PLOS ONE

RESEARCH ARTICLE

Impact of acute kidney injury on graft outcomes of deceased donor kidney transplantation: A nationwide registry-based matched cohort study in Korea

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Citation: Ha J, Jung CW, Choi S, Kim M-G, Gwon JG, Kim JK, et al. (2021) Impact of acute kidney injury on graft outcomes of deceased donor kidney transplantation: A nationwide registry-based matched cohort study in Korea. PLoS ONE 16(11): e0260076. https://doi.org/10.1371/journal.pone.0260076

Editor: Giuseppe Remuzzi, Istituto Di Ricerche Farmacologiche Mario Negri, ITALY

Received: March 12, 2021

Accepted: November 2, 2021

Published: November 17, 2021

Data Availability Statement: Data can be accessed through Korean Organ Transplantation Registry (KOTRY) website. To gain access to KOTRY data, an application form, a research proposal, and the applicant's institutional review board approval document should be submitted to and reviewed by the Committee of KOTRY. Contact information is as below. Korean Organ Transplantation Registry Website: http://www.kotry.org Tel: +82-2-3675-2194 Fax: +82-2-3675-2195 E-mail: kotry@kotry.org.

Abstract

Background

Favorable long-term and short-term graft survival and patient survival after kidney transplantation (KT) from deceased donors with acute kidney injury (AKI) have been reported. However, few studies have evaluated effects of donor AKI status on graft outcomes after KT in Asian population. Thus, the purpose of this study was to evaluate graft function after KTs from donors with AKI compared to matched KTs from donors without AKI using a multicenter cohort in Korea.

Methods

We analyzed a total of 1,466 KTs collected in Korean Organ Transplant Registry between April 2014 and December 2017. KTs from AKI donors (defined as donors with serum creatinine level $\geq$ 2 mg/dL) and non-AKI donors (275 cases for each group) were enrolled using a 1:1 propensity score matching. Graft outcomes including graft and patient survival, delayed graft function (DGF), rejection rate, and serially measured estimated glomerular filtration rate (eGFR) were evaluated.

Results

After propensity matching, KTs from AKI donors showed higher rate of DGF (44.7% vs. 24.0%, $p < 0.001$). However, the rejection rate was not significantly different between the two groups (KTs from AKI donors vs. KTs from non-AKI donors). eGFRs measured after 6

Funding: This research was supported by research grants (2014-ER6301-00, 2014-ER6301-01, 2014-ER6301-02, 2017-ER6301-00, 2017-ER6301-01, 2017-ER6301-02) funded by Korea Centers for Disease Control and Prevention and a Korea University Grant (for C.W.J.). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

months, 1 year, 2 years and 3 years were not significantly different by donor AKI status. With median follow-up duration of 3.52 years, cox proportional hazards models revealed hazard ratio of 0.973 (95% confidence interval [CI], 0.584 to 1.621), 1.004 (95% CI, 0.491 to 2.054) and 0.808 (95% confidence interval [CI], 0.426 to 1.532) for overall graft failure, death-censored graft failure and patient mortality, respectively, in KTs from AKI donors compared to KTs from non-AKI donors as a reference.

Conclusions

KTs from AKI donors showed comparable outcomes to KTs from non-AKI donors, despite a higher incidence of DGF. Results of this study supports the validity of using kidneys from deceased AKI donors in Asian population.

Introduction

Kidney transplantation (KT) is the treatment of choice for eligible patients with end-stage renal disease (ESRD) which is superior to any other treatment modalities including renal replacement therapies [1, 2]. However, the issue of organ shortage has been raised because the incidence of ESRD is increasing while the donor pool remains relatively unchanged. There have been efforts to maximize the utilization of donated kidneys. Formalized definition and use of expanded criteria donor (ECD) donor [3] have allowed more patients to benefit from KT.

Kidney discard rate from donors with acute kidney injury (AKI) is significantly higher than that from donors without AKI [4, 5] because serum creatinine level of donor has been recognized as one of critical factors contributing to poor outcomes after KT. However, accumulating clinical evidence including long-term observations supports comparable patient survival and graft survival of KT from donors with and without AKI [5–12]. Main concerns about using kidneys from donors with AKI have been primary non function [13]. However, many of previous reports had a single-center design [7, 12, 14–18]. There have not been sufficient studies for supporting the safety and efficacy of KTs from donors with AKI in Asian population [9, 14].

Therefore, we conducted a matched cohort study using a nationwide multicenter cohort in Korea to evaluate effects of deceased donor AKI status on graft function after KT presented by estimated glomerular filtration rate (eGFR) with minimized selection bias, and to assess adequacy of KT from donor with AKI in Asian population.

Patients and methods

Study population

The Korean Organ Transplant Registry (KOTRY) is a web-based national transplant registry established in 2014. It includes demographic and clinical data of donors and recipients from 32 centers. The database was accessed on January 2020 for data collection, and all cases of KT from deceased donors and registered in KOTRY between April 2014 and December 2017 were eligible for this study. Exclusion criteria were en-bloc or dual KTs, KTs from donor aged less than 19 years, and cases with missing variables including donor serum creatine, height, weight, presence of hypertension, or presence of diabetes. The KOTRY study was reviewed and approved by the Institutional Review Board of Korea University Anam Hospital (approval number: 2014-0272-024). All data were fully anonymized before researchers accessed the

database. The Institutional Review Board waived the requirement for informed consent. None of the transplant donors in the dataset was from a vulnerable population and all donors or next of kin provided written informed consent that was freely given. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Data collection

Primary data included information of donors, information of recipients, and transplantation-related factors. Donor factors included age, height, weight, body mass index (BMI), cause of death, serum creatinine, presence of diabetes or hypertension, smoking status, and human leukocyte antigen (HLA) types (HLA-A, -B, -DRB1). Kidney donor profile index (KDPI) and kidney donor risk index (KDRI) were calculated based on donor characteristics [19]. Recipient factors included primary cause of renal disease (diabetes, hypertension, glomerular disease, tubular interstitial disease, polycystic kidney disease, or others), history of kidney transplantation, presence of diabetes or hypertension, age, height, weight, BMI, and HLA types. Transplant-related factors included cold ischemia time (CIT), results of donor specific antigen (DSA) test, agents of induction therapy, and maintenance immunosuppressants. HLA mismatch score was calculated by counting the number of HLA matched loci of HLA-A, -B, and -DRB1 out of six. Clinical outcomes included serum creatinine levels of recipients measured at 6 months, 1 year, 2 years, and 3 years after KT, delayed graft function (DGF, defined as the need for renal replacement therapy during the first week after KT), primary nonfunction (PNF), graft loss, patient loss, biopsy proven rejections within 1-year post-KT (borderline rejections, T-cell mediated, antibody mediated, and mixed rejections), and BK nephropathy. eGFR in each follow-up period was calculated using demographic factors and serum creatinine level using the Modification of Diet in Renal Disease study equation [20].

Statistical analysis

Continuous variables and categorical variables are presented as means with standard deviations and frequency with percentages, respectively. AKI donor was defined as donor with terminal serum creatinine level (the last serum creatinine level measured before KT) $\geq$ 2.0 mg/dL. We used a 1 to 1 propensity score matching from a logistic regression to minimize the difference in baseline covariates between AKI donors and non-AKI donors. We performed propensity score matching in consideration of donor age, sex height, weight, presence of hypertension and diabetes, and cause of death using the caliper matching. To assess the balance of variables used in the matching, standardized mean differences (SMDs) were checked.

Differences in continuous outcomes and categorical outcomes between the two matched groups were investigated using independent t-test and chi-squared test, respectively. A generalized estimating equation model was used to estimate statistical significance of variance in eGFR between groups. Bonferroni correction was used for comparing eGFR at specific time point. Graft failure was defined as a return to dialysis or retransplantation. Kaplan-Meier log-rank tests were used to test differences in patient survival, graft survival and death-censored graft failure between groups. The hazard ratios (HRs) and 95% confidence intervals (CIs) of overall graft failure, death-censored graft failure and death after KT were estimated using Cox proportional hazards model. A p-value less than 0.05 in a two-sided test was regarded as statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.6.3 (Vienna, Austria, http://www.R-project.org).

Results

Baseline characteristics of included KTs

Among 1,466 deceased donor KTs performed between April 2014 and December 2017 and identified from the KOTRY database, 275 KTs from donors with AKI were matched at 1:1 to 275 from donors without AKI according to the propensity score. Fig 1 provides information of excluded cases in detail. Characteristics of matched variables including SMDs by donor AKI status before and after matching are presented in S1 Table.

Baseline characteristics of donors and recipients included in the analysis and transplantation-related characteristics are described in Table 1 according to group. The mean age of donors was 46.7±13.4 years. The majority (83.6%) of donors were males. Their mean BMI was 23.9 ± 3.5 kg/m^2. Of all donors, 42.6% died from cerebrovascular causes. Recipients were 51.1 ± 10.7 years old in average. Most (60.9%) of them were males. Their mean BMI was 23.1 ± 3.4 kg/m^2. There were three leading primary causes of renal disease: glomerular disease (35.4%), diabetes (30.7%), and hypertension (28.6%). Mean serum creatinine levels of AKI donors and non-AKI donors were 3.55 ± 1.44 mg/dL and 1.05 ± 0.44 mg/dL ($p < 0.001$),

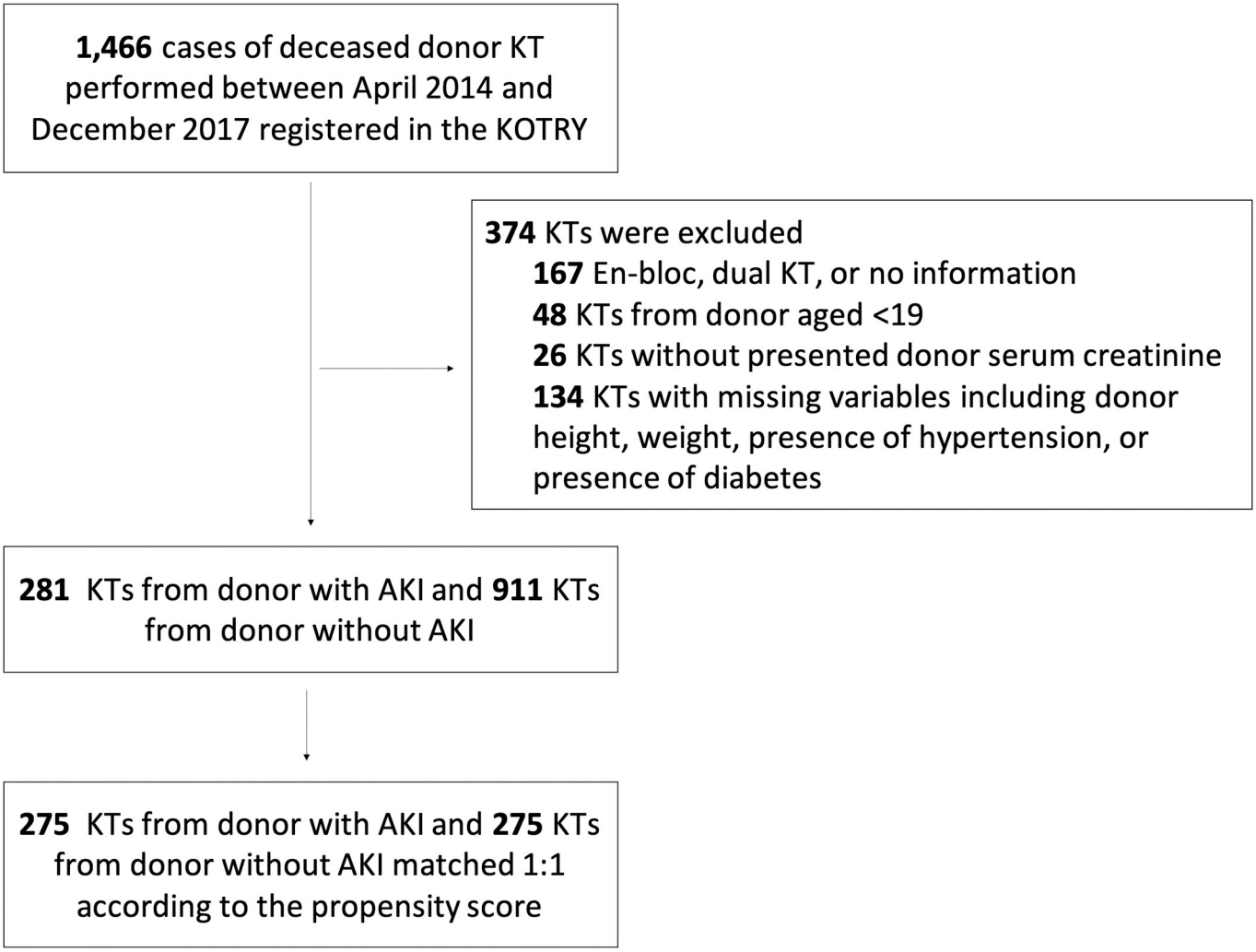

Fig 1. Flow diagram showing the selection of the study population.

https://doi.org/10.1371/journal.pone.0260076.g001

Table 1. Baseline characteristics of subjects in KT from AKI donor group and KT from non-AKI donor groups.

	KT from AKI donor (n = 275)	KT from non-AKI donor (n = 275)	*P*-value
Donor characteristics			
Age, years	47.17 ± 12.11	46.29 ± 14.58	0.443
Male, No. (%)	227 (82.5)	233 (84.7)	0.564
Height, cm	169.48 ± 8.86	170.20 ± 8.11	0.323
Weight, kg	69.40 ± 11.75	68.83 ± 12.35	0.577
BMI, kg/m^2	24.10 ± 3.48	23.66 ± 3.52	0.147
Diabetes, No. (%)	45 (16.4)	44 (16.0)	1.000
Hypertension, No. (%)	79 (28.7)	73 (26.5)	0.634
Serum creatinine, mg/dL	3.55 ± 1.44	1.05 ± 0.44	<0.001
Cerebrovascular death, No. (%)	119 (43.3)	115 (41.8)	0.796
Current or ex-smoker, No. (%)	145 (55.6)	127 (50.2)	0.259
ECMO, No. (%)	14 (5.1)	9 (3.3)	0.394
KDRI	1.66 ± 0.40	1.42 ± 0.38	<0.001
KDPI, %	75 ± 18	61 ± 22	<0.001
Recipient characteristics			
Age, years	51.83 ± 10.45	50.36 ± 10.72	0.106
Male, No. (%)	172 (62.5)	163 (59.3)	0.484
Height, cm	165.79 ± 8.25	164.65 ± 8.65	0.114
Weight, kg	63.12 ± 11.16	63.21 ± 12.23	0.935
BMI, kg/m^2	22.88 ± 3.14	23.22 ± 3.57	0.235
Diabetes, No. (%)	82 (29.7)	80 (29.1)	0.925
Hypertension, No. (%)	254 (92.7)	243 (88.4)	0.112
Current or ex-smoker, No. (%)	78 (28.6)	59 (21.5)	0.072
Past history of KT, No. (%)	22 (8.0)	20 (7.27)	0.748
Duration of dialysis before KT, years	7.45 ± 4.90	7.54 ± 4.74	0.832
Primary cause of renal disease, No. (%)			
Diabetes	71 (32.0)	62 (29.4)	P for trend 0.244
Hypertension	69 (31.1)	55 (26.1)	
Glomerular disease	70 (31.5)	83 (39.3)	
Tubulointerstitial disease	0 (0.0)	2 (0.9)	
Polycystic kidney disease	12 (5.4)	9 (4.3)	
Other or unknown	53 (19.3)	64 (23.3)	
Transplantation characteristics			
CIT, hours	4.90 ± 2.22	4.97 ± 2.09	0.748
HLA mismatch score, out of 6	2.29 ± 1.63	2.47 ± 1.71	0.202
Baseline DSA positive, No. (%)	18 (11.3)	26 (15.3)	0.370
Induction medication, No. (%)			
Anti-thymocyte globulin	123 (44.7)	66 (24.0)	<0.001
Basiliximab	152 (55.3)	209 (76.0)	<0.001
Maintenance immunosuppressants, No. (%)			
Tacrolimus	270 (98.2)	273 (99.3)	0.450
Cyclosporin	4 (1.5)	0 (0)	0.124
Mycophenolic acid	262 (95.3)	258 (93.8)	0.453
Steroid	272 (98.9)	268 (97.5)	0.202

KT, kidney transplantation; AKI, acute kidney injury; SMD, standardized mean difference; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; KDPI, kidney donor profile index; KDRI, kidney donor risk index; CIT, cold ischemic time; HLA, human leukocyte antigen; DSA, donor-specific antibody.

https://doi.org/10.1371/journal.pone.0260076.t001

Table 2. Graft outcomes by AKI status of deceased donor.

Variables	KT from AKI donor	KT from non-AKI donor	P-value
eGFR, mL/min/1.73 m^2			
6 months post-KT	53.29 ± 20.60	55.94 ± 23.44	0.172
1 year post-KT	55.20 ± 19.93	57.28 ± 22.69	0.279
2 years post-KT	56.53 ± 20.20	60.56 ± 22.80	0.064
3 years post-KT	55.71 ± 19.32	60.25 ± 22.19	0.099
PNF, No. (%)	2 (0.73)	0 (0.00)	0.157
DGF, No. (%)	67 (24.54)	17 (6.18)	<0.001
Biopsy-confirmed rejection within 1 year, No. (%)	43 (15.64)	54 (19.64)	0.2184
Borderline rejection within 1 year	17 (9.71)	20 (7.27)	0.7031
Acute T cell-mediated rejection	16 (5.82)	24 (8.73)	
Acute antibody-mediated rejection	5 (1.82)	7 (2.55)	
Mixed acute rejection	5 (1.82)	3 (1.09)	
Biopsy-confirmed BK nephropathy, No. (%)	3 (1.09)	6 (2.18)	0.504

KT, kidney transplantation; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; DGF, delayed graft function; PNF, primary nonfunction

https://doi.org/10.1371/journal.pone.0260076.t002

respectively. Compared to non-AKI donors, AKI donors had higher mean KDRI (1.66 ± 0.40 versus 1.42 ± 0.38, $p < 0.001$) and KDPI (75 ± 18% versus 61 ± 22%, $p < 0.001$). Anti-thymocyte globulin was more frequently used as an induction agent in KTs from AKI donors than in KTs from non-AKI donors (44.7% versus 24.0%, $p < 0.001$). No significant difference in the frequency of patients using each maintenance immunosuppressant was observed.

Allograft outcomes

Allograft outcomes according to donor AKI status are presented in Table 2. The incidence of DGF was significantly higher in the group of KTs from AKI donors than in the group of KTs from non-AKI donors (24.5% versus 6.2%, $p < 0.001$). However, the incidence of PNF was not significantly different between the two groups ($p = 0.157$). There was a significant difference in eGFR by time ($p = 0.006$, Fig 2), although the variance in eGFR was not significantly different between KTs from AKI and non-AKI donors ($p = 0.427$). After KTs from non-AKI donors, eGFR was improved at 3 years compared to that at 6 months after KT ($p = 0.002$). There was no significant difference in the incidence of biopsy-confirmed rejection within 1 year or biopsy-confirmed BK nephropathy.

Allograft and patient survival

The median follow-up duration of recipients was 3.52 (interquartile range, 2.69–4.28) years. Graft and patient survivals by donor AKI status are shown in Fig 3. The risk of overall graft failure (HR, 0.973; 95% CI, 0.584 to 1.621), death-censored graft failure (HR, 1.004; 95% CI, 0.491 to 2.054) and mortality (HR, 0.808; 95% CI, 0.426 to 1.532) were not significantly different by donor AKI status.

Discussion

The discard rate of deceased kidneys is increasing without showing significant difference in the quality between transplanted and discarded kidneys [21], implying that better assessment and distribution of such limited resource could increase the donor pool. Given that AKI donor is one of common causes of kidney discard, the impact of donor AKI status on outcomes of

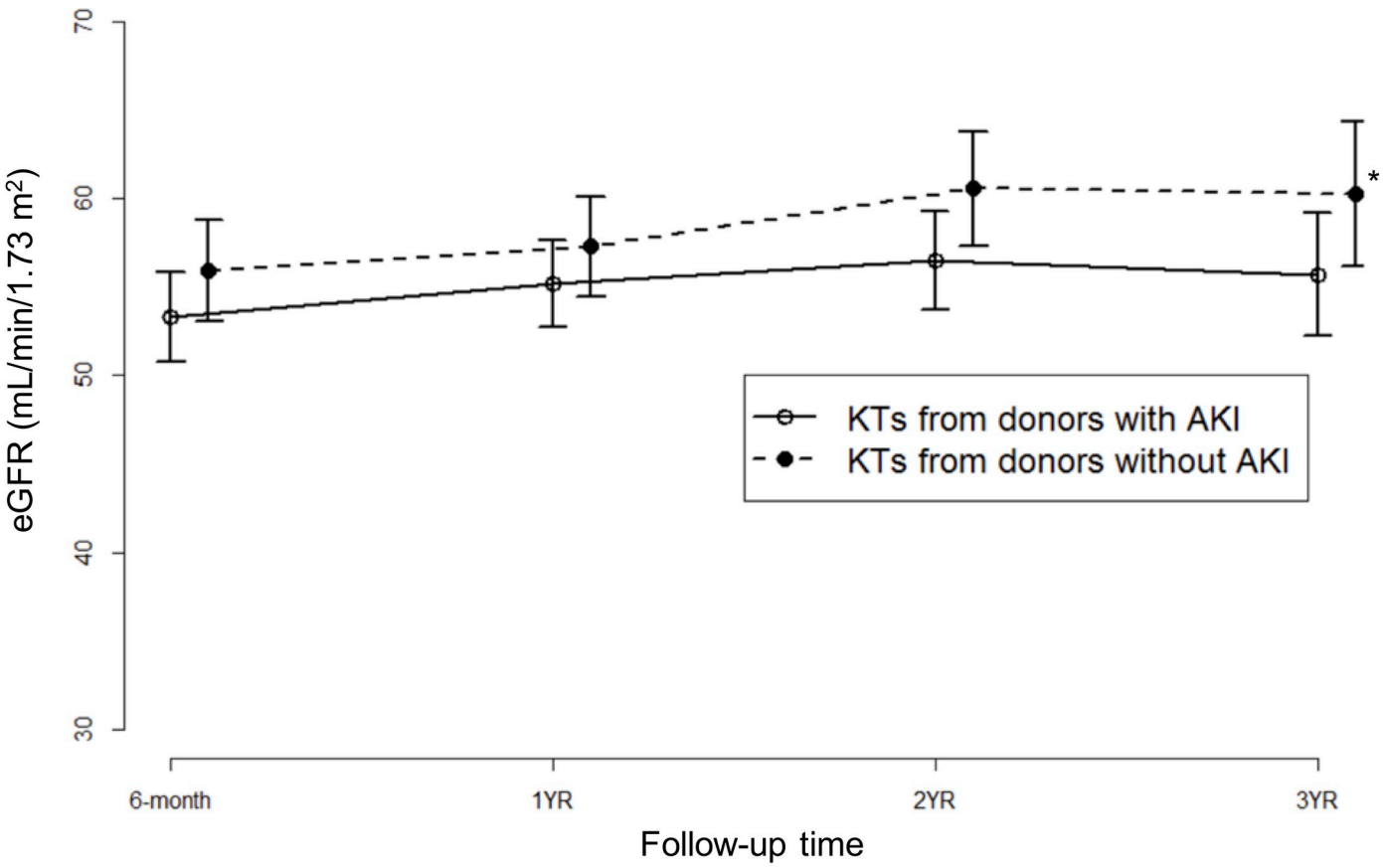

Fig 2. Mean eGFR in KT from AKI donors and non-AKI donors. eGFR, estimated glomerular filtration rate; KT, kidney transplantation; AKI, acute kidney injury. Generalized estimating equation showed significant difference in eGFR by time ($p = 0.006$). However, group versus time interaction was insignificant ($p = 0.427$). eGFR showed a significant difference (*, $p < 0.05$) at 6 months and 3 years after KT.

https://doi.org/10.1371/journal.pone.0260076.g002

KT comes to the fore. Although preceding studies have reported favorable outcomes of KTs from AKI donors [4–8, 10, 12–14, 17, 18] and feasible mechanisms have been proposed [11, 22], there have been considerable discordances in the selection criteria for kidneys from AKI

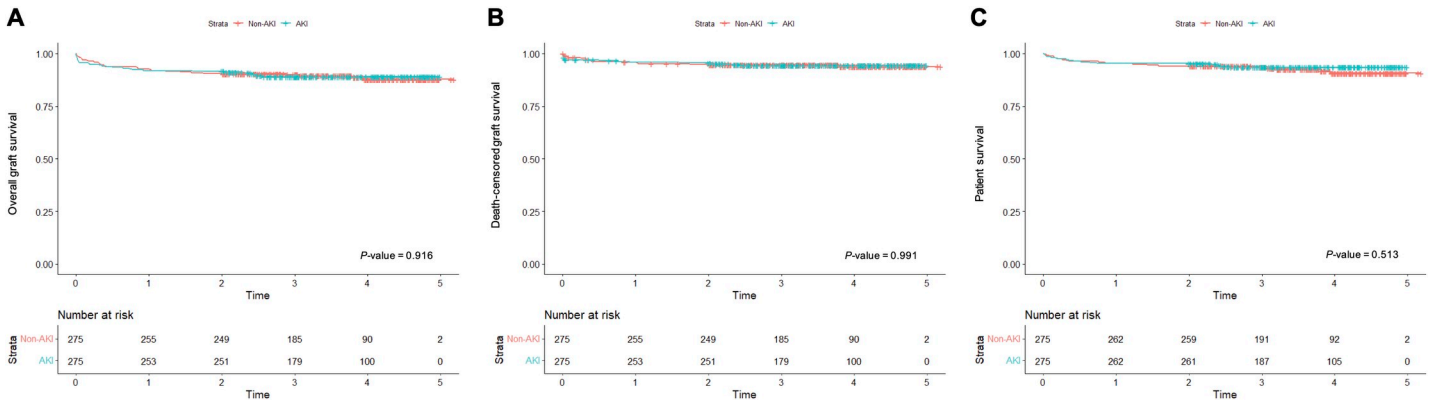

Fig 3. Overall graft survival (A), death-censored graft survival (B) and patient survival (C) after KT from donor with AKI and without AKI.

https://doi.org/10.1371/journal.pone.0260076.g003

donors across centers [7, 12]. Due to low feasibility of randomized controlled trials, well-designed observational studies with low risk of bias and confounders could provide decisive evidence.

To the best of our knowledge, this is the first nationwide cohort study reporting serial graft function after KTs according to donor AKI status in an Asian population. We found that KTs from AKI donors resulted in comparable outcomes to propensity score-matched KTs from non-AKI donors in an Asian population. According to our findings, despite higher incidence of DGF in KTs from AKI donors, the rejection rate, eGFR, graft survival, and patient survival were not significantly affected by donor AKI status. These findings are in line with prior studies including one study on 6,722 deceased donors with AKI matched to donors without AKI showing that AKI status of donor can significantly increase the risk of DGF (29% versus 22%, $p < 0.001$), while AKI status was not related to death-censored graft failure (HR: 1.01; 95% CI: 0.95 to 1.08) or all-cause graft failure (HR: 0.97; 95% CI: 0.93 to 1.02) [11]. Higher incidence of DGF relevant to donor AKI has been consistently featured in abundant studies. However, convincing short-term and long-term outcomes justify the use of AKI kidneys [23].

Our study population composed of Asian with short CIT (mean, 4.94 ± 2.16 hours), one of the most important factors affecting graft survival and function [24, 25]. In addition, basiliximab was predominantly prescribed as an induction agent attributing to a low immunologic risk of Asian [26]. Before cases were matched by propensity score, the study cohort showed that AKI donors tended to be taller and heavier than non-AKI donors (S1 Table). This tendency can be explained by choosing favorable characteristics offsetting higher risk of poor prognosis after KT. The size of kidney, which is proportional to the body size of the donor, is related to better prognosis after KT [27, 28].

We observed a significant increase in kidney function measured at 3 years compared to 6 months after KTs from non-AKI donors (Fig 2), which was also reported in recent studies [29, 30]. Although the exact mechanism has not been elucidated yet and its clinical significance is controversial, several plausible explanations could be suggested. First, improved kidney function over time could be explained as a compensatory hyperfiltration of the graft in a fashion similar to improvement of renal function in live donors after nephrectomy [31]. Second, improvements in general medical care for transplant patients and management for high immunologic risk patients and acute rejection episodes with better choice of immune suppression [32, 33] might have contributed to better graft functions after KT. Third, increase in eGFR within 3 years after KTs could be explained as a natural course of recovery from pre-, intra-, and post-transplant graft injury such as ischemic insults during the donor/recipient management and ischemia reperfusion injury which is an inevitable consequence following KTs [33].

In this study, there was no significant difference in the mean eGFR measured at each follow-up period between KTs from AKI and KTs from non-AKI donors. Previous long-term observation studies with multiple eGFR measurements to compare graft functions between KTs from AKI and non-AKI donors have shown inconsistent results. Some studies showed that eGFR after KTs from AKI donors was comparable to that after KTs from non-AKI donors until 5 years [12, 17]. In contrast, Bauer et al. [18] found that KTs from AKI and non-AKI donors did not show significant difference in eGFR measured at 1 year after KT; however, eGFR at 3 and 5 years after KT was significantly higher in the non-AKI group than in the AKI group. Schütte-Nütgen et al. [34] also reported that KTs from AKI donors consistently show lower eGFR than KTs from non-AKI donors at 3-year follow-up.

Some limitations of this study should be acknowledged. First, we used dichotomized definition of AKI donors without considering chronicity, severity, or dynamic changes in donor kidney function as donor serum creatinine level was reported only once in the registry. Second,

although bias from the retrospective design of this study was partially resolved by propensity score matching, there might be effects of known and unknown variables. Third, a considerable number of cases were excluded due to missing variables. Fourth, the small cohort size decreased the statistical power of this study.

Taken together, this study supports the validity of using kidneys from deceased AKI donors in Asian population. Further studies with long term follow-up duration are needed to investigate graft function according to donor AKI status.

Supporting information

S1 Table. Characteristics of matched variables according to donor AKI status before and after propensity score matching.
(DOCX)

Acknowledgments

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