was used. A CMV event was defined as any treatment registered in medical records preemptive or CMV disease treatment with antivirus therapy with ganciclovir registered in (Levin et al, 2013).

2.5 Bacterial allograft pyelonephritis (ICU) in CKD-T

ICU was determined by a value >105 colony-forming unit per milliliter in the urine culture, and fever associated with one of the following signs or symptoms: painful allograft, worsening of serum Cr or biopsy detecting bacterial neutrophilic nephritis.

2.6 Monitoring of BK-polyomavirus (BKPyV) and BK-polyomavirus nephropathy

BKPyV was screened after 90, 120, 150, 270 and 360 days of aABMR or aTCMR treatment or when there was an unexplained increase in serum Cr. A BKPyV event was defined as viremia >10,000 copies/mL. When associated with renal biopsy compatible diagnosis of polyomavirus nephropathy was made. The Dose reduction of serum levels of

immunosuppressants with or without changes in immunosuppressants was performed according to clinical judgment and biopsy result (Ramanan & Razonable, 2013).

2.7 Statistical analysis

Statistical analysis was conducted using Stata version 14.0 (StataCorpLLC™, College Station, Texas, USA). Absolute and relative frequencies were used to describe the clinical characteristics associated with kidney disease.

Quantitative variables were classified into categories and measurements were standardized. Mortality rates (MR) were expressed as incidence density of deaths with a 95% confidence interval (CI95%) and the number of cases standardized per 100 or 1,000 person-years of observation time. Pearson's chi-square (X^2) or Fisher's exact tests were used to assess associations of clinical factors related to CKD-T pre- and post-KT. The measures of the association of hazard ratio (HR) were also estimated for each covariate.

Survival functions were presented by the Kaplan-Meier graph and the differences were tested using the logrank test (Mantel-Cox) (Chuang, Parikh & Langone, 2005). In the survival analysis, the outcome variable was death and covariate dependent on time until death or the end of the cohort follow-up. Cases of loss to follow-up or abandonment of treatment were censored. The risk of death was estimated using the Cox-model and the measure of association of covariates was HR with CI95%. The Schoenfeld residue test was used to determine the proportional hazards assumption (Armitage, Berry & Matthews, 2013).

The HR of the association of mortality with clinical and CKD-T related pre- and post-KT factors was adjusted by stepwise-forward modelling. For input criterion, $P < 0.20$ was used in the bivariate stage while $P < 0.10$ was used as exit criterion. A bilateral P value < 0.05 was considered statistically significant. Biological plausibility served as a basis for interpreting concomitance at the stages (Schoenfeld, 1982). The quality of the goodness-of-fit adjustment was performed after modelling. Harrel's probability (Harrel's C index) was used to assess the discriminatory power and predictive accuracy of the mortality model. Gönen & Heller's K concordance coefficient was used to correct censoring interference and intensify the modelling power (Gönen & Heller, 2005).

3. Results

3.1 Description of the general characteristics of the population

From 605 CKD-T recruited between 2011 and 2018, 553 were selected for analysis. The general profile of the recipient population was composed of 78.5% of individuals < 60 years old, 61.7% of males and 72% multiracial (Table 1).

Table 1. Description of the chronic kidney disease transplant-recipients treated between 2011 to 2018 at a referral center in Brazil included in the retrospective cohort study (n = 553)

Kidney recipient characteristics	**n (%)**
Age ≥ 60 years	434 (78.5%)
Male sex	341 (61.7%)
Race (self-referenced)	
White	109 (19.7%)
Multiracial	398 (72.0%)
Black	46 (8.3%)
Pre-transplant body mass index (kg/m^2)	
Underweight (<18.5)	42 (7.6%)
Normal (18.5-24.9)	302 (54.6%)
Overweight (25.0-29.9)	161 (29.1%)
Obesity ≥ 30	48 (8.7%)
Etiological diagnosis	
Indeterminate	267 (48.3%)
Diabetes mellitus (DM)	45 (8.1%)
Systemic arterial hypertension (SAH)	85 (15.4%)
DM + SAH	13 (2.3%)
Nonspecific chronic glomerulonephritis	26 (4.7%)
Focal and segmental glomerulosclerosis	19 (3.4%)
Polycystic kidney disease	34 (6.1%)
Alport syndrome	4 (0.7%)
Others	60 (10.8%)
Donor type (n = 546)	
Living donor	41 (7.5%)
Standard deceased donor	424 (77.7%)
Expanded deceased donor	81 (14.8%)
Kidney replacement therapy (n = 546)	
Hemodialysis	499 (91.4%)
Peritonial dialysis	13 (2.6%)
Hemodialysis + peritonial dialysis	16 (2.9%)
Preemptive treatment	18 (3.3%)
ΔT-KRT&KT (n = 544)	
Less than 5 years	347 (63.8%)
Between 5 and 10 years	140 (25.7%)
More than 10 years	57 (10.5%)

ΔT-KRT&KT: time between kidney replacement therapy and kidney transplantation.
Source: Authors

When CKD-T-fast (n=126) and CKD-T-slow (n=427) progressors were compared, 77.2% of patients had a CKD-T-slow behavior with a CKD-T-slow/fast ratio estimated of 3.4. Elderly patients were a minority in both groups. The most frequent etiologies were DM and SAH. SDD predominated in both groups and the recipients had < 5 years of KRT (Table 2).

Table 2. Comparison between chronic kidney disease transplant-recipients with slow progression behavior and fast progression behavior treated at a referral center in Brazil from 2011 to 2018 (n = 553).

Covariables	**Fast progression** (n = 126)	**Slow progression** (n = 427)
Age ≥ 60 years	20 (15.9%)	99 (23.3%)
Male sex	71 (56.3%)	270 (63.2%)
Race (self-referenced)		
White	24 (19.1%)	85 (19.9%)
Multiracial	86 (68.2%)	312 (73.1%)
Black	16 (12.7%)	30 (7.0%)
Pre-transplant body mass index (kg/m^2)		
Underweight (< 18.5)	16 (12.7%)	26 (6.1%)
Normal (18.5 a 24.9)	76 (60.3%)	226 (52.9%)
Overweight (25.0 a 29.9)	23 (18.2%)	138 (32.3%)
Obesity (≥ 30)	11 (08.7%)	37 (8.7%)
Etiological diagnosis		
Indeterminate	70 (55.6%)	197 (46.1%)
Diabetes mellitus (DM)	7 (5.6%)	38 (8.9%)
Systemic arterial hypertension (SAH)	19 (15.1%)	66 (15.5%)
DM + SAH	2 (1.6%)	11 (2.6%)
Nonspecific chronic glomerulonephritis	6 (4.8%)	200 (4.7%)
Focal and segmental glomerulosclerosis	4 (3.2%)	15 (3.5%)
Polycystic kidney disease	6 (4.8%)	28 (6.6%)
Alport syndrome	1 (0.8%)	3 (0.7%)
Others	11 (8.7%)	49 (11.5%)
Donor type (n = 546)		
Living	11 (8.9%)	30 (7.1%)
Standard deceased	95 (77.2%)	329 (77.8%)
Expanded deceased criteria	17 (13.8%)	64 (15.1%)
Kidney replacement therapy (n = 546)		
Hemodialysis	111 (91.0%)	388 (91.5%)
Peritoneal Dialysis	2 (1.6%)	11 (2.6%)
Hemodialysis + peritoneal dialysis	5 (4.1%)	11 (2.6%)
Preemptive treatment	4 (3.3%)	14 (3.3%)
ΔT-KRT&KT (n = 544)		
Less than 5 years	72 (58.5%)	275 (65.3%)
Between 5 and 10 years	31 (25.2%)	109 (25.9%)
More than 10 years	20 (16.3%)	37 (8.8%)

ΔT-KRT&KT: time between renal replacement therapy and kidney transplantation.
Source: Authors

3.2 Analysis of the survival function and characteristics related to death

Fifteen patients died during follow-up and the 5-year survival probability is 93.2%. The standardized MR was 10 per 1,000 person-years, with death from CKD-T occurring within the first three years after transplant. Death was more prevalent in men aged ≥ 60 years with an MR of 1.55 (CI95%: 0.64–3.73) (Table 3).

Table 3. Pre-kidney transplant covariates associated with the risk of death in chronic kidney disease transplant-recipients in the post-kidney transplant period (n = 15).

Covariables	Deaths	Incidence density (CI95%)[a]	Hazard ratio (CI95%)	P
Age ≥ 60 years	5	1.55 (0.64 – 3.73)	1.10 (0.65 – 1.85)	0.718
Male sex	9	0.94 (0.49 – 1.81)	0.83 (0.29 – 2.33)	0.720
Progression				
Slow	9	0.80 (0.40 – 1.48)	Reference	-
Fast	6	1.87 (0.84 – 4.16)	2.40 (0.85 – 6.74)	0.097
Race(self-referred)				
White	3	1.22 (0.39 – 3.78)	Reference	-
Multiracial	10	0.91 (0.49 – 1.69)	0.75 (0.21 – 2.74)	0.663
Black	2	1.41 (0.35 – 5.63)	1.19 (0.19 – 7.14)	0.851
Body mass index (kg/m^2)				
Normal (18.5-24.9)	8	0.99 (0.49 – 1.98)	Reference	-
Underweight (<18.5)	3	0.70 (0.23 – 2.19)	0.72 (0.19 – 2.69)	0.621
Overweight (25.0-29.9)	3	2.50 (0.81 – 7.75)	2.48 (066 – 9.35)	0.180
Obesity (≥ 30)	1	0.77 (0.11 – 5.46)	0.76 (0.10 – 6.11)	0.798
Etiological diagnosis				
DM pre-KT	6	1.39 (0.74 – 2.57)	Reference	-
SAH	2	1.65 (0.41 – 6.61)	1.19 (0.26 – 5.45)	0.819
DM pre-KT + SAH	2	0.75 (0.19 – 3.01)	0.55 (0.12 – 2.52)	0.443
Others	1	0.68 (0.09 – 4.86)	0.49 (0.06 – 3.85)	0.499
ΔT-KRT&KT				
Less than 5 years	7	0.80 (0.38 – 1.67)	Reference	-
Between 5 and 10 years	5	1.19 (0.49 – 2.86)	1.51 (0.48 – 4.75)	0.486
More than 10 years	2	1.25 (0.31 – 5.00)	1.57 (0.33 – 7.55)	0.575

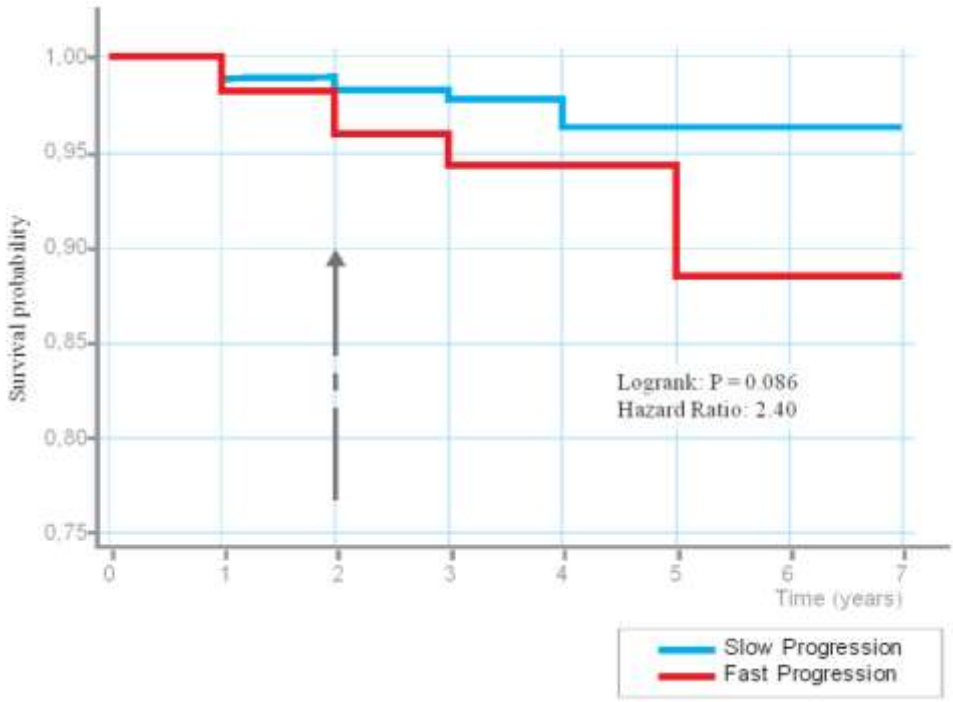
[a]The incidence density of deaths is per 100 person-years. CI95%: confidence interval at 95%; DM: diabetes mellitus; SAH: systemic arterial hypertension; KT: kidney transplantation; ΔT-KRT&KT: time between renal replacement therapy and kidney transplantation
Source: Authors.

3.3 Analysis of the eGFR and rapid progression behavior

Forty percent of deaths in this cohort occurred in transplant recipients who exhibited CKD-T-fast behavior, estimating the MR in 1.87 (CI95%: 0.84–4.16) and the HR in 2.4

(CI95%: 0.85–6.74). Survival curves diverged between CKD-T-fast and CKD-T-slow progressors from the second year post-KT (Figure 2).

Figure 2. Survival analysis among chronic kidney disease transplant recipients with slow progression behavior (n=427) and fast progression behavior (n = 126).



Arrow shows the critical point between kidney transplant-recipients slow progressors and fast progressor. Chronic kidney disease transplant-recipients with fast progressing behavior have average decline in annual glomerular filtration rate > 5mL/min/1.73m2/year.
Source: Authors

3.4 Covariables correlated with death

DM accounted for to 66% of CKD-T deaths with MR estimated at 1.39 (CI95%: 0.74–2.57). The mean time between KRT and RR was < 5 years, and a greater MR was observed among patients who were on KRT ≥10 years (HR: 1.57; CI95%: 0.33–7.55) (Table 1). Pre-KT obesity was the comorbidity with the highest MR (3.9; CI95%: 1.45–10.3) and HR (4.81; CI95%: 1.53–15.1). 40% of the patients who died had their grafts perfused with HPPM (MR: 1.82; CI95%: 0.82–4.06) (Table 4).

Table 4. Covariables pre- and post-kidney transplantation related to the highest risk of death for recipients in the post-kidney transplant period (n = 15).

Covariables	Deaths	Incidence density (CI95%)[a]	Hazard ratio (CI95%)[b]	P
Hypothermic machine perfusion	6	1.82 (0.82 – 4.06)	3.42 (1.09 – 10.8)	0.036
Mismatches				
Human leukocyte antigen-A				
0 mm	0	-	-	-
1 mm	4	0.63 (0.81 – 2.80)	Reference	-
2 mm	10	2.00 (0.28 – 14.2)	2.40 (0.74 – 7.67)	0.138
Human leukocyte antigen-B				
0 mm	1	0.75 (0.11 – 5.29)	Reference	-
1 mm	3	0.46 (0.15 – 1.42)	0.62 (0.06 – 5.93)	0.675
2 mm	10	1.56 (0.84 – 2.90)	2.09 (0.27 – 16.3)	0.482
Human leukocyte antigen-DR				
0 mm	5	1.08 (0.45 – 2.58)	Reference	-
1 mm	6	0.79 (0.35 – 1.75)	0.73 (0.22 – 2.40)	0.607
2 mm	3	1.49 (0.48 – 4.63)	1.39 (0.33 – 5.83)	0.653
Systemic arterial pressure (mmHg)				
SBP 150-159 and DBP 100-110	7	0.80 (0.38 – 1.67)	Reference	-
SBP ≥ 160 and DBP ≥ 110	5	1.84 (0.77 – 4.42)	2.32 (0.73 – 7.32)	0.151
Cold ischemia				
Less than 12 hours	1	0.54 (0.08 – 3.82)	Reference	-
Between 12 and 18 hours	5	1.12 (0.47 – 2.70)	2.01 (0.23 – 17.2)	0.524
Between 18 and 24 hours	6	1.68 (0.75 – 3.73)	3.03 (0.36 – 25.2)	0.305
Between 24 and 30 hours	1	0.52 (0.07 – 3.68)	0.93 (0.06 – 14.9)	0.962
More than 30 hours	1	0.79 (0.11 – 5.59)	1.47 (0.09 – 23.6)	0.787
Panel-reactive antibody				
Not sensitized recipients	13	1.01 (0.57 – 1.78)	Reference	-
Moderate sensitized	2	0.97 (0.24 – 3.88)	0.95 (0.21 – 4.26)	0.947
Hypersensitized	0	-	-	-
Donor type				
Living donor	0	-	Reference	-
Standard deceased donor	12	-	-	-
Expanded deceased criteria	3	-	-	-

[a]The incidence density of deaths is per 100 person-years. [b]Hazard ratio was not calculated for all deaths in kidney transplant recipients among non-transplanted patients. CI95%: confidence interval at 95%; HLA: human leukocyte antigen; SBP: systolic blood pressure; DBP: diastolic blood pressure.
Source: Authors.

The delay graft function (DGF) >4 weeks was associated with a higher MR (5.42; CI95%: 2.82–10.4). 53% of the patients who died had been diagnosed with ICU up to six months post-KT (MR: 1.57; CI95%: 0.78–3.13 and HR: 3.65; CI95%: 1.10–12.1) (Table 5).

Table 5. Incidence rate of deaths and covariates pre- and post-transplant associated with the risk of death in chronic kidney disease transplant recipients up to one year (n = 15).

Covariables	**Deaths**	**Incidence density (CI95%)[a]**	**Hazard ratio (CI95%)**	**P**
Progression				
Slow	9	0.80 (0.40 – 1.48)	Reference	-
Fast	6	1.87 (0.84 – 4.16)	2.40 (0.85 – 6.74)	0.097
BMI ≥ 30 kg/m^2 pre-KT	4	3.88 (1.45 – 10.3)	4.81 (1.53 – 15.1)	
ICU up to 6 months post-KT	8	1.57 (0.78 – 3.13)	3.65 (1.10 – 12.1)	0.034
Delay graft function				
Less than one week	2	0.27 (0.07 – 1.07)	Reference	-
Between 1 and 2 weeks	2	0.61 (0.15 - 2.42)	2.20 (0.31 – 15.6)	0.432
Between 2 and 3 weeks	2	1.08 (0.27 – 4.29)	4.06 (0.57 – 28.9)	0.161
Between 3 and 4 weeks	0	-	-	-
More than 4 weeks	9	5.42 (2.82 – 10.4)	20.2 (4.35 – 94.1)	<0.001
Cytomegalovirus event	5	0.83 (0.34 – 1.99)	0.85 (0.28 – 2.59)	0.769
BKPyV nephropathy	2	1.63 (0.41 – 6.50)	1.94 (0.43 – 8.77)	0.388
aTCMR	5	1.87 (0.77 – 4.48)	2.39 (0.80 – 7.14)	0.118
NODAT	7	1.14 (0.54 – 2.38)	3.12 (0.80 – 12.1)	0.100

[a]The incidence density of deaths is per 100 person-years. [b]CMV event was symptomatic infection or preemptive treatment or biopsy with cytomegalovirus nephritis.[c]BKyP - polyomavirus is considered serum viremia > 10.000 copies/mL with biopsy with BKyP nephropathy. CI95%: confidence interval at 95%; BMI: body mass index; KT: kidney transplantation; ICU: allograft pyelonephritis; aTCMR: acute T cell-mediated rejection; NODAT: new-onset diabetes after transplantation.
Source: Authors

FBG ≥ 126 mg/dL (≥6.99 mmol/L) or NODAT diagnosis was associated with both higher MR (2.67; CI95%: 1.11–6.42) and HR (3.81; CI95%: 1.16–12.5) (Table 6). Results from the serum laboratory measurements one-year post-KT are also available in Table 6.

Table 6. Serum laboratory covariates related to the risk of death results up to one after kidney transplantation (n = 15).

Covariables	Deaths	Incidence density (CI95%)[a]	Hazard Ratio (CI95%)[b]	P
Fasting blood glycose				
< 99 mg/dL	6	0.71 (0.32 – 1.57)	Reference	-
100-125 mg/dL	3	0.69 (0.22 – 2.14)	0.99 (0.25 – 3.97)	0.985
≥ 126 mg/dL	5	2.67 (1.11 – 6.42)	3.81 (1.16 – 12.5)	0.028
Hemoglobin				
10-11mg/dL	4	0.97 (0.36 – 2.57)	Reference	-
< 10mg/dL	3	2.42 (0.78 – 7.50)	2.56 (0.57 – 11.5)	0.218
> 12 mg/dL	8	0.85 (0.43 – 1.71)	0.89 (0.27 – 2.98)	0.862
Hematocrit				
30-36 mg/dL	4	1.04 (0.39 – 2.78)	Reference	-
< 30mg/dL	3	3.22 (1.05 – 10.0)	3.12 (0.70 – 13.9)	0.137
> 36 mg/dL	7	0.71 (0.33 – 1.48)	0.68 (0.20 – 2.33)	0.542
Serum total calcium				
8.5-10.5 mg/dL	3	0.42 (0.13 - 1.29)	Reference	-
< 8.5 mg/dL	3	1.15 (0.36 – 3.55)	2.71 (0.55 – 13.5)	0.223
> 10.5 mg/dL	3	1.23 (0.40 – 3.83)	2.98 (0.60 – 14.8)	0.182
Serum phosphorus				
2.5-4.5 mg/dL	4	0.49 (0.18 – 1.30)	Reference	-
< 2.5 mg/dL	2	0.65 (0.16 – 2.59)	1.33 (0.24 – 7.28)	0.740
> 4.5 mg/dL	1	2.43 (0.35 – 17.3)	5.07 (0.56 – 45.4)	0.147
Serum albumin				
3.5-4.5 mg/dL	7	1.11 (0.53 – 2.32)	Reference	-
< 3.5 mg/dL	2	2.98 (0.75 – 11.9)	2.65 (0.55 – 12.8)	0.224
> 4.5 mg/dL	0	-	-	-
HbA1c				
4.0-5.6 %	1	0.44 (0.06 – 3.13)	Reference	-
< 4.0 %	1	0.51 (0.07 – 3.66)	1.16 (0.07 – 18.5)	0.917
> 5.6 %	4	1.27 (0.48 – 3.39)	2.89 (0.32 – 25.9)	0.342

[a]The incidence density of deaths is per 100 person-years, [b]Hazard ratio was not calculated for all deaths in kidney transplant recipients with proteinuria above 300 mg/24h; CI95**%**: confidence interval at 95%; HbA1c: serum glycated hemoglobin.
Source: Authors.

3.5 Selection of the composition of covariates correlated to death

Multivariate modelling demonstrated that the pre-KT obesity, use of MPPH, ICU up to six months post-KT, fasting blood glycose ≥ 126 mg/dL (≥ 6.99 mmol/L) or NODAT, and CKD-T-fast behavior were associated with a higher risk of death (Table 7). However, only pre-KT obesity (P = 0.023) and the use of HPPM (P = 0.035) were independent risk factors.

Table 7. Multivariate analysis by Cox proportional hazard model with the covariables more closely associated with the risk of death in chronic kidney disease transplant-recipients

Covariables	Hazard ratio (CI95%)	P
Fast progression	1.82 (0.59 – 5.55)	0.294
Pre-kidney transplant obesity	4.32 (1.22 – 15.3)	0.023
Hypothermic pulsatile machine perfusion	3.51 (1.09 – 11.3)	0.035
Pyelonephritis post-kidney transplantation until six months	3.28 (0.97 – 11.1)	0.056
Fasting blood glycose ≥ 126 mg/dL or NODAT	3.18 (0.92 – 11.0)	0.068

CI95%: confidence interval at 95%; NODAT: new-onset diabetes after transplantation.
Harrell's C index = 0.8538; Gönen & Heller's K concordance coefficient = 0.7401
Source: Authors.

4. Discussion

4.1 Main causes of death in kidney recipients-transplant

A study conducted by Bicalho et al. (2019) with 944 Brazilian patients have found a survival rate of 90.2%. Infectious and cardiovascular diseases accounted for 90% of the causes of death in the population studied. In a research study conducted in Germany, involving populations with socioeconomic and ethnic characteristics different from the present study, Abeling et al. (2019) have also found an accelerated loss of renal function post-KT in addition to infectious and cardiovascular factors. These study with a follow-up between 2000 and 2007 observed a drop in the survival rate from 90% in the fifth year post-KT to 78% in the 10-year period among CKD-T with fast renal loss behavior. The CKD-T survival curve of the present study corroborates findings from well-reputed reference centers, such as the Hospital do Rim de São Paulo, which found a 93.2% in the five-year survival rate for CKD-T of LV and 79.6% for CKD-T of SDD (Jolissaint & Tullius, 2017).

4.2 CKD-T fast-progressor behavior

There is still no consensus over a clear characterization of CKD-T-fast patients. Renal function progression in these patients follows the general guidelines of KDIGO 2012 (Levin et al., 2013), considering a rate of decline in renal function >5 mL/min/1.73m^2/year was a rapid decline in renal function (Stevens & Levin, 2013). The mechanisms underlying such rapid progression and the risk of death remain unclear.

The rate of decline in CKD may be a marker of subclinical atherosclerosis, endothelial dysfunction or oxidative stress. The Atherosclerosis Risk in Communities (ARIC) study,

which involved more than 13,000 patients, pointed to a risk of peripheral arterial disease and death in the group of patients with the greatest annual rate of decline in renal function (Matsushita et al., 2009). Shlipak et al. (2009) have demonstrated an association between accelerated rate of decline in eGFR and increased risk of heart failure, heart attack and death.

In a 34-month follow-up, Khan et al. (2006) also noticed an increase in mortality when associated with an accelerated rate of decline in renal function. In the study, a value >15 mL/min/1.73m^2/year was a reference point for defining rapid progression, which was found in 12% of the 6,640 individuals studied. The increase in MR was not verified by the authors in subjects defined as CKD-T-slow.

In the present study, a higher risk of death was found for CKD-T fast progressors or patients with eGFR > 5 mL/min/1.73m^2/year and this phenomenon was detected after the second year of post-KT follow-up (Figure 2). We should like to emphasize the importance of analyzing the survival function curve, not only by the logrank, but by the configuration of its trajectory, since survival function is impacted by the censored group and by time of analysis of the probabilistic comparison pairs. A simple analysis may at first seem to invalidate the discriminatory analysis, but it is at the inflection point on the curve that care needs to be intensified. The critical point of the trajectory favors the determination of CKD-T-fast with a higher risk of rapid graft loss and leads to a greater likelihood of death (Park et al., 2013).

4.3 New-onset diabetes after transplantation and pre-kidney transplant obesity

NODAT is a growing problem in KT recipients, since this is a serious complication during follow-up (Ducloux et al., 2005). The NODAT continually increases after KT, as demonstrated by the cumulative incidence of cardiovascular events and increased risk of death associated with FBG higher levels (Cia et al., 2016). The present study corroborates these findings, since FBG levels ≥126 mg/dL (>6.99 mmol/L) were also associated with a higher risk of death. In the literature, NODAT has been found to increase the risk of death from cardiovascular diseases by 1.5 to 3 times (Srinivasan et al., 2019).

The modern global epidemic of obesity is yet another serious risk factor for loss of transplanted kidney and death. Although the pathophysiology of obesity and the risk of death are multifactorial,24 the present study found that obesity was the post-KT comorbidity associated with greatest MR. As shown in other studies, obesity in CKD-T increases the risk of SAH, DM, dyslipidemia and coronary artery diseases. Post-KT obesity is an independent

risk factor for allograft dysfunction and death from cardiovascular events (Ducloux et al., 2005).

4.4 Allograft pyelonephritis (ICU) up to six months after six months post-KT

In the present cohort, the ICU represented a 3.65 times greater risk and was present in 53% of the CKD-T who died. Infectious complications represent a challenge to KT and are associated with longer hospital stays and increased health costs, with CKD-T patients presenting increased risk for ICU. This condition is the major of source of bacteremia and infectious complications, increasing the death risk for CKD-T patients (Ojo, 2005).

According to Srinivasan et al. (2019) genitourinary infections up to six months post-RT are associated with an increase in MR, with CKD-T affected by ICU showing a drop-in survival rate, with survival coefficients estimated at 82.7% after five years post-KT. Furthermore, the single center survey conducted in Brazil by the authors recorded 162 deaths among with 1,873 CKD-T (Srinivasan et al., 2019).

4.5 Hypothermic pulsatile perfusion preservation machine

In our study, HPPM was used only in selected cases of higher risk of DGF, including ECD kidney-recipients, and only after a period under static preservation, i.e., hybrid preservation. Thus, the value found in the Cox model may be an indirect measure of the quality of the received kidney, and not a linear risk factor for death.

In a multicenter randomized study, involving a kidney donation after circulatory death (DCD-donor), Watson et al. (2010) have found no difference in the incidence of DGF between the kidneys assigned for HPPM or static preservation, with percentages of 58% and 56% respectively. Kidney function at three and twelve months was similar between groups, as well as graft and patient survival.

In a study carried out by Jochmans et al. (2010) also involving DCD-donor kidneys, HPPM reduced the incidence of DGF from 69.5% to 53.7% (OR: 0.43; CI95%: 0.20–0.89; P = 0.025). In addition, the DGF had a reduction in four days in the CKD-T perfused by HPPM (P = 0.082) and the kidneys perfused by HPPM showed better clearance of Cr up to one-month post-KT (P = 0.027). Regarding graft survival and CKD-T one-year post-KT, there was no difference between the groups (93.9% vs. 95.1%). However, both studies were conducted with DCD-donors, a modality not yet regulated in Brazil. The greatest applicability

of HPPM lies in kidneys of brain-dead donors, immediately after surgical extraction. Apparently, there is a benefit for selected groups regarding reductions in DGF, length of hospital stays and renal function after the first year post-KT (Sandal et al., 2018; Watson et al., 2010).

4.6 Effectiveness of the prediction model

Regarding the covariables associated with fatal outcomes, the Harrell's C index of the model was calculated at 85% and Gönen & Heller's K concordance coefficient at 74.0% (Armitage, Berry & Matthews, 2013; Gönen & Heller, 2005; Schoenfeld, 1982). The combination of the two indices demonstrates that the model is both solid and consistent for adjusting the prediction for risk of death in the pre- and post-KT assessment up to one year.

The survival trajectory curve and the survival coefficient of the CKD-T showed a smooth slope in five years. This fact generated a discrete injector function in the codomain (CKD-T who died). As a result, there was both a reduction in MR and in the absolute number of deaths. However, Cox modelling combined with Harrell's C index and Gönen & Heller's K-concordance coefficient helped to correct biases related to deaths and counterbalance the limitations of the Kaplan-Meyer curve analysis.

5. Final Considerations

A five-year probability of survival rate of 93% was identified among chronic kidney disease transplant recipients. The composition of covariates related to worst probability of survival was demonstrated using Cox's modelling: decline in eGFR >5 mL/min/1.73m^2/year, ICU up to six months post-KT, pre-KT obesity, FBG ≥ 126 mg/dL (≥ 6.99 mmol/L) or NODAT. Rapid decline in eGFR reduces substantially the survival probability in these population.

In addition, to improving the knowledge of transplantation, we will also have the introduction of techniques and artificial intelligence and data validation using machine learning techniques. Several studies are using regression robots and techniques with complex algorithms to predict kidney allograft graft failure and the patient's risk of death. The tendency is for the biomedical context to appropriate the new knowledge of "Big Data" and computer science for the benefit of kidney-recipients.

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References

Abeling, T., Scheffner, I., Karch, A., Broecker, V., Koch, A., Haller, H., Schwarz, A., & Gwinner, W. (2019). Risk factors for death in kidney transplant patients: analysis from a large protocol biopsy registry. *Nephrology Dialysis Transplantation*, 34(7), 1171–1181. https://doi.org/10.1093/ndt/gfy131

Ariza-Heredia, E. J., Beam, E. N., Lesnick, T. G., Cosio, F. G., Kremers, W. K., & Razonable, R. R. (2014). Impact of urinary tract infection on allograft function after kidney transplantation. *Clinical Transplantation*, 28(6), 683–690. https://doi.org/10.1111/ctr.12366

Armitage, P., Berry, G., & Matthews, J. N. S. (2013). *Statistical methods in medical research* (4th Edition). Massachusetts: Wiley-Blackwell.

Ashby, V. B., Leichtman, A. B., Rees, M. A., Song, P. X.-K., Bray, M., Wang, W., & Kalbfleisch, J. D. (2017). A kidney graft survival calculator that accounts for mismatches in age, sex, HLA, and body size. *Clinical Journal of the American Society of Nephrology*, 12(7), 1148–1160. https://doi.org/10.2215/CJN.09330916

Bicalho, P. R., Requião-Moura, L. R., Arruda, É. F., Chinen, R., Mello, L., Bertocchi, A. P. F., Lamkowski Naka, E., Tonato, E. J., & Pacheco-Silva, A. (2019). Long-term outcomes among kidney transplant recipients and after graft failure: a single-center cohort study in Brazil. *BioMed Research International*, 2019, 7105084. https://doi.org/10.1155/2019/7105084

Chuang, P., Parikh, C. R., & Langone, A. (2005). Urinary tract infections after renal transplantation: a retrospective review at two US transplant centers. *Clinical Transplantation*, 19(2), 230–235. https://doi.org/10.1111/j.1399-0012.2005.00327.x

Cia, C.-T., Li, M.-J., Li, C.-W., Lee, N.-Y., Chang, S.-S., Lee, C.-C., & Ko, W.-C. (2016). Community-onset bacteremia in kidney transplant recipients: The recipients fare well in terms of mortality and kidney injury. *Journal of Microbiology, Immunology and Infection*, 49(5), 685–691. https://doi.org/10.1016/j.jmii.2014.08.027

Davidson, J. A., & Wilkinson, A. (2004). New-onset diabetes after transplantation 2003 International Consensus Guidelines: an endocrinologist's view. *Diabetes Care*, 27(3), 805–812. https://doi.org/10.2337/diacare.27.3.805

Djamali, A., Samaniego, M., Muth, B., Muehrer, R., Hofmann, R. M., Pirsch, J., Howard, A., Mourad, G., & Becker, B. N. (2006). Medical care of kidney transplant recipients after the first posttransplant year. *Clinical Journal of the American Society of Nephrology*, 1(4), 623–640. https://doi.org/10.2215/CJN.01371005

Ducloux, D., Kazory, A., & Chalopin, J.-M. (2005). Posttransplant diabetes mellitus and atherosclerotic events in renal transplant recipients: a prospective study. *Transplantation*, 79(4), 438–443. https://doi.org/10.1097/01.TP.0000151799.98612.EB

Gönen, M., & Heller, G. (2005). Concordance probability and discriminatory power in proportional hazards regression. *Biometrika*, 92(4), 965–970. https://doi.org/10.1093/biomet/92.4.965

Jochmans, I., Moers, C., Smits, J. M., Leuvenink, H. G. D., Treckmann, J., Paul, A., Rahmel, A., Squifflet, J.-P., van Heurn, E., Monbaliu, D., Ploeg, R. J., & Pirenne, J. (2010). Machine perfusion versus cold storage for the preservation of kidneys donated after cardiac death. *Annals of Surgery*, 252(5), 756–764. https://doi.org/10.1097/SLA.0b013e3181ffc256

Jolissaint, J. S., & Tullius, S. G. (2017). Hospital do Rim, São Paulo: a world leader in kidney transplantation. *Jornal Brasileiro de Nefrologia*, 39(3), 234–235. https://doi.org/10.5935/0101-2800.20170047

Khan, N. A., Ma, I., Thompson, C. R., Humphries, K., Salem, D. N., Sarnak, M. J., & Levin, A. (2006). Kidney function and mortality among patients with left ventricular systolic

dysfunction. *Journal of the American Society of Nephrology*, 17(1), 244–253. https://doi.org/10.1681/ASN.2005030270

Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F. 3rd, Feldman, H. I., Kusek, J. W., Eggers, P., Van Lente, F., Greene, T., & Coresh, J. (2009). A new equation to estimate glomerular filtration rate. *Annals of Internal Medicine*, 150(9), 604–612. https://doi.org/10.7326/0003-4819-150-9-200905050-00006

Levin, A., Stevens, P. E., Bilous, R. W., Coresh, J., De Francisco, A. L. M., De Jong, P. E., Griffith, K. E., Hemmelgarn, B. R., Iseki, K., Lamb, E. J., Levey, A. S., Riella, M. C., Shlipak, M. G., Wang, H., White, C. T., & Winearls, C. G. (2013). Kidney disease: improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International Supplements*, 3(1), 1–150. https://doi.org/10.1038/kisup.2012.73

Matsushita, K., Selvin, E., Bash, L. D., Franceschini, N., Astor, B. C., & Coresh, J. (2009). Change in estimated GFR associates with coronary heart disease and mortality. *Journal of the American Society of Nephrology*, 20(12), 2617–2624. https://doi.org/10.1681/ASN.2009010025

Ojo, A. O. (2005). Expanded criteria donors: process and outcomes. *Seminars in Dialysis*, 18(6), 463–468. https://doi.org/10.1111/j.1525-139X.2005.00090.x

Orlandi, P. F., Cristelli, M. P., Aldworth, C. A. R., Freitas, T. V. de S., Felipe, C. R., Silva Junior, H. T., & Pestana, J. O. M. de A. (2015). Long-term outcomes of elderly kidney transplant recipients. *Jornal Brasileiro de Nefrologia*, 37(2), 212–220. https://doi.org/10.5935/0101-2800.20150034

Park, J.-S., Oh, I. H., Lee, C. H., Kim, G.-H., & Kang, C. M. (2013). The rate of decline of glomerular filtration rate is a predictor of long-term graft outcome after kidney transplantation. *Transplantation Proceedings*, 45(4), 1438–1441. https://doi.org/10.1016/j.transproceed.2012.10.052

Port, F. K., Bragg-Gresham, J. L., Metzger, R. A., Dykstra, D. M., Gillespie, B. W., Young, E. W., Delmonico, F. L., Wynn, J. J., Merion, R. M., Wolfe, R. A., & Held, P. J. (2002). Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors1. *Transplantation*, 74(9), 1281–1286. https://doi.org/10.1097/00007890-200211150-00014

Ramanan, P., & Razonable, R. R. (2013). Cytomegalovirus infections in solid organ transplantation: a review. *Infection & Chemotherapy*, 45(3), 260–271. https://doi.org/10.3947/ic.2013.45.3.260

Sampieri, R. H., Collado, C. F., & Lucio, M. P. B. (2013). *Metodologia de pesquisa* (5th Edition). Porto Alegre: Penso.

Sandal, S., Luo, X., Massie, A. B., Paraskevas, S., Cantarovich, M., & Segev, D. L. (2018). Machine perfusion and long-term kidney transplant recipient outcomes across allograft risk strata. *Nephrology, Dialysis, Transplantation*, 33(7), 1251–1259. https://doi.org/10.1093/ndt/gfy010

Schoenfeld, D. (1982). Partial residuals for the proportional hazards regression model. *Biometrika*, 69(1), 239–241. https://doi.org/10.1093/biomet/69.1.239

Shlipak, M. G., Katz, R., Kestenbaum, B., Siscovick, D., Fried, L., Newman, A., Rifkin, D., & Sarnak, M. J. (2009). Rapid decline of kidney function increases cardiovascular risk in the elderly. *Journal of the American Society of Nephrology*, 20(12), 2625–2630. https://doi.org/10.1681/ASN.2009050546

Srinivasan, D., Stoffel, J. T., Bradley, K., & Sung, R. S. (2019). Outcomes of kidney transplant recipients with posttransplant genitourinary infectious complications: a single center study. *Experimental and Clinical Transplantation*, 17(4), 470–477. https://doi.org/10.6002/ect.2017.0196

Stevens, P. E., & Levin, A. (2013). Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline.

Annals of Internal Medicine, 158(11), 825–830. https://doi.org/10.7326/0003-4819-158-11-201306040-00007

Van Loon, E., Senev, A., Lerut, E., Coemans, M., Callemeyn, J., Van Keer, J. M., Daniëls, L., Kuypers, D., Sprangers, B., Emonds, M.-P., & Naesens, M. (2020). Assessing the complex causes of kidney allograft loss. *Transplantation*, 104(12), 2557–2566. https://doi.org/10.1097/TP.0000000000003192

Watson, C. J. E., Wells, A. C., Roberts, R. J., Akoh, J. A., Friend, P. J., Akyol, M., Calder, F. R., Allen, J. E., Jones, M. N., Collett, D., & Bradley, J. A. (2010). Cold machine perfusion versus static cold storage of kidneys donated after cardiac death: a UK multicenter randomized controlled trial. *American Journal of Transplantation*, 10(9), 1991–1999. https://doi.org/10.1111/j.1600-6143.2010.03165.x

Wekerle, T., Segev, D., Lechler, R., & Oberbauer, R. (2017). Strategies for long-term preservation of kidney graft function. *The Lancet*, 389(10084), 2152–2162. https://doi.org/10.1016/S0140-6736(17)31283-7

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