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ORIGINAL ARTICLE

Function and longevity of renal grafts from high-KDPI donors

Michele Molinari[1] | Christof Kaltenmeier[1] | Hao Liu[4] | Eishan Ashwat[1] | Dana Jorgensen[1,2] | Chethan Puttarajappa[3] | Christine M. Wu[3] | Rajil Mehta[3] | Puneet Sood[3] | Nirav Shah[3] | Akhil Sharma[3] | Ann Thompson[1] | Dheera Reddy[4] | Sundaram Hariharan[3]

[1]Department of Surgery, Division of Transplantation, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA (Email: thompsonam13@upmc.edu)

[2]Biostatistics, Division of Transplantation, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

[3]Department of Medicine, Division of Nephrology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

[4]Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Correspondence
Michele Molinari, University of Pittsburgh Medical Center, 3459 Fifth Avenue, N758, Pittsburgh, PA 15213, USA.
Email: molinarim@upmc.edu

Abstract

Background: High kidney-donor profile index (KDPI) kidneys have a shorter survival than grafts with lower KDPI values. It is still unclear, however, whether their shorter longevity depends on an inferior baseline function, faster functional decline, or the combination of both.

Methods: We analyzed the estimated glomerular filtration rate (eGFR) of 605 consecutive recipients of deceased donor kidney transplants (KT) at 1, 3, 6, 12, 18, 24, 36, 48, and 60 months. Comparisons were performed among four groups based on KDPI quartile: Group I-KDPI ≤ 25% ($n = 151$), Group II-KDPI 26–50% ($n = 182$), Group III-KDPI 51–75% ($n = 176$), and Group IV-KDPI 〉 75% ($n = 96$). Linear mixed model analysis was subsequently used to assess whether KDPI was independently associated with the decline in eGFR during the first 5-years after KT. We also analyzed the incidence of delayed graft function (DGF), rejection within the first year after KT, patient survival, graft survival, and death censored graft survival based on KDPI group.

Findings: High-KDPI grafts had lower eGFR immediately after KT, had a higher incidence of DGF and rejection. However, there were no signifcant differences in the adjusted rate (slope) of decline in eGFR among the four KDPI groups ($P = .06$). Although patient survival was signigicantly lower for recipients of high-KDPI grafts, death-censored graft survival was similar among the four KDPI groups ($P = .33$).

Conclusions: The shorter functional survival of high-KDPI grafts seems to be due to their lower baseline eGFR rather than a more rapid functional decline after KT.

KEYWORDS
kidney donor profile index, renal transplantation

1 | INTRODUCTION

Kidney transplantation (KT) provides the best quality of life and the longest survival for patients with end-stage renal disease (ESRD).[1] The overall success of KT, however, is thwarted by the shortage of donors.[2,3] To correct this limitation, transplant centers have expanded the donor pool by accepting donors previously considered unsuitable due to their age or comorbidities.[4] As organs from elderly donors or donors with multiple comorbidities are at a higher risk of primary graft non-function and shorter survival,[5–7] determining

the quality of the grafts prior to their use is critical to avoid poor outcomes.

Among the many models developed to predict the quality of renal grafts, the Kidney Donor Risk Index **(KDRI)** is the instrument currently used in the United States.[5] The KDRI incorporates ten donor parameters that are easily attainable before surgery.[5]

The KDRI was subsequently converted into a cumulative measure ranging from 0% (high-quality grafts) to 100% (low-quality grafts), named the Kidney Donor Profile Index **(KDPI)**.[8] The KDPI estimates the average relative risk of post-transplant graft failure.

Several studies have shown an inverse relationship between KDPI and graft survival.[9–11] It is still unclear, however, whether the shorter longevity of high-KDPI grafts is due to a lower baseline renal function or a more rapid functional decline after surgery, or both.[12]

Since the speed of decline of the estimated glomerular filtration rate **(eGFR)** can predict renal failure or graft loss,[13,14] we analyzed the eGFR at different intervals in a consecutive cohort of adult recipients of deceased-donor KTs. Our primary aim was to analyze the relationship between KDPI and changes in the eGFR over time by comparing high-KDPI kidneys to grafts with lower KDPI values.

2 | PATIENTS AND METHODS

2.1 | Study population and settings

Between January 1, 2013, and December 31, 2017, a total of 1000 consecutive KTs were performed on adult recipients at the University of Pittsburgh Medical Center and were screened for this study.

No standardized policies were used to guide the acceptance or the decline of organs based on KDPI values. The decisions to accept or decline renal grafts were made by on-call providers based on their assessment of donors' hemodynamic status, the trend of donor serum creatinine, hourly urinary output, and the distance between the donor and our center. For grafts put on pulsatile perfusion pumps, parameters considered acceptable for transplantation were a flow of > 90 ml/min with the resistance of < .5 mmHg/ml/min. Graft biopsies were obtained only on demand based on providers' preferences and pathology availability. Renal graft biopsies with <20% of glomerulosclerosis were considered satisfactory.

The immunosuppression therapy used at our center has been described in detail in previous publications.[15,16] A total of 577/605 (95.3%) patients received thymoglobulin (total dose of 6 mg/kg divided into four different sessions) over 4–5 days starting at the date of surgery. Basiliximab was used for 18 patients (2.9%) and Alemtuzumab for 10 (1.6%). All recipients received a rapid 7-day corticosteroid taper. Maintenance immunosuppression with prednisone (5 mg daily), was recommended only for highly sensitized patients defined as recipients with calculated panel reactive antibody **(cPRA)** > 90% and for patients diagnosed with T-cell mediated rejection (TCMR) (> Banff IA). Mycophenolate (maximum dose of 1000 mg twice daily) was started on the day of the transplant and Tacrolimus was added within 72 h after surgery (*n*. patients = 567/605, 93.7%). Maintenance immunosuppression with Mycophenolate (maximum dose of 1000 mg twice daily) and Cyclosporine or mTOR inhibitors (Sirolimus or Everolimus) was used for patients intolerant to Tacrolimus (*n*. patients = 38/605, 6.3%). Serum Tacrolimus trough levels were maintained between 8 and 12 ng/ml during the first 6 months and 6–10 ng/ml thereafter irrespective of KDPI values.

2.2 | Inclusion and exclusion criteria

Inclusion criteria were age ≥ 18 years, a single renal graft from compatible ABO blood group donors. Exclusion criteria were grafts from live donors, dual or multiorgan transplants, and en-bloc renal grafts (Figure 1).

2.3 | Groups

The study population was stratified into four groups based on the quartiles of the KDPI values. We also performed sub-analyses using KDPI values traditionally employed by Organ Procurement and Transplant Network **(OPTN)** to stratify the quality of deceased donor grafts. These values were KDPI < 20%, KDPI between 21% and 85%, and KDPI > 85%.[8,17]

2.4 | Data collection

Recipient date of birth, date of transplantation, date of discharge, date of death or last follow-up, date of relisting or re-transplantation, sex, height and weight, ethnicity (categorized as Caucasian, African American, Asian, Hispanic, or Other), the primary indication for renal transplant, need for dialysis within the first week after KT, serum creatinine at 3, 6, 12, 18, 24, 36, 48, and 60 months after KT were collected.

Other clinical parameters were the duration of preoperative dialysis (measured in days), the highest **cPRA** value reported in percentage and calculated using the **OPTN** calculator publicly available on the US Department of Health and Human Services website (https://optn.transplant.hrsa.gov/resources/allocation-calculators/cpra-calculator/).

Donor variables were age, ethnicity, history of hypertension or diabetes, the main cause of death, type of donation (donation after brain death **(DBD)** or donation after cardiac death **(DCD)**), terminal serum creatinine, and history of viral hepatitis C. The KDPI score was obtained using the KDPI calculator available on the OPTN website (https://optn.transplant.hrsa.gov/resources/allocation-calculators/kdpi-calculator/).[5,18]

Operative variables were cold ischemia time **(CIT)** and warm ischemia times **(WIT)**. CIT was defined as the interval between the time when the donor aorta was cross-clamped and the time when the graft was removed from the cold preservation solution. WIT was defined as the interval between the time when the renal graft was brought to the surgical field and the time when the organ was reperfused after completion of all the vascular anastomoses. Postoperative variables

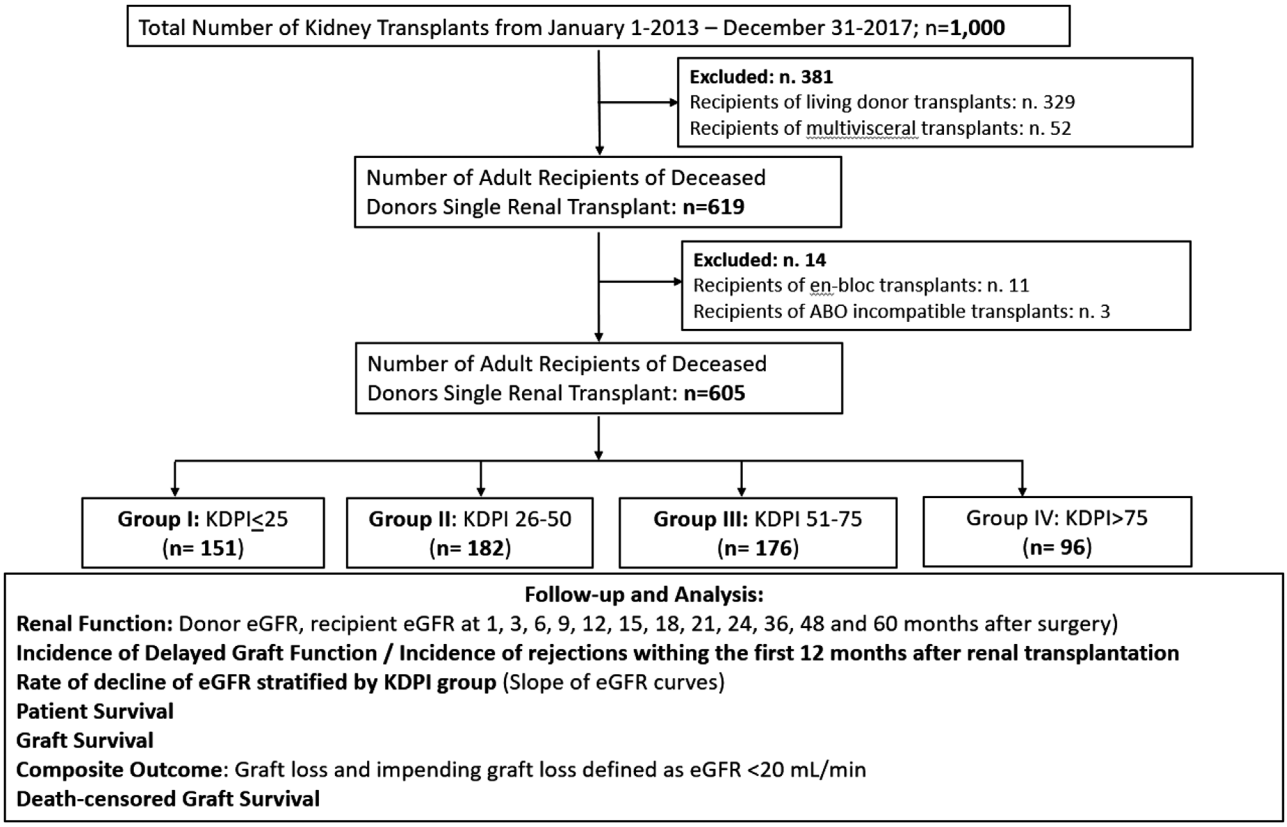

FIGURE 1 Flowchart of all adult recipients of kidney grafts transplanted between January 1–2013 and December 31–2017 at the University of Pittsburgh Medical Center. Among 1000 potentially suitable candidates, 381 were excluded because they received grafts from live donors or multi-visceral organs (e.g., simultaneous kidney and pancreas, simultaneous kidney, and liver), 14 were excluded because they received en-bloc kidneys from pediatric donors or ABO-incompatible organs. All patients were followed until December 31, 2019.

included hospital stay defined as the time between hospital admission and patient discharge after the index operation.

2.5 | Outcomes

The main outcome was the rate of decline of eGFR during the first 5 years after KT. The rate of decline in eGFR was measured using the slopes of the functions representing the mean values of eGFR calculated at 3, 6, 12, 18, 24, 36, 48, and 60 months stratified by KDPI. EGFR was calculated using the CKD-Epi equation that utilizes the serum creatinine, sex, race, and age to estimate the eGFR.[19] For eGFR at 1, 3, and 6 months, recipients' serum creatinine levels were measured within 2 weeks from the pre-established date. For the calculation of eGFR at 12, 18, 24, 36, 48, and 60 months, the serum creatinine levels were measured within 4 weeks from the pre-established date. Secondary outcomes were: (1) Donors' eGFR was measured at the time of organ allocation using terminal serum creatinine, (2) the incidence of delayed graft function **(DGF)** was defined as the need for dialysis within 7 days after KT,[20] (3) the rate of rejection during the first year after KT. Rejections were diagnosed by renal biopsies that were obtained for patients with a new-onset of renal dysfunction defined as the rise in serum creatinine >25% from baseline and/or new or worsening proteinuria [>1 g/day and/or >1 g/g urine protein to creatinine ratio]. Renal biopsies were not routinely requested for patients with isolated donor-specific antibodies. Surveillance allograft biopsies were also performed at 3 and 12 months in the absence of systemic anticoagulation, dual antiplatelet therapy, intra-abdominal kidney location, serious infections, or lack of transportation. Biopsies were scored using Banff 2013 and later 2017 classifications by experienced transplant pathologists.[21,22] Histological findings were classified as normal, subclinical allograft inflammation defined as the presence of histological changes that did not satisfy Banff IA criteria, TCMR, antibody-mediated rejection, or mixed rejection (coexistence of TCMR and antibody-mediated rejection). For this study, we defined rejection all types of rejection irrespective of the grade of the Banff classification. We also did not differentiate whether rejections were diagnosed by clinically indicated or by surveillance biopsies. Other secondary outcomes were (a) the 5-year graft survival, (b) the 5-year death-censored graft survival, (c) the 5-year patient survival, and (d) the 5-year graft loss or impending graft loss. Graft loss was defined as the irreversible need for dialysis, allograft nephrectomy, or patient death. Impending graft loss was defined as the presence of eGFR $\leq$ 20 ml/min in patients with previously sustained eGFR $\geq$ 20 ml/min.

2.6 | Statistical analysis

Shapiro-Wilk test was used to assess whether continuous variables were normally distributed. Continuous variables with normal distribution are presented as mean and standard deviation **(SD)**, whereas those with a non-normal distribution are presented as median values with an interquartile range **[IQR]**. Trends were evaluated using ANOVA and pairwise comparisons were obtained using least squared means for normally distributed variables and the Wilcoxon rank-sum test for differences in medians.

Categorical variables are presented as counts and percentages. The Chi-square test or Fisher's exact test was used when appropriate to analyze categorical variables.

Logistic regression analysis was used to assess whether KDPI group was an independent parameter associated with the risk of DGF after accounting for clinically relevant confounders such as age, sex, body mass index **(BMI)**, type of donor, CIT, WIT, and cPRA.

Multivariable linear mixed models were used to assess the mean change in kidney function (measured by eGFR) over the first 5 years post-transplant in each KDPI group. We tested changes over time in the eGFR based on both adjusted and unadjusted models that included the KDPI Group as the primary explanatory variable. Independent parameters included in the model were recipient age, sex, BMI, type of donor, CIT, WIT, cPRA, and DGF. These confounders were selected based on their clinical relevance as reported in the literature. To assess the longitudinal effect on eGFR for each KDPI category, we defined the KDPI group, post-transplant time, and the interaction between the KDPI group and time as fixed effects. Each recipient level rate of change in eGFR was specified as a random effect. Variance-covariance matrix structures were defined as first-order autoregressive structures.[23] For patients who required dialysis after KT due to DGF or graft failure, eGFR was set at 10 ml/min/1.73m^2.

Time-dependent events were graft loss, impending graft loss, death, or last follow-up. Censoring was used for patients who were still alive at their last follow-up and for grafts that were still functioning at the end of the study or during their last follow-up.

The Kaplan-Meier method was used to represent survival function and the Log-rank test was used to assess differences in patient survival, graft survival, death-censored graft survival, and the composite outcome of graft loss or impending graft loss. Cox proportional hazards regression analysis was used to examine whether the KDPI group was an independent factor associated with the risk of graft loss or impending graft loss after adjusting for type of donor, recipient age, recipient sex, CIT, WIT, recipient BMI, cPRA and DGF.

For all comparisons[1] patients in the lowest KDPI quartile (Group I) represented the reference group performed in this study and Bonferroni method was used to correct all the *P*-values when multiple comparisons were performed. Only *P*-values < .05 were considered statistically significant. All statistical analyses were performed using SAS software, Version 9, (SAS Institute Inc. Cary, NC, USA) or SPSS Statistics, for Windows, version 28, (IBM Corp, Armonk, NY, USA).

[1] For all comparisons performed in this study, patients in the lowest KDPI quartile (Group I) represented the reference group, and Bonferroni method was used to correct all the *P*-values.

2.7 | Ethical guidelines, privacy protection, and institution ethics review board approval

All the data were obtained from a prospectively maintained transplant registry containing de-identified demographic and clinical data of renal transplant recipients operated at our center. Privacy and data protection were secured by limiting access to the registry to investigators with personalized two-step codes to open the dataset. The need for individual patient consent was waived by the local institutional ethics review board that approved the study protocol (Approval number PRO 13060220). This study was performed in compliance with the declaration of Helsinki on ethical principles for medical research involving human subjects.[24] The strengthening of the reporting of observational studies in epidemiology **(STROBE)** statement was used for the reporting of this study.[25]

3 | RESULTS

3.1 | Patient characteristics

The baseline demographic and clinical characteristics of the study population and respective donors are summarized in Table 1. The recipient's age at transplantation was 53.8 years and females were 40.3%. The most frequent indication for KT was diabetic nephropathy (23.1%), hypertensive nephropathy (18.5%), and polycystic renal disease (9.8%). The average waiting time was 4.9 years, CIT was 12.1 h, WIT was 38 min and cPRA was 39%. Kidneys from brain-dead donors represented the most common type of grafts. DCD grafts represented 16% of organs in Group I, 29% in Group II, 38% in Group III, and 17% in Group IV ($P < .01$). Due to the new kidney allocation system, recipients of grafts with KDPI > 75% were significantly older than recipients of grafts with KDPI < 25% (60 vs. 46 years; $P < .01$).

Overall, KDPI values in our population were not normally distributed as illustrated in Figure 1 of the Supplement (Shapiro-Wilk test $P < .001$).

3.2 | Immunosuppression

The percentage of patients who received induction therapy with Thymoglobulin, Basiliximab, or Alemtuzumab was similar among the KDPI groups. Similarly, the serum levels of maintenance immunosuppression were not statistically different among the four KDPI groups (Data not shown due to space limitations).

3.3 | Donor eGFR

Donor eGFR was 113 (±30.1) for Group I, 98.9 (±41.3) for Group II, 89.0 (±38.7) for Group III, and 82.3 (±37.4) ml/min/1.73 m^2 for Group IV ($P < .001$) (Figure 2A). EGFR was 116.5 (+27.4) for donors

TABLE 1 Demographic and clinical characteristics of the study population

	Entire cohort	KDPI 1-25	KDPI 26-50	KDPI 51-75	KDPI 76-100	
	n. 605	*n.* 151	*n.* 182	*n.* 176	*n.* 96	
Characteristics	**Group**	**I**	**II**	**III**	**IV**	***P-value***
Recipient age, years, mean (SD)	53.8 (13.7)	46.3 (14.5)	55.3 (11.9)	55.4 (13.6)	60.2 (10.4)	<.001
Recipient sex, female, *n.* (%)	244 (40.3)	58 (38.4)	75 (41.2)	71 (40.3)	40 (41.7)	.948
Recipient body mass index, mean (SD)	28.9 (5.6)	28.1 (5.7)	29.1 (5.3)	28.9 (5.6)	29.8 (5.7)	.114
Recipient ethnicity, *n.* (%)						
Caucasian	426 (70.4)	106 (70.2)	131 (72.0)	130 (73.9)	59 (61.5)	.277
African American	163 (26.9)	41 (27.2)	47 (25.8)	43 (24.4)	32 (33.3)	
Asian	4 (.7)	1 (.7)	2 (1.1)	1 (.6)	0	
Hispanic	0	–	–	–	–	
Other	12 (2.0)	3 (2.0)	2 (1.1)	2 (1.1)	5 (5.2)	
Primary indication for transplant, *n.* (%)						
Diabetic nephropathy	140 (23.1)	18 (11.9)	44 (24.2)	44 (25.0)	34 (35.4)	.021
Hypertension	112 (18.5)	24(15.9)	36 (19.8)	30 (17.0)	22 (22.9)	
Polycystic renal disease	59 (9.8)	11 (7.3)	22 (12.1)	21 (11.9)	5 (5.2)	
Membranous glomerulonephritis	13 (2.1)	3 (2.0)	2 (1.1)	8 (4.5)	0	
IgA nephropathy	24 (4.0)	7 (4.6)	7 (3.8)	7 (4.0)	3 (3.1)	
Focal glomerulosclerosis	24 (4.0)	8 (5.3)	8 (4.4)	6 (3.4)	2 (2.1)	
Chronic glomerulonephritis	17 (2.8)	5 (3.3)	4 (2.2)	5 (2.8)	3 (3.1)	
Medication induced renal failure	9 (1.5)	2 (1.3)	3 (1.6)	3 (1.7)	1 (1.0)	
Systemic lupus erythematous	14 (2.3)	4 (2.6)	5 (2.7)	3 (1.7)	2 (2.1)	
Obstructive / Reflux disease	22 (3.6)	6 (4.0)	7 (3.8)	4 (2.3)	5 (5.2)	
Chronic allograft nephropathy	4 (.7)	3 (2.0)	1 (.5)	0	0	
Other	167 (27.6)	60 (39.7)	43 (23.6)	45 (25.6)	19 (19.8)	

(Continues)

TABLE 1 (Continued)

Characteristics	Entire cohort *n.* 605 Group	KDPI 1-25 *n.* 151 I	KDPI 26-50 *n.* 182 II	KDPI 51-75 *n.* 176 III	KDPI 76-100 *n.* 96 IV	*P-value*
Number of previous renal transplants, *n.* (%)						
0	433 (71.6)	94 (66.7)	133 (72.7)	136 (69.7)	70 (81.4)	.10
1	129 (21.3)	29 (20.6)	41 (22.4)	44 (22.6)	15 (17.4)	
2	31 (5.1)	13 (9.2)	7 (3.8)	10 (5.1)	1 (1.2)	
3	8 (1.3)	4 (2.8)	2 (1.1)	2 (1.0)	0	
4	4 (.7)	1 (.7)	0	3 (1.5)	0	
Renal replacement therapy duration, days, mean (SD)	1811 (1246)	1832 (1505)	1829 (1270)	1795 (1053)	1777 (1115)	.878
Cold ischemia time, minutes, median (Range)	727 (326)	758 (341)	713 (333)	703 (328)	749 (279)	.422
Warm ischemia time, minutes, mean (SD)	38.2 (10.5)	37.9 (10.3)	38.0 (10.4)	38.4 (10.8)	38.4 (10.6)	.774
Type of donation						
Donation after brain death, *n.* (%)	445 (73.6)	127 (84.1)	129 (70.9)	109 (61.9)	80 (83.3)	<.001
Donation after cardiac death, *n.* (%)	160 (26.4)	24 (15.9)	53 (29.1)	67 (38.1)	16 (16.7)	
Donor age, mean (SD)	40.1 (14.4)	24.9 (6.5)	37.9 (10.9)	46.7 (11.1)	56.2 (9.4)	<.001
Donor sex, female, *n.* (%)	230 (38)	38 (25.2)	70 (38.5)	66 (37.5)	56 (58.3)	<.001
Donor ethnicity						
Caucasian	547 (90.4)	137 (90.7)	168 (92.3)	161 (91.5)	81 (84.4)	.023
African American	44 (7.3)	6 (4.0)	12 (6.6)	13 (7.4)	44 (13.5)	
Hispanic	10 (1.7)	7 (4.6)	1 (.5)	1 (.6)	1 (1.0)	
Other	4 (.7)	1 (.7)	1 (.5)	1 (.6)	1 (1.0)	
Hospital stay, days, mean (SD)	5.0 (3.5)	4.5 (2.8)	5.3 (3.7)	4.6 (2.5)	5.7 (5.0)	.035
n. missing values	61 (10.0)	11 (7.2)	24 (13.1)	22 (12.5)	4 (4.1)	
Calculated PRA, mean (SD)	39.9 (40.4)	42.0 (41.2)	39.2 (41.2)	40.4 (40.6)	37.0 (37.2)	.810

Abbreviations: KDPI, Kidney Donor Profile Index; cPRA, calculated Panel Reactive Antibodies.

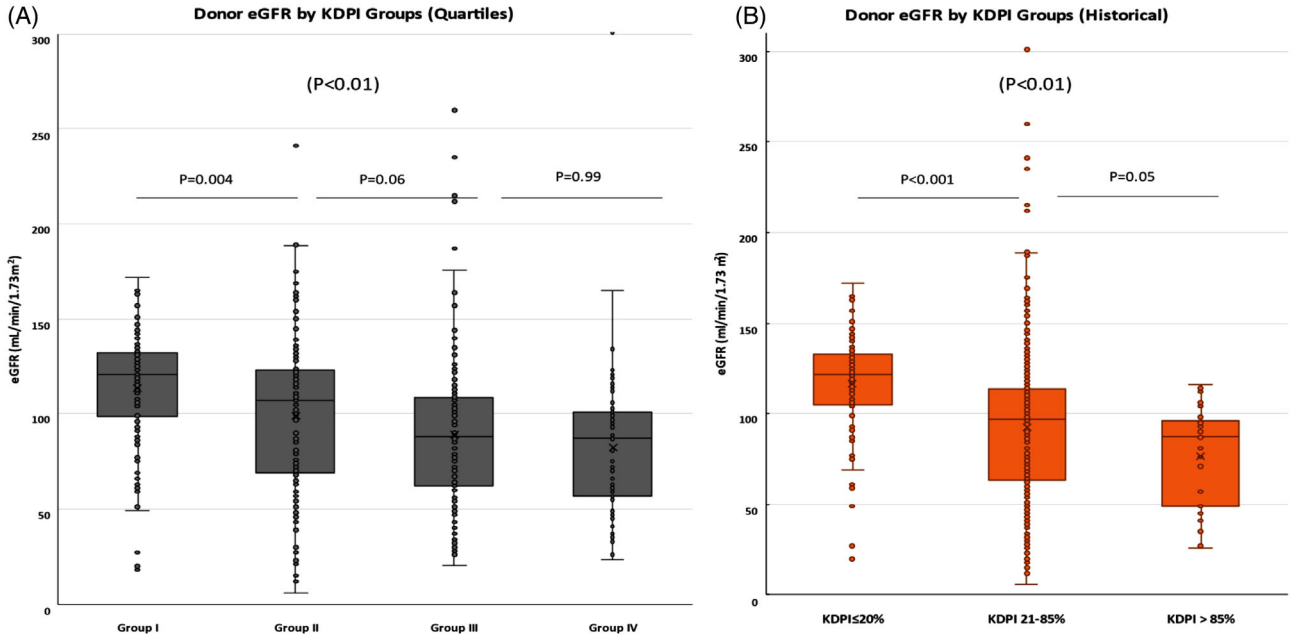

FIGURE 2 Box and whisker plot illustrating the quartiles, median, and 95% confidence intervals of the donors' estimated glomerular filtration rate (eGFR) calculated using the terminal serum creatinine stratified by KDPI quartiles (**Panel A**). Box and whisker plot illustrating the quartiles, median, and 95% confidence intervals of donors' eGFR stratified by historical KDPI cut-offs KDPI < 20%, KDPI 21–85%, and KDPI > 85% **(Panel B)**.

with KDPI < 20%, 92.5 (+40.5) for donors with KDPI 21–85% and 76.5 (+28.0) ml/min/1.73 m^2 for donors with KDPI > 85% ($P < .001$) (Figure 2B).

3.4 | DGF

The incidence of DGF was 14.5% for Group I, 27.4% for Group II, 27.2% for Group III, and 31.2% for Group IV ($P < .001$). At 1 year after KT, the mean difference in eGFR between patients with and without DGF was 6 ml/min (95%CI 4.6–7.8) for Group I, 11.0 ml/min (95%CI 7.8-14.4) for Group II, 16.5 ml/min (95%CI 11.7–21.6) for Group III and 22.0 ml/min (95%CI 15.6-28.8) for Group IV (All pairwise comparisons P values < .001). In multivariate analysis, KDPI remained an independent risk factor for DGF after adjusting for recipient age, sex, CIT, WIT, BMI, cPRA, and donor type (Figure 3).

3.5 | eGFR

The mean eGFR at 1 month was 49.9 (±18.6) for Group I, 37.5 (±14.8) for Group II, 32.8 (±15.1) for Group III, and 29.5 (±13.9) ml/min/1.73m^2 for Group IV (All pairwise comparisons P values ≤.01) (Figure 4A). At 1 year, the mean eGFR was 56.2 (±21.0) for Group I, 46.4 (±16.6) for Group II, 42.2 (±18.5) for Group III, and 38.1 (±15.0) ml/min/1.73m^2 for Group IV (All pairwise comparisons all P values ≤.01). A progressive decline in eGFR was observed for all four Groups after the first year.

Linear mixed model analysis using the deltas eGFR as the dependent variables showed that there were no statistically significant differences in the speed of functional decline (slope of the eGFR curve) among the four KDPI groups after adjusting for recipient age, sex, BMI, type of organ donation, CIT, WIT, cPRA, and DGF ($P = .06$).

Sub-analysis using the stratification of the cohort in three groups (KDPI < 20%, KDPI 21–85%, and KDPI > 85%) also confirmed that the slopes of the eGFR curves were similar among the three KDPI groups (Figure 4B) ($P = .34$).

3.6 | Rejection

During the first year, the rejection rate was 17.8% for Group I, 21.9% for Group II, 31.8% for Group III, and 33.3% for Group IV ($P < .001$). Sub-analysis showed that the rejection rate was 18.7% for recipients of grafts with KDPI < 20%, 27.0% for recipients of grafts with KDPI 21–85%, and 32.3% for recipients of grafts with KDPI > 86% ($P = .03$) (Table 2).

3.7 | Patient and graft survival

The median follow-up for the entire cohort was 44 months (range 10–78 months). During this period, 55 patients (9%) died, 20 with functional grafts and 35 with impending graft loss while 550 patients were still alive, 476 with functional grafts, and 74 with impending graft loss.

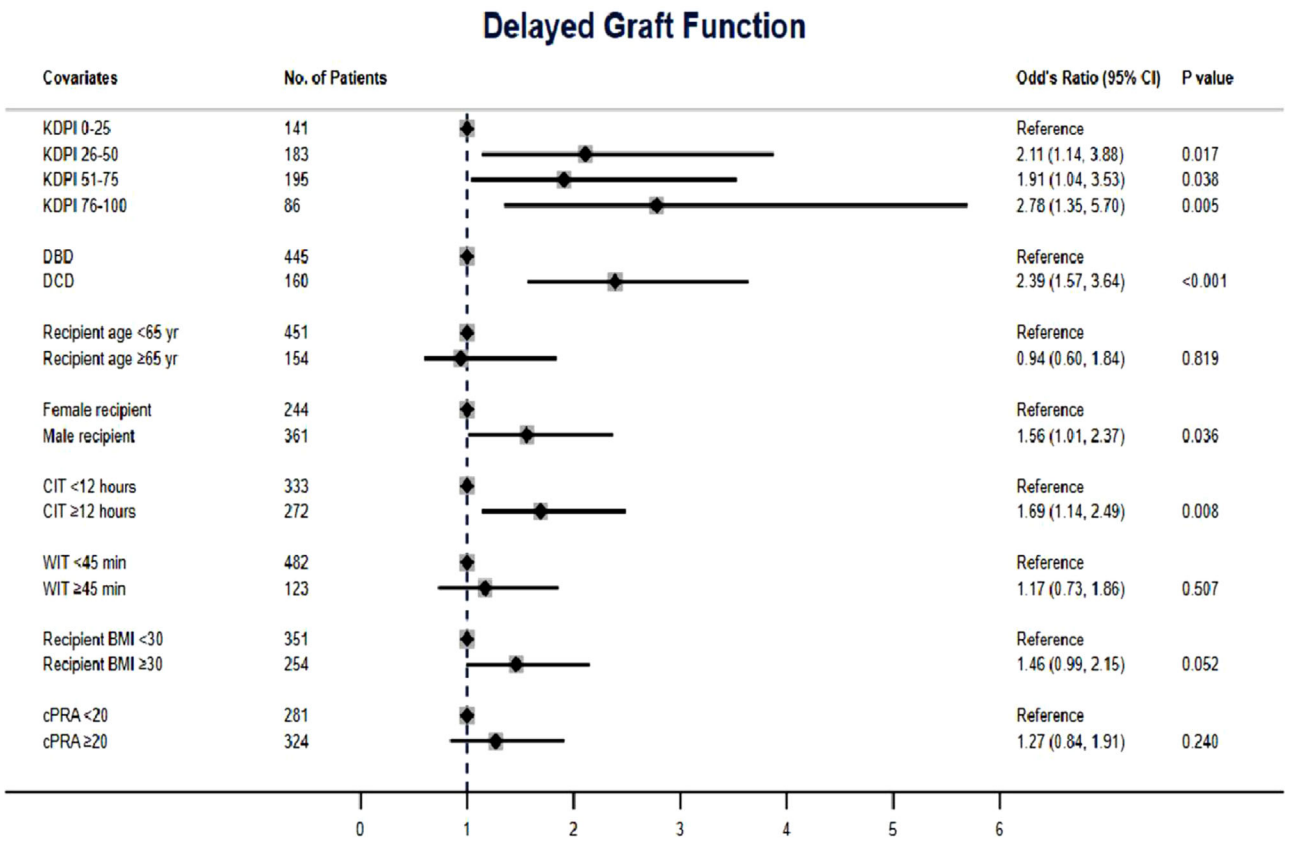

FIGURE 3 Forest plot illustrating the adjusted odds ratios (OR) for the development of delayed graft function (DGF) for each KDPI Group after accounting for the type of donation, recipient age, recipient sex, duration of cold ischemia time (CIT), duration of warm ischemia time (WIT), recipient body mass index (BMI) and the calculated panel of reactive antibodies (cPRA). Kidney donor profile index (KPDI), donation after brain death (DBD), donation after cardiocirculatory death (DCD), cold ischemia time (CIT), warm ischemia time (WIT), body mass index (BMI), the calculated panel of reactive antibodies (cPRA).

TABLE 2 Biopsy proven rejection rates stratified by donor KDPI values

Immunological events within the first year after KT, *n.* (%)	All patients *n.* 605	KDPI 1-25 *n.* 151	KDPI 26-50 *n.* 182	KDPI 51-75 *n.* 176	KDPI 76-100 *n.* 96	*P value*
No rejection	214 (35.3)	58 (38.4)	73 (40.1)	55 (31.2)	28 (29.1)	<.001
Subclinical inflammation	236 (39.0)	66 (43.7)	69 (37.9)	65 (36.9)	36 (37.5)	
T-cell mediated / Antibody mediated rejection	155 (25.6)	27 (17.8)	40 (21.9)	56 (31.8)	32 (33.3)	

Immunological events within the first year after KT, *n.* (%)	KDPI 0-20% *n.* 128	KDPI 21-85% *n.* 443	KDPI 86-100% *n.* 34	*P value*
No rejection	47 (36.7)	155 (34.9)	12 (35.2)	.03
Subclinical inflammation	57 (44.5)	168 (37.9)	11 (32.3)	
T-cell mediated, or Antibody mediated rejection	24 (18.7)	120 (27.0)	11 (32.3)	

The 5-year patient survival was 95% for Group I, 86% for Group II, 73% for Group III, and 76% for Group IV ($P = .03$) (Figure 5A). The 5-year graft survival was 86% for Group I, 71% for Group II, 67% for Group III, and 68% for Group IV (Figure 5B) ($P = .009$). In contrast to previous findings, death-censored graft survival was not statistically significant different among groups ($P = .338$). After 5 years, death censored graft survival was 92% for patients in Group I, 85% for patients in Group II, 90% for patients in Group III, and 92.3% for patients in Group IV (Figure 5C). The cumulative probability of graft loss or impending graft loss was 22% for patients in Group I, 36% for patients in Group II,

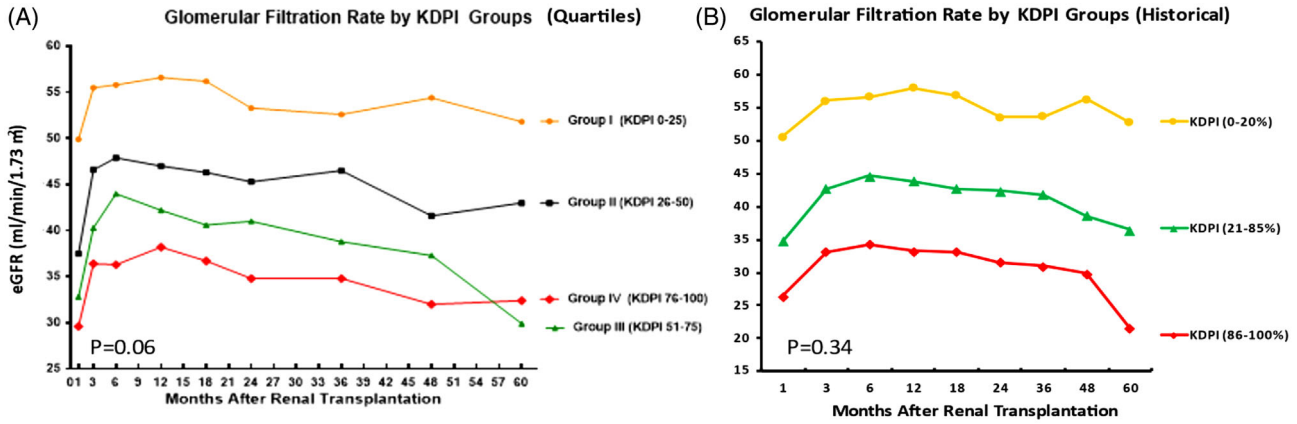

FIGURE 4 Estimated glomerular filtration (eGFR) stratified by quartiles of kidney profile index (KDPI) over time. Comparisons of the slopes of the curves were performed using linear mixed model analysis. No significant differences were found among groups suggesting that the rate of decline of the eGFR over time was not different among KDPI quartiles ($P = .06$) **(Panel A)**. Sub-analysis performed using historical KDPI groups (KPDI < 20%, KDPI 21–85%, and KDPI > 85%) confirmed that the decline of the eGFR was similar among the three strata ($P = .34$).

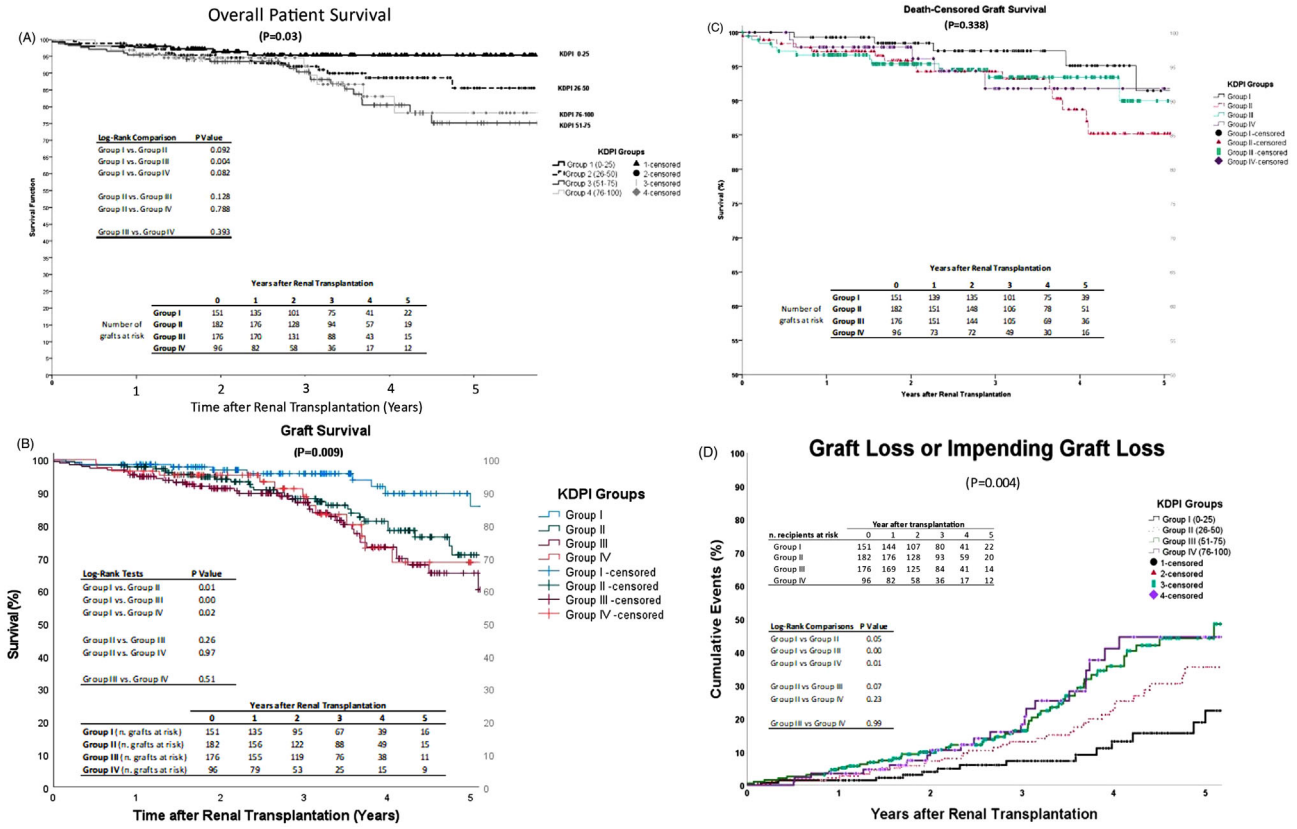

FIGURE 5 Kaplan-Meier survival curves of patients undergoing compatible blood group deceased donor renal transplants stratified by kidney donor profile index (KDPI) group. The 5-year patient survival was 95% for Group I (KDPI 0–25%), 86% for Group II (KDPI 26–50%), 73% for Group III (KDPI 51–75%) and 76% for Group IV (KDPI > 75%) ($P = .03$) **(Panel A)**. The 5-year graft survival was 86% for Group I (KDPI 0–25%), 71% for Group II (KDPI 26–50%), 67% for Group III (KDPI 51–75%) and 68% for Group IV (KDPI > 75%) ($P = .009$) **(Panel B)**. The 5-year death censored graft survival was 92% for Group I (KDPI 0–25%), 85% for Group II (KDPI 26–50%), 90% for Group III (KDPI 51–75%), and 92% for Group IV (KDPI > 75%)($P = .338$) **(Panel C)**. The 5-year graft loss or impending graft loss was 22% for Group I (KDPI 0–25%), 36% for Group II (KDPI 26–50%), 46% for Group III (KDPI 51–75%), and 45% Group IV (KDPI > 75%)($P < .004$) **(Panel D)**.

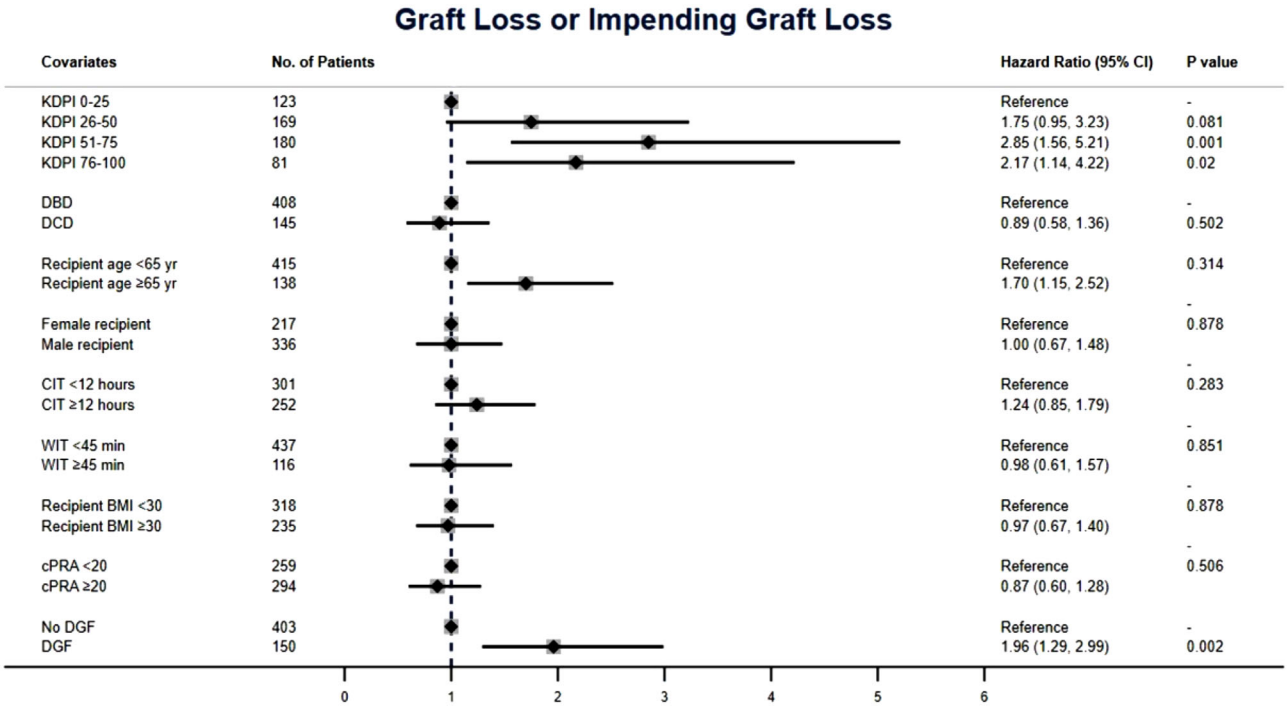

FIGURE 6 Forest plot illustrating the adjusted hazard ratios (HR) for graft loss or impending graft loss for each KDPI Group after accounting for the type of donation, recipient age, recipient sex, duration of cold ischemia time (CIT), duration of warm ischemia time (WIT), recipient body mass index (BMI), the calculated panel of reactive antibodies (cPRA) and delayed graft function (DGF). Kidney donor profile index (KPDI), donation after brain death (DBD), donation after cardiocirculatory death (DCD), cold ischemia time (CIT), warm ischemia time (WIT), body mass index (BMI), the calculated panel of reactive antibodies (cPRA), delayed graft function (DGF).

46% of patients in Group III, and 45% of patients in Group IV ($P < .01$) (Figure 5D). Multivariate cox regression analysis showed that KDPI was an independent factor associated with graft loss or impending graft loss after adjusting for recipient age, sex, type of donation, presence of DGF, CIT, WIT, BMI, and cPRA (Figure 6).

4 | DISCUSSION

KDPI is currently used as a measure of the quality of renal grafts in the United States.[26] Since its introduction in 2014, the decision to accept or decline kidney offers has been heavily influenced by the value of KDPI.[26] While grafts with KDPI < 75% are usually considered acceptable for transplantation in most centers, more than 30% of kidneys with KDPI > 75% are discarded because regarded as of insufficient quality.[27] Since KDPI plays an essential role in the acceptance or decline of kidney grafts,[27] the relationship between KDPI and postoperative outcomes requires scrutiny.

While the association between KDPI and the longevity of renal transplants has been extensively investigated in the past,[28–30] many other important clinical aspects have been overlooked. In this study, we aimed to analyze how the eGFR of high-KDPI kidneys changed over time compared to kidneys with lower KDPI values. Our hypothesis was that a more rapid functional decline of high-KDPI kidneys would explain their shorter survival.[14]

In this study, we analyzed the changes of the eGFR of a large cohort of adult KT recipients operated at a single transplant center from the time of organ allocation to a maximum of 5 years. Several key findings are innovative and clinically relevant. The first one is that KDPI values were inversely associated with donors' eGFR. This observation might seem self-evident, but it is important to keep in mind that donors' serum creatinine and donors' age are only two out of ten variables used to calculate KDPI values. Therefore, the relationship between high KDPI values and lower donors' renal function is not as obvious as initially thought. Second, there were significant differences in eGFR among KDPI groups from the very beginning after KT. While high KDPI-kidneys had a significantly lower eGFR after renal transplantation, their rate of functional decline was not different than the rate of function decline of grafts with lower KDPI values.

Based on these findings, we concluded that the shorter survival of high-KDPI grafts is mainly due to their lower baseline renal function rather than mechanisms that cause a faster deterioration of these organs. This observation is very important because it provides the rationale that these organs should not be discarded because of their intrinsic lower quality but should be offered to patients with shorter expected survival due to advanced age or comorbidities. This approach would significantly reduce the discard rate of valuable organs without having a negative effect on graft survival. In fact, in our study we observed that the death-censored graft survival was not significantly

different among KDPI groups as the majority of recipients of high-KDPI grafts died from causes non-related to renal graft failure.

Contrary to other studies that stratified patients using historical cut-off for low (<20%) versus high-KDPI (>86%), we grouped our population using KDPI-quartiles to better assess the clinical effects of smaller increments in KDPI values. Another important advantage of using KDPI quartiles was the creation of more balanced groups. We recognize that the stratification of the study population into four quartiles did not reflect the definition of extended criteria donors (ECD) applied to donors with KDPI > 85%.[31] We addressed this limitation by performing sub-analyses using more established cut-off values of KDPI (< 20%, KDPI 21–85%, and KDPI > 85%). These subsequent analyses also confirmed that grafts from high-KDPI donors had a lower baseline eGFR but that their functional decline was comparable to the functional decline of organs with lower KDPI values.

Although innovative, this study is limited by its retrospective design and by the fact that it is a single-center study with a relatively small number of high-KDPI grafts. Although the granularity and the quality of the data were high, with less than one percent of missing variables and less than three percent of attrition rate, our findings might not be generalizable to other centers. Another limitation is that we used indirect methods to estimate the eGFR.[24] Indirect estimates of the eGFR are not as accurate as the use of exogenous markers such as inulin to directly determine the renal clearance.[32] Nevertheless, formulas such as the MDRD or CKD-EPI equations[19,33] are universally used in clinical practice as they are valid alternatives to the more expensive and often not attainable direct measure of eGFR.[19,34,35] In addition, although the reliability of the CKD-EPI equation declines for very low or a very high values of eGFR,[36–40] it is unlikely that the results of this study were critically affected by the limitations of the formula, since the same instrument was used for all measurements.

Another limitation is the inability to eliminate the risk of selection bias. At our transplant center, high-KDPI grafts are accepted by physicians on call, based on their clinical judgment. In an ideal situation, the clinical impact of high-KDPI grafts should be determined when all grafts are transplanted, irrespective of KDPI values. This is not the case in most centers in the United States and other countries. In fact, a significant proportion of kidneys from donors with high-KDPI values are declined every day based on the findings of kidney biopsies or other clinical parameters that are not completely captured in registries. However, it is important to recognize that the scenario where all high-KDPI grafts are transplanted is probably impractical and we anticipate that the same risks of selection bias will continue to limit future investigations in this field. Another weakness is that the overall number of high-KDPI grafts, defined as KDPI > 75%, was only a small percentage (15.8%) of the study population. Consequently, the statistical power to detect significant differences among groups might have been inadequate, especially for comparisons of the long-term outcomes. The presence of multicollinearity between KDPI and eGFR might also have decreased the power to detect significant differences using regression analyses. Other limitations were the fact that the baseline histology of the biopsies of the grafts was not available for most recipients.

Despite these limitations, we believe that this study has several strengths. The granular data on both clinical and functional characteristics of the study population in combination with the data provided by protocol biopsies performed at 3 and 12 months after KT allowed us to analyze the functional trajectory of a consecutive cohort of deceased donors after adjusting for important clinical confounders. We believe that this study represents an important step toward a better understanding of what are the main factors associated with the longevity of high-KDPI grafts. Potential future ramifications of our study would be to identify recipients' and donors' key factors that could be used to optimize the outcomes of recipients of high-KDPI organs.

In conclusion, we found that KDPI values are inversely associated with donors' eGFR. We also found that high KDPI grafts have a higher rate of DGF, rejections within the first year after KT and that their eGFR is significantly lower immediately after surgery when compared to kidneys with lower KDPI values. The lower eGFR of high-KDPI kidneys persists over time, but the magnitude of the gap remains unchanged. More importantly, after accounting for common confounders such as CIT, WIT, cPRA, and other clinically significant parameters, we did not identify any significant difference in how the eGFR declines among different KDPI groups. These results suggest that the shorter longevity of high-KDPI kidneys is mainly due to their inferior inherent graft function at the time of organ allocation, rather than an accelerated loss of eGFR after transplantation.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest to disclose.

AUTHORS' CONTRIBUTION

Michele Molinari: study design, statistical analysis, interpretation, and writing of the manuscript. Dana Jorgensen: statistical analysis. Chethan Puttarajappa: statistical analysis, interpretation, and revision of the manuscript. Christine Wu: revision of the manuscript. Rajil Mehta: revision of the manuscript. Christof Kaltenmeier: revision of the manuscript. Puneet Sood: revision of the manuscript. Nirav Shah: revision of the manuscript. Akhil Sharma: revision of the manuscript. Eishan Ashwat: revision of the manuscript. Hao Liu: revision of the manuscript. Ann Thompson: revision of the manuscript. Dhera Reddy: revision of the manuscript. Sundaram Hariharan: study design, interpretation, and revision of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Michele Molinari https://orcid.org/0000-0002-9763-6253
Chethan Puttarajappa https://orcid.org/0000-0002-4856-9242
Rajil Mehta https://orcid.org/0000-0002-3770-8446
Puneet Sood https://orcid.org/0000-0002-0503-4707
Sundaram Hariharan https://orcid.org/0000-0001-5175-525X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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