



Impact of acute kidney injury in deceased donors with high Kidney Donor Profile Index on posttransplant clinical outcomes: a multicenter cohort study

Woo Yeong Park¹, Yoon Kyung Chang², Young Soo Kim³, Kyubok Jin¹, Chul Woo Yang⁴, Seungyeup Han¹,
Byung Ha Chung⁴

¹Division of Nephrology, Department of Internal Medicine, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, Republic of Korea

²Division of Nephrology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon, Republic of Korea

³Division of Nephrology, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, Republic of Korea

⁴Transplant Research Center, Division of Nephrology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Background: This study evaluated the impact of acute kidney injury (AKI) on posttransplant clinical outcomes for deceased donor (DD) kidney transplantation (KT) using the Kidney Donor Profile Index (KDPI) system.

Methods: Overall, 657 kidney transplant recipients (KTRs) receiving kidneys from 526 DDs from four transplant centers were included. We divided them into the high and low KDPI donor groups by 65%, the KDPI score, and both groups were subdivided into the AKI-DDKT and non-AKI-DDKT subgroups according to AKI in DDs.

Results: There was no significant difference in the incidence of delayed graft function (DGF) between the high and low KDPI-KTR groups; however, the AKI-DDKT subgroup showed significantly higher incidence of DGF than the non-AKI-DDKT subgroup in both groups ($p = 0.001$, $p < 0.001$, respectively). The death-censored graft survival rate was significantly lower in the high KDPI-KTR group than in the low KDPI-KTR group ($p = 0.005$). Only in the high KDPI-KTR group, the death-censored graft survival rate was significantly lower in the KT from DDs with AKI stage 3 than KT from DDs with non-AKI or AKI stage 1 or 2 ($p = 0.040$). The interaction between AKI stage 3 in DDs and high KDPI on the allograft outcome was significant ($p = 0.002$).

Conclusion: KTs from DDs with AKI stage 3 showed an adverse impact on the allograft outcome in the high KDPI-KTR group. Therefore, DDs with a high KDPI score should be managed carefully so that severe AKI does not occur prior to KT.

Keywords: Acute kidney injury, Brain death, Graft survival, Kidney transplantation, Mortality

Received: May 19, 2020; **Revised:** November 3, 2020; **Accepted:** December 7, 2020

Editor: Sang Ho Lee, Kyung Hee University College of Medicine, Seoul, Republic of Korea

Correspondence:

Byung Ha Chung

Department of Internal Medicine, Seoul St. Mary's Hospital, 222 Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea. E-mail: chungbh@catholic.ac.kr

ORCID: <https://orcid.org/0000-0003-0048-5717>

Seungyeup Han

Department of Internal Medicine, Keimyung University School of Medicine, Keimyung University Kidney Institute, 1035 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Republic of Korea. E-mail: hansy@dsmc.or.kr

Seungyeup Han and Byung Ha Chung contributed equally to this article as co-corresponding author.

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Introduction

Although one of the biggest drawbacks of kidney transplantation (KT) is the problem of organ shortage, the number of discarded kidneys still increases worldwide [1–3]. In 2014, the Kidney Donor Profile Index (KDPI) system, a new allocation system in the United States (US), was introduced, but the number of discarded kidneys in the US is not decreasing, and there is still a disagreement about the utility of this system [1,4–6]. The major factor of this discard is reported as the donor kidney function at the time of KT [7–9]. Recently, the efficacy of conducting procurement biopsy before transplantation has been reported, but it is still not commercialized [10]. Thus, it is important to trust and actively apply the current allocation system [4]. In particular, a kidney injury during donor management affects the condition of the donor kidney, which is mainly affected by the hemodynamic condition [11].

Several researches have recently been published regarding the clinical impact of KT from deceased donors (DDs) with acute kidney injury (AKI) in deceased donor KT (DDKT) [12,13]. AKI is very commonly detected in individuals with brain death state for various causes [14,15]. The shortage of donor kidney has also driven the use of the kidney from DDs with AKI. In addition, some research demonstrated that AKI does not affect the long-term allograft outcome although it results in lower allograft function in the early period after KT [16,17]. Our previous studies also showed that there was no significant difference in the long-term allograft outcome between the AKI-DDKT and non-AKI-DDKT groups or between the expanded criteria donor (ECD)-KT and standard criteria donor-KT groups, but AKI superimposed on ECDs or occurring in elderly DDs has a synergistically adverse impact on the long-term posttransplant allograft outcomes in the corresponding recipients [18]. Finally, the state of donor at the time of KT is important when AKI developed, but this issue is still controversial.

Recently, Koyawala and Parikh [12] have so far addressed this issue and insisted that there was no influence of DD with AKI on the long-term outcome. However, there are various limitations in this study, and it is still difficult to draw a clear conclusion on this issue as the new allocation system, KDPI score, has been published for approximately 4 years. In a previous study, the KDPI score was a useful tool to predict the allograft outcome in DDKT [19], but there was

no significant difference in the long-term allograft outcome between the high and low KDPI-kidney transplant recipient (KTR) groups [20]. Based on these studies, we investigated the impact of AKI in DDs with a high or low KDPI score on posttransplant clinical outcomes. The short- and long-term clinical outcomes according to the presence of AKI on DDs in the low and high KDPI-KTR groups were analyzed. In addition, the association between AKI and high KDPI in DDs on posttransplant allograft survival was evaluated.

Methods

Study population

A total of 657 KTRs receiving kidneys from 526 DDs between October 1996 and December 2017 from four transplant centers (Seoul St. Mary's Hospital, Uijeongbu St. Mary's Hospital, Daejeon St. Mary's Hospital, and Keimyung University Dongsan Hospital) were included. We divided them into the high and low KDPI donor groups by 65%, which is the median value of the KDPI score, and both groups were subdivided into the AKI-DDKT and non-AKI-DDKT subgroups according to AKI in DDs. AKI in DDs was defined and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as described in previous reports [21]. The KTRs according to the KDPI score or presence of AKI in DDs are shown in Fig. 1. Among all DDs, there were 257 high KDPI donors (48.9%) and 269 low KDPI donors (51.1%). Among all KTRs, there were 338 high KDPI-KTRs (51.4%) and 319 low KDPI-KTRs (48.6%). In the high KDPI-KTR group, there were 239 cases (36.4%) in the high KDPI-AKI-DDKT subgroup and 99 cases (15.1%) in the high KDPI-non-AKI-DDKT subgroup. In the low KDPI-KTR group, there were 148 cases (22.5%) in the low KDPI-AKI-DDKT subgroup and 171 cases (26.0%) in the low KDPI-non-AKI-DDKT subgroup.

Clinical and laboratory parameters and clinical outcomes

The medical records of the study population were retrospectively analyzed. We investigated the data of DDs: age, sex, height, weight, body mass index (BMI, kg/m²), ethnicity, history of diabetes mellitus (DM) and hypertension (HTN), causes of brain death, serum creatinine, estimated glomerular filtration rate (eGFR) by the Chronic Kidney

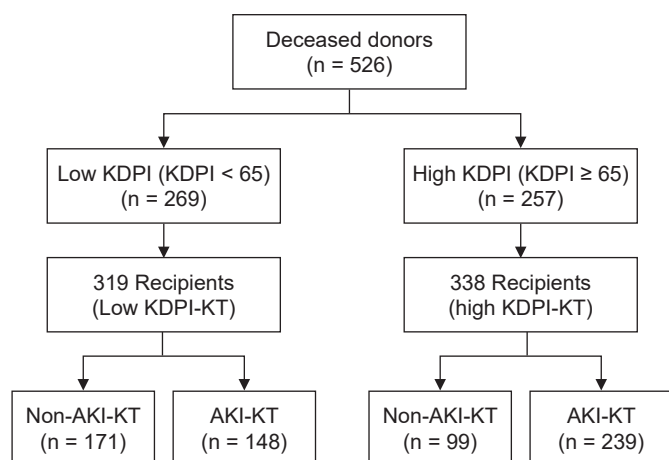


Figure 1. Patient algorithm and distribution in this study. Deceased donors were classified into high KDPI and low KDPI donor groups based on the median value of KDPI of 65%. In addition, KTRs were divided into AKI-KT and non-AKI-KT subgroups.

KDPI, Kidney Donor Profile Index; KTRs, kidney transplant recipients; AKI, acute kidney injury; KT, kidney transplantation.

Disease Epidemiology Collaboration (CKD-EPI) at baseline and the admission day and prior to KT, hepatitis C virus state, and donation after cardiac death. When serum creatinine was normal at the time of admission, the serum creatinine at admission was defined as baseline creatinine even if there was no previous baseline creatinine, and serum creatinine was measured at least 2 to 3 times until KT. AKI was defined by the KDIGO guideline based on the serum creatinine at the time of admission regardless of the presence or absence of a baseline creatinine. CKD was defined when estimated GFR less than 60 mL/min/1.73 m² continued for 3 months after measuring baseline creatinine. We used the ECD criteria according to the United Network for Organ Sharing for the definition of marginal donors [22]. We calculated the KDPI score with the terminal serum creatinine level through the KDPI calculator in the website of the Organ Procurement and Transplantation Network [23]. When the KDPI score is calculated, the factors are used as follows; age, height, weight, ethnicity, history of HTN or DM, cause of death, serum creatinine, hepatitis C virus serology, and donation after cardiac death in the DD [6]. The data of KTRs were also investigated; age, sex, height, weight, BMI, ethnicity, dialysis vintage prior to KT, frequency of KT, causes of end-stage renal disease, history of DM and HTN, cold ischemic time, number of human leukocyte antigen

(HLA) mismatches, types of immunosuppressive agents for induction and maintenance, and rate of panel-reactive antibodies (PRAs).

Biopsy-proven acute rejection (BPAR) was diagnosed according to the Banff classification [24,25]. Delayed graft function (DGF) was defined as at least one dialysis requirement within the first week after KT [26]. Death-censored allograft survival rate was defined as the proportion considering the return to the dialysis or retransplantation during the study period, except for patient death with a functioning allograft. Patient survival rate was defined as the proportion considering the death from all causes during the study period.

The primary outcome of this study was to investigate the impact of AKI in DDs on the death-censored allograft survival between the high and low KDPI-KTR groups. Therefore, we compared the death-censored allograft survival between the AKI-DDKT and non-AKI-DDKT subgroups in both high and low KDPI-KTR groups and analyzed the interaction between AKI and high KDPI score. The secondary outcomes were to investigate the incidences of DGF and BPAR and changes in allograft function during the first year after KT (1 week, 2 weeks, 1 month, 3 months, 6 months, and 12 months after KT; assessed by eGFR, calculated using the CKD-EPI [27]) between the AKI-DDKT and non-AKI-DDKT subgroups in both high and low KDPI-KTR groups. Patient survival between AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group was compared.

This study was approved by the Institutional Review Boards (IRBs) of Seoul St. Mary's Hospital (No. XC15RIMI0061K), Uijeongbu St. Mary's Hospital (No. XC15RIMI0061U), Daejeon St. Mary's Hospital (No. XC15RIMI0061K), and Dongsan Hospital, Keimyung University School of Medicine (No. 2020-05-047). The requirements for informed consent were waived by the IRBs of the aforementioned four centers because the use of the patient's data for research was informed to all donors' families and all recipients prior to KT to protect the personal information. Our study did not contain any distinguishable personal information, and all methods were performed according to the relevant guidelines and regulations.

Statistical analysis

Continuous variables are expressed as mean ± standard

deviation or median (interquartile range) and analyzed using the Student t test or the Mann-Whitney test. Categorical variables are expressed as count and percentage and analyzed using the chi-square test and Fisher exact test. The death-censored graft survival and patient survival rates were analyzed using the Kaplan-Meier curves and log-rank tests. All missing data were excluded. The Cox proportional hazards regression analysis was performed to investigate the relationship of the KDPI score and AKI for the clinical outcomes in DDKT, considering the confounding factors such as recipient age, transplant year (1996–2005 vs. 2006–2010 vs. 2011–2017), transplant center, recipient HTN, and acute rejection. Interaction effects between AKI and high KDPI score were explored by adding interaction terms to the Cox proportional hazards model with backward elimination of variables. In other words, AKI * high KDPI score as an interaction effect was included in the Cox proportional hazards model. The p-values less than 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Comparison of baseline characteristics between the high and low KDPI donors and between the high and low KDPI-KTR groups

The median follow-up duration of the study population was 48.0 months (interquartile range, 22.3–68.0). The mean age of the high KDPI donor group was significantly higher than that of the low KDPI donor group (55.0 ± 8.9 years vs. 35.5 ± 12.2 years, $p < 0.001$). The proportions of donors with HTN, DM, and death due to cerebrovascular accident (CVA) were significantly higher in the high KDPI donor group than in the low KDPI donor group (37.4% vs. 4.1%, $p < 0.001$; 17.1% vs. 2.1%, $p < 0.001$; 76.3% vs. 62.1%, $p < 0.001$, respectively). The baseline and allocation CKD-EPI eGFRs in DDs were significantly lower in the high KDPI donor group than in the low KDPI donor group (79.7 ± 20.1 mL/min/1.73 m² vs. 87.8 ± 28.9 mL/min/1.73 m², $p = 0.001$; 51.6 ± 29.6 mL/min/1.73 m² vs. 94.9 ± 44.6 mL/min/1.73 m², $p < 0.001$). The proportion of DDs with CKD stage 3 or above at allocation was significantly higher in the high KDPI donor group than in the low KDPI donor group (67.7% vs. 30.9%, $p < 0.001$).

The proportion of AKI was also significantly higher in the high KDPI donor group than in the low KDPI donor group (69.3% vs. 42.8%, $p < 0.001$). The proportion of ECD donors was significantly higher in the high KDPI donor group than in the low KDPI donor group (57.6% vs. 0.4%, $p < 0.001$). There were no significant differences in donor sex and BMI between the high and low KDPI donor groups (Table 1).

In corresponding recipients, the mean age was also higher in the high KDPI-KTR group than in the low KDPI-KTR group (51.3 ± 10.1 years vs. 47.6 ± 9.8 years, $p < 0.001$). The proportions of KTRs with DM and use of antithymocyte globulin for induction immunosuppressant were significantly higher in the high KDPI-KTR group than in the low KDPI-KTR group (24.3% vs. 17.2%, $p = 0.028$; 33.7% vs. 25.1%, $p = 0.017$), but the proportion of retransplantation was significantly higher in the low KDPI-KTR group than in the high KDPI-KTR group (14.1% vs. 7.4%, $p = 0.008$). The mean HLA mismatch number was significantly higher in the high KDPI-KTR group than in the low KDPI-KTR group (3.8 ± 1.5 vs. 3.5 ± 1.5 , $p = 0.014$). There was no significant difference in the distribution of recipient sex, dialysis duration before KT, cold ischemic time, and proportion of PRA > 50% between the high and low KDPI-KTR groups (Table 1).

Comparison of baseline characteristics between the high and low KDPI-KTR groups and between the AKI-DDKT and non-AKI-DDKT subgroups

In the high KDPI donor group, the proportions of male sex and cause of donor death by CVA were significantly higher in the AKI donor subgroup compared with those in the non-AKI donor subgroup (71.3% vs. 55.6%, $p = 0.016$; 78.7% vs. 70.9%, $p = 0.024$). The proportions of HTN and eGFR at baseline and allocation were significantly lower in the AKI donor subgroup compared with those in the non-AKI donor subgroup (30.9% vs. 51.9%, $p = 0.002$; 45.4 ± 26.6 vs. 81.0 ± 27.0 , $p < 0.001$; 34.0 ± 21.0 vs. 77.7 ± 24.7 , $p < 0.001$). On the contrary, in the low KDPI donor group, the BMI and proportion of CKD stage 3 or above were significantly higher in the AKI donor subgroup compared with those in the non-AKI donor subgroup (24.1 ± 4.0 vs. 22.2 ± 3.9 , $p < 0.001$; 48.7% vs. 36.4%, $p = 0.046$), but eGFRs at baseline and allocation were significantly lower in the AKI donor subgroup compared with those in the non-AKI donor subgroup (59.0 ± 36.0 vs. 102.3 ± 34.5 , $p < 0.001$; 50.5 ± 32.0 vs. 106.7 ± 31.4 ,

Table 1. Comparison of clinical and laboratory parameters between high KDPI donor (or recipient) and low KDPI donor (or recipient)

Variable	High KDPI	Low KDPI	p-value
Donor	257	269	
Age at KT (yr)	55.0 ± 8.9	35.5 ± 12.3	<0.001
Sex, male:female	171:86	197:72	0.106
BMI (kg/m ²)	23.1 ± 3.2	22.6 ± 3.9	0.223
HTN	96 (37.4)	11 (4.1)	<0.001
DM	44 (17.1)	6 (2.2)	<0.001
Cause of donor death, CVA	196 (76.3)	167 (62.1)	<0.001
eGFR (mL/min/1.73 m ²)			
Baseline	79.7 ± 20.1	87.8 ± 28.9	0.001
At allocation	51.6 ± 29.6	94.9 ± 44.6	<0.001
CKD stage 3 or above stage	174 (67.7)	83 (30.9)	<0.001
AKI	178 (69.3)	115 (42.8)	<0.001
Stage 1	61 (23.7)	52 (19.3)	
Stage 2	55 (21.4)	27 (10.0)	
Stage 3	62 (24.1)	36 (13.4)	
ECD	148 (57.6)	1 (0.4)	<0.001
Recipient	338	319	
Transplant year			0.004
1996–2005	0 (0)	8 (2.5)	
2006–2010	44 (13.0)	55 (17.2)	
2011–2016	294 (87.0)	256 (80.3)	
Age at KT (yr)	51.3 ± 10.1	47.6 ± 9.8	<0.001
Sex, male:female	201:137	188:131	0.937
BMI (kg/m ²)	23.3 ± 3.5	23.0 ± 4.1	0.297
HTN	290 (85.8)	263 (82.4)	0.242
DM	82 (24.3)	55 (17.2)	0.028
Dialysis duration before KT (yr)	7.3 ± 11.7	8.8 ± 8.6	0.289
Previous KT	25 (7.4)	45 (14.1)	0.008
Cause of ESRD			0.003
Glomerulonephritis	142 (42.0)	156 (48.9)	
DM	70 (20.7)	44 (13.8)	
HTN	70 (20.7)	45 (14.1)	
Others	56 (16.6)	74 (23.2)	
Cold ischemic time (min)	247.9 ± 118.7	254.2 ± 129.8	0.531
HLA mismatch number	3.8 ± 1.5	3.5 ± 1.5	0.014
Induction			0.017
Basiliximab	224 (66.3)	239 (74.9)	
ATG	114 (33.7)	80 (25.1)	
Major immunosuppressant, tacrolimus:cyclosporine	335:3	312:6	0.251
PRA > 50 %	50 (14.8)	64 (20.1)	0.048
Follow-up duration (mo)	44.1 ± 28.7	52.2 ± 39.9	0.003

Data are expressed as number only, mean ± standard deviation, or number (%). eGFR is calculated using Chronic Kidney Disease Epidemiology Collaboration. AKI, acute kidney injury; ATG, antithymocyte globulin; BMI, body mass index; CKD, chronic kidney disease; CVA, cerebrovascular accident; DM, diabetes mellitus; ECD, expanded criteria donor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HLA, human leukocyte antigen; HTN, hypertension; KDPI, Kidney Donor Profile Index; KT, kidney transplantation; PRA, panel-reactive antibody.

p < 0.001).

In corresponding recipients, the proportions of antithymocyte globulin were significantly higher in the AKI-DDKT subgroup compared with those in the non-AKI-DDKT subgroup in both high and low KDPI-KTR groups (41.0% vs. 16.2%, p < 0.001; 33.8% vs. 17.5%, p = 0.001, respectively). There was no significant difference in the distribution of recipient age, sex, HTN, DM, dialysis duration before KT, previous KT, cold ischemic time, main immunosuppressant, and proportion of PRA > 50% between the high and low KDPI-KTR groups (Table 2).

Comparison of the effect of AKI in DDs on the incidences of DGF and BPAR and changes in allograft function between the high and low KDPI-KTR groups

The incidence of DGF was not significantly different between the high and low KDPI-KTR groups (18.0% vs. 18.2%, p > 0.999) (Fig. 2A). In the subgroup analysis, the incidence of DGF was significantly higher in the AKI-DDKT subgroup compared with that in the non-AKI-DDKT subgroup in both high and low KDPI-KTR groups (23.0% vs. 6.1%, p < 0.001; 25.7% vs. 11.7%, p = 0.001) (Fig. 2B).

The incidence of BPAR within the first year after KT did not differ significantly between the high and low KDPI-KTR groups (12.7% vs. 12.5%, p > 0.999) (Fig. 2C). Moreover, there was no significant difference in the incidence of BPAR between the AKI-DDKT and non-AKI-DDKT subgroups in both high and low KDPI-KTR groups (13.0% vs. 12.1%, p > 0.999; 16.2% vs. 9.4%, p = 0.089) (Fig. 2D).

Allograft function for 12 months (1 week, 2 weeks, 1 month, 3 months, 6 months, and 12 months) after KT was significantly lower in the high KDPI-KTR group compared with that in the low KDPI-KTR group (39.4 ± 28.3 vs. 56.2 ± 33.3, p < 0.001; 52.0 ± 24.4 vs. 68.1 ± 29.0, p < 0.001; 48.4 ± 20.8 vs. 63.5 ± 23.6, p < 0.001; 56.0 ± 18.8 vs. 72.5 ± 20.5, p < 0.001; 54.8 ± 18.4 vs. 71.5 ± 20.1, p < 0.001; 57.6 ± 19.7 vs. 75.0 ± 22.5, p < 0.001) (Fig. 2E). In the high KDPI-KTR group, allograft function within 3 months (1 week, 2 weeks, 1 month) after KT was significantly lower in the AKI-DDKT subgroup compared with that in the non-AKI-DDKT subgroup (33.7 ± 27.0 vs. 53.3 ± 26.5, p < 0.001; 48.4 ± 24.7 vs. 60.9 ± 21.5, p < 0.001; 46.1 ± 20.9 vs. 54.2 ± 19.6, p = 0.001), but there was no significant difference between 3 and 12 months (3 months, 6 months, and 12 months) (55.3 ± 18.5 vs. 57.8 ± 19.5, p = 0.273; 54.3 ± 18.0 vs. 56.1 ± 19.4, p = 0.413; 57.6 ± 19.3 vs. 57.4 ± 20.9,

Table 2. Comparison of clinical and laboratory parameters according to AKI in high or low KDPI donor KTR

Variable	High KDPI-KTR			Low KDPI-KTR		
	Non-AKI-DDKT	AKI-DDKT	p-value	Non-AKI-DDKT	AKI-DDKT	p-value
Donor	79	178		154	115	
Age at KT (yr)	56.2 ± 10.0	54.5 ± 8.3	0.173	34.8 ± 13.7	36.4 ± 10.7	0.261
Sex, male:female	44:35	127:51	0.016	107:47	90:25	0.126
BMI (kg/m ²)	23.3 ± 3.3	23.1 ± 3.1	0.653	22.2 ± 3.9	24.1 ± 4.0	<0.001
HTN	41 (51.9)	55 (30.9)	0.002	8 (5.2)	3 (2.6)	0.362
DM	14 (17.7)	30 (16.9)	0.859	4 (2.6)	2 (1.7)	>0.999
Cause of donor death, CVA	56 (70.9)	140 (78.7)	0.024	92 (59.7)	75 (65.2)	0.377
eGFR (mL/min/1.73 m ²)						
Baseline	81.0 ± 27.0	45.4 ± 26.6	<0.001	102.3 ± 34.5	59.0 ± 36.0	<0.001
At allocation	77.7 ± 24.7	34.0 ± 21.0	<0.001	106.7 ± 31.4	50.5 ± 32.0	<0.001
CKD stage 3 or above stage	37 (46.8)	85 (47.8)	1	56 (36.4)	56 (48.7)	0.046
ECD	39 (49.4)	109 (61.2)	0.1	0 (0)	1 (0.9)	0.428
Recipient	99	239		171	148	
Transplant year			0.157			0.098
1996–2005	0 (0)	0 (0)		7 (4.1)	1 (0.7)	
2006–2010	17 (17.2)	27 (11.3)		34 (19.9)	21 (14.2)	
2011–2016	82 (82.8)	212 (88.7)		130 (76.0)	126 (85.1)	
Age at KT (yr)	51.4 ± 10.7	51.3 ± 9.9	0.878	47.0 ± 8.8	48.3 ± 10.7	0.261
Sex, male:female	60:39	141:98	0.809	103:68	85:63	0.649
BMI (kg/m ²)	23.3 ± 3.4	23.3 ± 3.5	0.981	22.7 ± 3.2	23.4 ± 4.9	0.141
HTN	84 (84.8)	206 (86.2)	0.735	141 (82.5)	122 (82.4)	>0.999
DM	18 (18.2)	64 (26.8)	0.097	29 (17.0)	26 (17.6)	0.883
Dialysis duration before KT (yr)	7.0 ± 4.5	8.3 ± 13.6	0.895	9.0 ± 9.8	8.6 ± 7.1	0.728
Previous KT	6 (6.1)	19 (7.9)	0.652	18 (10.5)	27 (18.2)	0.054
Cause of ESRD			0.290			0.022
Glomerulonephritis	45 (45.5)	97 (40.6)		95 (55.6)	61 (41.2)	
DM	15 (15.2)	55 (23.0)		24 (14.0)	20 (13.5)	
HTN	19 (19.2)	51 (21.3)		23 (13.5)	22 (14.9)	
Others	20 (20.2)	36 (15.1)		29 (17.0)	45 (30.4)	
Cold ischemic time (min)	250.2 ± 112.6	247.0 ± 121.4	0.828	262.3 ± 124.7	245.1 ± 135.2	0.257
HLA mismatch number	3.7 ± 1.6	3.8 ± 1.4	0.541	3.5 ± 1.5	3.5 ± 1.4	0.634
Induction			<0.001			0.001
Basiliximab	83 (83.8)	141 (59.0)		141 (82.5)	98 (66.2)	
ATG	16 (16.2)	98 (41.0)		30 (17.5)	50 (33.8)	
Main immunosuppressant, tacrolimus:cyclosporine	97:2	238:1	0.206	165:6	147:1	0.222
PRA > 50%	13 (13.1)	37 (15.5)	0.864	32 (18.7)	32 (21.6)	0.779

Data are expressed as number only, mean ± standard deviation, or number (%).

eGFR is calculated using Chronic Kidney Disease Epidemiology Collaboration.

AKI, acute kidney injury; ATG, antithymocyte globulin; BMI, body mass index; CKD, chronic kidney disease; CVA, cerebrovascular accident; DDKT, deceased donor kidney transplantation; DM, diabetes mellitus; ECD, expanded criteria donor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HLA, human leukocyte antigen; HTN, hypertension; KDPI, Kidney Donor Profile Index; KT, kidney transplantation; KTR, kidney transplant recipient; PRA, panel-reactive antibody.

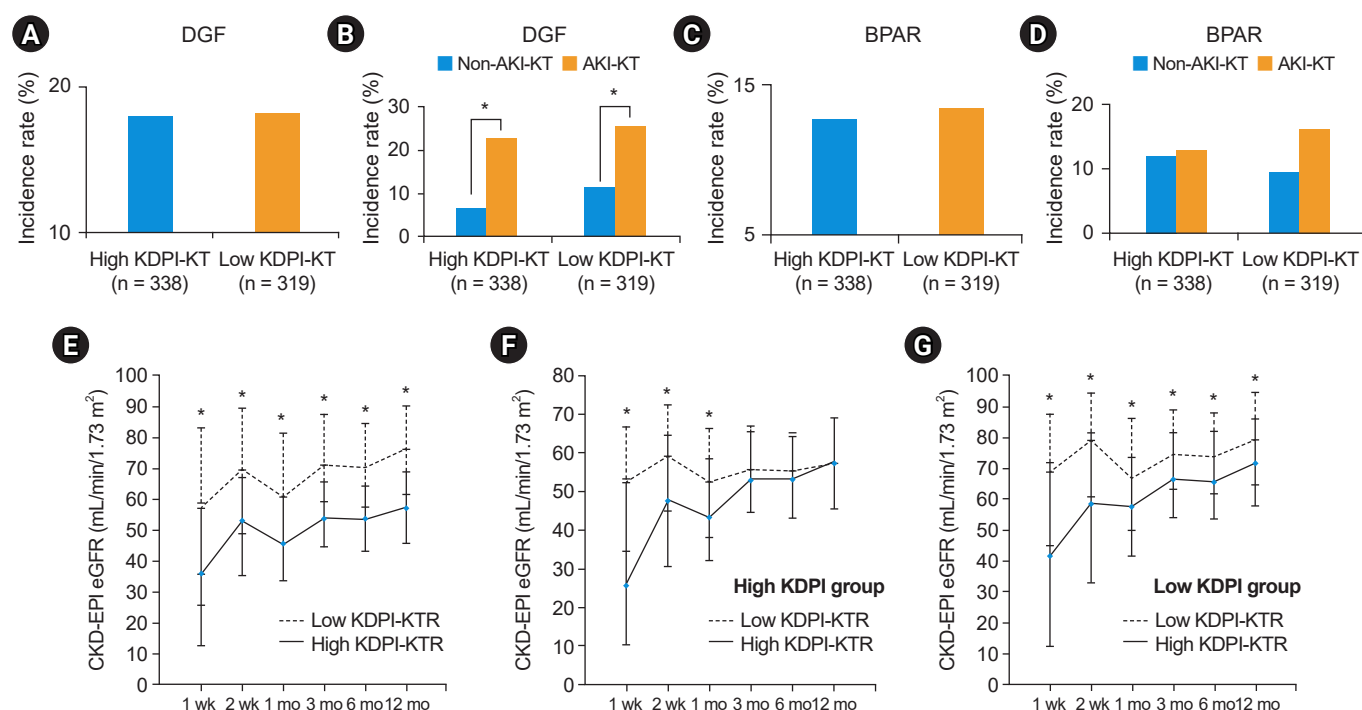


Figure 2. Comparison of the DGF incidence rates, BPAR incidence rates, and the changes in allograft function after kidney transplant. (A, B) Comparison of DGF incidence rates (A) between high KDPI-KTR and low KDPI-KTR groups and (B) between AKI-DDKT and non-AKI-DDKT subgroups in the high KDPI-KTR or low KDPI-KTR group. (C, D) Comparison of BPAR incidence rate (C) between high KDPI-KTR and low KDPI-KTR groups and (D) between AKI-DDKT and non-AKI-DDKT subgroups in the high KDPI-KTR or low KDPI-KTR group. (E-G) Comparison of the change in allograft function after kidney transplant (E) between high KDPI-KTR and low KDPI-KTR groups, (F) between AKI-DDKT and non-AKI-DDKT subgroups in the high KDPI-KTR group, and (G) between AKI-DDKT and non-AKI-DDKT subgroups in the low KDPI-KTR group.

AKI, acute kidney injury; BPAR, biopsy-proven acute rejection; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DDKT, deceased donor kidney transplantation; DGF, delayed graft function; KDPI, Kidney Donor Profile Index; KTR, kidney transplant recipient.

* $p < 0.001$ vs. non-AKI-DDKT.

$p = 0.905$) (Fig. 2F). In the low KDPI-KTR group, allograft function for 12 months (1 week, 2 weeks, 1 month, 3 months, 6 months, and 12 months) after KT was significantly lower in the AKI-DDKT subgroup compared with that in the non-AKI-DDKT subgroup ($p < 0.001$) (45.2 ± 34.6 vs. 65.7 ± 29.1 , $p < 0.001$; 58.5 ± 30.4 vs. 76.4 ± 24.9 , $p < 0.001$; 58.1 ± 23.9 vs. 68.1 ± 22.4 , $p < 0.001$; 68.2 ± 21.6 vs. 76.2 ± 18.7 , $p < 0.001$; 67.5 ± 21.2 vs. 74.8 ± 18.6 , $p = 0.002$; 70.4 ± 23.3 vs. 78.7 ± 21.1 , $p = 0.001$) (Fig. 2G).

Comparison of the impact of AKI in DDs on the death-censored allograft survival between the high and low KDPI-KTR groups

A total of 49 cases (49 of 657, 7.5%) of graft failure developed,

including 31 cases (4.7%) in the high KDPI-KTR group (20 and 11 patients in the AKI-DDKT and non-AKI-DDKT subgroups, respectively) and 18 cases (2.7%) in the low KDPI-KTR group (7 and 11 patients in the AKI-DDKT and non-AKI-DDKT subgroups, respectively). There were no significant differences in the distribution of the causes of allograft failure between the AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group (Table 3). The death-censored graft survival rate was significantly lower in the high KDPI-KTR group compared with that in the low KDPI-KTR group ($p = 0.005$) (Fig. 3A). However, there was no significant difference in the death-censored graft survival rates between the AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group (Fig. 3B, C). In the multivariate analysis, a high KDPI score was an

Table 3. Comparison of clinical outcomes according to AKI in high or low KDPI donor KTR

Variable	High KDPI-KTR			Low KDPI-KTR		
	Non-AKI-DDKT	AKI-DDKT	p-value	Non-AKI-DDKT	AKI-DDKT	p-value
Causes of graft failure			0.170			0.952
Acute rejection	4 (36.4)	8 (40.0)		6 (54.5)	3 (42.9)	
Chronic rejection	1 (9.1)	8 (40.0)		1 (9.1)	1 (14.3)	
Recurrent glomerulonephritis	2 (18.2)	2 (10.0)		1 (9.1)	0 (0)	
Ischemia	0 (0)	0 (0)		2 (18.2)	2 (28.6)	
Infection	1 (9.1)	1 (5.0)		0 (0)	1 (14.3)	
BK virus-associated nephropathy	3 (27.3)	1 (5.0)		1 (9.1)	0 (0)	
Causes of death			0.530			>0.999
Cardiovascular disease	2 (50.0)	4 (28.6)		2 (16.7)	0 (0)	
Cerebrovascular accident	0 (0)	1 (7.1)		0 (0)	0 (0)	
Infection	1 (25.0)	5 (35.7)		5 (41.7)	3 (100)	
Malignancy	0 (0)	1 (7.1)		2 (16.7)	0 (0)	
Gastrointestinal bleeding	1 (25.0)	0 (0)		1 (8.3)	0 (0)	
Unknown	0 (0)	3 (21.4)		2 (16.7)	0 (0)	

Data are expressed as number (%).

KDPI, Kidney Donor Profile Index; KTR, kidney transplant recipient; AKI, acute kidney injury; DDKT, deceased donor kidney transplantation

independent risk factor for allograft failure after adjustment for recipient age, transplant year, transplant center, recipient HTN, and acute rejection (hazard ratio [HR], 3.096; 95% confidence interval [CI], 1.642–5.838; $p < 0.001$), not donor AKI. There was not a significant interaction between AKI in DDs and high KDPI DDs for allograft failure (p for interaction = 0.088). There was no significant difference in the incidence of death-censored graft failure according to the AKI stage in the high and low KDPI-KTR groups (Supplementary Table 1, available online). However, in the high KDPI-KTR group, AKI stage 3 showed the lowest death-censored allograft survival rate in comparison with non-AKI and AKI stages 1 and 2 ($P = 0.040$) (Fig. 3D), but not in the low KDPI-KTR group (Fig. 3E). In the multivariate analysis, the combination of high KDPI score and AKI stage 3 was an independent risk factor for allograft failure after adjustment for recipient age, transplant year, transplant center, recipient HTN, acute rejection, PRA > 50%, HLA mismatch, and induction immunosuppressant (HR, 2.707; 95% CI, 1.324–5.536; $p = 0.006$). There was a significant interaction between AKI stage 3 in DDs and high KDPI DDs for allograft failure (p for interaction = 0.002) (Table 4).

Comparison of the impact of AKI in DDs on the patient survival between the high and low KDPI-KTR groups

A total of 33 patients (33 of 657, 5.0%) died, 18 cases (2.7%) of

whom were in the high KDPI-KTR group (14 and 4 patients in the AKI-DDKT and non-AKI-DDKT subgroups, respectively) and 15 cases (2.3%) of whom were in the low KDPI-KTR group (3 and 12 patients in the AKI-DDKT and non-AKI-DDKT subgroups, respectively). There were no significant differences in the distribution of the cause of patient death between the AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group (Table 3). There was no significant difference in the patient survival rate between the high and low KDPI-KTR groups (Fig. 4A). In the high KDPI-KTR group, there was no significant difference in the patient survival rate between the AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group (Fig. 4B, C).

Discussion

For a long time, the ECD criteria have been used to determine to accept or discard DD kidneys. Our previous study reported that the allograft outcome was poor when ECD was accompanied by AKI [18]. Our other study also reported that the elderly donor had a poor allograft outcome when accompanied by AKI [28]. In other words, the poor kidney state of the DDs prior to KT can have a synergistic effect when this situation is accompanied by AKI. Therefore, it is very important to evaluate the kidney state of the DDs prior to KT. We have reported on the usefulness of KDPI for evaluating the kidney state of the DDs prior to KT

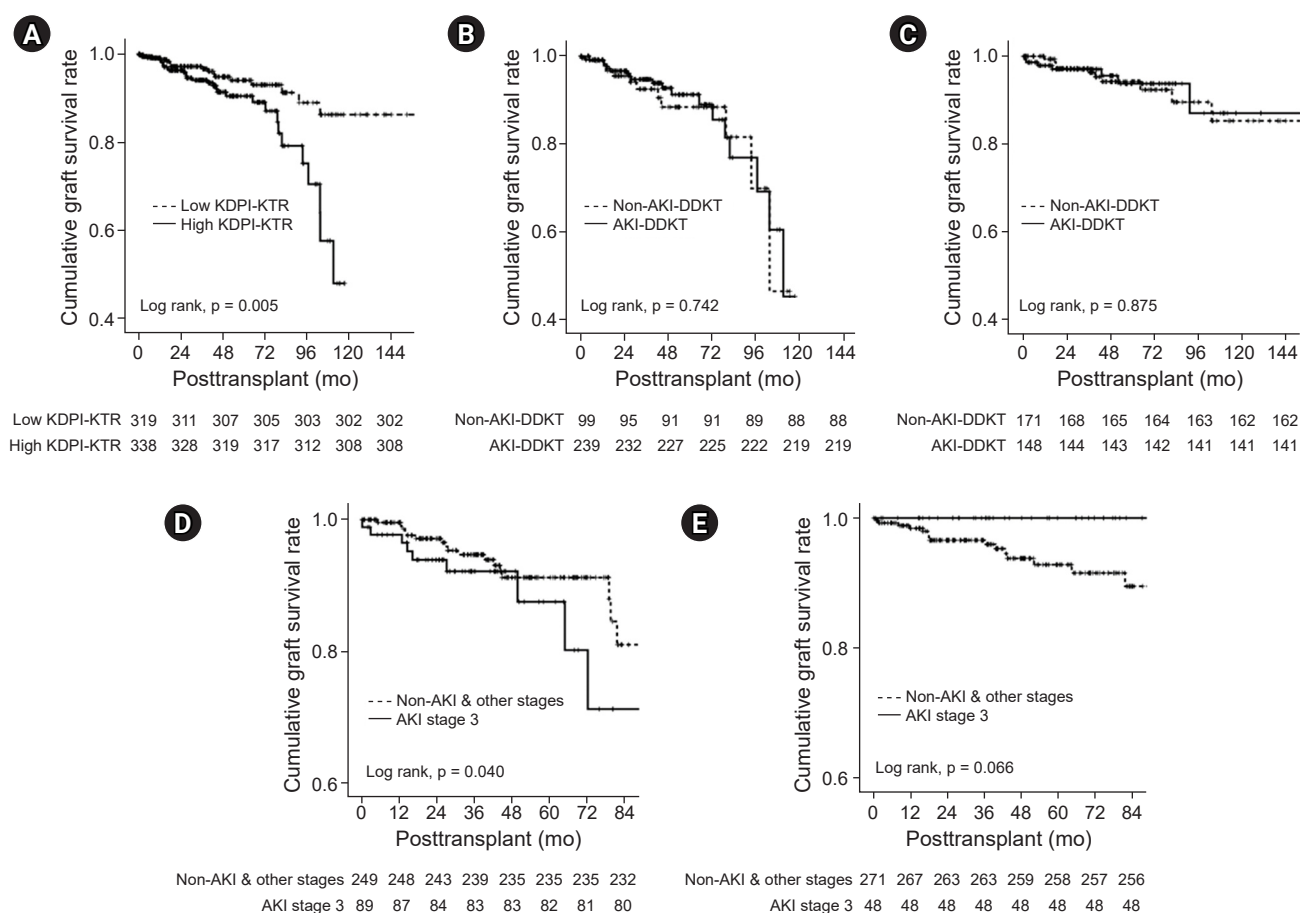


Figure 3. Comparison of the death-censored graft survival rates according to the KDPI group and AKI subgroup and the death-censored graft survival rates according to the AKI stage. (A–C) Comparison of the death-censored graft survival rate (A) between the high KDPI-KTR and low KDPI-KTR groups, (B) between AKI-DDKT and non-AKI-DDKT subgroups in the high KDPI-KTR group, and (C) between AKI-DDKT and non-AKI-DDKT subgroups in the low KDPI-KTR group. (D, E) Comparison of the death-censored graft survival rate according to the AKI stage (D) in the high KDPI-KTR group and (E) in the low KDPI-KTR group.

AKI, acute kidney injury; DDKT, deceased donor kidney transplantation; KDPI, Kidney Donor Profile Index; KTR, kidney transplant recipient.

Table 4. Odds ratios (OR) for allograft failure on the status of AKI or high KDPI donor in deceased donor

	Unadjusted OR (95% CI)	p-value	Adjusted OR ^a (95% CI)	p-value	p-value for interaction
AKI-KT	0.884 (0.422–1.849)	0.742	1.011 (0.484–2.114)	0.976	0.088 ^b
AKI stage 3-KT	1.349 (0.701–2.596)	0.370	1.357 (0.583–3.155)	0.479	0.002 ^c
High KDPI-KT	2.304 (1.262–4.205)	0.007	3.096 (1.642–5.838)	<0.001	

AKI, acute kidney injury; CI, confidence interval; KDPI, Kidney Donor Profile Index; KT, kidney transplantation.

^aAdjusted by recipient age, transplant year, transplant center, recipient hypertension, acute rejection, panel-reactive antibody of >50%, human leukocyte antigen mismatch, and induction immunosuppressant. ^bAn interaction between AKI in deceased donors and high KDPI deceased donors for allograft failure. ^cAn interaction between AKI stage 3 in deceased donors and high KDPI deceased donors for allograft failure.

and predicting allograft outcome [19]. Furthermore, we performed this current study based on the previous one.

First, we compared the clinical characteristics of the high and low KDPI donors. The mean age of donor at KT

and proportions of HTN, DM, CVA, AKI, and ECD were significantly higher, and the mean CKD-EPI eGFRs at baseline and allocation were significantly lower in the high KDPI donors than in the low KDPI donors perhaps because

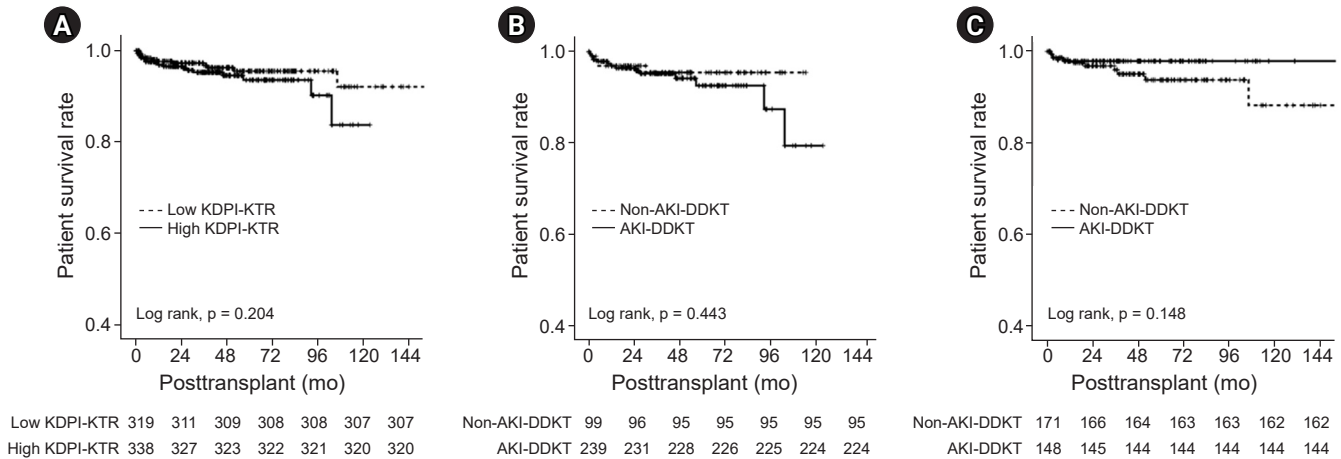


Figure 4. Comparison of the patient survival rates. Comparison of (A) between the high KDPI-KTR and low KDPI-KTR groups, (B) between AKI-DDKT and non-AKI-DDKT subgroups in the high KDPI-KTR group, and (C) between AKI-DDKT and non-AKI-DDKT subgroups in the low KDPI-KTR group.

AKI, acute kidney injury; DDKT, deceased donor kidney transplantation; KDPI, Kidney Donor Profile Index; KTR, kidney transplant recipient.

the KDPI score contains donor age, creatinine, history of HTN and DM, and cause of death (CVA) [29]. The mean age of recipient at KT was significantly higher in the high KDPI-KTR group than in the low KDPI-KTR group. Most elderly candidates received KT from marginal donors because of the benefit of old for old KT and the prevention of death prior to KT during the waiting period for DDKT [30–33]. Since the presence of DM or HTN can suggest an underlying chronic tissue injury irrespective of allograft function, such donors could be diagnosed with CKD [34]. In addition, the allograft function at baseline and allocation, as calculated by the CKD-EPI equation, was significantly lower and proportion of donors with CKD stage 3 or above was higher in the high KDPI donor group than in the low KDPI donor group. These findings showed that a significantly higher proportion of DDs with a high KDPI score had underlying CKD compared with DDs with a low KDPI score.

In the short-term clinical outcomes between the high and low KDPI-KTR groups, the occurrence of AKI in high or low KDPI score led to a higher incidence of DGF after KT. These findings suggested that AKI or high KDPI score on DDs was an independent risk factor for DGF, and this result is consistent with previous studies [26,35,36]. Recently, AKI on DDs and the recipients' factors may have a more significant impact on the development of DGF compared with the baseline chronic damage of the allograft [37]. However, there was no difference in the development of BPAR according to

the occurrence of AKI on DDs in the high or low KDPI-KTR groups. This finding suggests that the donor state prior to KT does not significantly affect the immunological response after KT.

A research reported that allograft function in the early period after KT was significantly lower in the KT from marginal DDs [35]. On the contrary, another research reported that the poor kidney state of the DDs prior to KT can cause persistent low graft function after KT [38]. In our previous study, there was no difference in the allograft function among KTs from DDs with a stable kidney state, but KT from DDs with a poor kidney state such as elderly DDs or high KDPI DDs showed persistent low allograft function after KT [19,28]. In our study, the high KDPI-KTR group showed significantly lower allograft function compared with the low KDPI-KTR group. However, the AKI-DDKT subgroup showed lower allograft function within 3 months after KT compared with the non-AKI-DDKT subgroup in the high KDPI-KTR group. On the contrary, the AKI-DDKT subgroup showed lower allograft function for 12 months after KT compared with the non-AKI-DDKT subgroup in the low KDPI-KTR group.

Our main hypothesis is that AKI in DDs has a different impact on the long-term allograft survival in the high and low KDPI-KTR groups. The death-censored graft survival rate was significantly lower in the high KDPI-KTR group than in the low KDPI-KTR group. However, in the subgroup

analysis, there was no significant difference in the death-censored graft survival rates between the AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group. Interestingly, in the high KDPI-KTR group, AKI stage 3 was the lowest in the death-censored graft survival rate in comparison with non-AKI and AKI stages 1 and 2 but not in the low KDPI-KTR group. In the multivariate analysis using the Cox proportional hazards regression model, the coexistence of high KDPI and AKI stage 3 in DDs was a significant contributor to allograft failure, and we found a significant interaction between high KDPI and AKI stage 3 in DDs on allograft failure as suggested in Table 4. The aforementioned findings suggest that AKI stage 3 in DDs has a significant impact on the allograft outcomes in the high KDPI-KTR group but not in the low KDPI-KTR group.

In contrast to the death-censored allograft survival rate, the patient survival rate was not significantly different between the high and low KDPI-KTR groups, and the distribution of the cause of death did not depend on the KDPI score. There was also no significant difference in the patient survival rate between the AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group. It may be because the number of patient death was too small to evaluate the impact of AKI in DDs for the patient survival in the high and low KDPI-KTR groups. Therefore, a large, well-designed prospective study is required to overcome the small sample size.

Both donor and recipient factors are important in the prognosis of DDKT, but donor factors are particularly important for short-term outcomes such as DGF or allograft function at the time of early stage after KT. Therefore, an allocation system for selecting an appropriate donor is currently needed above all. In 2014, the KDPI score was introduced as a new allocation system in the US and it has been studied not only in the US but also in various countries around the world. We demonstrated that the presence of AKI in ECDs significantly impacted the long-term allograft outcomes of KTRs [18]. Furthermore, we also demonstrated that AKI in elderly DDs can significantly affect long-term allograft outcomes of KTRs [28]. In other words, when the underlying kidney status of the donor was bad, the prognosis was poor when AKI occurred. In evaluating these underlying kidney status, KDPI was more effective than the ECD criteria. Comparing ECD criteria with KDPI score, ECD criteria is a binary score that takes into account

the factors of four donors, and on the other hand, the KDPI score is a continuous score that considers 10 donor factors. Therefore, the KDPI score can determine the donor status more diversely than the ECD criteria. Finally, among the variables of KDPI score, donor age and kidney function at allocation with chronic change were very important factors according to our studies. Furthermore, AKI in DDs was also an important factor. In addition, we reported that the KDPI score is effective in predicting the long-term prognosis as well as the short-term clinical course. In our previous research, we demonstrated that the KDPI scoring system was useful in predicting allograft outcomes in a Korean DDKT cohort, in particular, KT from DDs with a marginal kidney [19].

Although the KDPI score is helpful to evaluate the effect of the DD factors and predict the prognosis of posttransplant clinical outcomes, there were some limitations in our studies. First, these were retrospective studies, so the KDPI score was calculated retrograde after KT. Therefore, well-designed large-scale prospective study is needed because the KDPI score is a prospective predictor. Second, it is known that the predictive power of the KDPI is only moderate (c-statistic = 0.60). Third, all donor factors associated with graft outcomes are not included with pathologic findings. Fourth, there is a selection bias for the prognosis of KT since clinicians want to selectively perform DDKT with good quality of kidney although they consider the KDPI score.

Our study has some limitations like our previous reports using this cohort. First, because this was a retrospective cohort study, this could have selection bias. However, we analyzed the medical records of four centers considering the characteristics such as multiple transplant centers and transplant year without the loss of KTRs during the study period in the multivariate analysis. Second, because KT from both kidneys in the same transplant center was not performed, the clinical outcome of the contralateral kidney transplanted in the other transplant center could not be known. The tracking system for all transplanted or discarded kidneys is needed to overcome this problem. Lastly, the Korean allocation rule has been applied for the allocation when the brain death donor occurred. Because the KDPI system has not been validated in Korea, it has not been used in the real world. We only used the KDPI score for the research retrospectively. In spite of these limitations, this study is valuable because it is a very useful research as basic

data for improving the allocation system, given the reality that the allocation criteria are not clear although DDKT with donor AKI is expanding year by year in Korea.

In conclusion, KT from DDs with AKI stage 3 showed an adverse impact on the allograft outcome in the high KDPI-KTR group. Therefore, although AKI occurs in DDs with a high KDPI score, it is recommended to perform KT from donor kidney with AKI stages 1 and 2, and it would be better to judge more carefully for donor kidney with AKI stage 3 using additional tools such as procurement biopsy. In addition, donor management should be performed more carefully not to proceed to AKI stage 3 during donor management before allocation.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI20C0317) and also was supported by the First Research Support Project of the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT in 2018 (NRF-2017R1C1B5076739).

Authors' contributions

Conceptualization: All authors

Data curation: WYP, YKC, YSK, KJ, CWY

Funding acquisition: WYP, BHC

Investigation: YKC, YSK, KJ

Writing—original draft: WYP, SH, BHC

Writing—review & editing: WYP, CWY, SH, BHC

All authors read and approved the final manuscript.

ORCID

Woo Yeong Park, <https://orcid.org/0000-0003-2662-2898>

Yoon Kyung Chang, <https://orcid.org/0000-0003-4193-2034>

Young Soo Kim, <https://orcid.org/0000-0001-8478-0566>

Kyubok Jin, <https://orcid.org/0000-0002-7836-8863>

Chul Woo Yang, <https://orcid.org/0000-0001-9796-636X>

Seungyeup Han, <https://orcid.org/0000-0002-7561-6534>

Byung Ha Chung, <https://orcid.org/0000-0003-0048-5717>

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