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Young donors with severe acute kidney injury offer an opportunity to expand the donor pool

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ABSTRACT

Background: This study assessed our experience transplanting kidneys from young donors with severe acute kidney injury.
Methods: We performed a single center retrospective analysis of 315 kidney transplants between 1/1/2014-12/31/2016. Donor kidneys were classified according to the Acute Kidney Injury Network (AKIN) criteria. A case-matched cohort was created using recipient age, history of diabetes, donor specific antibody, donor age and donor after cardiac death. Primary endpoints were graft function measured by eGFR at 90 days and at 1-year.
Results: Stage 3 AKIN recipients had significantly greater eGFR at one year (63.9 ml/min v. 51.2 ml/min, $p < 0.001$) compared to those with Stage 0 AKIN. This difference was abrogated when compared to a case matched cohort (eGFR at 90 days or 1 year; $p > 0.05$). Donor and recipient characteristics on eGFR at 1 year were analyzed using linear and logistic regression. Only donor age had a significant impact on recipient eGFR.
Conclusions: Donor kidneys with severe acute injury can achieve optimal 1-year outcomes. Donor age is the most significant predictor of eGFR >45 ml/min after transplant.

Introduction

Timely kidney transplantation is recognized as the optimal form of renal replacement therapy for people with end stage renal disease (ESRD).[1] However, demand for kidney transplantation continues to rise due to increasing age of the general population and increasing incidence of risk factors like diabetes.[2,3]

Meanwhile it is well known that the number of organ donors has been relatively unchanged, leading to acceptance of alternative strategies to expand the donor pool. Extended criteria donors (ECD), donors after cardiac death (DCD), and donors with long cold ischemia times (CIT) represent some of these approaches. However, while transplanting these donor grafts may confer a survival advantage as compared to remaining on the wait list, published outcomes have been highly variable.[4] It is known, for example, that kidneys from DCD donors have higher rates of delayed graft function (DGF) but have acceptable long-term survival.[5,6] Similarly, long CIT results in increased rates of DGF without a substantial difference in outcomes as compared to donors with shorter CITs.[6–8] Public Health Service Centers for Disease Control (PHS CDC) high risks donors have also used to expand the donor pool with increased and more effective serum testing to minimize donor disease transference.[9,10] Finally, dual kidney transplantation from marginal donors has been shown to offer comparable outcomes to solitary kidney transplantation in highly selected donors and recipients.[11,12]

Despite efforts to increase utilization of available organs and reduce discard rates, potentially transplantable grafts continue to be discarded. The new kidney allocation system was implemented by UNOS in 2014 partly to address high discard rates.[13] KAS utilized Kidney Donor Profile Index (KDPI) as a more objective numerical score, replacing SCD and ECD designations. However, three years after KAS, kidney discard rate is actually higher than before implementation. Graft discard increased in the 35–85% and 85–100% KDPI categories.[14] Particularly concerning was the rise in

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Abbreviations

AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network Criteria
CKD	Chronic kidney disease
DCD	Donor after cardiac death
DD	Deceased donor
DGF	Delayed graft function
CIT	Cold ischemic time
ECD	Expanded criteria donor
ESRD	End stage renal disease
KAS	Kidney Allocation System
KDPI	Kidney donor profile index
SCD	Standard criteria donor

discard in the 35–85% KDPI group given that these kidneys were generally considered to be SCD grafts. Given that KDPI represents a derivation from regression modeling, many variables affect the score. Serum creatinine has the largest contribution to KDPI {All Donors KDRI β coefficient = 0.22; "Xβ" component = 0.22 * (creat-1)}. However, the Xβ summation for KDPI accounts for donors with serum creatinine >1.5 mg/dL {KDRI Xβ = −0.209 * (creat −1.5)}. Therefore, as serum creatinine increases over 1.5 mg/dL the increase in KDPI is not as pronounced.

Our effort to counter the current graft shortage has focused on the use of kidneys from donors with high terminal creatinine.[15] It is well known that deceased kidney donors often suffer from reversible insults. Several studies have shown that donor mechanism of death, brain death and hemodynamic instability can lead to and exacerbate AKI. In patients considered for deceased donors, AKI commonly developed during their stay in the intensive care unit because of ischemic and nephrotoxic insults.[16]

Given the multifactorial mechanisms that lead to AKI, the predictability of reversibility of this pathophysiology is imprecise. However, it is generally accepted that patients who have underlying chronic kidney disease and suffer AKI have increased rates of late-stage ESRD.[17] Conversely, AKI in healthy individuals often results in normalization serum creatinine after removal of the causative agent.[18,19]

However, the transplant community has not universally embraced the reversibility of AKI in some donors. Resultantly, kidneys with high terminal creatinine with KDPI ~35%–85% are often discarded and not used for transplantation.[20,21] Current studies have assessed the expansion of the viable pool using kidneys with severe AKI with varying outcomes[16,22–24]

Here we present our single center experience with deceased donor renal transplantation utilizing donors with AKI. We aimed to investigate the clinical outcome in patients who received kidneys from deceased donors with AKI based on the AKIN criteria and try to clarify which donor characteristics result in preserved post-transplant renal function.

Methods

Study population

A retrospective cohort of patients 18 years of age and older who received a deceased donor renal transplant between January 2014 through July 2016 at Montefiore Medical Center (MMC) were included in this study. Patients who received multi-organ transplants were excluded from the cohort. Additionally, 4 patients were excluded because initial donor creatinine was not available, thus the kidneys could not be classified according to AKIN criteria. Donor initial creatinine and terminal creatinine was used to stage the AKI following the AKIN criteria.[25] A 1.5–2 fold increase of serum creatinine is defined as Stage 1 AKI, a 2–3 fold increase is Stage 2 AKI and a 3-fold increase or a serum creatinine of 4 mg/dL is a Stage 3 AKI. Kidneys from donors that had calculated values below the stated criteria were described as "non-AKI".

At the time of transplantation, all patients were tested for reactivity to their donor via flow cytometric cross match and testing using LABScreen beads to indicate the presence of pre-transplantation donor specific antibody. As per our protocol, positive complement-dependent cytotoxicity crossmatch (XM) is a contraindication to transplant, but we accept positive flow XM up to 100 MCS for T-cell and 150 MCS for B-cell.

Per protocol, patients with a panel reactive antibody (PRA) of less than 20% received basiliximab induction, whereas patients with a PRA of more than 20% received rabbit anti-thymocyte globulin induction (Thymo). Patients with preformed donor specific antibodies present at the time of transplant receiving IVIG in addition to Thymo. Maintenance immunosuppression included a calcineurin inhibitor, a mycophenolic acid derivative, and a prednisone taper starting at the time of transplantation that was reduced to and then maintained a level of 5 mg/day by 3 months after transplantation.

Data analysis

Data variables of recipient gender, race, induction therapy, history of hypertension (HTN), history of diabetes, age and BMI were collected. Donor characteristics including KDPI, CIT, warm ischemic time (WIT), donor specific antibody (DSA), PHS CDC high risk, DCD, age, and BMI were also collected from patient charts and/or UNOS DonorNet®. Biopsy scores of glomerular sclerosis, arteriosclerosis and interstitial fibrosis and tubular atrophy (IFTA) were collected from DonorNet®. Glomerular sclerosis was recorded as a percentage. IFTA and arteriosclerosis were recorded in ranges of 0–10% and >11%. Analysis used a binary measure of above or below 10% to compare groups. Primary endpoints collected were eGFR at 90 days, 1-year and graft failure. Secondary endpoints included DGF, acute rejection, BK infections and patient deaths within one year of transplant were recorded. DGF was defined classically as the need for dialysis within one-week post-transplant. Estimated GFR (eGFR) was calculated using serum creatinine at 90 days and 1 year using the MDRD formula.[26] Patients with graft loss or patients who were deceased at the 90 day and 1 year endpoints had no serum creatinine readings and thus were not included in eGFR analysis.

The different AKIN stages were all compared to the non-AKI group as the reference group for evaluation of graft and patient outcomes. To compare recipient demographics, donor demographics, and outcomes, a two-tailed *t*-test was used to determine significance. Levene's Test was used to determine if equal or unequal variances were to be used. Gender, induction and race were compared using a Chi-Squared test. To create a case matched cohort, the Stage 3 AKIN were randomly matched on recipient age, DSA and history of diabetes and on donor characteristics of age and DCD status to the non-AKI group. The tolerance values ± 7 years for both recipient and donor age. These two cohorts were compared in according to the aforementioned methodology.

SPSS version 24.0 was used for analysis.

Results

Donor and recipient demographics

Of the 315 renal transplant recipients, there were 193 non-AKI

Table 1
Recipient demographics.

AKIN Stage	0	1	2	3
n	193	39	33	50
Gender (M/F)	129/64	24/15	19/14	35/15
Age	56.9 ± 12.1	58.3 ± 13.6	56.5 ± 13.7	53.6 ± 13.7 *
BMI	29.0 ± 6.2	29.6 ± 7.1	28.3 ± 5.7	30.86 ± 6.2*
Race (%)				
Black	46	44	55	54
Hispanic	32	46	30	30
Asian	4	0	6	2
White	10	3	6	6
Other/Unknown	8	8	3	8
Diabetes (%)	25	36	33	14*
Hypertension (%)	67	67	73	57
DSA (%)	30	13**	20	15**
Induction (Simulect/Thymo)	81/112	20/18	15/18	18/32

* for a p-value of between 0.05 and 0.10.
** for a p-value less than 0.05.

recipients and 122 recipients who received a kidney with AKI. Within the AKI cohort there were 39 Stage 1 AKIN kidneys, 33 Stage 2 AKIN kidneys and 50 Stage 3 AKIN kidneys (Table 1). All three AKIN stages were compared to the non-AKI group as a reference group. When analyzing recipient characteristics, there was no significant difference in history of DM, HTN, age, and BMI between in patients who received a Stage 1, 2 and 3 AKIN kidney as compared to those that received a non-AKI graft. DSA incidence was significantly lower in both Stage 1 and 3 AKIN as compared to the non-AKI group.

Demographics of the donors were also analyzed with several significant differences immediately noticeably (Table 2). The non-AKI group was the reference group for the AKI groups. There was a lower prevalence of DCD donors for all AKIN stages as compared to the non-AKI group. Donor age of Stage 3 AKIN donors was significantly lower. Biopsy scores of Stage 3 AKIN donors showed significantly lower percentage of glomerular sclerosis and interstitial fibrosis/tubular atrophy but comparable rates of arteriosclerosis (Table 2). Biopsy scores between of Stage 1 and 2 AKIN groups were comparable to those of the non-AKI group with the exception IFTA score of Stage 1 group, though this may be to low n in the group.

Regarding outcomes, recipients of Stage 1 and 2 AKIN kidneys had no significant differences in DGF or eGFR at 90 days and 1-year post transplant. Conversely, patients in the Stage 3 AKIN had an increased occurrence of DGF of 72% compared to 54% in the non-AKI group ($p = 0.016$). Moreover, eGFR was significantly higher in the Stage 3 AKIN group as compared to the non AKI group at both 90 days (57.2 ml/min v. 48.4 ml/min; $p < 0.001$) and 1-year (63.9 ml/min v. 51.2 ml/min; $p < 0.001$). The number of patients in each group with GFR under 30 ml/min was assessed at 90 days and 1 year (Table 3). The non-AKI group had 16.1% and 14.5% of patients with GFR under 30 ml/min at 90 days and 1 year respectively. AKIN groups were comparable to the non-AKIN group except the Stage 2 group at 90 days had 33.3% incidence of low GFR ($p = 0.02$), which decreased to 18.2% at 1 year ($p = 0.59$). The Stage 3 AKIN group had a lower incidence of GFR <30 ml/min at 90 days of 8.0% ($p = 0.09$) and 6.0% at 1 year ($p = 0.05$).

Patient outcomes were also assessed with regard to acute rejection episodes and BK viremia (Table 4). Given that these occurrences were relatively few, there was no discernable difference between groups. Patient deaths and graft losses within one year following transplant were also recorded (Table 4). The only significant difference between these groups was Stage 2 AKIN group had 0 patient deaths and thus a significant p-value was observed between non-AKI and Stage 2 AKIN recipients. Given the similarities in the recipient characteristics and concordant rates of graft rejection and BK viremia, further of analysis of the donor was needed to better understand the increased eGFR seen in the Stage 3 AKIN group.

Regression analysis demonstrate that donor age is the most significant variable

To better understand which variables contributed most significantly to eGFR at 1 year, a linear regression was performed, which included the variables: donor age, DCD, AKIN stage and CIT (Table 5). Notably, KDPI was excluded because variables several of the variables used in the model are utilized in the calculation of KDPI, thus their inclusion would have been redundant. The only variable that was a significant predictor was donor age ($\beta = -0.51$,

Table 2
Donor demographics.

AKIN Stage	0		1		2		3	
		std		std		std		std
KDPI (%)	56.4	25.1	65.0	26.9	60.1	25.7	46.7**	21.4
CIT (min)	1737.4	655.6	1897.4	561.7	2017.8**	467.9	1957.7**	552.7
WIT (min)	36.8	10.5	34.5	9.0	38.2	8.4	38.2	11.5
CDC high risk %	31.0		28.0		33		50**	
DCD %	27		5*		6**		8**	
Donor Age	42.5	16.2	48.4	15.4	42.3	11.4	33.1**	13.0
Donor BMI	29.2	7.5	31.0	8.4	33.2*	11.5	30.2	7.1
Glomerular Sclerosis %	2.3		2.4		1.8		0.65**	
Interstitial Fibrosis and Tubular Atrophy % (>10%)	2.8		0**		3.1		0**	
Arteriosclerosis % (>10%)	13.0		8.0		12.0		9.0	

* for a p-value of between 0.05 and 0.10.
** for a p-value less than 0.05.

Table 3
Outcomes.

AKIN Stage	0			1				2				3			
	n	Mean	std	n	Mean	std	*p*	n	Mean	std	*p*	n	Mean	std	*p*
DGF (%)	104	54.0		24	62.0		0.38	21	64.0		0.30	36	72.0		**0.016**
90 day GFR	184	48.4	20.4	38	47.1	20.8	0.72	33	43.6	21.7	0.21	48	57.2	16.1	**0.001**
1 year GFR	175	51.2	21.2	37	49.7	22.1	0.69	31	50.3	20.7	0.83	48	63.9	20.5	**0.001**
GFR < 30 at 90 days (%)	31	16.1		7	17.9		0.77	11	33.3		**0.02**	4	8.0		0.09
GFR < 30 at 1 year (%)	28	14.5		7	17.9		0.57	6	18.2		0.59	3	6.0		**0.05**

Table 4
Complications.

AKIN Stage	0		1			2			3		
	n	%	n	%	p	n	%	p	n	%	p
Graft Failure	4	2.1	2	5.1	0.42	3	9.1	0.19	1	2.0	0.97
Patient Deaths	14	7.3	1	2.6	0.14	0	0.0	**0.01**	2	7.3	0.41
Acute Rejection	9	4.7	1	2.6	0.56	2	6.1	0.73	2	4.0	0.84
BK infection	5	2.6	4	10.3	0.14	1	3.0	0.89	3	6.0	0.35

Table 5
Linear and logistic regressions.

Linear Regression		
	B	p - value
Donor Age	−0.51	0.001
DCD	−3.89	0.20
AKIN Stage	1.87	0.083
CIT	−0.002	0.29
Constant	77.16	0.01
Logistic Regression		
	B	p - value
Donor Age	0.044	0.001
DCD	0.41	0.22
AKIN Stage	−0.12	0.37
CIT	0.00	0.11
Constant	−3.19	0.01

$p < 0.001$). Additionally, a binary logistic regression model was used to predict whether recipient eGFR would be greater than 45 ml/min at 1-year post transplant. The 45 ml/min mark was used as the cut-off for an optimally functioning graft, as this mark serves as the division point between Stage 3a and 3b CKD and a suitable indicator of concern for graft performance. When performing the logistic regression, donor age was again the only significant predictor of eGFR at 1 year ($\beta = 0.044$, $p < 0.001$).

Comparisons of case-matched cohort against the stage 3 AKIN group

In order to offer a more compelling comparison a case-matched cohort from the non-AKIN group was created to assess differences in the Stage 3 AKIN group. Patients from the non-AKI group were matched to the Stage 3 AKIN group. Recipient variables of age, DSA and history of diabetes, and donor variables of age and DCD status were all used to match Stage 3 AKIN recipients to create a cohort of 70 patients. Characteristics of donors and recipients were not significantly different in the case matched cohort (Table 6).

DGF was not significantly higher in the Stage 3 AKIN group with a frequency of 68.5% compared to 57.1% in the non-AKI group (case-matched) ($p = 0.33$). Moreover, at 90 days, eGFR was comparable with no significant difference. At 1-year eGFR was the same between the Stage 3 AKI cohort (64.0 ml/min) as compared to the case-matched non-AKIN group ($p = 0.089$) (Table 7). The same case match cohort was created excluding donor age as a matching variable.(Table 8) In this cohort, the rates of DGF were comparable. However, eGFR at both 90 days and 1 year were significantly higher in the Stage 3 AKIN group (Table 9).

Table 6
Case matched recipient and donor characteristics.

Recipient (n = 35)					
AKIN Stage	0		3		
	Mean	std	Mean	std	*p*
DM %	8.57	0.28	8.57	0.28	1.00
HTN %	65.7	0.48	60	0.50	0.63
Age	55.0	12.27	55.1	11.99	0.97
BMI	29.3	5.39	30.8	6.60	0.30
Donor					
AKIN Stage	**0**		**3**		
	Mean	std	Mean	std	*p*
KDPI	52.2	25.8	47.4	21.7	0.39
CIT	1832	656	1861	492	0.84
WIT	36	11	39	13	0.25
DSA %	14.28	0.4	14.29	0.4	1.00
CDC high risk%	31.43	0.5	45.71	0.5	0.23
DCD %	5.71	0.2	5.71	0.2	1.00
Donor Age	35.7	14.8	34.6	12.6	0.74
Donor BMI	28.2	9.2	30.0	7.3	0.39

Table 7
Case matched outcomes.

AKIN Stage	0		3		
	Mean	std	Mean	std	*p*
DGF %	57.1	0.5	68.5	0.5	0.33
90 day GFR	51.0	22.0	57.6	18.4	0.18
1 year GFR	54.2	23.9	64.0	22.8	0.09

Discussion

Recent studies have been conflicting regarding the use of high terminal creatinine donors (severe AKI) in deceased donor renal transplantation.[16] Our results confirm the findings of Boffa et al., Farney et al. and Ali et al. who found that selective use of kidneys with high terminal creatinine due to AKI offers comparable outcomes to standard criteria donors.[22–24] In a large study of 12,308 first-time, adult kidney transplants, Boffa et al. found small but statistically lower graft function at the 1, 3 and 5 years, but the authors questioned the clinical significance of these differences given the higher morbidity associated with longer waiting times.[22]

Ali et al. reviewed 284 DD kidney recipients stratified by AKIN classification: recipients of AKI kidneys had increased DGF and longer hospital stays. Though about half of patients were lost to follow up, over a ten-years there were no significant differences in acute rejection rates, graft survival, patient survival or serum

Table 8
Recipient and donor characteristics of case matched cohort excluding donor age.

Recipient (n=47)					
AKIN Stage	0		3		
	Mean	std	Mean	std	*p*
DM%	10.6	31.2	10.6	31.2	1
HTN%	57.5	50.0	55.3	50.3	0.84
DSA%	14.9	36.0	14.9	36.0	1.00
Age	55.4	13.0	54.3	13.7	0.69
BMI	30.6	6.8	30.7	6.0	0.95
Donor					
AKIN Stage	**0**		**3**		
	Mean	std	Mean	std	*p*
KDPI	57.4	24.6	46.8	21.7	0.03
CIT	1785	678	1972	545	0.14
WIT	31.3	9.9	38.5	11.3	0.01
CDC high risk	29.8	46.2	48.9	50.5	0.06
DCD	8.5	28.0	8.5	28.2	1.00
Age	44.2	16.7	32.7	13.3	0.01
BMI	29.4	8.2	30.0	6.9	0.70

Table 9
Outcomes of case matched cohort excluding donor age.

AKIN Stage	0		3		
	Mean	std	Mean	std	*p*
DGF %	59.6	49.6	72.3	45.2	0.20
90 day GFR	46.5	22.1	57.3	16.4	0.01
1 year GFR	49.4	25.3	64.5	20.9	0.01

creatinine levels between AKI and non-AKI groups.[23]

Farney et al. compared outcomes of recipients receiving AKI kidneys in a cohort of 367 patients. Rather than implementing the AKIN criteria to classify their kidneys, they utilized a cutoff of terminal SCr >2.0 mg/dL. They found higher rates of DGF in AKI donor kidneys, but comparable 1 month, 1 year and 2 year serum creatinine levels.[24] Kolonko et al. found worse outcomes for AKI recipients, however the scope of their study was limited to 61 patients, only 10 of which were classified as AKI kidneys.[16] Through our single center experience, recipients of high terminal creatinine donors experienced increased DGF in comparison to non-AKI donors, but had better eGFRs at the 90 day and 1-year mark (Table 3).

Though long-term outcomes of recipients receiving high terminal creatinine donors were excellent in our experience, especially at the 1-year eGFR mark, this may be attributable to inherent selection bias. The mean age of the Stage 3 AKIN donor cohort was significantly lower than the non-AKI cohort (Table 2), contributing to the advantageous outcomes seen in our non-matched cohort.

Linear and logistic regression model of eGFR at 1-year found that donor age was the only variable associated with better kidney function post-transplant, and AKIN stage had no significant impact on 1-year eGFR. Our data suggests that severe acute kidney injury is not predictive of long-term outcomes in young donors.

Use of young donors with a high terminal creatinine may be a strategy to expand the donor pool. These findings corroborate those of Si Nga et al.[13] Patients in this study of 53 AKI donor kidneys, increasing donor age was associated with higher rates of DGF and reduced creatinine clearance at 6 months, validating the preferential use of younger donor kidneys with AKI.[13]

In our smaller case-matched cohort, both donor and recipient characteristics were matched to analyze outcomes in transplanted patients, where donor AKIN stage was the only significant independent variable (Table 6). Rates of DGF were higher (not significantly) in Stage 3 AKIN recipients than the non-AKI group. Stage 3 AKIN recipients had comparable eGFR to the non-AKI group at both 90 days and 1 year (Table 7).

As donor age is the major factor associated with 90 day and 1 year eGFR, normalizing for this variable (Stage 3 AKIN: 34.6 years, Non-AKI: 35.7 years, $p = 0.74$) abrogates the eGFR advantage seen in the comparing unmatched cohorts. Based on the results in this study, one can expect equivalent long-term results when using kidney grafts from young donors, regardless of AKIN stage at the time of acquisition. This case-match cohort analysis supports that AKIN stage alone has little impact on clinical outcomes.

Our study validates the regression model of KDPI when assessing donors. KDPI was introduced as a multivariate model weighting variant factors differently to predict graft quality.[27] In our cohort, mean KDPI of the Stage 3 AKIN group was significantly lower than that of the non-AKI group. This difference was likely driven by the difference in age between the two groups, despite higher terminal creatinine. In our case matched cohort, there was no difference in KDPI after matching on age, despite higher terminal creatinine.

KDPI has limitations as some donor factors are not included, such a kidney biopsy and pump parameters. Additionally, its predictive power is only 0.6 and is better at predicting grafts on the extreme ends of the spectrum. Grafts in the middle of the KDPI spectrum (20%–80%) are more difficult to predict. In fact, some studies have shown that high KDPI grafts (>85%) behave comparably to moderate KDPI grafts (35–85%).[28] The KDPI model heavily weights serum creatinine with a βcoefficient = 0.22 for all donors and βcoefficient = - 0.209 for donors with serum creatinine > 1.5 mg/dL.[27] Thus a donor that is suffering from a reversible kidney injury who would otherwise make an excellent donor, will result in a high KDPI from elevated serum creatinine.

The mechanism by which AKI occurs and resolves is complex and multifactorial.[29] Though decreased renal function attributable to AKI is generally thought to be reversible following resolution of the injury, variability in kidney function following AKI is observed.[30] Those with underlying kidney dysfunction are more likely to progress to CKD and experience adverse outcomes after an AKI.[31,32] However, patients experiencing AKI may be sicker in general. Experiencing AKI as a manifestation of other comorbidities could also contribute to an increased risk in progression to CKD. Additionally, older individuals, who are also more likely to have underlying kidney dysfunction or comorbidities, are at higher risk of CKD following AKI.[33,34] Age is a negative predictor for kidney function, with eGFR steadily declining at age 30 to 40 and accelerating in decline after age 65–70.[35] Therefore, older age patients are more susceptible to long term renal consequences following an AKI.

Several molecular mechanisms have been proposed that may explain higher rates of CKD in older individuals following AKI.[36] Age related decline in nephron mass and epithelial proliferative capability in the kidney tubule has been suggested to contribute to diminished renal repair following AKI. Surprisingly however, in experimental animal models, reduced nephron mass has been shown to be protective for ischemia/reperfusion injuries.[37]

Decreased ability to proliferate following tubular cells death is another mechanism by which old kidneys may experience damage that is more permanent. Older mice have shown decreased capacity for cell proximal tubule cell proliferation via increased expression of zinc-alpha glycoprotein (Zag).[38] AKI induces G2/M arrest in proximal tubular cells; this checkpoint arrest activates increased fibrosis. This increase in fibrotic tissue contributes to permanent defective tissue organization.[39] Decreased proliferative capacity following insult is may also be attributable to telomere shortening. A study in mice demonstrates that telomere shortening reduced

the ability of tubular, glomerular and interstitial cells to proliferative, thus reducing restoration of renal function.[40]

Animal studies have shown increased tendency for apoptosis of tubule cells in older rats. It is theorized that this increased disposition for cell death may result in decreased ability to recover from AKI induced tubular damage. Aging rats show increased expression of different apoptotic factors such cytochrome c and caspases-3 and -9.[41] Inhibiting caspase-3 has been shown to decrease apoptosis following AKI.[42] Thus, it can be proposed that renal transplants utilizing older donors have an increased risk for tubular apoptosis and permanent damage following AKI due to the increased presence of apoptotic factors in relation to younger kidneys. Older rats also showed increased pro-apoptotic Bax/Bcl2 ratio in addition to expression of the apoptotic factors.[41] Rats were also used to investigate ischemia/reperfusion injury. Older rats suffered higher rates of apoptosis following renal ischemia/reperfusion injuries.[41] While much is unknown about the mechanisms leading to poorer renal function in older kidneys following AKI, animal models provide some insight to the molecular mechanisms by which this occurs.

There are limitations of our study given that this is a single center experience. Additionally, the comparison of AKI and non-AKI kidneys is only after stringent donor selection for both groups. It is possible that more stringent donor selection is applied to the AKI group to compensate for high creatinine, as seen in the younger age of AKI donors in our cohort.

While it has been established that AKI alone should not preclude graft discard, we find that donor age is the most important factor in graft outcomes. However, some donors may have presented with rising creatinine at the time of admission and thus these criteria would underestimate the AKI when calculating the stage when comparing initial and terminal creatinine levels. Therefore, we must acknowledge that the assessment of the donor pool at MMC is possibly a conservative approximation of donor AKIN stages. As such, when considering the use of a high terminal creatinine kidney the larger clinical picture of the donor should be taken into account.

In our experience rates of DGF are higher in Stage 3 AKIN recipients compared to the no AKI recipients. Though the occurrence of DGF had no negative impact on long term outcomes observed in the Stage 3 AKIN group (Table 3), patients that are frail or have severe cardiac disease may not be the best candidates for these kidneys given the lack of immediate function.

While traditionally implicated in worse long term outcomes, the mechanisms leading to DGF in non-AKI and AKI recipients are purportedly different.[43] The DGF in high terminal creatinine donors has been attributed to acute, reversible causes leading to ATN. The impact of this reversible injury on long term outcomes is variable.[30] DGF in the non-AKI cohort may be related to other pre-existing conditions or irreversible intrinsic causes, whereas DGF in traditional donors can be an early predictor of poor long-term graft performance.[24,44] As such, kidneys from young donors with severe AKI and expected DGF offer excellent long-term results.

Authorship

Julia Torabi —Participated in the writing of the paper, Participated in the performance of the research, Participated in data analysis.

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Conflicts of interest

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Appendix A. Supplementary data

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References

1. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*. 1999;341(23):1725–1730.
2. Leichtman AB, Cohen D, Keith D, et al. Kidney and pancreas transplantation in the United States, 1997-2006: the HRSA breakthrough collaboratives and the 58 DSA challenge. *Am J Transplant : Off J Am Soc Transplant Am Soc Transpl Surg*. 2008;8(4 Pt 2):946–957.
3. Axelrod DA, McCullough KP, Brewer ED, Becker BN, Segev DL, Rao PS. Kidney and pancreas transplantation in the United States, 1999-2008: the changing face of living donation. *Am J Transplant : Off J Am Soc Transplant Am Soc Transpl Surg*. 2010;10(4 Pt 2):987–1002.
4. Ojo AO, Hanson JA, Meier-Kriesche H, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol : JASN*. 2001;12(3):589–597.
5. Kayler L, Yu X, Cortes C, Lubetzky M, Friedmann P. Impact of cold ischemia time in kidney transplants from donation after circulatory death donors. *Transpl Dir*. 2017;3(7):e177.
6. Kim SM, Ahn S, Min SI, et al. Cold ischemic time is critical in outcomes of expanded criteria donor renal transplantation. *Clin Transplant*. 2013;27(1):132–139.
7. Roodnat JI, Mulder PG, Van Riemsdijk IC, JN IJ, van Gelder T, Weimar W. Ischemia times and donor serum creatinine in relation to renal graft failure. *Transplantation*. 2003;75(6):799–804.
8. Kayler LK, Magliocca J, Zendejas I, Srinivas TR, Schold JD. Impact of cold ischemia time on graft survival among ECD transplant recipients: a paired kidney analysis. *Am J Transplant : Off J Am Soc Transplant Am Soc Transpl Surg*. 2011;11(12):2647–2656.
9. Schweitzer EJ, Perencevich EN, Philosophe B, Bartlett ST. Estimated benefits of transplantation of kidneys from donors at increased risk for HIV or hepatitis C infection. *Am J Transplant : Off J Am Soc Transplant Am Soc Transpl Surg*. 2007;7(6):1515–1525.
10. Duan KI, Englesbe MJ, Volk ML. Centers for Disease Control 'high-risk' donors and kidney utilization. *Am J Transplant : Off J Am Soc Transplant Am Soc Transpl Surg*. 2010;10(2):416–420.
11. Moore PS, Farney AC, Sundberg AK, et al. Experience with dual kidney transplants from donors at the extremes of age. *Surgery*. 2006;140(4):597–605. discussion 605-596.
12. Ekser B, Furian L, Broggiato A, et al. Technical aspects of unilateral dual kidney transplantation from expanded criteria donors: experience of 100 patients. *Am J Transplant : Off J Am Soc Transpl Am Soc Transpl Surg*. 2010;10(9):2000–2007.
13. Si Nga H, Takase HM, Bravin AM, et al. Good outcomes in kidney transplantation with deceased donor with acute kidney injury: donor's age and not

acute kidney injury predicts graft function. *Transplant Proc*. 2016;48(7):2262–2266.
14. Amber R, Wilk JB, Kucheryavaya Anna Y. The kidney allocation system (KAS). In: *OPTN Kidney Transplantation Committee*. April 19, 2017.
15. Chen G, Bridenbaugh EA, Akintola AD, et al. Increased susceptibility of aging kidney to ischemic injury: identification of candidate genes changed during aging, but corrected by caloric restriction. *Am J Physiol Renal Physiol*. 2007;293(4):F1272–F1281.
16. Kolonko A, Chudek J, Pawlik A, Wilk J, Jalowiecki P, Wiecek A. Acute kidney injury before organ procurement is associated with worse long-term kidney graft outcome. *Transplant Proc*. 2011;43(8):2871–2874.
17. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. *J Clin Investig*. 2011;121(11):4210–4221.
18. Abosaif NY, Tolba YA, Heap M, Russell J, El Nahas AM. The outcome of acute renal failure in the intensive care unit according to RIFLE: model application, sensitivity, and predictability. *Am J Kidney Dis : Off J Natl Kidney Found*. 2005;46(6):1038–1048.
19. Ali T, Khan I, Simpson W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol : JASN*. 2007;18(4):1292–1298.
20. de Mendonca A, Vincent JL, Suter PM, et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. *Intensive Care Med*. 2000;26(7):915–921.
21. Rodrigo E, Minambres E, Pinera C, et al. Using RIFLE criteria to evaluate acute kidney injury in brain-deceased kidney donors. *Nephrol Dial Transplant : Off Publ Eur Dial Transpl Assoc - Eur Renal Assoc*. 2010;25(5):1531–1537.
22. Boffa C, van de Leemkolk F, Curnow E, et al. Transplantation of kidneys from donors with acute kidney injury: friend or foe? *Am J Transplant : Off J Am Soc Transplant Am Soc Transpl Surg*. 2017;17(2):411–419.
23. Ali T, Dimassi W, Elgamal H, et al. Outcomes of kidneys utilized from deceased donors with severe acute kidney injury. *QJM : Mon J Assoc Phys*. 2015;108(10):803–811.
24. Farney AC, Rogers J, Orlando G, et al. Evolving experience using kidneys from deceased donors with terminal acute kidney injury. *J Am Coll Surg*. 2013;216(4):645–655. discussion 655-646.
25. Joannidis M, Metnitz B, Bauer P, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med*. 2009;35(10):1692–1702.
26. Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem*. 2007;53(4):766–772.
27. Rao PS, Schaubel DE, Guidinger MK, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. *Transplantation*. 2009;88(2):231–236.
28. Gupta A, Francos G, Frank AM, Shah AP. KDPI score is a strong predictor of future graft function: moderate KDPI (35 - 85) and high KDPI (> 85) grafts yield similar graft function and survival. *Clin Nephrol*. 2016;86(10):175–182.
29. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. *Compre Physiol*. 2012;2(2):1303–1353.
30. Macedo E, Mehta RL. Renal recovery after acute kidney injury. *Contrib Nephrol*. 2016;187:24–35.
31. Hsu CY, Chertow GM, McCulloch CE, Fan D, Ordonez JD, Go AS. Nonrecovery of kidney function and death after acute on chronic renal failure. *Clin J Am Soc Nephrol : CJASN*. 2009;4(5):891–898.
32. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis : Off J Natl Kidney Found*. 2009;53(6):961–973.
33. Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol : JASN*. 2009;20(1):223–228.
34. Amdur RL, Chawla LS, Amodeo S, Kimmel PL, Palant CE. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. *Kidney Int*. 2009;76(10):1089–1097.
35. Glassock RJ, Winearls C. Ageing and the glomerular filtration rate: truths and consequences. *Trans Am Clin Climatol Assoc*. 2009;120:419–428.
36. Schmitt R, Cantley LG. The impact of aging on kidney repair. *Am J Physiol Renal Physiol*. 2008;294(6):F1265–F1272.
37. Vercauteren SR, Ysebaert DK, De Greef KE, Eyskens EJ, De Broe ME. Chronic reduction in renal mass in the rat attenuates ischemia/reperfusion injury and does not impair tubular regeneration. *J Am Soc Nephrol : JASN*. 1999;10(12):2551–2561.
38. Schmitt R, Marlier A, Cantley LG. Zag expression during aging suppresses proliferation after kidney injury. *J Am Soc Nephrol : JASN*. 2008;19(12):2375–2383.
39. Yang L, Besschetnova TY, Brooks CR, Shah JV, Bonventre JV. Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. *Nat Med*. 2010;16(5):535–543, 531p following 143.
40. Westhoff JH, Schildhorn C, Jacobi C, et al. Telomere shortening reduces regenerative capacity after acute kidney injury. *J Am Soc Nephrol : JASN*. 2010;21(2):327–336.
41. Qiao X, Chen X, Wu D, et al. Mitochondrial pathway is responsible for aging-related increase of tubular cell apoptosis in renal ischemia/reperfusion injury. *J Gerontol Series A, Biol Sci Med Sci*. 2005;60(7):830–839.
42. Guo R, Wang Y, Minto AW, Quigg RJ, Cunningham PN. Acute renal failure in endotoxemia is dependent on caspase activation. *J Am Soc Nephrol : JASN*. 2004;15(12):3093–3102.
43. Farney AC, Hines MH, al-Geizawi S, Rogers J, Stratta RJ. Lessons learned from a single center's experience with 134 donation after cardiac death donor kidney transplants. *J Am Coll Surg*. 2011;212(4):440–451. discussion 451-443.
44. Singh RP, Farney AC, Rogers J, et al. Kidney transplantation from donation after cardiac death donors: lack of impact of delayed graft function on post-transplant outcomes. *Clin Transplant*. 2011;25(2):255–264.