Impact of Donor Age on the Outcomes of Kidney Transplantation From Deceased Donors With Histologic Acute Kidney Injury

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ABSTRACT

Purpose. Kidney transplantation from elderly donors with acute kidney injury (AKI) has increased recently due to donor shortage, but the safety and prognosis are not well known. We examined the effect of donor age on the outcomes of kidney transplantation (KT) from donors with histologic AKI.

Materials and methods. We retrospectively analyzed the medical records of 59 deceased-donor KTs with acute tubular necrosis (ATN) on preimplantation donor kidney biopsy between March 2012 and October 2017. Histologic evaluations of ATN, inflammation, glomerulosclerosis (GS), interstitial fibrosis, tubular atrophy, and arterial sclerosis were performed.

Results. Twenty and 39 recipients received kidneys from elderly (> 60, 68.9 ± 5.0 years) and young (≤ 60, 45.9 ± 9.6 years) donors with ATN, respectively. Among the elderly donors, significantly increased donor creatinine was observed in only 44% donors, and there were more diabetic patients and women and a higher proportion of GS than among the young donors. Six months after KT, estimated glomerular filtration rate was significantly lower in recipients who received kidneys from elderly donors compared to young donors. Donor creatinine level and AKI severity did not significantly affect the recipient outcomes in either group. However, the presence of ATN and GS were significant factors that exacerbated renal outcomes after KT from elderly donors only. On multivariate analysis, severe ATN was the strongest independent predictor of elderly recipient renal function.

Conclusions. Histologic injury may predict renal outcomes in KT from elderly donors. A donor allocation protocol including preimplantation renal histology should be established for KT from elderly donors.

With the rapid increase in the number of individuals awaiting kidney transplantation (KT), the shortage of donors and excessive waiting time for deceased-donor KT have become major issues in the field of transplantation. Therefore, attempts have been made to use kidneys from donors selected on the basis of expanded criteria, and the concept of expanded-criteria donor (ECD) has been introduced to track graft survival [1–3].

Previous studies showed that KT using kidneys from donors selected on the basis of expanded criteria such as

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donor age of > 55 years, non-heart-beating donor, cold ischemia time of > 36 h, or donor hypertension or diabetes mellitus may have significant survival benefit for transplant-waitlisted dialysis patients [2]. As a result, the number of KTs with ECD kidneys has been increasing worldwide. However, the criteria for ECD defined by the Unified Network for Organ Sharing in 2002 must be reevaluated for each country with consideration of variable medical circumstances such as the accessibility of dialysis treatment, transplantation policies, waiting times, and cultural and ethnic differences.

In particular, difficulties activating deceased-donor KTs are more commonly encountered in Asian countries than in Western countries owing to cultural, religious, and policy issues, which results in severe donor shortage and prolonged waiting times of > 5 years for deceased-donor KT. Therefore, KT has been performed with more-expanded criteria, including donors with infectious diseases, old age, and renal insufficiency. In Korea, among 20,283 individuals awaiting KT in 2017, 2163 received a KT, of whom only 903 had deceased donors [4]. Recently, many centers in Korea have been actively performing KT from acute kidney injury (AKI) donors, with relatively good prognoses [5,6]; however, the safety and allocation criteria remain unclear. In addition, the number of KTs from aged deceased donors has been increasing, although effective methods of defining aged organs and predicting prognosis are uncertain. In recent years, even kidneys with AKI in elderly donors have been allocated for KT. However, given the lack of understanding as to whether AKI in elderly donors will recover or progress to chronic kidney disease (CKD), appropriate allocation guidelines should be established.

In this study, we investigated the effects of donor age on the outcomes of KT from donors with histologic AKI and the factors predictive of graft outcomes.

MATERIALS AND METHODS

Patients

We retrospectively analyzed the medical records of 59 deceased-donor KT recipients with acute tubular necrosis (ATN) on donor kidney histology obtained with preimplant wedge biopsy between March 2012 and October 2017. The mean follow-up after transplantation was 30.2 ± 18.4 months. This study was approved by our institutional review board and conducted in accordance with the principles of the Declaration of Helsinki. In Korea, for confirmation of brain death, 2 separate neurologic examinations, apnea tests, and electroencephalography are performed. During the first and second neurologic examinations, the recipients are selected and receive KT as soon as possible after brain death is declared.

Data Collection

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. AKI was defined in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The following recipient and donor variables were assessed: age and sex; HLA-A, HLA-B, and HLA-DR mismatches; initial, peak, and final creatinine (Cr) levels of the donor; and diabetes, hypertension, and renal function up to 6 months.

Histologic quantifications of ATN, inflammation, glomerulosclerosis (GS), interstitial fibrosis, tubular atrophy, and arterial sclerosis were performed retrospectively by an experienced renal pathologist blinded to the patients' clinical data. Urinary neutrophil gelatinase-associated lipocalin (NGAL) level was measured in the urine collected immediately after the operation. NGAL level was measured using an enzyme-linked immunosorbent assay kit in accordance with the manufacturer's instructions (NGAL: BioPorto, Gentofte, Denmark), and the amount of urinary NGAL was normalized to urine Cr concentration (ng/mg Cr).

Statistical Analysis

Numerical data were compared between the 2 recipient groups using the Student *t* or Mann-Whitney U test. Categorical data were evaluated using the χ^2 or Fisher exact test, as appropriate. Multiple logistic regression models were used to analyze prognostic factors for outcomes. Statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, USA).

RESULTS

Clinical Characteristics before and after Transplantation Between Young and Elderly Donors

A total of 78 patients received a deceased-donor KT in Korea University Anam Hospital during the study period. We performed KT after excluding kidneys with severe chronic lesions such as tubular atrophy, interstitial fibrosis, and glomerulosclerosis on pretransplantation biopsy at the time of harvest. Finally, 59 recipients who received kidneys from donors with histologic AKI were included in the study. Thirty-nine and twenty recipients received kidneys from young (≤ 60, 45.9 ± 9.6 years) and elderly (> 60, 68.9 ± 5.0 years) donors with ATN, respectively. The peak and final serum Cr levels before graft harvest were respectively 2.6 ± 1.6 and 2.2 ± 1.5 mg/dL in the young donors and 1.9 ± 1.2 mg/dL and 1.5 ± 0.8 mg/dL in the elderly donors (Table 1). Among the elderly donors, significantly increased donor Cr level was observed only in 44%, and the proportions of diabetic patients and women were higher. Despite the high prevalence of diabetes mellitus among the elderly donors, donor proteinuria did not significantly differ. No significant differences in age, sex, and HLA mismatch were found between the recipients of KT from elderly and young donors, but 6 months after KT, eGFR was significantly lower in the recipients who received kidneys from elderly donors than in those who received kidneys from young donors.

Histologic Scoring Between Young and Elderly Donors

According to histologic scoring of the donor kidneys at harvest time, the GS percentage was higher in the elderly donors, but the difference was not statistically significant (Table 2). No significant difference was found between the elderly and young donors in terms of ATN, interstitial fibrosis, tubular atrophy, or interstitial inflammation.

Table 1. Basal Characteristics of the Donors and Recipients and Renal Function According to Donor Age

	Young donors (< 60 years, n = 39)	Elderly donors (≥ 60 years, n = 20)	*P* Value
Donors			
Age (years)	45.9 ± 9.6	68.9 ± 5.0	<.001
Sex (female, %)	23.1	45.0	.083
Clinical AKI (%)	81.1	44.4	.006
Peak Cr (mg/dL)	2.6 ± 1.6	1.9 ± 1.2	.1
Last Cr (mg/dL)	2.2 ± 1.5	1.5 ± 0.8	.08
uNGAL/uCr	1668.1 ± 438.6	2179.6 ± 677.6	.537
DM (%)	10.5	55.6	.001
HTN (%)	28.9	36.8	.275
Proteinuria			.182
0 to +1	92.3	95.0	
≥ +2	7.7	5.0	
Recipients			
Age	49.1 ± 10.2	53.0 ± 10.1	.168
Sex (F, %)	30.8	35.0	.742
HLA MM ≥ 3 (%)	79.4	75.5	.274
3-month eGFR	45.0 ± 14.5	38.5 ± 14.1	.119
6-month eGFR	44.7 ± 14.7	35.3 ± 14.9	.042
proteinuria			.087
0 to +1	94.9	100	
≥ +2	5.1	0	

Abbreviations: AKI, acute kidney injury; Cr, creatinine; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

Risk Factors of Poor Graft Outcomes according to Donor Age

We analyzed the histologic and clinical parameters of the donors to predict post-transplant renal outcome in the elderly and young donors. The donor Cr level and AKI severity according to the KDIGO criteria and urinary NGAL level did not significantly impact the recipient outcomes in either group at 6 months post-transplant. However, ATN and GS were found to be significant factors that exacerbated renal outcomes at 6 months only in the KTs from elderly donors (Table 3).

In particular, in the multivariate analysis, severe ATN was the strongest independent predictive factor of poor 6-month eGFR of < 30 mL/min in the recipients who received transplants from elderly donors, which suggests that donor aging is an important factor in modifying the outcomes of AKI (Table 4).

Table 2. Histologic Scoring of Donor Kidneys at the Time of Harvest

	Young donors (< 60 years)	Elderly donors (≥ 60 years)	*P* Value
Cold ischemic time (min)	236.2 ± 135.6	281.2 ± 119.1	.214
Acute tubular necrosis	2.2 ± 1.1	2.5 ± 0.9	.193
Glomerulosclerosis (%)	5.6 ± 6.1	12.9 ± 18.5	.097
Interstitial fibrosis/tubular atrophy	0.8 ± 0.4	0.9 ± 0.4	.369
Interstitial inflammation	1.5 ± 1.0	1.7 ± 1.1	.523

DISCUSSION

Recently, the number of KTs from unconventional ECDs such as those with AKI, diabetes, infection, or extremely old age has been increasing owing to severe donor shortages, especially in Asian countries [7].

Although large epidemiologic studies have shown that AKI is an important cause of CKD progression [8,9], acceptable graft function may confer a better survival benefit to end-stage renal disease patients than waiting for a transplant. In addition, donor AKI may show a different clinical course from general AKI owing to changes in the environment around the kidney after harvest, including exposure to immunosuppressants, disappearance of the AKI cause, and combined cold and warm ischemia.

In our investigation of the clinical outcomes of KT from donors with AKI, no significant difference in 1-year Cr level was found, even in the context of increasing donor Cr and peak donor Cr levels of > 4 mg/dL. This suggests that KT from donors with AKI should be more actively considered to expand the donor pool [5]. Recently, a large-scale study by the Mayo Clinic investigated 162 AKI donor transplant recipients over 10 years [10]. In the study, donors were classified as standard criteria donors or ECDs, and despite a high rate of delayed graft function in the AKI cohort, AKI was found to have almost no impact on graft survival for up to 8 years in both the standard criteria donor and ECD groups. However, the question remains as to whether these findings ensure the safety of KT using AKI donors, as the understanding or guideline as to the degree of AKI severity that is acceptable for KT is still unclear.

One limitation of the previous studies is that they used only Cr level or eGFR for the evaluation of AKI; therefore, they may have included patients with transient mild AKI due to dehydration or low blood pressure, which may be a reason why the kidneys from AKI donors showed relatively good function. Recently, a study evaluated the impact of AKI with histologic tubular injury [11]. They included 975 patients, and all biopsies were performed postreperfusion. They assessed acute and chronic histologic lesions, including acute tubular injury, vascular disease, interstitial fibrosis/tubular atrophy, and GS. Among the parameters, GS alone was predictive of the final serum Cr level in deceased-donor KT but not in living-donor KT. It is interesting that the presence of histologic AKI was not associated with poor graft outcomes at the final follow-up, which suggests that the use of histologic AKI evaluation for predicting allograft outcomes is limited. However, we should consider that age may be an important contributing factor to the aberrant response to AKI. Overall, the donors were relatively young in the previous studies. Moreover, AKI was found to significantly increase the risks of CKD and end-stage renal disease in older patients, even after adjusting for important

Table 3. Linear Regression Analysis of Donor Factors That Affected 6-Month eGFR

	Young donors (< 60 years)		Elderly donors (≥ 60 years)	
Donor factors	β	*P* Value	*B*	*P* Value
ATN	0.030	.877	−0.506	.032
GS	−0.131	.246	−0.408	.049
DM	0.057	.382	−0.154	.285
HTN	0.357	.026	−0.099	.358
Peak Cr	0.011	.478	−0.214	.213
Last Cr	0.053	.393	−0.403	.061
uNGAL/uCr	−0.142	.614	0.357	.432
KDIGO criteria	0.147	.561	−0.151	.722
HLA MM	−0.206	.138	−0.169	.258

Abbreviations: ATN, acute tubular necrosis; Cr, creatinine; DM, diabetes mellitus; GS, glomerulosclerosis; HTN, hypertension; KDIGO, Kidney Disease Improving Global Outcomes; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

covariates [12,13], which suggests that AKI in elderly donors may negatively impact graft outcomes after KT.

In contrast to previous studies, our study focused on and included more elderly donors with AKI. Moreover, only AKI patients identified as having histologic ATN were included, as functional markers such as Cr level and eGFR may be less useful in diagnosing AKI, especially in elderly donors with low muscle mass. Indeed, in the present study, the histologic ATN scores did not differ, but the proportion of AKI in elderly donors according to the clinical criteria based on Cr was significantly lower. Previous studies showed that the urinary NGAL level of donors with AKI could be a useful biomarker to predict poor graft outcomes [14,15]. Therefore, we measured NGAL level and compared its prognostic value with that of Cr level. We observed that the 6-month graft outcomes in the elderly donors with AKI were poorer than those in the young donors. In the subgroup analysis of young and elderly donors, we found that the implications of AKI-associated clinical and histologic parameters differed with age. AKI severity based on the KDIGO criteria was not significant in predicting graft outcomes for either young or elderly donors, which suggests that the clinical AKI criteria are limited in assessing donor AKI and may have little impact on kidney outcomes, although this is not the case with the general population of AKI patients. Histologic changes alone predicted poor graft outcomes for up to 6 months in the elderly donors but not in the young donors. Moreover, severe sclerosis and high ATN score were found to be important risk factors. These results suggest that aged kidneys with GS may not fully recover from ATN and may progress to CKD. Thus, graft survival is worse in the context of elderly donors with AKI, and histologic evaluation may be a critical predictor of prognosis.

Table 4. Multivariate Analyses for Predicting Poor Graft Outcomes (eGFR of < 30 mL/min at 6 Months Post Transplantation) in Recipients Who Received Kidneys From Elderly Donors

	Odds ratio (95% CI)	*P* Value
ATN	3.651 (1.024–13.021)	.046
Last Cr level before harvest	5.377 (0.847–34.121)	.074

Variables with *P* values of <.1 in the univariate analysis (ATN, glomerulosclerosis, last Cr) were included in multivariate analysis using backward selection.

Abbreviations: ATN, acute tubular necrosis; CI, confidence interval; Cr, creatinine.

Still no clear guidelines have been established on the allocation of AKI kidneys, and subjective assessment is solely responsible for the burden of nonrecovery, which leads to a high discard rate. Therefore, an allocation system based on the histologic scores of elderly donors must be established.

This study has several important limitations. First, it was a single-center study with a small number of patients. Furthermore, although histologic scoring was conducted by blinded pathologists, the process was difficult to standardize. Lastly, urinary NGAL level may not have accurately reflected the severity of AKI, as the first urine of the recipient rather than that of the donor was used.

In conclusion, the assessment of AKI based on Cr level is not useful for predicting prognosis. However, in KT from elderly donors, histologic evaluation for acute tissue injury and GS may predict renal outcomes. Therefore, the development of a donor allocation protocol, including the histologic evaluation of acute and chronic lesions using preimplantation donor kidney biopsy, is warranted to ensure optimal outcomes in KT from older donors.

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