ABCS HEALTH SCIENCES

ORIGINAL ARTICLE

OPEN ACCESS

Modeling of covariates predicting renal allograft failure within six months after transplantation

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ABSTRACT

Introduction: Kidney transplantation (KT) is the renal replacement therapy (RRT) of choice for patients with chronic kidney disease (CKD). However, not every KT is successful and some patients persist on RRT. **Objective:** To model a logistic regression with pre- and post-KT risk covariates capable of predicting secondary allograft dysfunction in need of RRT or reaching stage V of CKD until the first six months post-KT. **Methods:** Cohort with KT recipients from Northeastern Brazil. Medical records of KT performed between 2011-2018 were analyzed. KT-recipients with insufficient data or who abandoned follow-up were excluded. The covariables analyzed were: demographic; infectious; pre- and post-KT comorbidities; panel reactive-antibodies; number of HLA mismatches; acute rejection episodes mediated by T-cell (ACR) or antibodies (AAR) six months after KT; and laboratory tests six months after KT. **Results:** Covariates with higher risk for the analyzed outcomes six months after KT were: elderly KT recipients (OR:1.41; CI95%:1.01-1.99), time between onset of RRT and KT (ΔT-RRT&KT)>10years (OR:3.54; CI95%:1.27-9.87), diabetes mellitus (DM) pre-KT (OR:3.35; CI95%:1.51-7.46), pyelonephritis (OR:2.45; CI95%:1.24-4.84), polyomavirus nephropathy (OR:4.99; CI95%:1.87-13.3), AAS (OR:4.82; CI95%:1.35-17.2), 24h-proteinuria ≥300mg/24h (OR:5.05; CI95%:2.00-12.7) and serum calcium (Ca) <8.5mg/dL (OR:4.72; CI95%:2.00-11.1). The multivariate model presented an accuracy of 88.1% and the mean variance inflation factor is 1.81. **Conclusion:** Elderly-recipients, ΔT-RRT&KT>10 years, pre-KT DM, and post-KT aggressions until six months (pyelonephritis, polyomavirus nephropathy, ABMR, 24h-proteinuria≥300mg/24h, and Ca<8.5mg/dL) are associated with high predictive power for secondary allograft dysfunction in need of RRT or reaching CKD stage V until the first six months post-KT.

Keywords: kidney transplantation; disease progression; renal insufficiency, chronic; logistic models; risk factors.

How to cite this article: Elihimas Jr *et al*. Modeling of covariates predicting renal allograft failure within six months after transplantation. ABCS Health Sci. 2022;47:e022204 https://doi.org/10.7322/abcshs.2020112.1566

Received: Jul 10, 2020
Revised: Nov 16, 2020
Approved: Feb 08, 2021

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Declaration of interest: nothing to declare
Funding: CAPES (code 001), PFAUPE

INTRODUCTION

Chronic kidney disease (CKD) is an important public health problem and represents a challenge to management due to the increase in the number of patients and correlated psychosocial factors[1,2]. CKD is classified into five stages (I to V) according to the estimated glomerular filtration rate (eGFR). In stage V of CKD the renal function becomes unsatisfactory, with a eGFR<15mL/min/1.73m^2, thus requiring start renal replacement therapy (RRT) which can be hemodialysis (HD), peritoneal dialysis or kidney transplantation (KT)[2].

Despite the survival of patients in RRT and technological evolution, high mortality (19.9%) among Brazilians in RRT is still observed[3]. In this sense, KT confers the best quality of life and survival among RRTs[2,4]. In Brazil, studies indicate that successful KT is economically more viable after 2 years, when compared to maintenance in RRT[2,4]. However, a portion of transplanted patients return for dialysis or progress to death[4]. Unfortunately, some risk covariates may contribute to the failure of KT, such as viral infections, allograft dysfunctions and systemic diseases[5].

In view of the above, this study aimed to model a logistic regression with pre- and post-KT risk covariates capable of predicting secondary allograft dysfunction requiring RRT or reaching stage V of CKD until the first 6 months after KT.

METHODS

Study Design

This is a retrospective cohort study with transplanted recipients. Medical records of the post-KT outpatient clinic of a reference hospital located in Recife, PE, Brazil, were analyzed. The sample included KT receptors from 2011 to 2018 followed in the post-KT outpatient clinic. Transplanted with insufficient data or who abandoned follow-up were excluded (Figure 1).

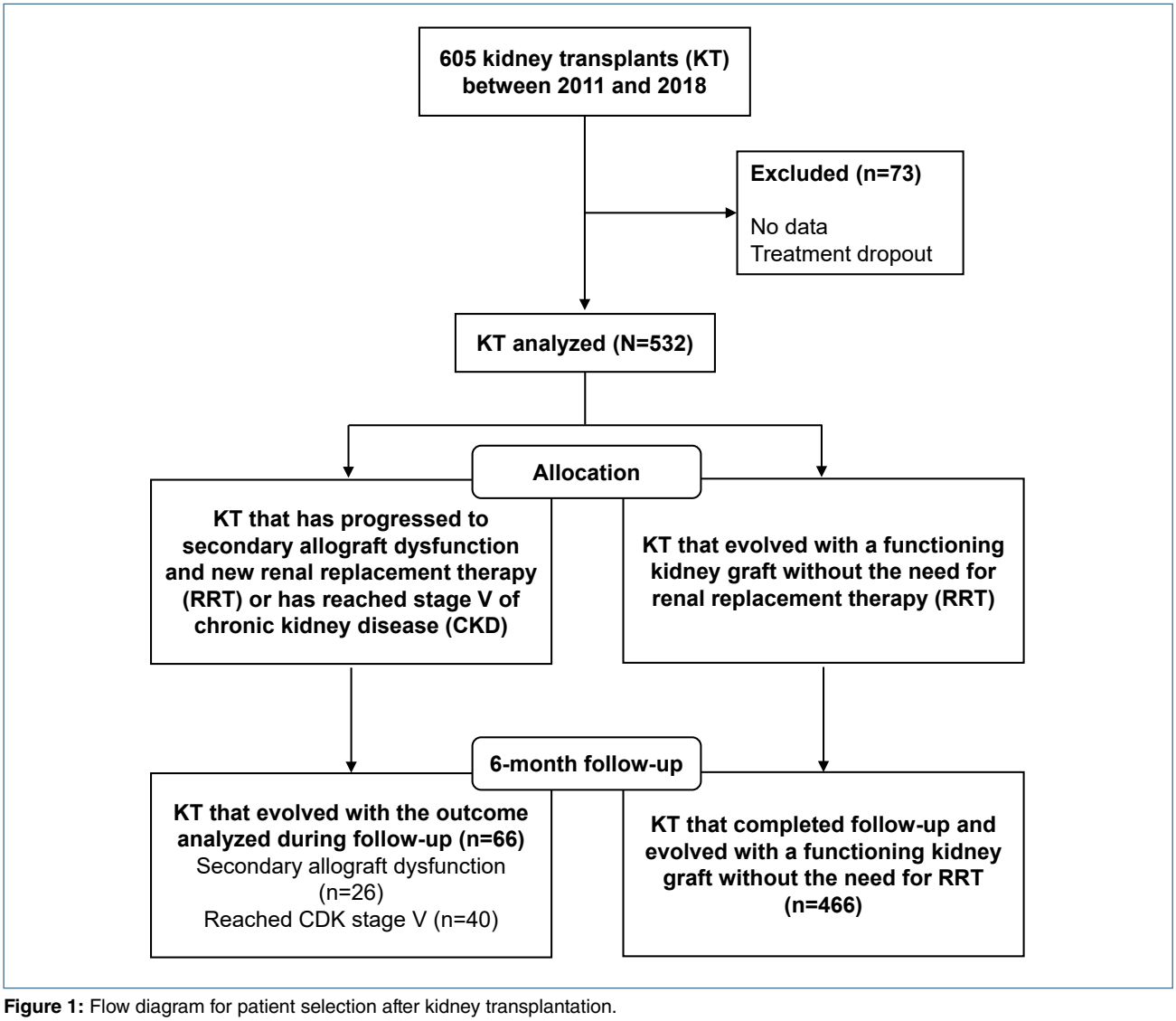

Figure 1: Flow diagram for patient selection after kidney transplantation.

The research was approved by the Research Ethics Committee of UPE according to process 2,520,459 (CAAE: 82587418.6.0000.5192), following the Brazilian ethic guidelines.

Outcome variable

KT patients who evolved the first 6 months after the transplant with secondary allograft dysfunction and new RRT or reach to stage V of CKD estimated by the equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[6]. The primary causes of renal graft dysfunction were excluded to avoid confounding factors[7].

Explanatory variables

They were grouped into the following categories: donor type, demographic, immunological, pre-KT and post-KT comorbidities, infectious and laboratory.

The type of donor was categorized as a living donor (LD), standard criteria deceased donor (SDD) or expanded criteria deceased donor (ECD)[5].

Age, biological sex and self-reported skin color comprised demographic covariates. Recipients ≥60 years were considered elderly[8].

Immunological covariates used data from the main histocompatibility complex and number of incompatibilities in the human leukocyte antigen system (HLA) class I (A and B) and class II (DR), the HLA panel reactive antibody (PRA) and the number of episodes of acute cell-mediated rejection (ACR) or acute antibody-mediated rejection (AAR) up to 6 months after KT. Suspected rejections were evaluated in renal biopsies by nephropathologists using Banff criteria, according to the most updated version at the time of KT. The last version adopted was from 2017[9].

Pre-KT comorbidities were nutritional status, systemic arterial hypertension (SAH) and diabetes mellitus (DM). Nutritional status was assessed according to body mass index (BMI) recorded in the medical records, being subdivided into low weight (BMI<18.5kg/m^2), normal weight (18.5≤BMI<25.0kg/m^2), overweight (25.0≤BMI<30.0kg/m^2) and obesity (BMI≥30kg/m^2). SAH and DM were obtained in the medical records of the pre-KT outpatient clinic.

Post-KT comorbidities were SAH and new-onset DM after transplant (NODAT). Post-KT SAH was identified in a non-hypertensive patient who presented a diagnosis recorded in the medical records by the nephrologist after KT. NODAT were considered the following cases: classic symptoms of DM added to casual glycemia with glucose concentration ≥200mg/dL; fasting glucose (FG) with at least 2 values ≥126mg/dL and at least 8 h of fasting; oral glucose tolerance test after 2h with glycemia ≥200mg/dL and glycated hemoglobin (HbA_{1C})≥6.5%[10].

Infectious covariates were bacterial pyelonephritis, cytomegalovirus nephritis (CMV) and poliomavirus nephropathy (BKPyV). Bacterial pyelonephritis was defined as the presence of urinary symptoms associated with positive uroculture with 10^5 colony-forming units/mL with increased serum creatinine associated. CMV DNA was quantified in plasma by polymerase chain reaction (PCR) in KT with a compatible clinical picture of CMV infection. As a worsening of renal function without further clinical explanation, BKPyV DNA was quantified also in plasma by PCR. Confirmation of the clinical diagnosis of infections was performed in renal biopsies by a nephropathologist.

Laboratory covariates were obtained from the values recorded in the medical records of the 6-month post-KT consultation. Hemoglobin (reference values [RV] for CKD: 10-12 g/dL), hematocrit (RV: 30-33%), phosphorus (RV: 2.5-4.5 mg/dL), calcium (RV: 5.5-10.5mg/dL), albumin (RV: 3,3.5-4.5g/dL), creatinine (RV: 0.6-1.3mg/dL), FG (RV: 70-99mg/dL), HbA_{1C} (RV: 4.0-5.6%) and 24-hour proteinuria (Pt24h) (<300mg/24h).

Institutional Protocol for Immunosuppression (PI-IMS) of the *Real Hospital Português de Beneficência* in Pernambuco (RHP/PE)

All KT were submitted to PI-IMS of RHP/PE consisting of 15mg/kg of methylprednisolone (MP) up to 2 hours before induction, maximum dose of 1g. Maintenance was performed with combinations of antimetabolic/antiproliferative mycophenolate sodium (MPS) or azathioprine (AZA), caucineurin inhibitor (I-CaN), and inhibitors of the target protein of rapamycin in mammals (I-mTOR). All immunosuppression regimens were associated with prednisone (PRED). The antimetabolic drugs used were AZA or MPS. The I-mTOR used were everolimus (EVE) or sirolimus (SIR) and I-CaN were cyclosporine-A (CyA) or tacrolimus (TAC). Until 2012 the second induction drug used was the α-chain blocker of interleukin-2 receptors (IL-2R) basiliximab and then replaced by human antithylobulin rabbit immunoglobulin called thymoglobulin (Thymo).

Sensitized receptors were considered: retransplanted with PRA ≥50% or with the presence of donor-specific antibody (DSA). Non-sensitized receptors were represented by PRA<50%, first KT and absence of DSA.

Tacrolimus was adjusted to a serum level between 4 and 8 ng/mL in sensitized receptors and between 3 and 5 ng/mL in non-sensitized receptors. EVE or SIR were adjusted to levels between 3 and 6 ng/mL.

Delayed graft function (DGF) was defined as renal transplant failure to function immediately, with the need for dialysis in the first week after KT[5]. The kidney of a deceased donor aged ≥60 years or aged between 50 and 59 years with 2 of the following criteria was considered: a) serum creatinine ≥1.5 mg/dL, b) history of SAH, c) death by stroke[11].

Between 2011 and 2015, induction was performed with MP and basiliximab, and maintenance with CyA or TAC+AZA+PRED for

non-sensitized recipients and CyA or TAC+MPS+PRED for sensitized. Between 2015 and 2018, induction was performed with MP+Thymo (3 mg/kg) for non-sensitized recipients and maintenance with EVE or SIR+TAC+PRED. Sensitized receptors were induced with Thymo (6 mg/kg), administered in doses of 2 mg/kg on days 0, 3 and 6 post-KT. The maintenance PI-IMS was instituted with TAC+MPS. In all maintenance the pred dose was 0.5 mg/kg, with a maximum dose of 30 mg/day[1,3].

Cold Ischemia Time

It was defined as the interval between the clamping of the aorta with infusion of cold preservation solution in the donor and the moment the renal graft was inserted into the abdominal cavity of the recipient.

Hypothermic Pulsatile Machine Perfusion (HPMP)

HPMP was indicated in the following situations: a) kidney from ECD; b) kidney from SDD if the presumed ischemia time was >24 hours; c) final serum creatinine of the donor ≥1.8 mg/dL. In the course of the capture process, these kidneys were installed in the HPMP after a cold storage period upon arrival at the hospital. The length of stay in the HPMP was 50% of the time in cold storage with at least 6 hours and maximum individualized time.

Statistical analysis

Data were entered and analyzed at Stata (StataCorp LP, College Station, Texas, USA, Release 14.0, 2015). Categorical variables were presented at absolute and relative frequencies, while continuous on average ± standard deviation after Kolmogorov-Smirnov test. The analysis of the curves is two-tailed with $p \leq 0.05$.

Continuous parameters were reclassified into categories following scientific standards. Associations between biological, clinical and CKD-related factors pre- and post-KT were established by Pearson's X^2 or Fisher's exact. In the association measures, the relative risk (RR) was used with a 95% confidence interval (95%CI). The multivariate analysis was modeled by stepwise-forward logistic regression[12] and the selection criteria was used $p \leq 0{,}20$ in the bivariate stage. In the second stage of the regression, p>0.10 was used as an exit criterion. From the definition of the explanatory variables present in the model, vertical collinearity was verified by means of the variance inflation factor (VIF), excluding those with VIF>5. The magnitude of the effect of each explanatory variable was estimated using the crude odds ratio (OR) and 95% CI[12]. In the final stage of the modeling, the adjusted OR were calculated. At all stages of modeling, biological plausibility was considered. Finally, the evaluation of the receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used to evaluate the accuracy and performance of the predictor model.

RESULTS

Of the 605 KT, 73 were excluded (12.1%; CI95%: 9.7–14.9) by insufficient data or abandonment of follow-up. The remaining 532 KT were included in the multivariate analysis. In the first 6 months after KT, 26 (4.9%; CI95%:3.3–7.1) receptors presented secondary allograft dysfunction requiring RRT and 40 (7.5%; CI95%:5.6–10.1) reached stage V of CKD, establishing in 12.4% (95%CI:9.9–15.5) the prevalence of the outcome variable.

Table 1 describes the pre-KT explanatory covariates related to the return to RRT or reach to stage V of CKD up to 6 months of KT. Elderly recipients, ECD, time between the onset of RRT and the KT (ΔT-RRT&KT) between 5 and 10 years and ΔT-RRT&TK>10 years are associated with the outcome variable. In addition, recipients with a history of DM have a risk approximately 3 times higher of presenting the outcomes analyzed.

Among the post-KT explanatory covariates, the presence of DGF doubles the risk of the analyzed outcomes, with a relative risk 9 times higher when the period is >4 weeks (Table 2).

Pyelonephritis of the allograft after KT is associated with the outcome variable. Aggressor events on allograft scans in the first 6 months after KT, both infectious and immunological, contributed significantly to unfavorable allograft outcomes (Table 3).

Laboratory covariates were obtained in the medical consultation 6 months after KT (Table 4). FG ≥126mg/dL, hemoglobin <10g/dL, serum calcium <8,5mg/dL, serum albumin <3,5g/dL and Pt24h ≥300mg/24h were risk covariates for the studied outcomes.

Table 5 presents the multivariate model of explanatory covariates related to the return to RRT or reach to stage V of CKD up to 6 months post-KT. Elderly recipients, ΔT-RRT&KT between 5 and 10 years, ΔT- RRT&KT>10 years, antecedent of DM increase the chance of the outcomes analyzed. When infectious covariates were analyzed within 6 months post-KT, allograft pyelonephritis and BKPyV nephropathy present a higher odds ratio for the combined outcome. Among the rejection mechanisms, AAR was the one that stood out the most with about 5 times the chance of returning to RRT or reaching stage V of CKD up to 6 months of KT. Serum calcium levels <8.5 mg/dL also presented a odds ratio close to 5 times for the outcome variable and Pt24h≥300mg/24h proved to be the main risk covariate among all analyzed. The AUC of the ROC curve of the predictive model presented accuracy of 88.07% (statistic C=0.8807) and the mean VIF of the explanatory variables inserted in the final model was 1.81.

DISCUSSION

The construction of the regressive model was based on predicting secondary allograft dysfunction in need of new RRT or reaching stage V of CKD until the sixth month after KT. The modeling identified recipients aged ≥60 years, ΔT-RRT&KT>5 years,

Table 1: Pre-transplant covariates related to secondary allograft dysfunction requiring RRT or reaching stage V of CKD within the first six months after kidney transplantation

Explanatory covariates	Outcome (n=66)	Functioning allograft (n=466)	RR (IC95%)	*P*
Age ≥ 60 years	25 (38.5%)	091 (19.6%)	1.39 (1.06–1.83)	0.017
Male	40 (60.6%)	286 (61.4%)	0.97 (0.57–1.64)	0.905
Diabetes mellitus	18 (33.3%)	072 (15.5%)	2.71(1.46–5.04)	0.002
Systemic arterial hypertension	47 (79.7%)	345 (74.0%)	1.37(0.70–2.67)	0.351
Obesity	07 (10.8%)	034 (7.3%)	1.53(0.65–3.62)	0.329
Self-reported skin colour				
White	19 (28.8%)	086 (18.4%)	Reference	-
Multiracial	41 (62.1%)	342 (73.4%)	0.54 (0.30–0.98)	0.043
Black	06 (9.1%)	038 (8,1%)	0.71 (0.26–1.93)	0.508
Nutritional status				
Normal	39 (59.1%)	251 (53.9%)	Reference	-
Low weight	19 (28.8%)	138 (29.6%)	0.89 (0.49–1.59)	0.686
Overweight	06 (9.1%)	039 (8.4%)	0.99 (0.39–2.49)	0.983
Obese	02 (3.0%)	038 (8.1%)	0.34 (0.08–1.46)	0.147
Donor status				
Alive	01 (1.6%)	040 (8.6%)	Reference	-
Deceased standard	40 (63.5%)	366 (78.7%)	4.37 (0.58–32.6)	0.151
Deceased of expanded criterion	22 (34.9%)	059 (12.7%)	14.9 (1.93–115.1)	0.010
ΔT-RRT&KT				
≤5 years	30 (47.6%)	306 (66.1%)	Reference	-
>5 and ≤10 years	21 (33.3%)	114 (24.6%)	1.87 (1.03–3.42)	0.039
>10 years	12 (19.1%)	043 (9.3%)	2.85 (1.35–5.97)	0.006
Mismatch between recipient and donor				
HLA A				
0 mm	03 (4.9%)	043 (9.4%)	Reference	-
1 mm	16 (26.2%)	219 (47.8%)	1.05 (0.29–3.75)	0.944
2 mm	42 (68.9%)	196 (42.8%)	3.07 (0.91–10.4)	0.071
HLA B				
0 mm	03 (4.9%)	047 (10.3%)	Reference	-
1 mm	28 (45.9%)	216 (47.3%)	2.03 (0.59–6.96)	0.260
2 mm	30 (49.2%)	194 (42.4%)	2.42 (0.71–8.29)	0.158
HLA DR				
0 mm	21 (34.4%)	144 (31.5%)	Reference	-
1 mm	30 (49.2%)	246 (53.8%)	0.83 (0.46–1.51)	0.555
2 mm	10 (16.4%)	067 (14.7%)	1.02 (0.47–2.29)	0.955
Receiver sensitization				
Not sensitized	46 (74.2%)	364 (79.0%)	Reference	-
Moderate sensitized	11 (17.7%)	071 (15.4%)	1.22 (0.61–2.48)	0.571
Hypersensitized	05 (8.1%)	026 (5.6%)	1.52 (0.56–4.16)	0.413
Retransplantation				
No	59 (96.7%)	448 (97.0%)	Reference	-
Yes	02 (3.3%)	014 (3.0%)	1.08 (0.24–4.89)	0.916
Cold ischemia in hours				
<12h	07 (12.3%)	057 (13.7%)	Reference	-
12-18h	15 (26.3%)	136 (32.7%)	0.89 (0.35–2.32)	0.824
18-14h	18 (31.6%)	117 (28.1%)	1.25 (0.49–3.17)	0.634
24-30h	08 (14.0%)	061 (14.7%)	1.07 (0.36–3.13)	0.905
>30h	09 (15.8%)	045 (10.8%)	1.62 (0.56–4.71)	0.368
Use of HPMP	18 (38.3%)	128 (28.1%)	1.58 (0.85–2.95)	0.147

RR: relative risk; CI95%: 95% confidence interval; ΔT-RRT&KT: time between initiation of renal replacement therapy and kidney transplantation; HLA: human leukocyte antigen; mm: mismatch; HPMP: hypothermic pulsatile machine perfusion.

Table 2: Clinical covariates, presence, and time of delayed graft function in the post-transplantation period related to secondary allograft dysfunction requiring RRT or reaching stage V of CKD within the first six months after kidney transplantation

Explanatory covariates	Outcome (n=66)	Functioning allograft (n=466)	RR (IC95%)	*P*
Systemic blood pressure*				
< 140/90 mmHg	04 (7.4%)	058 (12.6%)	Reference	-
140-149/90-99 mmHg	04 (7.4%)	064 (13.8%)	0.91 (0.22–3.79)	0.893
150-159/100-109 mmHg	32 (59.3%)	255 (55.2%)	1.82 (0.62–5.34)	0.276
≥ 160/110 mmHg	14 (25.9%)	085 (18.4%)	2.39 (0.75–7.62)	0.141
NODAT	24 (51.1%)	174 (37.8%)	1.72 (0.95–3.15)	0.075
Post-transplant hypertension**	42 (91.3%)	388 (85.6%)	1.75 (0.61–5.07)	0.296
Delayed graft function				
Absent	09 (18.0%)	148 (32.2%)	Reference	-
Present	41 (82.0%)	312 (67.8%)	2.16 (1.02–4.56)	0.043
Period in delayed graft function				
< 1 week	20 (30.3%)	239 (51.3%)	Reference	-
1-2 weeks	09 (13.6%)	105 (22.5%)	1.02 (0.45–2.32)	0.954
2-3 weeks	04 (6.1%)	064 (13.7%)	0.74 (0.25–2.26)	0.606
3-4 weeks	03 (4.5%)	019 (04.1%)	1.88 (0.51–6.92)	0.339
> 4 weeks	30 (45.4%)	039 (08.4%)	9.19 (4.75–17.8)	0.001

RR: relative risk; CI95%: 95% confidence interval; NODAT: new-onset diabetes mellitus after transplantation or diabetes of recent onset after kidney transplantation, requiring prescription of oral hypoglycemic or subcutaneous insulin; *Mean blood pressure measured in three subsequent consultations after kidney transplantation; **Hypertension after kidney transplantation in patients without a history of hypertension requiring prescription of antihypertensive medication.

Table 3: Post-transplant infectious and immunological covariates related to secondary allograft dysfunction requiring RRT or reaching stage V of CKD within the first six months after kidney transplantation.

Explanatory covariates	Outcome (n=66)	Functioning allograft (n=466)	RR (IC95%)	*P*
Nephritis by CMV	33 (55.9%)	199 (43.4%)	1.65 (0.96–2.86)	0.069
BKPyV nephropathy	13 (25.0%)	031 (6.8%)	4.58 (2.21–9.46)	0.001
Pyelonephritis within 6 months	34 (59.6%)	155 (33.5%)	2.92(1.67–5.14)	0.001
RAMC	19 (34.5%)	069 (15.3%)	2.91 (1.58–5.37)	0.001
RAMA	07 (13.0%)	020 (4.4%)	3.26 (1.31–8.11)	0.011
Immunosuppression				
Induction				
Methylprednisolone	01 (1.6%)	025 (5.4%)	Reference	-
Methylprednisolone + Thymoglobulin	49 (83.1%)	358 (77.5%)	2.32 (0.30–17.8)	0.417
Methylprednisolone + IL-2R	09 (15.3%)	079 (17.1%)	1.94 (0.23–16.3)	0.543
Maintenance				
Antimetabolic/antiproliferative				
None	05 (9.1%)	101 (22.2%)	Reference	-
Azathioprine	08 (14.5%)	055 (12.1%)	2.94 (0.92–9.42)	0.070
Sodium mycophenolate	42 (76.4%)	299 (65.7%)	2.83 (1.09–7.37)	0.032
Calcineurin inhibitor				
Cyclosporine or Tacrolimus				
No	02 (3.4%)	002 (0.4%)	Reference	-
Yes	57 (96.6%)	462 (99.6%)	0.12 (0.02–0.89)	0.038
I-mTOR				
Everolimus or Sirolimus				
No	26 (50.1%)	293 (63.8%)	Reference	-

RR: relative risk; CI95%: 95% confidence interval; CMV: cytomegalovirus; BKPyV: BK-poliomavirus; RAMC: acute rejection mediated by T-cells; RAMA: antibody-mediated acute rejection; IL-2R: interleukin-2 α-blocker (Basiliximab); I-mTOR: rapamycin target protein inhibitors in mammals.

previous DM, infectious and immunological aggressions on allograft after KT, hypocalcemia and Pt24h≥300mg/24h were the explanatory covariates for the outcome variable studied. Significant covariate will be detailed for better understanding of the model.

Elderly Receiver

Patients with CKD ≥60 years typically spend more time on RRT, a characteristic related to the KT waiting list. According to data provided by the Brazilian National System of Organ Transplants, from 25,163 patients on the waiting list for KT in December 2019,

Table 4: Post-transplant laboratory covariates related to secondary allograft dysfunction requiring RRT or reaching stage V of CKD within the first six months after kidney transplantation.

Explanatory covariates	Outcome (n=66)	Functioning allograft (n=466)	RR (IC95%)	*P*
Fasting glycemia				
≤99 mg/dL	33 (54.1%)	292 (63.1%)	Reference	-
100-125 mg/dL	15 (24.6%)	121 (26.1%)	1.10 (0.57–2.09)	0.779
≥126 mg/dL	13 (21.3%)	050 (10.8%)	2.30 (1.13–4.67)	0.021
Serum hemoglobin				
10-12 g/dL	26 (40.6%)	133 (28.6%)	Reference	-
<10 g/dL	18 (28.1%)	027 (5.8%)	3.41 (1.64–7.07)	0.001
>12 g/dL	20 (31.2%)	305 (65.6%)	0.33 (0.18–0.62)	0.001
Hematocrit				
30-36 %	28 (45.1%)	113 (24.3%)	Reference	-
<30 %	13 (21.0%)	024 (5.2%)	2.18 (1.00–4.82)	0.053
>36 %	21 (33.9%)	328 (70.5%)	0.26 (0.14–0.47)	0.001
Serum calcium				
8.5-10.5 mg/dL	22 (45.8%)	258 (64.8%)	Reference	-
<8.5 mg/dL	17 (35.4%)	065 (16.3%)	3.07 (1.54–6.11)	0.001
>10.5 mg/dL	09 (18.7%)	075 (18.8%)	1.41 (0.62–3.19)	0.412
Serum phosphorus				
2.5- 4.5 mg/dL	32 (71.1%)	266 (70.2%)	Reference	-
<2.5 mg/dL	09 (20.0%)	103 (27.2%)	0.73 (0.33–1.57)	0.418
>4.5 mg/dL	04 (8.9%)	010 (2.6%)	3.32 (0.99–11.2)	0.053
Serum albumin				
3.5-4.5 g/dL	25 (69.4%)	214 (91.8%)	Reference	-
<3.5 g/dL	11 (30.6%)	014 (6.0%)	6.72 (2.75–16.6)	0.001
>4.5 g/dL	00 (0%)	005 (2.1%)	Not calculated	-
Glycated hemoglobin				
4,0-5,6 %	08 (26.7%)	071 (31.0%)	Reference	-
<4.0 %	07 (23.3%)	066 (28.8%)	0.94 (0.32–2.74)	0.912
>5.6 %	15 (50.0%)	092 (40.2%)	1.45 (0.58–3.60)	0.427
24h proteinuria				
<300 mg/24h	12 (38.7%)	176 (68,2%)	Reference	-
≥300 mg/24h	19 (61.3%)	082 (31.8%)	3.39 (1.57–7.33)	0.002

RR: relative risk; IC95%: 95% confidence interval.

only 2,911 (9.5%) were 60 years or older. Elderly recipients in this cohort[8] are 1.4 times more likely to return to RRT or to reach CKD stage V up to 6 months post-KT.

Most elderly patients have more pre-KT comorbidities[13,14]. A Brazilian study demonstrated 3 times more post-KT cardiovascular events among the elderly[8]. Another risk factor for the elderly with CKD is the higher incidence of nephritis per CMV[15].

Oniscu et al.[13] point out that age is not a risk factor for KT. European studies point out that organs should not be used indiscriminately in elderly patients. However, the literature argues that access to RT should not be denied based solely on the age of the recipient[13,15]. Moreso et al.[15] showed a lower frequency of ACR episodes among kidney receptors at >60 years, and this result was possibly related to lower immunological reactivity regarding allograft in this population group[8,15].

This study was not designed to compare KT in the elderly, however most elderly patients had >5 years of RRT. Elderly recipients on the waiting list have higher mortality and KT is the therapeutic modality that offers higher quality of life and survival for this population.

Time Between Start of Dialysis and Renal Transplant

More than 5 years of waiting between the initial moment of RRT and KT was a risk factor for the outcome variable, a finding consistent with national and international studies[16,17]. The time in RRT is associated with increased cardiovascular diseases, as well as intensifies the risk of infections and malnutrition[18].

This knowledge is of paramount importance to encourage the improvement of the renal allocation system in Brazil since the average waiting list time for mortality-adjusted KT is 5.5 years. Without this estimate, the time increases to approximately 11 years[19]. Therefore, it is necessary that satellite clinics refer early patients admitted to RRT. In addition, health institutions need to increase the efficiency of the registration process on the KT waiting list. Finally, social awareness and awareness campaigns regarding voluntary donation are still necessary.

Table 5: Multivariate model of explanatory covariates related to secondary allograft dysfunction requiring RRT or reaching stage V of CKD within the first six months after kidney transplantation.

Covariates	OR justifiable (95% CI%)*	*P*
Age		
< 60 years	Reference	-
≥ 60 years	1.41 (1.01-1.99)	0.048
Self-reported skin colour		
White	Reference	-
Multiracial	0.42 (0.19-0.92)	0.029
Black	0.76 (0.22-2.63)	0.661
Type od donor		
Living donor	Reference	-
Standard criteria deceased donor	2.00 (0.24-16.5)	0.521
Expanded criteria deceased donor	7.97 (0.91-69.5)	0.061
Time between RRT and TK		
<5 years	Reference	-
>5 and <10 years	2.55 (1.12-5.81)	0.026
>10 years	3.54 (1.27-9.87)	0.016
Previous diabetes mellitus	3.35 (1.51-7.46)	0.003
Pyelonephritis within six months post-KT	2.45 (1.24-4.84)	0.010
BKPyV nephropathy post-transplant	4.99 (1.87-13.3)	0.001
AAR	4.82 (1.35-17.2)	0.015
Serum calcium		
8.5-10.5mg/dL	Reference	-
< 8.5mg/dL	4.72 (2.00-11.1)	0.001
> 10.5mg/dL	0.78 (0.26-2.31)	0.657
24-hour proteinuria		
< 300 mg/24h	Reference	-
≥ 300 mg/24h	5.05 (2.00-12.7)	0.001

*Statistics C=0.8807; AUC ROC=88.07%; VIF=1.81
OR: odds ratio; CI95%: 95% confidence interval; RRT: renal replacement therapy; KT: kidney transplantation; BKPyV: BK-poliomavirus; AAR: acute antibody-mediated rejection.

History of DM

History of DM is a risk factor for both secondary allograft dysfunction and hospital readmission due to infections[20], being a strong aggravating factor in elderly recipients[8].

Transplant recipients with a history of DM have lower mortality when compared to diabetics on the waiting list[1,2]. Due to this higher mortality, candidates with a history of DM are less likely to be transplanted, since they commonly die before the first KT[21]. It is important to highlight that KT is considered the treatment that provides greater survival and better quality of life for patients with pre-KT DM on a waiting list[21].

Bacterial Pyelonephritis

Bacterial urinary infections are the main post-KT infectious complications, besides increasing the chances of returning to RRT[22]. Bacterial pyelonephritis of the allograft in the post-KT represents a substantial burden on hospital costs, because its manifestation causes read hospitalizations, broad-spectrum antibiotic therapy and greater biopsychosocial risk[22].

In the literature, the commonly associated etiological agent is Escherichia coli[23], and this agent impacts in terms of acute kidney injury and deterioration of graft function after KT[22]. Cohort of 380 transplant recipients identified allograft bacterial pyelonephritis as an independent predictor of renal graft dysfunction[24]. Furthermore, recurrent symptomatic infections with increased serum creatinine during the first year after KT have a negative impact on long-term allograft function[24].

Nephropathy by BK Poliomavirus

The imbalance between the different viral infections throughout life and the immunosuppressive drugs used in the maintenance of KT are the main factors that corroborate BKPyV infection[25]. The combination TAC+MPS+PRED may be associated with a higher incidence of BKPyV infection[25], a maintenance regimen used in this cohort. The main prognosis of BKPyV is the outcome in nephropathy, which increases the chances of allograft loss[26]. In this group, the rapid diagnosis and reduction of immunosuppression are necessary measures to reduce the chances of renal graft loss[25,26].

An explanation for the increased risk of outcomes analyzed by BKPyV nephropathy is associated with pi-IMS adopted until 2015, which performed induction with MP+Thymo and maintenance with TAC+MPS+PRED. Higher frequency of BKPyV infections in kidney transplant recipients is associated with the use of more potent immunosuppressive regimens, in particular the combination of TAC and Mycophenolate[27]. After this period, I-mTOR were introduced as immunosuppressants in the service. In 2019 Transform study[27] demonstrated a decrease in CMV and BKPyV infection in 2,037 kidney transplant recipients who used I-mTOR in maintenance. The use of an immunosuppressive regimen with Thymo+MP and TAC+MPS+PRED may have favored the early incidence of BKPyV nephropathy and, consequently, the return to RRT.

AAR up to 6 months after KT

Although the frequency of AAR In the group that returned to RRT was 3 times higher than in the functioning allograft group after 6 months of RT, the frequency of AAR in the present study (5.1%) is within the internationally estimated range (3-10%).

AAR up to 6 months post-RT is a risk factor for return to RRT in other cohorts[28,29], although other covariates, such as the use of SDD with high time of cold ischemia and retransplantation, also correlate with increased risk of AAR and loss of renal function[28].

Hypocalcemia

Post-RT hypercalcemia is partly due to hypophosphatemia secondary to persistent hyperparathyroidism, which is a compensatory mechanism[30]. The persistence of high calcium levels has been confirmed in other studies as a risk factor for the return to dialysis and even for death[30,31]. In turn, post-RT hypocalcemia is poorly analyzed and the number of studies is still scarce. In this cohort, it

is associated with a nearly 5-fold higher risk of the outcome variable. Despite the strong correlation between the outcome and the explanatory covariate, this finding was not considered a new risk factor, but rather an indication of allograft failure.

In the progression of CKD when eGFR<50 mL/min/1.73m^2 changes in bone mineral metabolism are evident[32]. Both total and ionized serum calcium tend to change during the course of CKD due to phosphate retention, decreased calcitriol secretion, reduced intestinal calcium absorption, and skeletal resistance to the hypercalcemic action of parathyroid hormone[32]. Therefore, hypocalcemia is possibly related to progression to advanced stages of CKD.

Thus, the clinician should pay close regard to the onset of post-KT hypocalcemia and its possible relationship with allograft failure. Surveillance on elevated levels of intact parathyroid hormone is also necessary, which may be related to both persistent fibroblast growth factor-23 levels and post-TR tubulopathy[30,33].

24h proteinuria ≥ 300 mg

Elevated pt24h is the most important explanatory covariate for the recipients to evolve to the analyzed outcome, with a odds ratio 5 times higher. Proteinuria is a well-established marker of CKD progression and is associated with a reduction in the number of glomeruli and nephron mass and cardiovascular events[34].

Proteinuria soon after KT can already be identified, however, it tends to reduce or disappear after a few days. This condition, when persistent for more than 3 months post-KT, carries risks for the progression and failure of the allograft[35].

The causes of pt24h post-KT are diverse, and other risk factors may contribute to its development, such as post-KT SAH, age, number of episodes of acute rejection and NODAT[35]. Indirectly, these covariates affect allograft survival and should be considered before and after KT.

In the case of a post-KT prognosis, elevated Pt24h may be responsible for the shorter shelf life of renal function of transplanted CKD[35]. In this respect, therapy with angiotensin conversion enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) is discussed[35]. ACE Inhibitor and ARBs lead to blockade of the renin-angiotensin-aldosterone system (RAAS) and cause decreased blood pressure, intraglomerular capillary pressure, proteinuria and cardiovascular events[36]. Thus, the blockade of RAAS reduces the appearance of interstitial fibrosis and tubular atrophy[35]. However, these drugs may intensify or accentuate hyperkalemia present in patients with DGF[35]. In addition, they can reduce hematocrit in rates between 5 and 10%[35]. It is essential that the control of this covariate is established in the post-KT receptors early due to the greater chance of renal graft loss caused by elevated Pt24h[5].

Limitations

Initially, the risk of pre-KT care was different in dialysis units that refer patients to the referral center. However, the team followed the scientific rigors of validation, strict protocols with robust evaluation methodology to minimize biases. Despite using retrospective data, it is frequent to use this dataset model in RT when analyzing new drugs, implementation of protocols and cost-effectiveness of therapeutic innovations. HPMP was not included in all analyses due to restricted use and by PI-IMS prioritizing it for SDD kidneys with presumed cold ischemia period >24 hours or kidneys of ECD with creatinine >1.8 mg/dL. The impossibility of offering HPMP to all patients may have behaved as a confounding variable. However, it presented low vertical collinearity.

In addition, the use of Kidney Donor Profile Index (KDPI) and Estimated Post Transplant Survival (EPTS) score was not feasible because it was implemented only in 2014 for the USA and was not an allocation criterion adopted in the Brazilian National System of Organ Transplants.

Finally, the prediction process may present problems when variables are used to select significant attributes (CKD-EPI) and reuse themselves as predictors. Andrade and Tedesco[37] analyzed this issue and introduced criteria for the identification of collinear variables. However, the absence of significant collinearity between the predictive explanatory covariates (age and self-reported skin color) and the outcome variable (eGFR by CKD-EPI) is highlighted. However, in order to exclude the possibility of overadjustment, in new studies the train-test split method of machine learning should be considered for better interpretation of renal function estimates when the CKD-EPI equation is used.

Conclusion

The predictive model identified that the elderly receptors, ΔT-RRT&KT>5 years, pre-KT DM, bacterial pyelonephritis, BKPyV nephropathy, AAR, hypocalcemia and Pt24h≥300mg/24h are independent risk covariates for secondary renal graft dysfunction and reach to stage V of CKD in the first 6 months after KT. The modeling presents accuracy of 88.1% and average VIF of 1.81.

ACKNOWLEDGEMENTS

To the Real Hospital Portuguese de Beneficência in Pernambuco, which allowed the research to be conducted through the Alberto Ferreira da Costa Institute of Teaching and Research.

To the National Organ Transplant System and the Brazilian Society of Organ Transplantation. Special thanks to Thiago Quintas Câmara (data analyst of the Brazilian Registry of Transplants), Noemy Gomes (Coordinator of the Transplant Center of the state of Pernambuco) and Melissa Albuquerque Moura (Manager of the Operational Technical Center of Solid Organs and Tissues of Pernambuco) for helping to access databases in the state of Pernambuco and the Ministry of Health of Brazil. We thank Prof. Dr. Paulo Hugo do Espírito Santo, from the Polytechnic School of Pernambuco (POLI), for his assistance in statistical analysis.

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