OPEN

The Association Between Kidney Donor Profile Index and 1-y Graft Function

Renato Demarchi Foresto, MD, MSc,[1,2] Maria Amelia Aguiar Hazin, MD, MSc,[1,2] Bianca Cristina Cassão, MD, MSc,[1,2] Ana Paula Aquino de Morais,[2] Claudia Rosso Felipe, PharmD, PhD,[2] Lucio R. Requião-Moura, MD, PhD,[1,2] José Medina Pestana, MD, PhD,[1,2] and Helio Tedesco-Silva, MD, PhD[1,2]

Background. The association between Kidney Donor Profile Index (KDPI) and 1-y estimated glomerular filtration rate (eGFR) with long-term kidney graft survival is well known. Yet, the association between KDPI and 1-y eGFR remains uncertain considering the several concurrent competing risk factors. **Methods.** This single-center, retrospective cohort study analyzed data from 3059 consecutive deceased donor kidney transplant recipients with a 1-y follow-up from January 2013 to December 2017. The aim was to determine the association between the KDPI strata (0%–35%, 36%–50%, 51%–85%, 86%–100%) and 1-y eGFR estimated by the CKD-EPI equation. **Results.** The incidence of delayed graft function (50.6% versus 59.3% versus 62.7% versus 62.0%; $P < 0.001$) and cytomegalovirus infection (36.7% versus 36.6% versus 43.3% versus 57.8%; $P < 0.001$) increased with increasing KDPI strata but not biopsy-proven acute rejection (9.1% versus 9.8% versus 8.4% versus 9.1%; $P = 0.736$). The median 1-y eGFR decreased with increasing KDPI strata (64.8 versus 53.5 versus 46.9 versus 39.1 mL/min/1.73 m^2; $P < 0.001$). In the Cox regression, the higher the KDPI was, the lower the probability of a lower 1-y eGFR was. Assuming the 0%–35% strata as the reference, the likelihood of eGFR <50 mL/min/1.73 m^2 was increased by 76.6% (hazard ratio [HR] = 1.767, 95% confidence interval [CI] = 1.406–2.220), 2.24- and 2.87-fold higher for KDPI higher >35%–50% (HR = 2.239, 95% CI = 1.862–2.691), and >51%–85% (HR = 2.871, 95% CI = 2.361–3.491), respectively. Other variables associated with a lower graft function were donor sex (HR male versus female = 0.896, 95% CI = 0.813–0.989) and cold ischemia time (HR for each hour = 1.011, 95% CI = 1.004–1.019). This association was sustained after the Poisson mediation analysis, including delayed graft function, cytomegalovirus, and acute rejection as mediators. **Conclusions.** In this cohort of deceased donor kidney recipients, KDPI, and cold ischemia time were the major independent risk factors associated with lower 1-y kidney function.

(*Transplantation Direct* 2023;9: e1476; doi: 10.1097/TXD.0000000000001476.)

Received 23 January 2023.

Accepted 16 February 2023.

[1] *Hospital do Rim, Fundação Oswaldo Ramos, São Paulo, Brazil.*

[2] *Nephrology Division, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil.*

This study was financed in part by the Coordenação de Aperfeiçoamento Pessoal de Nível Superior, Brasil (CAPES), Finance Code 001.

The authors declare no conflicts of interest.

R.D.F., C.R.F., J.M.-P., and H.T.-S. designed the study. R.D.F., M.A.A.H., B.C.C., and A.P.A.d.M. were involved in data acquisition and analysis. R.D.F., L.R.R.-M., and H.T.-S. analyzed and interpreted the data. R.D.F. wrote the manuscript. L.R.R.-M. and H.T.-S. revised the manuscript. All authors read and approved the final version.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Correspondence: Renato Demarchi Foresto, MD, MSc, Hospital do Rim, Fundação Oswaldo Ramos, 960 Borges Lagoa St, São Paulo 04038-002, Brazil. (rdforesto@gmail.com).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001476

Organ shortage prompts transplant teams to seek new strategies to increase the donor pool, including the use of lower-quality kidneys recovered from expanded criteria donors, despite the known increased risk associated with poorer long-term outcomes.[1,2] Precise assessment of the quality of kidneys is challenging, suggesting that developing improved risk prediction models would be helpful in decision-making.

In 2009, Rao et al[3] developed the Kidney Donor Risk Index (KDRI) as a prediction model for long-term graft survival, a risk score derived from donor and transplant data. Later, the Kidney Donor Profile Index (KDPI) was derived from the KDRI, removing the transplant-related factors and converting 10 donor factors into a normalized percentile (0%–100%). The KDPI is currently used for recipient counseling, allocation policies, and graft survival assessment in the United States, and many other countries have already validated it for clinical practice.[3–7] In addition, the KDPI proved to perform better in predicting long-term graft survival than the traditional dichotomic classification of standard or expanded criteria.[3,8] Another key parameter associated with long-term kidney transplant outcomes is the 1-y estimated glomerular filtration

rate (eGFR).[9–12] Therefore, KDPI and eGFR are associated with long-term graft survival.[3,13] Although the association between KDPI and long-term outcomes has emerged as a possible milestone in the allocation system in a few countries, this index has not been validated in other ones, such as Brazil. Although the Brazilian transplantation system has one of the world's largest transplant programs, the KDPI has not previously been investigated as a predictor of kidney transplant success. The primary objective of this study was to determine the association of the KDPI with 1-y eGFR and to identify independent risk factors associated with reduced kidney function at the end of the first year of transplantation.

MATERIALS AND METHODS

Study Design

This single-center, retrospective cohort study compared the KDPI with the kidney function at the end of the first year after transplantation. The Federal University of São Paulo Research Ethics Committee approved this study (CAEE 10021419.0.0000.5505).

Population

For this analysis, we included data from all deceased donor kidney transplant recipients from January 2013 to December 2017. All patients were matched for ABO compatibility and received a transplant with a negative T and B complement-dependent cytotoxicity crossmatch, without donor-specific anti-HLA antibodies in loci A, B, and DR with MFI ≥1500. We excluded recipients younger than 18 y and those receiving combined liver or pancreas transplants. Static cold storage was used for graft preservation for all patients. Brazilian allocation policy discards HCV+ donors, as well as donation after circulatory death. Thus, here, all transplants were performed with HCV- and brain-dead donors.

Immunosuppressive Regimen

All patients received induction therapy with antithymocyte globulin. Maintenance therapy consisted of a combination of tacrolimus and prednisone for all patients, added with mycophenolate, azathioprine, or mammalian target of rapamycin inhibitors, based on donor type (standard criteria donor or expanded criteria donor) and perceived immunological risk.

Prevention of Infections

Preemptive therapy for cytomegalovirus (CMV) infection was used for patients using mycophenolate, patients with (D+/R–) CMV serostatus, or after treatment of acute rejection episodes. This strategy consisted of monitoring viral replication every other week up to the end of the third month, using CMV pp65 antigenemia assay or real-time polymerase chain reaction. All patients received oral trimethoprim/sulfamethoxazole for prophylaxis against *Pneumocystis jirovecii* and albendazole for parasitic infection prophylaxis.

Definitions

Patients were classified into 4 groups according to KDPI strata: 0%–35%, 36%–50%, 51%–85%, and 86%–100% (Figure 1). These KDPI strata were based on published cutoffs associated with good quality (KDPI <35%) and expanded criteria donor (KDPI >85%) kidneys.[3,5,14] The eGFR was calculated using the CKD-EPI equation.[15,16] Delayed graft function (DGF) was defined by the need for dialysis during the first week of transplantation, except for 1 dialysis during the first 24 h.[17] Episodes of CMV infection or disease were defined based on the Third International CMV Consensus.[18] CMV infection was diagnosed based on the CMV pp65 antigenemia (at least 10 positive cells per 200 000 cells) or DNAemia (>5000 UI/mL) in asymptomatic patients. CMV disease was based on the evidence of CMV replication, regardless of the number of pp65 positive cells or the DNAemia, and associated symptoms.[19] Graft loss was defined as the definitive need to return to dialysis. The biopsy-proven acute rejection (BPAR), including borderline changes, was categorized according to the Banff 2013 classification.[20] Presumed acute rejection was defined as a successfully treated episode of acute graft dysfunction without biopsy confirmation. Treated acute rejection included BPAR, borderline changes, and presumed acute rejection episodes. Low renal function was arbitrarily defined as <50 mL/min/1.73 m^2, based on investigators' criteria.

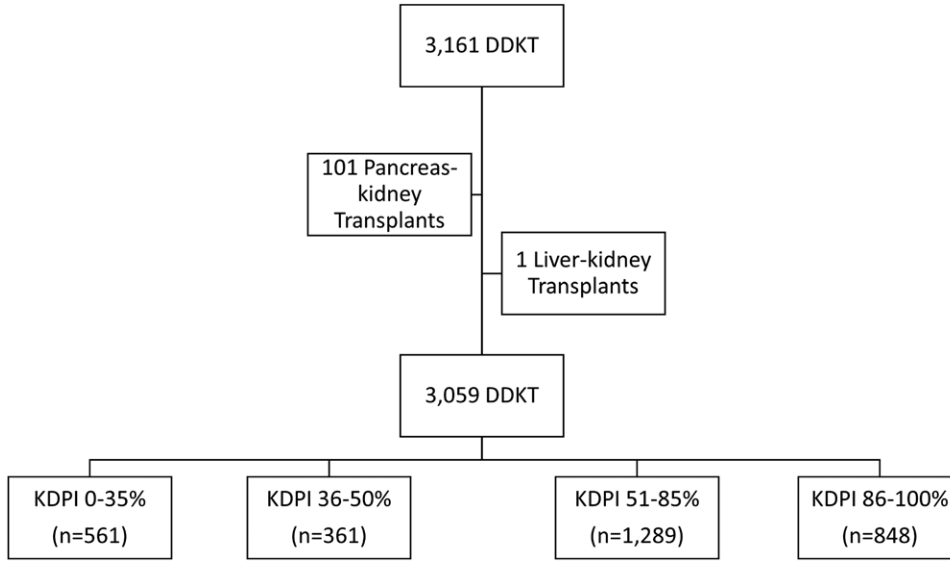


FIGURE 1. Flowchart of the study cohort. DDKT, deceased donor kidney transplant; KDPI, Kidney Donor Profile Index.

Statistical Analysis

Numerical variables were compared using the Kruskal-Wallis test with the Mann-Whitney post hoc pairwise test and Bonferroni correction and presented as medians and interquartile ranges. Categorical variables were compared using χ^2 and presented in absolute numbers and percentages. Linear regression was used to verify the association between the 1-y eGFR and KDPI. For this analysis, eGFR data were censored in patients with graft loss, death, or loss of follow-up. For patients who returned to dialysis, 1-y eGFR was considered 0. Patient and graft survivals were calculated using the Kaplan-Meier method and compared using the log-rank test. We performed univariate and multivariate Cox regression analyses to assess the variables associated with 1-y eGFR <50 mL/min/1.73 m², shown as hazard ratios. Collinear variables with the eGFR (recipient age, sex, and race) and KDPI (donor age, race, hypertension, diabetes, KDRI, expanded criteria donor, and brain death etiology) were excluded from the model. In an additional analysis, the events acute rejection, CMV infection, and DGF were considered in a Poisson mediation analysis to assess the role of these mediators on eGFR <50 mL/min/1.73 m², considering exposure time.[21] Poisson distributions with exposure to acute rejection and CMV infection were assumed. As for the DGF, the binomial distribution was adopted. The model was estimated via a system of generalized structural equations (generalized structural equation modeling). For all statistical tests, a significance level of 5% was used. The statistical analyses were performed using SPSS Statistics software version 28 (SPSS Inc, Chicago, IL) and STATA 17 statistical package (StataCorp, 2021, Stata Statistical Software: Release; 17; StataCorp LLC, College Station, TX).

RESULTS

Demographics

Between January 2013 and December 2017, 3161 deceased donor kidney transplants were performed, but 102 were excluded, resulting in 3059 patients eligible for this study (Figure 1). All donor-derived variables used for KDPI calculation were statistically different among the KDPI strata. There were no differences in cold ischemia time (CIT) and the proportion of donors with positive CMV serology. Median recipient age was higher in group KDPI 86%–100% than in groups KDPI 0%–35%, KDPI 36%–50%, and KDPI 51%–85%. Hemodialysis as a previous renal replacement therapy had a lower incidence in group KDPI 0%–35% than in groups KDPI 51%–85% and KDPI 86%–100%. Positive panel-reactivity antibodies class I was more frequent in KDPI 86%–100% than in the other strata. PRA class II was higher in KDPI 36%–50% than in KDPI 51%–85% and KDPI 86%–100%. Retransplantation was less frequent in KDPI 86%–100% than in the other groups (Table 1).

The distribution of kidney transplant recipients according to the KDPI followed a nonnormal pattern, shifting to the right (higher KDPI). Among the transplants performed, 18.34% used kidneys with a KDPI of 0% to 35%, 11.8% with a KDPI of 36% to 50%, 42.14% with a KDPI of 51% to 85%, and 27.72% with a KDPI of 86% to 100% (Figure 2A). In this cohort, 36.5% of transplants were derived from expanded criteria donors, comprising 27.2% of the kidneys with KDPI 51%–85% and comprising 90.2% of those with KDPI 86%–100% (Figure 2B).

Association Between KDPI Strata and Transplant Outcomes During the First Year After Transplantation

The overall incidence of DGF was 59.9%, with a lower incidence in the group KDPI 0%–35% (50.6%) than in the other KDPI strata. The median duration of DGF was 5 d, similar between the groups. The incidence of CMV infection or disease increased from 36.7% in the KDPI 0%–35% to 57.8% in the KDPI 86%–100%. The overall incidence of treated acute rejection episodes was 17.6%, whereas the incidence of BPAR was 9.1%. There was no difference in the incidence of acute rejection across KDPI strata (Table 2).

Association of KDPI With 1-y eGFR

The median 1-y eGFR was 47.8 mL/min/1.73 m² and was higher in patients without DGF and with shorter CIT (Table 2; **Table S1, SDC**, http://links.lww.com/TXD/A520). Simple linear regression showed the association between KDPI scores and 1-y eGFR (r^2 = 0.212, P < 0.001; Figure 3A), with no clear association with the occurrence of DGF (Figure 3B) or with higher CIT (Figure 3C). There was an inverse association between the median eGFR and the KDPI strata, decreasing from 64.8 mL/min/1.73 m² for patients receiving kidneys with KDPI 0%–35% to 39.1 mL/min/1.73 m² for those receiving kidneys with KPDI 86%–100% (Table 2; Figure 4A). The median eGFR decreased with increasing KDPI strata in patients with or without DGF and those who received kidneys with lower or higher CIT (**Table S1, SDC**, http://links.lww.com/TXD/A520). Interestingly, within the same stratum, a lower median eGFR was observed only in patients who developed DGF on the lower KDPI 0%–35% stratum (Figure 4B; **Table S1, SDC**, http://links.lww.com/TXD/A520), whereas the influence of CIT was observed only in the KDPI 51%–85% stratum (Figure 4C, **Table S1, SDC**, http://links.lww.com/TXD/A520).

Overall, 45.7% of the recipients achieved eGFR >50 mL/min/1.73 m². The proportion of patients with eGFR <50 mL/min/1.73 m² increased with increasing KDPI strata (Table 2). In a Cox regression analysis, an increase in KDPI strata and CIT were associated with an increased risk of reaching 1-y eGFR <50 mL/min/1.73 m², whereas receiving a kidney from a male donor was associated with a reduced risk (Table 3). This association persisted using CIT as a dichotomous variable (>22 h, **Table S2, SDC**, http://links.lww.com/TXD/A520) and with lower 1-y eGFR cutoffs of <40 and <30 mL/min/1.73 m² (P < 0.001, **Tables S3, S4, SDC**, http://links.lww.com/TXD/A520). The mediation analysis confirmed the association of KDPI and CIT with kidney function but also showed the acute rejection as an event associated with lower graft function at the end of the first year of transplantation (hazard ratio = 1.36; 1.21–1.53; P < 0.001; **Table S5, SDC**, http://links.lww.com/TXD/A520).

Survivals

The 1-y graft survival was 91.9% (Figure 5A), whereas death-censored graft survival was 95.1% (Figure 5B). In the KDPI 36%–50% stratum, there was an abnormally higher incidence of technical complications early in the posttransplantation period that reduced graft survival in this group, but these data were not related to the donor quality itself (Figure 5B; **Table S6, SDC**, http://links.lww.com/TXD/A520). The main cause of death was infectious (69.4%), followed

TABLE 1.

Demographic characteristics of the donors and recipients according to KDPI strata

	Total (n = 3059)	KDPI 0%–35% (n = 561)	KDPI 36%–50% (n = 361)	KDPI 51%–85% (n = 1289)	KDPI 86%–100% (n = 848)	*P*
Donors						
KDPI, %, median (IQR)	70 (44–87)	22 (14–29)	44 (40–47)	71 (61–79)	94 (90–98)	<0.001
KDRI, median (IQR)	1.22 (0.95–1.52)	0.76 (0.71–0.82)	0.94 (0.91–0.97)	1.23 (1.11–1.36)	1.76 (1.6–2.04)	<0.001
Expanded criteria, n (%)	1116 (36.5)	0 (0.0)	0 (0.0)	351 (27.2)	765 (90.2)	<0.001
Age, y, median (IQR)	49 (37–57)	27 (22–32)	39 (32–44)	49 (44–54)	61 (56–66)	<0.001
Male, n (%)	1737 (56.8)	438 (78.1)	213 (59.0)	692 (53.7)	394 (46.5)	<0.001
White, n (%)	1632 (53.4)	296 (52.8)	199 (55.1)	704 (54.6)	433 (51.1)	<0.001
Hypertension, n (%)	1249 (40.8)	9 (1.6)	39 (10.8)	577 (44.8)	624 (73.6)	<0.001
Diabetes mellitus, n (%)	242 (7.9)	4 (0.7)	7 (1.9)	73 (5.7)	158 (18.6)	<0.001
Positive CMV serology (IgG), n (%)	2687 (87.8)	482 (85.9)	317 (87.8)	1135 (88.1)	753 (88.8)	0.436
Brain death etiology, n (%)						<0.001
Cerebrovascular	1852 (60.5)	100 (17.8)	158 (43.8)	883 (68.5)	711 (83.8)	
Trauma	936 (30.6)	364 (64.9)	155 (42.9)	321 (24.9)	96 (11.3)	
Anoxia	181 (5.9)	58 (10.3)	30 (8.3)	64 (5.0)	29 (3.4)	
Others	90 (4.9)	39 (6.9)	18 (5.0)	21 (1.6)	12 (1.4)	
Creatinine, mg/dL, median (IQR)	1.50 (1.00–2.60)	1.20 (0.80–2.10)	1.40 (0.90–2.78)	1.53 (1.00–2.60)	1.70 (1.16–2.70)	<0.001
CIT, h, median (IQR)	23 (19–28)	23 (18–29)	22 (19–28)	23 (19–28)	23 (19–29)	0.513
Recipients						
Age, y, median (IQR)	49.7 (39.2–58.6)	47.8 (37.1–56.9)	48.0 (36.5–57.9)	49.7 (39.3–58.5)	51.4 (41.4–60.1)	<0.001
Male, n (%)	1872 (61.2)	327 (58.3)	225 (62.3)	781 (60.6)	539 (63.3)	0.222
White, n (%)	1392 (45.5)	251 (44.7)	161 (44.6)	583 (45.2)	397 (46.8)	0.116
CKD etiology, n (%)						0.127
Undetermined	1428 (46.7)	246 (43.9)	165 (45.7)	611 (47.4)	406 (47.9)	
Diabetes	539 (17.6)	99 (17.6)	49 (13.6)	236 (18.3)	155 (18.3)	
Glomerulonephritis	510 (16.7)	94 (16.8)	66 (18.3)	218 (16.9)	132 (15.6)	
Polycystic kidney disease	244 (8.0)	44 (7.8)	33 (9.1)	94 (7.3)	73 (8.6)	
Others	338 (11.0)	78 (13.9)	48 (13.3)	130 (10.1)	82 (9.6)	
Positive CMV serology (IgG), n (%)	2879 (94.1)	529 (94.3)	340 (94.2)	1216 (94.3)	794 (93.6)	0.917
Duration of dialysis, mo, median (IQR)	39.7 (22.3–70.3)	41.9 (23.2–75.1)	38.6 (20.4–69.6)	39.6 (22.0–71.8)	38.2 (23–65.9)	0.473
Renal replacement therapy, n (%)						0.024
Hemodialysis	2771 (90.6)	497 (88.6)	326 (90.3)	1166 (90.5)	782 (92.2)	
Hemodialysis/peritoneal dialysis	169 (5.5)	47 (8.4)	22 (6.1)	70 (5.4)	30 (3.5)	
Peritoneal dialysis	108 (3.5)	14 (2.5)	11 (3.0)	49 (3.8)	34 (4.0)	
Preemptive	11 (0.4)	3 (0.5)	2 (0.6)	4 (0.3)	2 (0.2)	
Panel-reactive antibodies >0%, n (%)						
Class I	731 (23.9)	159 (28.3)	92 (25.5)	312 (24.2)	168 (19.8)	0.002
Class II	329 (10.8)	66 (11.8)	54 (15.0)	135 (10.5)	74 (8.7)	0.012
HLA mismatch (ABDR), median (IQR)	2 (2–3)	2 (1–3)	2 (2–3)	2 (2–3)	2 (2–3)	0.103
Retransplantation, n (%)	225 (7.4)	52 (9.3)	34 (9.4)	114 (8.8)	25 (2.9)	<0.001

CIT, cold ischemia time; CKD, chronic kidney disease; CMV, cytomegalovirus; IQR, interquartile range; KDPI, Kidney Donor Profile Index; KDRI, Kidney Donor Risk Index.

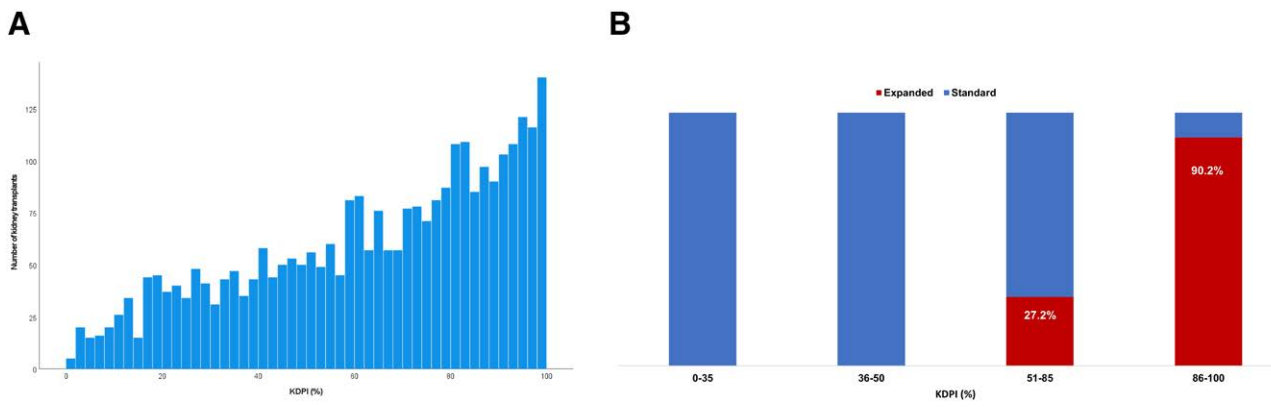


FIGURE 2. Donor distribution of this study by KDPI and standard/expanded criteria. A, Histogram of the distribution of kidney transplant recipients according to KDPI. B, Distribution of standard vs expanded criteria donors classification by KDPI strata. KDPI, Kidney Donor Profile Index.

TABLE 2.

Association between KDPI strata and transplant outcomes during the first year after transplantation

	Total (n = 3059)	KDPI 0%–35% (n = 561)	KDPI 36%–50% (n = 361)	KDPI 51%–85% (n = 1289)	KDPI 86%–100% (n = 848)	*P*
Transplant outcomes						
DGF, n (%)	1832 (59.9)	284 (50.6)	214 (59.3)	808 (62.7)	526 (62.0)	<0.001
Duration of DGF, d, median (IQR)	5 (2–9)	5 (2–9)	5 (2–9)	5 (2–9)	6 (2–9)	0.077
CMV infection or disease, n (%)	1386 (45.3)	206 (36.7)	132 (36.6)	558 (43.3)	490 (57.8)	<0.001
Treated acute rejection, n (%)	539 (17.6)	100 (17.8)	55 (15.2)	228 (17.7)	156 (18.4)	0.618
Presumed acute rejection, n (%)	34 (1.1)	10 (1.8)	3 (0.8)	14 (1.1)	7 (0.8)	0.362
Borderline changes, n (%)	232 (7.6)	38 (6.8)	17 (4.7)	105 (8.1)	72 (8.5)	0.106
Biopsy-proven acute rejection, n (%)	273 (9.1)	52 (9.1)	35 (9.8)	109 (8.4)	77 (9.1)	0.736
IA	100 (3.3)	18 (3.2)	15 (4.2)	41 (3.2)	26 (3.1)	
IB	72 (2.4)	13 (2.3)	9 (2.5)	23 (1.8)	27 (3.2)	
IIA	60 (2.0)	13 (2.3)	5 (1.4)	25 (1.9)	17 (2.0)	
IIB	20 (0.7)	3 (0.5)	5 (1.4)	8 (0.6)	4 (0.5)	
III	5 (0.2)	2 (0.4)	0 (0.0)	3 (0.2)	0 (0.0)	
Mixed	4 (0.1)	0 (0.0)	0 (0.0)	3 (0.2)	1 (0.1)	
Antibody-mediated acute rejection	11 (0.4)	2 (0.4)	1 (0.3)	6 (0.5)	2 (0.2)	
Chronic-active rejection	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Graft loss, n (%)	149 (4.9)	18 (3.2)	23 (6.4)	57 (4.4)	50 (5.9)	0.040
Death, n (%)	98 (3.2)	18 (3.2)	8 (2.2)	37 (2.9)	35 (4.1)	0.269
Loss of follow-up, n (%)	104 (3.4)	23 (4.1)	15 (4.2)	42 (3.3)	24 (2.8)	0.497
1-y eGFR, mL/min/1.73 m^2, median (IQR)	47.8 (34.3–62.6)	64.8 (50.1–82.4)	53.5 (38.8–68.6)	46.9 (34.5–59.6)	39.1 (26.8–50.8)	
1-y eGFR <50 mL/min/1.73 m^2, n (%)	1661 (54.3)	140 (25.0)	158 (43.8)	739 (57.3)	624 (73.6)	

CMV, cytomegalovirus; DGF, delayed graft function; eGFR, estimated glomerular filtration rate; KDPI, Kidney Donor Profile Index.

by cardiovascular disease (19.4%), whereas the main cause of graft loss was vascular thrombosis (32.9%), followed by immunological interstitial fibrosis/tubular atrophy (IFTA; 18.1%) and nonimmunological IFTA (14.8%), with no significant differences according to the KDPI (**Table S6, SDC**, http://links.lww.com/TXD/A520). Finally, the patient survival rate was 96.8% (Figure 5C).

DISCUSSION

In this retrospective, single-center analysis, we showed that increasing KDPI score was independently associated with a decreasing 1-y eGFR in kidney transplant recipients. This association was confirmed across increasing KDPI strata and after Cox regression analysis. Previous studies have shown this inverse relationship between KDRI/KDPI and kidney function in the US population and in recipients of high-KDPI kidneys or of grafts from donors with acute kidney injury.[22–24] In a cohort of 469 kidney transplants with a median KDPI of 67%, short CIT (4 h), and low incidence of DGF (<20%), those recipients of high-KDPI kidneys showed inferior kidney function compared with those who received kidneys with lower KDPI.[5] In another single-center cohort study including 580 kidney transplants with a median KDPI of 71%, short CIT (10 h), and low incidence of DGF, the mean 1-y eGFR decreased according to increasing KDPI strata (KDPI <35%: 65 mL/min/1.73 m^2, KDPI 35%–85%: 53 mL/min/1.73 m^2, KDPI >85%: 39 mL/min/1.73 m^2).[4] A retrospective Australian cohort study including 2923 recipients of kidneys with a median KDPI of 54% and a median CIT of 11 h also confirmed an inverse association between KDPI and 1-y reduced kidney function, defined by a GFR<30 mL/min/1.73 m^2.[25] Compared with these studies, our study population had a higher prevalence of high-KDPI kidneys, longer CIT (23 h), and, importantly, significantly higher incidences of DGF (60%). Considering these substantial differences in donor and transplant demographics, we sought to determine the association between KDPI and 1-y kidney function and whether this association is modified by associated risk factors, particularly CIT and DGF.

In our cohort, increasing KDPI stratum was consistently and independently associated with 1-y reduced kidney function, regardless of the defined threshold (<50, <40, and <30 mL/min/1.73 m^2). The donor male sex was associated with a lower risk of 1-y reduced kidney function; the larger number of nephrons[26,27] and the metabolic requirements of the recipient are involved,[28] directly influencing graft function and survival.[29,30]

Another risk factor associated with 1-y reduced kidney function was CIT. Although CIT is a known risk factor for DGF,[31] both have been associated with inferior graft survival.[32,33] In our analysis, the effect size of CIT on the incidence of 1-y reduced kidney function was relatively small (1.7% increased risk per additional hour), becoming more relevant after 22 h (28% increased risk). Interestingly, DGF, a major risk factor for graft loss,[32,34] was not associated with reduced 1-y kidney function, even when CIT was removed from the multivariate analysis. Although various studies have associated the incidence of DGF with inferior long-term graft survival,[35] its intuitive association with 1-y reduced kidney function is elusive. In a previous analysis including 1412 deceased donor kidney transplant recipients, we showed that only those who developed DGF lasting longer than 15 d showed 1-y reduced kidney function.[36] In a retrospective, Brazilian, multicenter cohort study, with an incidence of DGF of 54% and a median CIT of 22 h, increasing duration of DGF was associated with

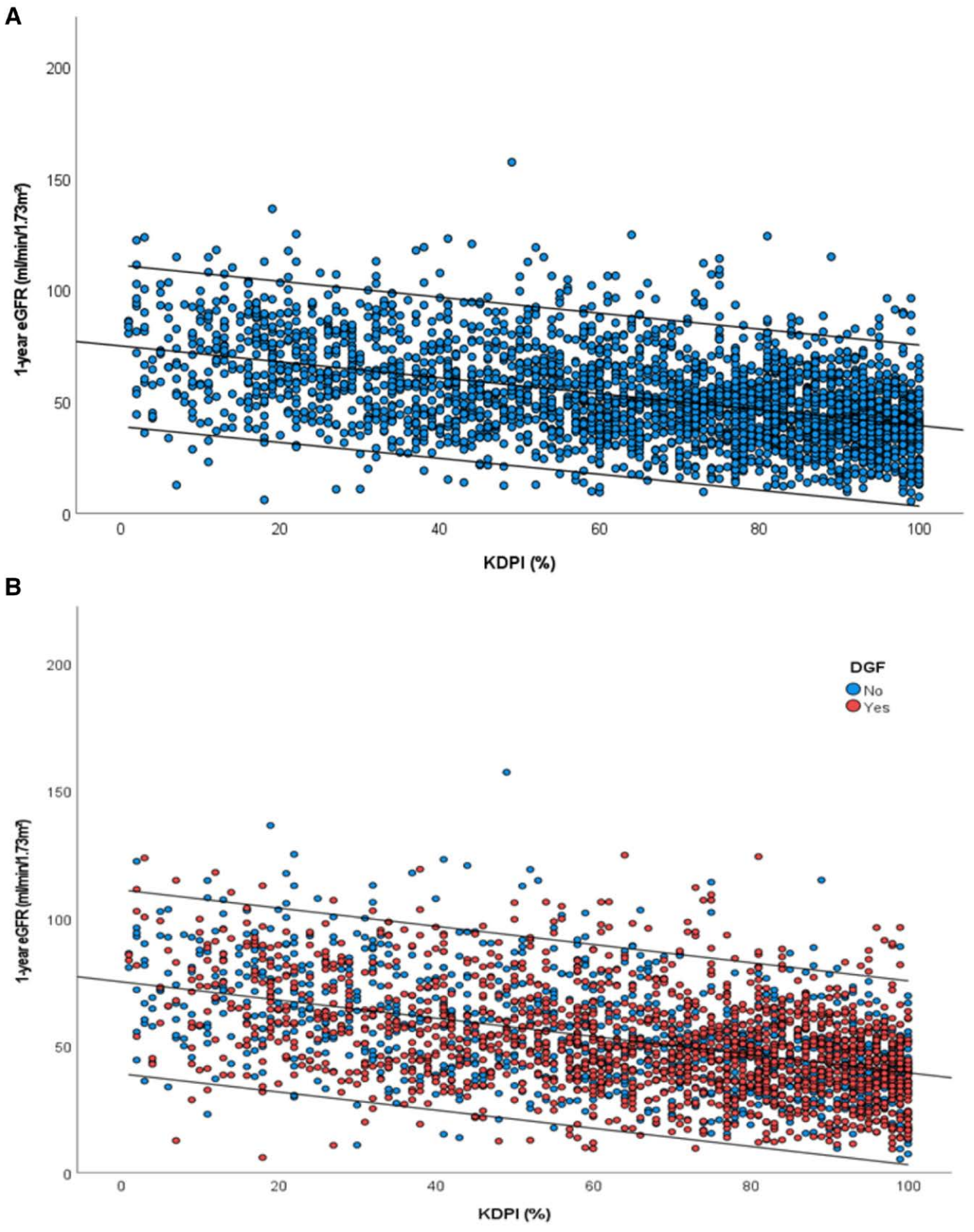


FIGURE 3. Association between KDPI and 1-y eGFR (A), stratified by the presence of DGF (B) and by the CIT (C). Deaths and graft losses were excluded from this analysis. CIT, cold ischemia time; DGF, delayed graft function; eGFR, estimated glomerular filtration rate; KDPI, Kidney Donor Profile Index.

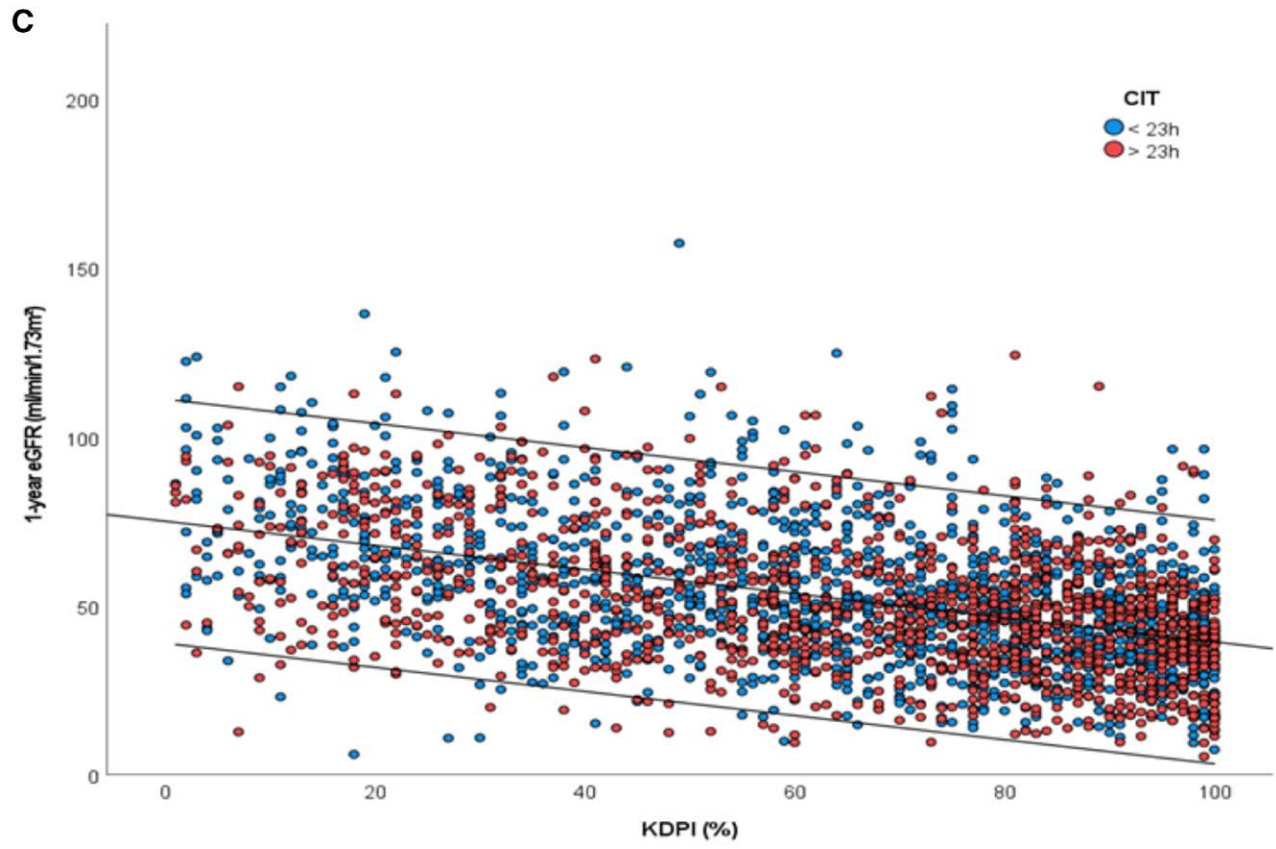


FIGURE 3. Continued.

decreasing 1-y kidney function.[37] In a German cohort study including 525 kidney transplant recipients with an incidence of DGF of 21% and a median CIT of 10 h, DGF was associated with reduced kidney function as early as 3 mo after transplantation.[38] Finally, in a US cohort study including 355 patients, DGF lasting >20 d was associated with a 5.73-fold increased risk of 1-y eGFR <40 mL/min/1.73 m^2.[39] Altogether, the lack of association between DGF and kidney function in our cohort analysis is intriguing. Considering the high incidence of DGF, we speculate that the fate of the kidney is already determined at the time of organ recovery. Previous studies have shown that this high incidence has been associated with late referral and inadequate maintenance of potential donors.[36,40] Therefore, even recipients who do not develop DGF, using the standard criteria, show slow and perhaps incomplete kidney function recovery that is not discernable compared with those with DGF. The relatively short median duration of DGF and the low incidence of primary nonfunction and early graft loss, regardless of KDPI strata, CIT, and DGF, support this hypothesis. Whether natural ischemic preconditioning plays any protective role is uncertain.[41]

The association between CMV infection and kidney transplant outcomes has been well documented.[42] However, whether current preventive strategies have changed this association is uncertain. The direct effect of viral infection, antiviral drug toxicity, immunosuppressive drug dose reduction, and concurrent risk of acute rejection are possible causal pathways leading to this observation.[43,44] Nonetheless, this association has been challenged, as there are functional and histological data suggesting that kidney function is already reduced before the diagnosis of CMV infection.[45,46] In our cohort, using the preemptive strategy, CMV infection increased with increasing KPDI strata but was not associated with 1-y reduced kidney function in the Poisson mediation analysis.

The overall incidence of acute rejection was low and similar across KDPI strata. This is perhaps associated with immunological selection and universal induction therapy. Nevertheless, acute rejection was still a major event associated with low 1-y kidney function.[47,48] Both clinical and subclinical acute rejection episodes might negatively influence renal function,[44] suggesting the need to further develop preventive and effective therapeutic strategies.

This analysis has several limitations involving its retrospective nature, single-center data source, unique donor demographic characteristics, and patient managements, including immunosuppressive regimens and CMV preventive strategies. On the other hand, considering the peculiar characteristics of the Brazilian transplantation program, notably the relative higher CIT and a high incidence of DGF, we could demonstrate that KDPI is independently associated with 1-y graft function, even when clinical events such as acute rejection and CMV infection were included in the mediation analysis.

In conclusion, in a population for whose the KDPI has not been validated, it was associated with 1-y graft function, independently of a high CIT, high incidence of DGF, or the occurrence of acute rejection.

REFERENCES

1. Ojo AO, Hanson JA, Meier-Kriesche H, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other

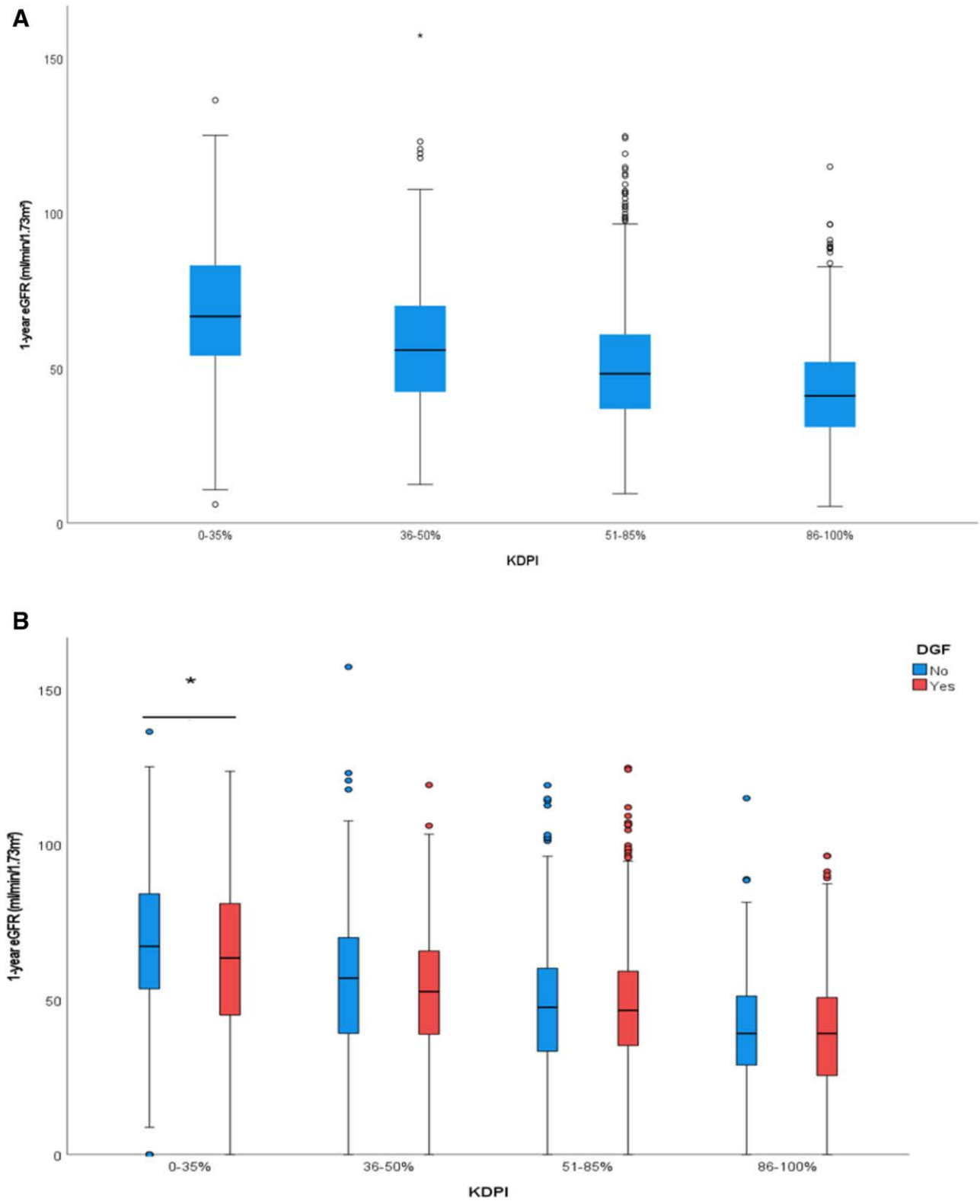


FIGURE 4. Box plots comparing median 1-y eGFR (CKD-EPI) after kidney transplantation according to KDPI strata ([A] $P < 0.001$), stratified by the presence of DGF ([B] $P = 0.015$ no DGF vs DGF, KDPI 0%–35%) and by the CIT ([C] $P < 0{,}001$, CIT<23 vs >23 h, KDPI 51%–85%). CIT, cold ischemia time; CKD, chronic kidney disease; DGF, delayed graft function; eGFR, estimated glomerular filtration rate; EPI, epidemiology; KDPI, Kidney Donor Profile Index.

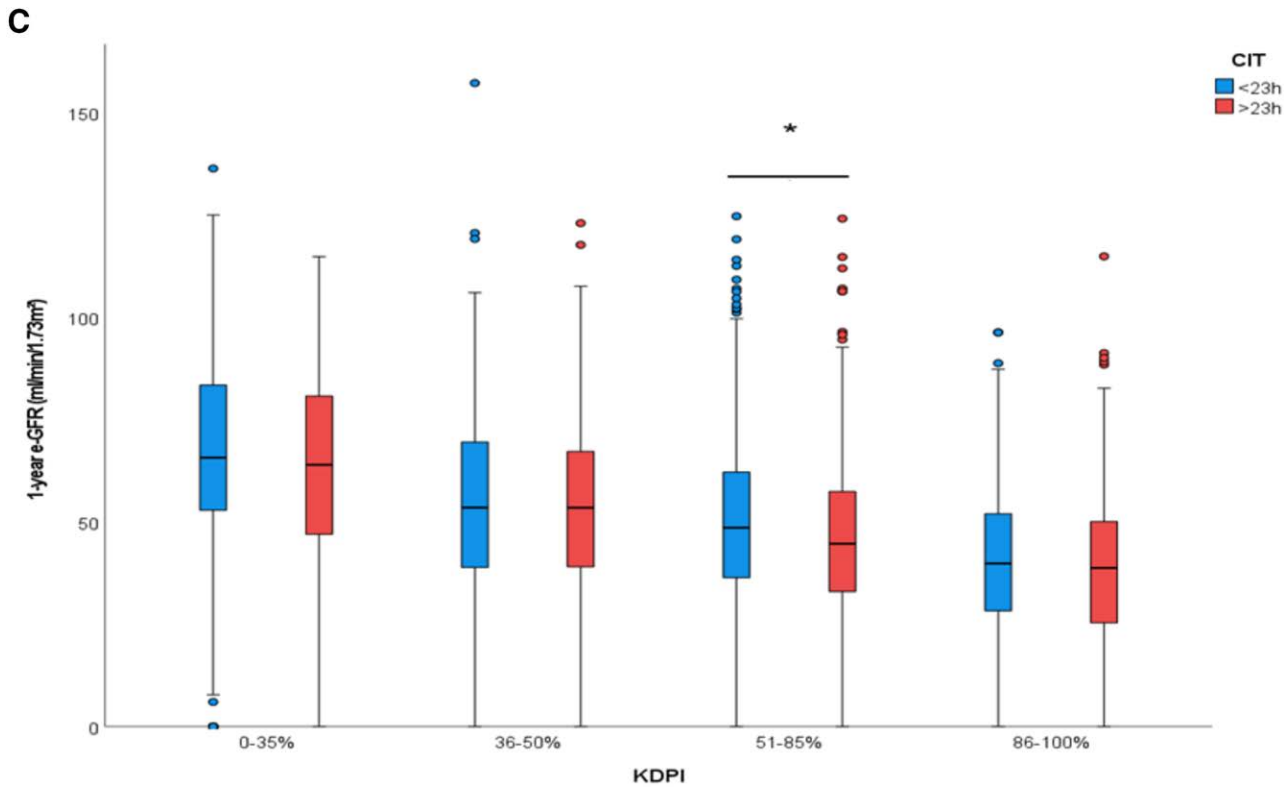


FIGURE 4. Continued.

TABLE 3.

Risk factors associated with 1-y eGFR <50 mL/min/1.73 m²

		95% CI		
	HR	Lower	Upper	*P*[a]
KDPI				
0%–35% (ref.)	1.0	-	-	-
36%–50%	1.767	1.406	2.220	<0.001
51%–85%	2.239	1.862	2.691	<0.001
86%–100%	2.871	2.361	3.491	<0.001
CIT, h	1.011	1.004	1.019	0.003
Donor sex (male)	0.896	0.813	0.989	0.028
Maintenance immunosuppression				
MPS + TAC + Pred	1.0	-	-	-
AZA + TAC + Pred	0.957	0.846	1.082	0.485
mTORi + TAC + Pred	1.055	0.897	1.242	0.518
Other	1.930	0.719	5.181	0.192

[a]*P* values were calculated by Cox proportional hazard model with steps backward Wald statistics.
Variables included: donor sex (male), KDPI, CIT (h), and maintenance immunosuppression.
AZA, azathioprine; CI, confidence interval; CIT, cold ischemia time; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KDPI, Kidney Donor Profile Index; MPS, sodium mycophenolate; mTORi, mammalian target of rapamycin inhibitor; Pred, prednisone; ref., reference; TAC, tacrolimus.

recipients and wait-listed transplant candidates. *J Am Soc Nephrol.* 2001;12:589–597.
2. Port FK, Bragg-Gresham JL, Metzger RA, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation.* 2002;74:1281–1286.
3. Rao PS, Schaubel DE, Guidinger MK, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. *Transplantation.* 2009;88:231–236.
4. Dahmen M, Becker F, Pavenstadt H, et al. Validation of the kidney donor profile index (KDPI) to assess a deceased donor's kidneys' outcome in a European cohort. *Sci Rep.* 2019;9:11234.
5. Lee JH, Park WY, Kim YS, et al. Clinical significance of the kidney donor profile index in deceased donors for prediction of post-transplant clinical outcomes: a multicenter cohort study. *PLoS One.* 2018;13:e0205011.
6. Lehner LJ, Kleinsteuber A, Halleck F, et al. Assessment of the Kidney Donor Profile Index in a European cohort. *Nephrol Dial Transplant.* 2018;33:1465–1472.
7. Philipse E, Lee APK, Bracke B, et al. Does kidney donor risk index implementation lead to the transplantation of more and higher-quality donor kidneys? *Nephrol Dial Transplant.* 2017;32:1934–1938.
8. Arias-Cabrales C, Perez-Saez MJ, Redondo-Pachon D, et al. Usefulness of the KDPI in Spain: a comparison with donor age and definition of standard/expanded criteria donor. *Nefrología (Engl Ed).* 2018;38:503–513.
9. Hariharan S, McBride MA, Cherikh WS, et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int.* 2002;62:311–318.
10. Ibrahim A, Garg AX, Knoll GA, et al. Kidney function endpoints in kidney transplant trials: a struggle for power. *Am J Transplant.* 2013;13:707–713.
11. Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation.* 2003;75:1291–1295.
12. Salvadori M, Rosati A, Bock A, et al. One-year posttransplant renal function is a strong predictor of long-term kidney function: results from the Neoral-MOST Observational Study. *Transplant Proc.* 2003;35:2863–2867.
13. Hwang JK, Park SC, Kwon KH, et al. Long-term outcomes of kidney transplantation from expanded criteria deceased donors at a single center: comparison with standard criteria deceased donors. *Transplant Proc.* 2014;46:431–436.
14. Jay CL, Washburn K, Dean PG, et al. Survival benefit in older patients associated with earlier transplant with high KDPI kidneys. *Transplantation.* 2017;101:867–872.
15. Levey AS, Stevens LA, Schmid CH, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604–612.

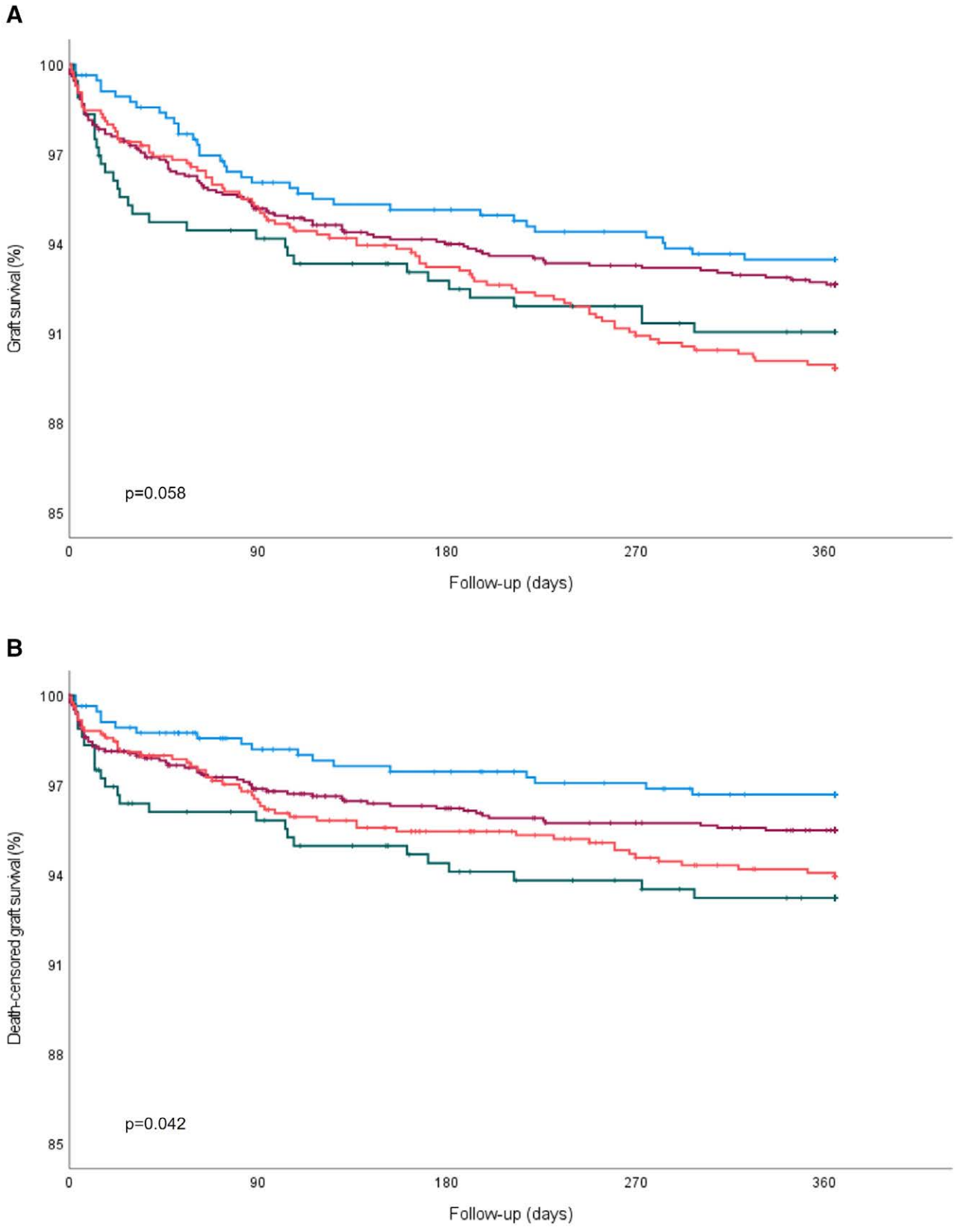
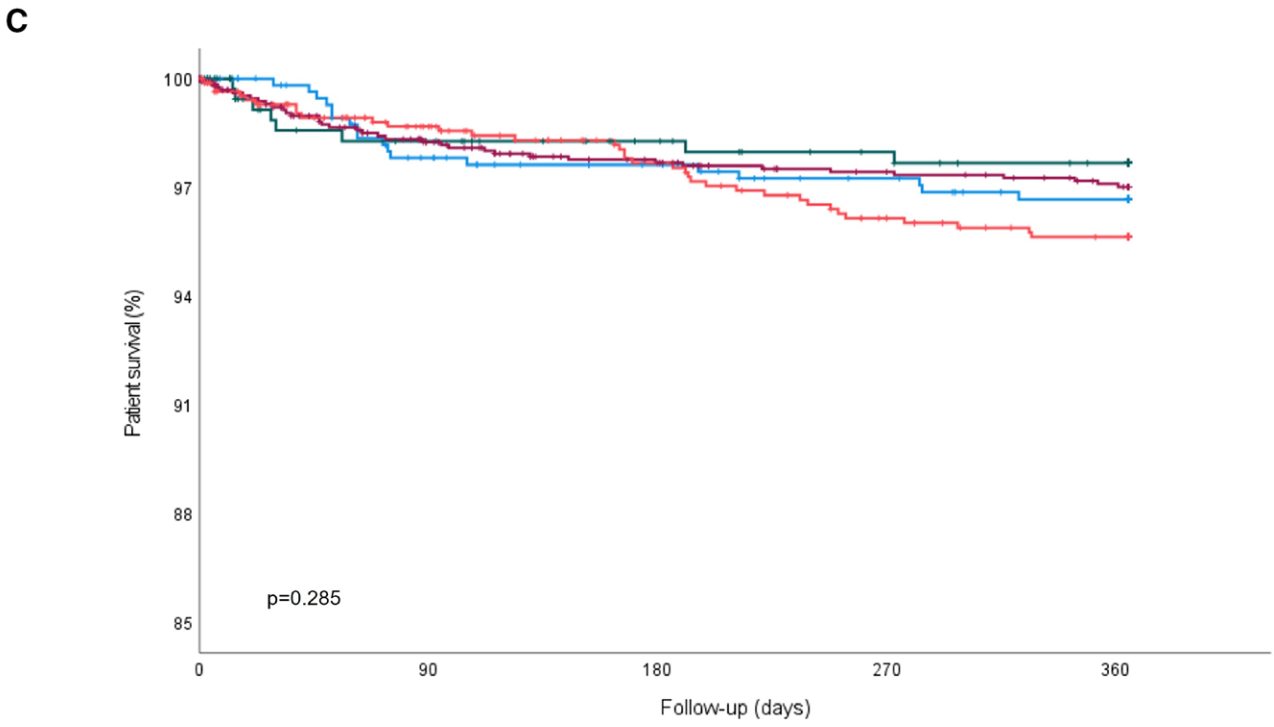


FIGURE 5. Kaplan-Meier plots of patient and graft survival categorized by KDPI strata. A, Kaplan-Meier analysis of 1-y patient survival by KDPI strata. B, Kaplan-Meier analysis of 1-y death-censored graft survival by KDPI strata. C, Kaplan-Meier analysis of 1-y graft survival by KDPI strata. The *P* value was obtained by the log-rank test. KDPI, Kidney Donor Profile Index.



Number at risk, n					
KDPI 0-35%	561	531	520	510	501
KDPI 36-50%	361	338	327	320	313
KDPI 51-85%	1,289	1,215	1,183	1,166	1,152
KDPI 86-100%	848	799	773	751	739

FIGURE 5. Continued.

16. White CA, Akbari A, Doucette S, et al. Estimating glomerular filtration rate in kidney transplantation: is the new chronic kidney disease epidemiology collaboration equation any better? *Clin Chem.* 2010;56:474–477.
17. Yarlagadda SG, Coca SG, Garg AX, et al. Marked variation in the definition and diagnosis of delayed graft function: a systematic review. *Nephrol Dial Transplant.* 2008;23:2995–3003.
18. Kotton CN, Kumar D, Caliendo AM, et al. The Transplantation Society International CMV Consensus Group. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation.* 2018;102:900–931.
19. Nakamura MR, Requiao-Moura LR, Gallo RM, et al. Transition from antigenemia to quantitative nucleic acid amplification testing in cytomegalovirus-seropositive kidney transplant recipients receiving preemptive therapy for cytomegalovirus infection. *Sci Rep.* 2022;12:12783.
20. Haas M, Sis B, Racusen LC, et al.; Banff meeting report writing committee. Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. *Am J Transplant.* 2014;14:272–283.
21. Lambert PC, Smith LK, Jones DR, et al. Additive and multiplicative covariate regression models for relative survival incorporating fractional polynomials for time-dependent effects. *Stat Med.* 2005;24:3871–3885.
22. Jun H, Jung CW, Lim S, et al. Kidney Donor Risk Index as the predictor for the short-term clinical outcomes after kidney transplant from deceased donor with acute kidney injury. *Transplant Proc.* 2017;49:88–91.
23. Keith DS, Vranic G, Nishio-Lucar A. Graft function and intermediate-term outcomes of kidney transplants improved in the last decade: analysis of the United States kidney transplant database. *Transplant Direct.* 2017;3:e166.
24. Molinari M, Kaltenmeier C, Liu H, et al. Function and longevity of renal grafts from high-KDPI donors. *Clin Transplant.* 2022;36:e14759.
25. Tully EK, Hayes IP, Hughes PD, et al. Beyond graft survival: a national cohort study quantifying the impact of increasing Kidney Donor Profile Index on recipient outcomes 1 year post-transplantation. *Transplant Direct.* 2022;8:e1308.
26. Hoy WE, Hughson MD, Bertram JF, et al. Nephron number, hypertension, renal disease, and renal failure. *J Am Soc Nephrol.* 2005;16:2557–2564.
27. Kalucki SA, Lardi C, Garessus J, et al. Reference values and sex differences in absolute and relative kidney size. A Swiss autopsy study. *BMC Nephrol.* 2020;21:289.
28. Brenner BM, Cohen RA, Milford EL. In renal transplantation, one size may not fit all. *J Am Soc Nephrol.* 1992;3:162–169.
29. Lepeytre F, Delmas-Frenette C, Zhang X, et al. Donor age, donor-recipient size mismatch, and kidney graft survival. *Clin J Am Soc Nephrol.* 2020;15:1455–1463.
30. Narasimhamurthy M, Smith LM, Machan JT, et al. Does size matter? Kidney transplant donor size determines kidney function among living donors. *Clin Kidney J.* 2017;10:116–123.
31. Perico N, Cattaneo D, Sayegh MH, et al. Delayed graft function in kidney transplantation. *Lancet.* 2004;364:1814–1827.
32. Debout A, Foucher Y, Trebern-Launay K, et al. Each additional hour of cold ischemia time significantly increases the risk of graft failure and mortality following renal transplantation. *Kidney Int.* 2015;87:343–349.
33. Liu L, Cheng K, Huang J. Effect of long cold ischemia time of kidneys from aged donors on prognosis of kidney transplantation. *Ann Transplant.* 2021;26:e928735.
34. Quiroga I, McShane P, Koo DD, et al. Major effects of delayed graft function and cold ischaemia time on renal allograft survival. *Nephrol Dial Transplant.* 2006;21:1689–1696.
35. Foroutan F, Friesen EL, Clark KE, et al. Risk factors for 1-year graft loss after kidney transplantation: systematic review and meta-analysis. *Clin J Am Soc Nephrol.* 2019;14:1642–1650.
36. de Sandes-Freitas TV, Felipe CR, Aguiar WF, et al. Prolonged delayed graft function is associated with inferior patient and kidney allograft survivals. *PLoS One.* 2015;10:e0144188.
37. de Sandes-Freitas TV, Mazzali M, Manfro RC, et al. DGF-Brazil Study Group†. Exploring the causes of the high incidence of delayed graft

function after kidney transplantation in Brazil: a multicenter study. *Transpl Int.* 2021;34:1093–1104.
38. Jahn L, Ruster C, Schlosser M, et al. Rate, factors, and outcome of delayed graft function after kidney transplantation of deceased donors. *Transplant Proc.* 2021;53:1454–1461.
39. Donnelly CV, Keller M, Kayler L. Kidney transplant outcomes after prolonged delayed graft function. *J Clin Med.* 2022;11:1535.
40. Baptista AP, Silva HT, Jr, Pestana JO. Influence of deceased donor hemodynamic factors in transplant recipients renal function. *J Bras Nefrol.* 2013;35:289–298.
41. Farooqui W, Pommergaard HC, Rasmussen A. Remote ischemic preconditioning of transplant recipients to reduce graft ischemia and reperfusion injuries: a systematic review. *Transplant Rev (Orlando).* 2018;32:10–15.
42. Raval AD, Kistler KD, Tang Y, et al. Epidemiology, risk factors, and outcomes associated with cytomegalovirus in adult kidney transplant recipients: a systematic literature review of real-world evidence. *Transpl Infect Dis.* 2021;23:e13483.
43. Vanhove T, Kuypers D, Claes KJ, et al. Reasons for dose reduction of mycophenolate mofetil during the first year after renal transplantation and its impact on graft outcome. *Transpl Int.* 2013;26:813–821.
44. Hoffman W, Mehta R, Jorgensen DR, et al. The impact of early clinical and subclinical T cell-mediated rejection after kidney transplantation. *Transplantation.* 2019;103:1457–1467.
45. Felipe CR, Ferreira AN, Bessa A, et al. The current burden of cytomegalovirus infection in kidney transplant recipients receiving no pharmacological prophylaxis. *J Bras Nefrol.* 2017;39:413–423.
46. Erdbrugger U, Scheffner I, Mengel M, et al. Long-term impact of CMV infection on allografts and on patient survival in renal transplant patients with protocol biopsies. *Am J Physiol Renal Physiol.* 2015;309:F925–F932.
47. Irish W, Nickerson P, Astor BC, et al. Change in estimated GFR and risk of allograft failure in patients diagnosed with late active antibody-mediated rejection following kidney transplantation. *Transplantation.* 2021;105:648–659.
48. Lindholm A, Ohlman S, Albrechtsen D, et al. The impact of acute rejection episodes on long-term graft function and outcome in 1347 primary renal transplants treated by 3 cyclosporine regimens. *Transplantation.* 1993;56:307–315.