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Original Article

Common predictors of adverse outcomes in adult deceased donor kidney transplant recipients with varying sensitization

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Abstract: Objective: Our objective was to identify consistent predictors of multiple adverse outcomes of adult deceased donor (DD) kidney transplant recipients (KTRs) of varying sensitization status. Methods: We used the national transplant database in studying 62037 adult DD-KTRs between Dec. 2007 and Jun. 2015 stratified into sensitization cohorts based on calculated panel reactive antibody (CPRA) of <10%, 10%-79%, and ≥80%. We used multivariable logistic regressions for the analysis of risks for delayed graft function (DGF), and of acute rejection (AR) and hospitalization in the first year of transplant, and Cox hazard regression for 5-year overall graft loss (OAGL) and death. Results: The kidney donor risk index (KDRI) highest two quartiles ≥1.45 and 1.15-1.44 were the most consistent predictors for 100% of adverse outcomes (OAGL, death, DGF, AR, and hospitalization) with high significance (P<0.0001) across all sensitization cohorts. The two risk factors that were consistently associated with 80% of adverse outcomes across sensitization cohorts were: (1) pre-transplant dialysis duration >2 years was significantly associated with increased risks of overall graft loss, death, DGF, and hospitalization; and (2) Black KTR race was significantly associated with increased risks of DGF, AR, and hospitalization, and decreased risk of death. Diabetes and KTR age >65 (years) were significant risk factors for overall loss and death across sensitization cohorts. Conclusions: The two highest KDRI quartiles, pre-transplant dialysis duration >2 years, and African American recipient race are consistent predictors of multiple adverse outcomes in adult DDKTRs across sensitization strata and should be among the factors considered in clinical decision-making and research models in kidney transplantation.

Keywords: Outcomes, sensitization, risk factors in transplants, predictors

Introduction

Kidney transplant (KT) provides survival, quality of life, and economic advantages over dialysis for patients with end-stage renal disease although there are still adverse complications hindering its long-term benefits [1, 2]. Sensitized kidney transplant recipients (KTRs) are more likely to suffer post-transplant complications and calculated panel reactive antibody (CPRA) level, later supplanted by calculated PRA (CPRA), has been the most frequently used objective parameter to gauge sensitization [3, 4]. The success of KT is profoundly undermined by adverse outcomes such as delayed graft function (DGF), acute rejection (AR), hospitalization, death, and overall graft loss (OAGL). And mitigation strategies could be employed to target these undesirable transplant outcomes. However, the success of interventions for the reduction of adverse KT outcomes would depend on the clinician's timely identification of KT recipients (KTRs) at risk for post-transplant complications. Therefore, clinicians need to have simple, easily accessible, and usable predictors of multiple adverse outcomes that are highly consistent to be applicable across sensitization strata of KTRs. The current literature has studies associating risk factors with single or few transplant outcomes. Unfortunately, no study has identified risk factors that can concurrently predict multiple adverse kidney transplant outcomes in adult DDKTRs of varying

degrees of sensitization as evidenced by the CPRA level [5-11].

Our objective for this study was to identify risk factors that could consistently predict multiple adverse outcomes: overall graft loss, death, delayed graft function, acute rejection, and hospitalization in adult deceased-donor (DD) KTRs belonging to different CPRA strata [12]. We hypothesized that only a few variables could consistently predict multiple outcomes across the KTRs' sensitization strata. To answer our study questions, we analyzed 7.5-year data of adult deceased donor kidney transplants in the United States from the Organ Procurement Transplantation Network (OPTN) [13]. We identified independent risk factors predicting adverse outcomes including recipient characteristics, clinical variables, and a composite indicator of donor characteristics, the kidney donor risk index (KDRI) [14]. The findings of this study would provide high-yield risk factors useful in identifying adult DDKTRs who could benefit from preventive or risk mitigation strategies post-transplant. This report would also provide data on the impact of recipient sensitization status on the associations between independent risk factors and adverse outcomes in deceased-donor KTRs [12].

Methods

Data source

The University of Florida Institutional Review Board approved this study, which used data from the Organ Procurement Transplantation Network (OPTN). The OPTN system includes data on all donors, wait-listed candidates, and transplant recipients in the US submitted by the members of the Organ Procurement and Transplantation Network (OPTN) and has been described elsewhere [13]. The Health Resources and Services Administration oversees the activities of the OPTN and SRTR contractors. This study was performed following the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Study design and population

This observational retrospective cohort study that utilized data from OPTN included adult patients (age ≥18 years) who received a deceased-donor kidney transplant (DDKT) between 5 Dec. 2007 and 16 Jun. 2015 with complete information on CPRA, induction immunosuppression, and kidney donor risk index (KDRI). KTRs were excluded from analysis if they: (1) did not receive any of the following induction agents: anti-thymocyte globulin (ATG), alemtuzumab (ALM), or an interleukin-2 receptor antagonist (IL2-RA); (2) had received a living donor kidney transplant; (3) had received multi-organ transplants; or (4) had experienced graft loss or died within the first transplant year of KT, thereby not attaining conditional one-year survival. Based on the Scientific Registry of Transplant Recipients program-specific report technical classification, adult DDKTRs were stratified into three sensitization cohorts based on their CPRA level at the time of kidney transplant as <10%, 10-79%, and ≥80% [15].

Outcomes

The primary outcome was overall graft loss defined as the time from transplant to return to dialysis, re-transplantation, or death with a functioning graft censored for a maximum of five-year follow-up. The secondary outcomes were: (1) patient death defined as the time from transplantation to death, censored for a maximum 5-year follow-up; (2) delayed graft function (DGF) defined as the need for dialysis in the first week of transplant; (3) biopsy-proven acute rejection (BPAR) within the first post-transplant year; and (4) hospitalization within the first post-transplant year.

Covariates

Covariates were selected a priori based on known clinical significance and relevance and included the following: (1) induction agent classified as anti-thymocyte globulin, alemtuzumab, or interleukin-2 receptor antagonist; (2) recipient age, stratified into 18-49 years, 50-64 years, or ≥65 years; (3) body mass index (BMI) of recipients classified as <30 kg/m^2 or ≥30 kg/m^2; (4) recipient's race/ethnicity classified as White, Black, Hispanic, or others; (5) primary (native) renal diagnosis namely: hypertension, glomerulonephritis, diabetes mellitus, polycystic kidney disease, or other; (6) the number of human leukocyte antigen (HLA) mismatches between donor and recipient classified into 0, 1-3, or 4-6; (7) calendar year of transplant either 2007-2010 or 2011-2015; (8) history of previous kidney transplant (yes or

no); (9) steroids maintenance immunosuppression use or not; (10) maintenance immunosuppressive regimen containing calcineurin inhibitor (CNI) with mycophenolate, mammalian target of rapamycin inhibitor, or other; (11) primary insurance coverage is classified as private, public, or other; (12) cold ischemic time is classified as <20 hours or ≥20 hours and; (13) kidney donor risk index (KDRI) as reported in the OPTN database was stratified into <0.96, 0.96-1.14, 1.15-1.44, or ≥1.45. Based on the published OPTN guide, KDRI is derived from a validated formula that includes age, height, weight, ethnicity, history of hypertension and diabetes, cause of death, creatinine, hepatitis C virus (HCV) status, and circulatory death status for deceased donor [16].

Statistical analysis

Baseline counts and percentages of risk factors in CPRA categories are depicted in **Table 1**. No P statistic was computed since the CPRA cohorts were analyzed separately and inter-cohort comparisons were not performed. Within cohorts, data were presented as counts and percentages and compared using the Chi-square test.

Association of risk factors with DGF, AR, and hospitalization were analyzed using multivariable logistic regression models in adult DDKTRs with at least 1 year of graft survival based on being at risk for these events since no exact dates were available for these outcomes in the OPTN dataset [17] and were reported as odds ratio (OR) and 95% confidence interval (CI). The risks of KTR death and overall graft loss (OAGL) were analyzed using Cox multivariable hazard regression models and were reported as Hazards ratio (HR) and 95% CI. In all analyses, Statistical Analysis System software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used, and the significance was at the two-sided *p*-value of <.05.

Results

Baseline characteristics

This study included 62037 deceased-donor KTRs of whom at the time of transplant, 41310 (66.6%), 11093 (17.9%), and 9634 (15.5%) had CPRA levels of <10%, 10-79%, and ≥80%; respectively. The baseline demographic and transplant-related clinical characteristics for KTRs categorized by CPRA cohorts are presented in **Table 1**. Specific indications for kidney transplantation were diabetes mellitus (in 30.6%, 24.3%, and 17.2%); hypertension (in 27.3%, 25.2%, and 18.3%); glomerulonephritis (in 19.9%, 22.2%, and 21.3%); and polycystic kidney disease (in 8.5%, 7.9%, and 6.5%) in <10%, 10-79%, and ≥80% of CPRA cohorts, respectively. Immunosuppression induction agent was ATG in 38708 (62%), alemtuzumab in 9878 (16%), and IL2-RA in 9878 (16%) of KTRs. IL2-RA agent utilization was highest in the CPRA <10% cohort (26.5%) and lowest in the CPRA ≥80% cohort (6.8%). The utilization of ATG induction and maintenance steroids increased in parallel with the CPRA strata. Alemtuzumab utilization was proportionally similar across CPRA strata (**Table 1**).

Delayed graft function

The odds of delayed graft function (DGF) were increased uniformly across CPRA cohorts in association with any pre-transplant dialysis duration (vs. no dialysis), highest two (2) KDRI quartiles (≥1.45 and 1.15-1.44 vs. <0.96), cold ischemic time (CIT) of ≥20 hours, and obesity or Black race/ethnicity of KTRs. In the <10% CPRA cohort, lymphocyte-depleting (either ATG or ALM) induction increased the odds of DGF compared with a non-lymphocyte-depleting agent (**Table 2**) while in the 10-79% and ≥80% CPRA cohorts, the type of induction agent did not change the odds of DGF (**Table 2**).

Acute rejection in the first post-transplant year

Risk factors that increased the odds of acute rejection in the first year of KT across CPRA cohorts were human leukocyte antigen (HLA) mismatches numbering 1-3 and 4-6 (vs. 0); all KDRI quartiles >0.96; and KTR's obesity or AA race/ethnicity. Factors that decreased the odds of acute rejection across CPRA cohorts were KTR age ≥50 years; standard calcineurin inhibitor + mycophenolate immunosuppression, and lymphocyte-depleting (either ATG or ALM) induction (**Table 3**).

Hospitalization in the first post-transplant year

Risk factors associated with the highest odds of hospitalization across CPRA cohorts were the mammalian target of rapamycin inhibitors

Table 1. Baseline patient and transplant-related characteristics

	CPRA[a] 0-9%	CPRA[a] 10-79%	CPRA[a] ≥80%
	N = 41310 (66.6%)	N = 11093 (17.9%)	N = 9634 (15.5%)
Induction Agent			
Antithymocyte Globulin	23764 (57.53)	7504 (67.65)	7440 (77.23)
Alemtuzumab	6601 (15.98)	1734 (15.63)	1543 (16.02)
IL-2RA[b]	10945 (26.49)	1855 (16.72)	651 (6.76)
Kidney Donor Risk Index (Rao)			
<0.96	9523 (23.05)	2934 (26.45)	3280 (34.05)
0.96-1.14	8075 (19.55)	2450 (22.09)	2307 (23.95)
1.15-1.44	10915 (26.42)	2929 (26.40)	2585 (26.83)
≥1.45	12797 (30.98)	2780 (25.06)	1462 (15.18)
Recipient Age Group			
18-49 years	13827 (33.47)	4230 (38.13)	4717 (48.96)
50-64 years	18033 (43.65)	4746 (42.78)	3671 (38.10)
≥65 years	9450 (22.88)	2117 (19.08)	1246 (12.93)
Recipient Body Mass Index ≥30 (kg/m^2)	14998 (36.31)	3915 (35.29)	3145 (32.64)
Recipient Ethnicity			
White	17801 (43.09)	4755 (42.86)	4356 (45.21)
Black	13200 (31.95)	3760 (33.90)	3054 (31.70)
Hispanic	6594 (15.96)	1617 (14.58)	1538 (15.96)
Other	3715 (8.99)	961 (8.66)	686 (7.12)
Primary Renal Diagnosis			
Hypertension	11274 (27.29)	2800 (25.24)	1760 (18.27)
Glomerulonephritis	8248 (19.97)	2459 (22.17)	2052 (21.30)
Polycystic Kidney Disease	3491 (8.45)	886 (7.99)	628 (6.52)
Diabetes Mellitus	12650 (30.62)	2692 (24.27)	1661 (17.24)
Other	5486 (13.28)	2214 (19.96)	3500 (36.33)
Missing	161 (0.39)	42 (0.38)	33 (0.34)
Pre-Transplant Dialysis			
None	8810 (21.33)	2619 (23.61)	2015 (20.92)
1-730 Days	4763 (11.53)	1043 (9.40)	1302 (13.51)
>730 days	27737 (67.14)	7431 (66.99)	6317 (65.57)
No. of Human Leukocyte			
Antigen Mismatch/es			
0	1974 (4.78)	1724 (15.54)	1731 (17.97)
1-3	6949 (16.82)	1871 (16.87)	2813 (29.20)
4-6	32387 (78.40)	7498 (67.59)	5090 (52.83)
Transplant Year			
2007-2010	16797 (40.66)	4101 (36.97)	2902 (30.12)
2011-2015	24513 (59.34)	6992 (63.03)	6732 (69.88)
Kidney Re-Transplant	1627 (3.94)	1962 (17.69)	4473 (46.43)
Steroids Use, Maintenance	27252 (65.97)	8139 (73.37)	7585 (78.73)
Maintenance Regimen			
CNI[c] + MPA[d]	38140 (92.33)	10311 (92.95)	8984 (93.25)
MTORI[e]-containing	1131 (2.74)	262 (2.36)	189 (1.96)
Other	1848 (4.47)	478 (4.31)	420 (4.36)
Missing	191 (0.46)	42 (0.38)	41 (0.43)

Primary Insurance			
Private	10296 (24.92)	2595 (23.39)	2184 (22.67)
Public	30965 (74.96)	8480 (76.44)	7431 (77.13)
Other	49 (0.12)	18 (0.16)	19 (0.20)
CIT[f]			
<20 hours	27005 (65.37)	7393 (66.65)	6435 (66.79)
≥20 hours	14305 (34.63)	3700 (33.35)	3199 (33.21)

[a]CPRA, Calculated Panel Reactive Antibody; [b]IL-2RA, Interleukin-2 receptor antagonist; [c]CNI, Calcineurin inhibitor; [d]MPA, Mycophenolate; [e]MTORI, Mammalian target of rapamycin inhibitor-containing; [f]CIT, Cold ischemia time.

Table 2. Adjusted odds ratios and 95% confidence intervals from logistic regression models for delayed graft function

	CPRA 0-9%			CPRA 10-79%			CPRA ≥80%		
	OR	95%	CI	OR	95%	CI	OR	95%	CI
ATG induction	1.38	*1.30*	*1.46*	1.01	*0.88*	*1.16*	0.91	*0.74*	*1.13*
ALM induction	1.36	*1.25*	*1.48*	1.18	*0.99*	*1.40*	0.99	*0.77*	*1.26*
KDRI 0.96-1.14	1.56	*1.45*	*1.68*	1.32	*1.14*	*1.52*	1.61	*1.40*	*1.86*
KDRI 1.15-1.44	1.80	*1.67*	*1.93*	1.60	*1.40*	*1.84*	1.91	*1.67*	*2.20*
KDRI ≥1.45	1.76	*1.64*	*1.89*	1.71	*1.49*	*1.97*	2.25	*1.92*	*2.63*
Recip. 50-64-yr.	1.04	*0.98*	*1.10*	1.05	*0.94*	*1.18*	1.09	*0.97*	*1.23*
Recip. ≥65 yr.	1.03	*0.96*	*1.10*	1.14	*0.98*	*1.31*	1.07	*0.90*	*1.28*
Recip. BMI ≥30	1.45	*1.38*	*1.53*	1.46	*1.32*	*1.62*	1.67	*1.50*	*1.87*
Recip. Black	1.31	*1.23*	*1.39*	1.46	*1.29*	*1.65*	1.20	*1.05*	*1.36*
Recip. Hispanic	1.22	*1.13*	*1.31*	1.35	*1.16*	*1.56*	1.16	*0.99*	*1.35*
Recip. Another Ethnicity	1.28	*1.17*	*1.40*	1.28	*1.06*	*1.54*	1.08	*0.87*	*1.34*
Diabetes	1.27	*1.16*	*1.38*	1.25	*1.06*	*1.47*	1.04	*0.87*	*1.24*
Glomeruloneph.	0.94	*0.86*	*1.03*	0.88	*0.75*	*1.04*	0.94	*0.81*	*1.09*
Hypertension	0.99	*0.91*	*1.08*	1.00	*0.85*	*1.18*	0.82	*0.69*	*0.96*
PKD	1.01	*0.90*	*1.13*	1.04	*0.83*	*1.31*	0.90	*0.71*	*1.16*
Dialysis <2 years	1.28	*1.16*	*1.41*	1.43	*1.16*	*1.77*	1.28	*1.04*	*1.58*
Dialysis ≥2 years	2.21	*2.06*	*2.37*	2.16	*1.87*	*2.48*	2.21	*1.89*	*2.59*
HLA MM = 1-3	1.22	*1.06*	*1.40*	1.37	*1.14*	*1.64*	1.10	*0.94*	*1.30*
HMA MM = 4-6	1.31	*1.15*	*1.49*	1.24	*1.06*	*1.46*	1.03	*0.89*	*1.21*
Transplant 2011-2015 yr.	1.03	*0.98*	*1.08*	1.09	*0.99*	*1.21*	1.05	*0.93*	*1.18*
Re-transplant	0.94	*0.82*	*1.08*	1.45	*1.25*	*1.67*	1.67	*1.47*	*1.89*
Private Insurance	1.03	*0.49*	*2.17*	1.27	*0.36*	*4.53*	0.59	*0.20*	*1.70*
Public Insurance	1.23	*0.59*	*2.61*	1.53	*0.43*	*5.43*	0.75	*0.26*	*2.15*
CIT ≥20	1.51	*1.43*	*1.58*	1.37	*1.24*	*1.51*	1.41	*1.26*	*1.57*

and the highest two KDRI quartiles ≥1.45 and 1.15-1.44 (vs. <0.96) (**Table 4**). Other risk factors associated with increased odds of hospitalization across CPRA cohorts were KTR Black race/ethnicity, obesity, and pre-transplant dialysis >2 years (**Table 4**). In the <10% CPRA cohort, induction with ATG or IL2-RA was associated with higher odds of hospitalization compared with ALM induction. In the ≥80% CPRA cohort, induction with ATG was associated with higher odds of hospitalization than induction with IL2-RA (**Table 4**).

Death and overall graft loss five years after transplant

Over a 5-year follow-up, the risk factors associated with the highest hazards of death across CPRA cohorts were KTR age ≥65 and 50-64 years and KDRI ≥1.45. Other risks factors associated with higher hazards of death across

Table 3. Adjusted odds ratios and 95% confidence intervals from logistic regression models for acute rejection

	CPRA 0-9%			CPRA 10-79%			CPRA ≥80%		
	OR	95%	CI	OR	95%	CI	OR	95%	CI
ATG induction	0.66	*0.60*	*0.72*	0.57	*0.48*	*0.68*	0.61	*0.47*	*0.79*
ALM induction	0.64	*0.56*	*0.73*	0.54	*0.42*	*0.69*	0.62	*0.46*	*0.85*
KDRI 0.96-1.14	1.16	*1.03*	*1.31*	1.35	*1.10*	*1.67*	1.31	*1.08*	*1.59*
KDRI 1.15-1.44	1.33	*1.19*	*1.48*	1.44	*1.18*	*1.77*	1.28	*1.06*	*1.55*
KDRI ≥1.45	1.55	*1.39*	*1.73*	1.72	*1.40*	*2.12*	1.66	*1.33*	*2.06*
Recip. 50-64 yr.	0.71	*0.65*	*0.78*	0.72	*0.61*	*0.85*	0.60	*0.50*	*0.70*
Recip. ≥65 yr.	0.60	*0.53*	*0.67*	0.68	*0.54*	*0.85*	0.48	*0.37*	*0.64*
Recip. BMI ≥30	1.27	*1.17*	*1.37*	1.33	*1.15*	*1.54*	1.23	*1.05*	*1.43*
Recip. Black	1.21	*1.10*	*1.32*	1.34	*1.13*	*1.60*	1.26	*1.06*	*1.50*
Recip. Hispanic	0.92	*0.81*	*1.03*	0.96	*0.76*	*1.21*	0.82	*0.65*	*1.03*
Recip. Other Race	0.72	*0.61*	*0.84*	0.71	*0.52*	*0.97*	0.80	*0.58*	*1.10*
Diabetes	0.90	*0.79*	*1.02*	0.80	*0.63*	*1.02*	0.64	*0.50*	*0.84*
Glomeruloneph.	1.02	*0.89*	*1.17*	1.04	*0.84*	*1.30*	0.82	*0.68*	*1.01*
Hypertension	0.90	*0.79*	*1.03*	0.77	*0.61*	*0.97*	0.67	*0.53*	*0.84*
PKD	0.82	*0.68*	*0.98*	0.77	*0.55*	*1.08*	0.70	*0.48*	*1.00*
Dialysis <2 yrs.	1.12	*0.98*	*1.30*	1.30	*0.98*	*1.73*	1.05	*0.79*	*1.39*
Dialysis ≥2 yrs.	1.10	*0.99*	*1.22*	1.20	*0.99*	*1.45*	1.29	*1.05*	*1.58*
HLA MM = 1-3	1.74	*1.35*	*2.25*	1.48	*1.11*	*1.98*	1.29	*1.02*	*1.64*
HMA MM = 4-6	2.15	*1.69*	*2.73*	1.76	*1.37*	*2.26*	1.50	*1.19*	*1.88*
Transpl 2011-15	0.92	*0.85*	*0.99*	0.93	*0.81*	*1.08*	0.89	*0.76*	*1.04*
Retransplant	1.21	*1.00*	*1.46*	1.58	*1.30*	*1.92*	1.17	*0.98*	*1.39*
Maint. Steroids	0.89	*0.82*	*0.98*	0.85	*0.71*	*1.01*	0.73	*0.61*	*0.88*
Maint. CNI + MP	0.64	*0.54*	*0.74*	0.58	*0.43*	*0.78*	0.62	*0.45*	*0.84*
Maint. MTORI	0.63	*0.48*	*0.83*	0.71	*0.43*	*1.19*	0.53	*0.29*	*0.98*
Private Insurance	3.78	*0.52*	*27.58*	0.58	*0.13*	*2.61*	0.36	*0.11*	*1.14*
Public Insurance	4.40	*0.60*	*32.05*	0.64	*0.14*	*2.85*	0.50	*0.16*	*1.56*
CIT ≥20	1.05	*0.97*	*1.13*	0.99	*0.85*	*1.15*	1.11	*0.95*	*1.30*

Table 4. Adjusted odds ratios and 95% confidence intervals from logistic regression models for hospitalization

	CPRA 0-9%			CPRA 10-79%			CPRA ≥80%		
	OR	95%	CI	OR	95%	CI	OR	95%	CI
ATG induction	0.99	0.94	1.04	1.07	0.95	1.19	1.22	1.02	1.45
ALM induction	0.91	0.85	0.98	1.01	0.87	1.17	1.10	0.90	1.35
KDRI 0.96-1.14	1.12	1.05	1.19	1.10	0.98	1.23	1.28	1.14	1.43
KDRI 1.15-1.44	1.29	1.21	1.37	1.27	1.14	1.42	1.45	1.29	1.61
KDRI ≥1.45	1.54	1.45	1.64	1.51	1.34	1.69	1.88	1.65	2.15
Recip. 50-64 yr.	1.01	0.96	1.06	1.04	0.95	1.15	0.97	0.89	1.07
Recip. ≥65 yr.	1.05	0.99	1.12	1.20	1.06	1.35	1.14	0.99	1.32
Recip. BMI ≥30	1.09	1.04	1.13	1.10	1.01	1.20	1.06	0.97	1.16
Recip. Black	1.12	1.07	1.18	1.15	1.03	1.27	1.22	1.09	1.36
Recip. Hispanic	0.90	0.84	0.96	0.89	0.79	1.02	0.96	0.85	1.10
Recip. Other	0.73	0.67	0.79	0.68	0.58	0.80	0.84	0.70	1.01
Diabetes	1.17	*1.09*	*1.26*	0.68	0.58	0.80	1.01	0.88	1.17
Glomeruloneph.	0.87	*0.80*	*0.94*	0.89	0.78	1.02	0.79	0.70	0.90

Hypertension	0.89	*0.82*	*0.96*	0.90	0.79	1.03	0.76	0.67	0.88
PKD	0.90	*0.82*	*0.99*	0.97	0.81	1.16	0.84	0.69	1.02
Dialysis <2 yrs.	1.09	1.01	1.18	1.07	0.91	1.25	0.98	0.84	1.14
Dialysis ≥2 yrs.	1.12	1.06	1.19	1.24	1.11	1.38	1.19	1.06	1.33
HLA MM = 1-3	1.20	1.07	1.34	1.01	0.87	1.17	1.01	0.89	1.16
HMA MM = 4-6	1.27	1.15	1.41	1.10	0.97	1.24	1.05	0.92	1.19
Transpl 2011-15	0.97	0.93	1.01	0.92	0.85	1.00	0.91	0.83	1.00
Retransplant	1.19	1.06	1.33	1.18	1.04	1.33	1.04	0.94	1.16
Maint. Steroids	0.98	0.94	1.03	0.86	0.78	0.95	0.96	0.85	1.07
CNI + MPA	0.91	0.82	1.00	1.07	0.88	1.31	0.95	0.77	1.17
MTORI	1.66	1.42	1.94	2.13	1.55	2.94	1.65	1.14	2.38
Private Insurance	1.26	0.65	2.44	2.21	0.63	7.77	0.93	0.36	2.41
Public Insurance	1.59	0.82	3.08	2.74	0.78	9.62	1.29	0.50	3.31
CIT ≥20	1.02	0.98	1.04	1.04	0.96	1.14	1.00	0.91	1.09

Table 5. Adjusted hazard ratios and 95% confidence intervals from cox regression models for death

	CPRA 0-9%			CPRA 10-79%			CPRA ≥80%		
	OR	95%	CI	OR	95%	CI	OR	95%	CI
ATG induction	0.93	*0.88*	*0.98*	0.94	*0.83*	*1.06*	0.99	*0.81*	*1.22*
ALM induction	0.95	*0.88*	*1.03*	0.99	*0.84*	*1.18*	0.91	*0.71*	*1.17*
KDRI 0.96-1.14	1.10	*1.02*	*1.20*	1.10	*0.95*	*1.29*	1.09	*0.93*	*1.28*
KDRI 1.15-1.44	1.27	*1.18*	*1.37*	1.33	*1.15*	*1.53*	1.42	*1.23*	*1.65*
KDRI ≥1.45	1.59	*1.49*	*1.71*	1.72	*1.50*	*1.97*	1.70	*1.44*	*2.00*
Recip. 50-64 yr.	2.01	*1.87*	*2.16*	1.91	*1.67*	*2.18*	2.08	*1.80*	*2.40*
Recip. ≥65 yr.	3.35	*3.10*	*3.61*	3.21	*2.77*	*3.72*	3.68	*3.13*	*4.33*
Recip. BMI ≥30	1.05	*1.00*	*1.10*	1.01	*0.91*	*1.11*	1.05	*0.93*	*1.19*
Recip. Black	0.85	*0.80*	*0.90*	0.82	*0.73*	*0.92*	0.83	*0.72*	*0.96*
Recip. Hispanic	0.62	*0.57*	*0.67*	0.65	*0.55*	*0.76*	0.68	*0.57*	*0.81*
Recip. Other	0.58	*0.53*	*0.64*	0.61	*0.50*	*0.75*	0.57	*0.43*	*0.75*
Diabetes	1.59	*1.46*	*1.73*	1.51	*1.29*	*1.76*	1.54	*1.30*	*1.83*
Glomeruloneph.	0.76	*0.68*	*0.84*	0.75	*0.63*	*0.89*	0.79	*0.66*	*0.95*
Hypertension	1.04	*0.95*	*1.14*	0.96	*0.82*	*1.13*	0.86	*0.71*	*1.03*
PKD	0.68	*0.60*	*0.76*	0.69	*0.54*	*0.87*	0.68	*0.52*	*0.91*
Dialysis <2 yrs.	1.19	*1.09*	*1.29*	1.15	*0.96*	*1.38*	0.97	*0.78*	*1.20*
Dialysis ≥2 yrs.	1.49	*1.39*	*1.59*	1.30	*1.15*	*1.48*	1.47	*1.26*	*1.72*
HLA MM = 1-3	1.07	*0.95*	*1.20*	1.13	*0.95*	*1.34*	1.01	*0.85*	*1.20*
HMA MM = 4-6	1.17	*1.04*	*1.30*	1.07	*0.92*	*1.24*	1.05	*0.89*	*1.23*
Transpl 2011-15	1.10	*1.04*	*1.16*	1.17	*1.05*	*1.31*	1.09	*0.96*	*1.24*
Retransplant	1.39	*1.22*	*1.57*	1.20	*1.03*	*1.39*	1.00	*0.87*	*1.15*
Maint. Steroids	1.12	*1.06*	*1.19*	1.04	*0.92*	*1.17*	1.06	*0.91*	*1.23*
CNI + MPA	0.86	*0.78*	*0.95*	0.75	*0.61*	*0.92*	0.83	*0.65*	*1.06*
MTORI	1.16	*0.98*	*1.37*	0.99	*0.69*	*1.42*	1.23	*0.78*	*1.92*
Private Insurance	1.19	*0.38*	*3.69*	1.16	*0.16*	*8.30*	0.73	*0.10*	*5.22*
Public Insurance	1.43	*0.46*	*4.44*	1.48	*0.21*	*10.59*	1.05	*0.15*	*7.46*
CIT ≥20	1.10	*1.05*	*1.16*	1.13	*1.02*	*1.25*	1.15	*1.02*	*1.30*

CPRA cohorts were primary renal diagnosis of diabetes, pre-transplant dialysis >2 years, KDRI 1.15-1.44, and cold ischemic time (CIT) ≥20 hours (**Table 5**). KTR Black race/ethnicity was associated with a lower hazard of death across CPRA cohorts (**Table 5**).

Table 6. Adjusted hazard ratios and 95% confidence intervals from cox regression models for overall graft loss

	CPRA 0-9%			CPRA 10-79%			CPRA ≥80%		
	OR	95%	CI	OR	95%	CI	OR	95%	CI
ATG induction	0.95	*0.91*	*0.99*	0.92	0.83	1.02	1.05	0.89	1.24
ALM induction	0.98	*0.92*	*1.05*	1.03	0.90	1.19	1.03	0.84	1.26
KDRI 0.96-1.14	1.10	*1.03*	*1.18*	1.22	1.08	1.38	1.10	0.97	1.24
KDRI 1.15-1.44	1.35	*1.27*	*1.43*	1.42	1.27	1.59	1.48	1.32	1.66
KDRI ≥1.45	1.76	*1.66*	*1.86*	1.93	1.73	2.16	1.92	1.70	2.18
Recip. 50-64 yr.	1.11	*1.06*	*1.17*	1.05	0.95	1.15	1.04	0.94	1.15
Recip. ≥65 yr.	1.54	*1.46*	*1.63*	1.52	1.36	1.70	1.64	1.44	1.86
Recip. BMI ≥30	1.11	*1.06*	*1.15*	1.02	0.94	1.11	1.10	1.00	1.21
Recip. Black	1.10	*1.05*	*1.15*	1.03	0.94	1.13	1.13	1.01	1.25
Recip. Hispanic	0.74	*0.70*	*0.79*	0.76	0.67	0.87	0.78	0.68	0.90
Recip. Other	0.68	*0.63*	*0.74*	0.71	0.61	0.84	0.67	0.55	0.83
Diabetes	1.39	*1.30*	*1.49*	1.30	1.15	1.48	1.21	1.05	1.39
Glomeruloneph.	0.91	*0.84*	*0.98*	0.91	0.80	1.04	0.90	0.79	1.02
Hypertension	1.07	*0.99*	*1.14*	0.96	0.84	1.09	0.79	0.69	0.90
PKD	0.68	*0.62*	*0.76*	0.74	0.61	0.90	0.73	0.59	0.91
Dialysis <2 yrs.	1.25	*1.16*	*1.34*	1.24	1.07	1.44	1.06	0.90	1.24
Dialysis ≥2 yrs.	1.39	*1.32*	*1.47*	1.30	1.17	1.45	1.40	1.25	1.58
HLA MM = 1-3	1.13	*1.02*	*1.25*	1.13	0.98	1.30	0.93	0.81	1.07
HMA MM = 4-6	1.24	*1.13*	*1.37*	1.14	1.00	1.29	1.07	0.94	1.21
Transpl 2011-15	1.07	*1.02*	*1.12*	1.07	0.98	1.16	1.00	0.91	1.10
Retransplant	1.27	*1.15*	*1.41*	1.20	1.07	1.34	1.03	0.93	1.15
Maint. Steroids	1.06	*1.01*	*1.11*	1.02	0.74	0.61	0.90	0.84	1.06
CNI + MPA	0.85	*0.78*	*0.93*	0.80	1.24	1.07	1.44	0.68	1.00
MTORI	1.20	*1.04*	*1.37*	1.15	1.30	1.17	1.45	0.66	1.39
Private Insurance	1.08	*0.51*	*2.26*	0.80	0.20	3.23	0.83	0.21	3.33
Public Insurance	1.27	*0.61*	*2.68*	1.09	0.27	4.36	1.13	0.28	4.53
CIT ≥20	1.09	*1.05*	*1.14*	1.13	1.04	1.22	1.05	0.95	1.15

The risk factors associated with the highest hazards of overall graft loss across CPRA cohorts were KDRI ≥1.45, KTR ≥65 age, primary renal diagnosis of diabetes, pre-transplant dialysis >2 years, KDRI 1.15-1.44, and prior transplant (**Table 6**). KTR Black race/ethnicity was associated with increased risk of OAGL than Caucasian race/ethnicity only in the <10% and ≥80% CPRA cohorts.

Risk factors as high yield predictors across outcomes in CPRA strata

The most consistently significant predictors of 100% (5 of 5) adverse outcomes in all CPRA strata were the two highest KDRI quartiles ≥1.45 and 1.15-1.44 (**Figure 1**). Consistent predictors of 80% (4 of 5) adverse outcomes in all CPRA cohorts were (1) pre-transplant dialysis duration >2 years that predicted increased risks of overall graft loss, death, DGF, and hospitalization; and (2) Black KTR (Kidney Transplant Recipients) race that predicted increased risks of DGF, AR, and hospitalization; and, paradoxically, decreased risk of death. KTR age ≥65 years predicted 60% (3 of 5) outcomes across CPRA cohorts, including increased risks of overall graft loss and death and a decreased risk of acute rejection. In all CPRA cohorts, KTR primary kidney disease of diabetes or age ≥65 years were both predictors of death and overall graft loss. Prolonged graft cold ischemic time (>20 hours) predicted consistently delayed graft function and death (**Figure 1**).

Box: significant increased risk Grey highlight: significant decreased risk Strike through: ~~not significant risk~~

Sensitization based on:	GRAFT LOSS			DEATH			DELAYED GRAFT FUNCTION			ACUTE REJECTION			HOSPITALIZATION		
CPRA ---→	<10%	10-79%	>80%	<10%	10-79%	>80%	<10%	10-79%	>80%	<10%	10-79%	>80%	<10%	10-79%	>80%
RISK FACTORS	HR[e]/P	HR[e]/P	HR[e]/P	HR[e]/P	HR[e]/P	HR[e]/P	OR[f]/P	OR[f]/P	OR[f]/P	OR[f]/P	OR[f]/P	OR[f]/P	OR[f]/P	OR[f]/P	OR[f]/P
KDRI [a] 1.15-1.44	1.35	1.42	1.48	1.27	1.33	1.42	1.80	1.60	1.91	1.33	1.44	1.28	1.29	1.27	1.45
	<0.001	<0.001	<0.001	0.021	<0.001	<0.001	<0.001	<0.001	<0.001	0.044	0.005	0.006	<0.001	0.013	<0.001
KDRI [a] >= 1.45	1.76	1.93	1.92	1.59	1.72	1.70	1.76	1.71	2.25	1.55	1.72	1.66	1.54	1.51	1.88
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.011	0.03	<0.001	<0.001
Dialysis >/=2 years	1.39	1.30	1.40	1.49	1.30	1.47	2.21	2.16	2.21	~~1.10~~	~~1.20~~	1.29	1.12	1.24	1.19
	<.0001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.422	0.618	0.010	0.005	<0.001	<0.001
CIT [b] >= 20	1.09	1.13	~~1.05~~	1.10	1.13	1.15	1.51	1.37	1.41	~~1.05~~	~~0.99~~	~~1.11~~	~~1.02~~	~~1.04~~	~~1.00~~
	<0.001	0.005	0.328	<0.001	0.015	0.027	<0.001	<0.001	<0.001	0.264	0.843	0.191	0.368	0.325	0.934
Diabetes	1.39	1.30	1.21	1.59	1.51	1.54	1.27	1.25	~~1.04~~	~~0.90~~	~~0.80~~	~~0.64~~	1.17	~~1.11~~	~~1.01~~
	<0.001	<0.001	0.007	<0.001	<0.001	<0.001	<0.001	0.037	0.667	0.108	0.260	0.962	<0.001	0.128	0.891
ATG 'induction	0.95	~~0.92~~	~~1.05~~	0.93	~~0.94~~	~~0.99~~	1.38	~~1.01~~	~~0.91~~	0.66	0.57	0.61	~~0.99~~	~~1.07~~	1.22
	0.024	0.132	0.588	0.011	0.316	0.923	<0.001	0.179	0.221	<0.001	<0.001	0.004	0.065	0.174	0.010
ALM [d] induction	~~0.98~~	~~1.03~~	~~1.03~~	~~0.95~~	~~0.99~~	~~0.91~~	1.36	~~1.18~~	~~0.99~~	0.64	0.54	0.62	0.91	~~1.01~~	~~1.10~~
	0.532	0.655	0.775	0.236	0.944	0.458	<0.001	0.061	0.719	<0.001	<0.001	0.002	0.005	0.705	0.986
Recip. 50 - 64-yr.	1.11	~~1.05~~	~~1.04~~	2.01	1.91	2.08	~~1.04~~	~~1.05~~	~~1.09~~	0.71	0.72	0.60	~~1.01~~	~~1.04~~	~~0.97~~
	<0.001	0.319	0.419	<0.001	<0.001	<0.001	0.249	0.829	0.371	0.023	<0.001	<0.001	0.504	0.281	0.062
Recip. >/=65 yr.	1.54	1.52	1.64	3.35	3.21	3.68	~~1.03~~	~~1.14~~	~~1.07~~	0.60	0.68	0.48	~~1.05~~	1.20	~~1.14~~
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.888	0.124	0.775	<0.001	<0.001	<0.001	0.0835	0.004	0.063
Recip. Black	1.10	~~1.03~~	1.13	0.85	0.82	0.83	1.31	1.46	1.20	1.21	1.34	1.26	1.12	1.15	1.22
	<0.001	0.545	0.028	<0.001	0.001	0.009	<0.001	<0.001	0.006	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Recip. Hispanic	0.74	0.76	0.78	0.62	0.65	0.68	~~1.22~~	~~1.35~~	~~1.16~~	~~0.92~~	~~0.96~~	~~0.82~~	~~0.90~~	~~0.89~~	~~0.96~~
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.466	0.202	0.416	0.483	0.843	0.079	0.168	0.627	0.492

Figure 1. Summary, risk factors for outcomes in deceased-donor kidney transplant sensitization groups. [a]kidney donor risk index (Rau); [b]cold ischemia time; [c]anti-thymocyte globulin; [d]alemtuzumab; [e]hazard ratio; [f]odds ratio.

Discussion

In this large database study of the United States OPTN, we aimed to identify risk factors that could consistently predict multiple adverse outcomes of deceased-donor kidney transplants across KTR (CPRA-based) sensitization strata. Our hypothesis that only a few risk factors could consistently or simultaneously predict multiple adverse DDKT outcomes across the sensitization strata of recipients was confirmed: out of 14 variables analyzed, only KDRI predicted 100% of complications in all CPRA strata; only two variables, duration of pre-KT dialysis and KTR race/ethnicity predicted 80% of complications across CPRA strata.

We found in this study that the highest two KDRI quartiles (≥1.45 and 1.15-1.44) were the most consistent predictors of all adverse outcomes investigated across all DDKTR strata. When proposed by Rao and others, the original

intention was for KDRI to quantify the risk of graft loss [18] and objectively assess the suitability of deceased donor kidneys for transplantation [19]. Values of KDRI or its derivative, the kidney donor performance index (KDPI) are directly associated with donor organ quality and longevity [20, 21]. The KDRI/KDPI score has correlated well with histological lesions in post-perfusion kidney biopsies [22] and has strongly driven "longevity matching" of deceased donor kidneys to recipients [23].

Multiple studies have confirmed the durable utility of KDRI or KDPI (Kidney Donor Profile Index) for organ allocation [11, 24-26] and the prediction of allograft function and survival in subgroups with varying recipient characteristics [27-31]. The predictive value of KDRI/KDPI for DGF, allograft loss, or recipient death has been studied previously in donation after brain or cardiac death transplants, elderly or younger donors, and recipients with or without diabetes [9, 30, 32, 33]. Our findings have added information that KDRI retains its attributes as a strong and high-yield predictor of multiple KT outcomes across sensitization strata [11]. We postulate that the highly consistent and strong predictive performance of KDRI found in our study is due to the inclusion in its formula of factors associated individually with organ quality, renal mass, and transplant outcomes [14, 27-34].

In this study, the second most consistent predictor of DDKTR outcomes was pre-transplant dialysis >2 years which predicted DGF, hospitalization, death, and overall graft loss in all CPRA strata. Our results relating prolonged dialysis duration to increased risks of death and graft loss after KT are consistent with the findings of a study by Meier-Kriesche et al. in the US [35]. Research from Japan and the Australia and New Zealand dialysis and transplant registry (ANZDATA) have yielded comparable results [36, 37].

Our findings that prolonged pre-transplant dialysis duration of >2 years was associated with increased odds of DGF and hospitalization conform with reports in the literature [9, 38-40, 42, 43]. It is conceivable that prolonged dialysis exposure before transplant had predisposed patients to progressive iliac artery calcification, loss of residual kidney function, and cardiac dysfunction: all contributing to increased risk of DGF post-transplant [44].

Other authors have shown that pre-transplant dialysis increases the likelihood of early (30-day) post-KT readmission with varying point estimates of risk. Our results showed that the odds of readmission within one-year post-KT in DDKTRs with >2 years of dialysis vintage were 12%, 24%, and 19% in DDKTRs with 0-9%, 10-79%, and ≥80% CPRA, respectively (**Table 4**). In a prior study, infection was the primary cause of increased admissions in KTRs with prolonged pre-transplant dialysis [45].

Although the prolonged duration of dialysis pre-transplant has been associated with an increased risk of KT acute rejection [41, 46], our study has clarified that dialysis vintage is a risk for acute rejection only in the broadly sensitized KTRs (with ≥80% CPRA). We theorize that KTRs with high CPRA stayed longer on the transplant waitlist due to a scarcity of matching donors. And after KT, their high acute rejection risk was a function of their high degree of sensitization. In our analysis, the most consistent risk factors of acute rejection were high KDRI quartiles, 1-3 and 4-6 HLA mismatch/es, and recipient obesity or age <50 years. For KTRs with one or more of these risk factors, the use of lymphocyte-depleting (either ATG or ALM) induction and standard calcineurin inhibitor, mycophenolate, and steroids maintenance regimens may be considered based on our multivariable model (**Table 3**).

The third most consistent predictor of DDKT outcomes in our study, Black KTR race/ethnicity was associated with increased risks of DGF, AR, and hospitalization in all CPRA strata, and overall graft loss in the <10% and >80% CPRA strata. Our findings may be explained by high immunologic risk, long waiting times, and lower rates of living donor transplants in Black KTRs [10, 47-50]. On the other hand, we found that across CPRA strata, Black race/ethnicity was associated with a lower risk of death compared with the Caucasian race/ethnicity of KTRs. Our results are consistent with those of previous studies demonstrating that AA race/ethnicity was associated with either a lower or insignificant risk of all-cause death or death due to infection or cardiovascular causes [51-53].

The limitations of our study include those inherent in retrospective analyses including information and selection biases. The strength of our study includes the considerable number (over 62000) of kidney transplants studied that provided statistical power to allow the analysis of multiple covariates. This study would have been logistically daunting, if performed as a clinical trial. We present novel and clinically applicable findings by identifying common risk factors predictive of multiple adverse outcomes across DDKTR sensitization strata. DDKTs (Deceased Donor Kidney Transplant).

Conclusions

In adult DDKTRs, the two highest KDRI quartiles ≥1.45 and 1.15-1.44 consistently and strongly predict adverse transplant outcomes (namely: DGF, 1-year AR, 1-year hospitalization, 5-year death, and 5-year overall graft loss) across CPRA strata. Other robust predictors of adverse post-transplant outcomes across CPRA strata included pre-transplant dialysis duration of >2 years and Black race/ethnicity of KTR. Due to their consistency in predicting transplant outcomes, the identified risk factors should be considered in risk assessment and clinical decision-making related to deceased-donor kidney transplantation.

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Disclosure of conflict of interest

None.

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