The challenge of quality assessment and regional perfusion to increase donor organ utilisation

Leemkolk, F.E.M. van de

Part I

Improving quality assessment of donor organs

Chapter 2

Transplantation of kidneys from donors with acute kidney injury: Friend or foe?

Fenna E.M. van de Leemkolk*, Catherine Boffa*, Elinor Curnow, Jaap Homan van der Heide, James Gilbert, Edward Sharples, Rutger J. Ploeg

* Both authors contributed equally to this work

American Journal of Transplantation. 2017; doi: 10.1111/ajt.13966

Abstract

Background

The gap between supply and demand in kidney transplantation has led to increased use of marginal kidneys; however, kidneys with acute kidney injury are often declined/discarded. To determine whether this policy is justified, we analysed outcomes of donor kidneys with acute kidney injury (AKI) in a large UK cohort.

Material & Methods

A retrospective analysis of the UK Transplant Registry evaluated deceased donors between 2003 and 2013. Donors were classified as no AKI, or AKI stage 1–3 according to Acute Kidney Injury Network (AKIN) criteria. Relationship of AKI with delayed graft function/primary non-function (DGF/PNF), estimated glomerular filtration rate (eGFR), and graft survival at 90 days and 1 year was analysed.

Results

There were 11,219 kidneys (1,869 [17%] with AKI) included. Graft failure at 1 year is greater for donors with AKI than for those without (graft survival 89% vs. 91%, $p = 0.02$; odds ratio (OR) 1.20 [95% confidence interval (CI): 1.03–1.41]). DGF rates increase with donor AKI stage ($p < 0.005$), and PNF rates are significantly higher for AKIN stage 3 kidneys (9% vs. 4%, $p = 0.04$). Analysis of association between AKI and recipient eGFR suggests a risk of inferior eGFR with AKI versus no AKI ($p < 0.005$; OR 1.25 [95% CI: 1.08–1.31]).

Conclusions

We report a small reduction in 1-year graft survival of kidneys from donors with AKI. We conclude that AKI stage 1 or 2 kidneys should be used, however, caution is advised for AKI stage 3 donors.

Introduction

There remains a wide gap between supply and demand in kidney transplantation. As of March 31, 2015, there were over 5,000 patients on the transplant waiting list, with less than 3,000 kidney transplants performed annually in the United Kingdom.[1] Kidney transplantation remains the treatment of choice for end-stage renal disease (ESRD), as it improves quality of life and reduces the mortality rate of patients with ESRD, compared to being on dialysis.[2] To bridge this gap between supply and demand, the donor pool has been expanded with the utilisation of donors after circulatory death (DCD) and extended criteria donors (ECD). Results following DCD donation are comparable to those following DBD donation.[3] Transplantation with ECD donors has reduced graft survival versus standard criteria donors (SCD) [4-7], although this donor source still offers a survival benefit when compared to staying on dialysis or the waiting list.[8,9]

Despite the persistent donor shortage, however, most transplant centres in many countries will decline donor kidneys with an acute kidney injury (AKI) at time of offering, due to a perception that this condition is not compatible with successful transplantation. This uncertainty leads to the frequent discard of many potentially viable donor kidneys.[10] In the United Kingdom, donation after brain death (DBD) kidneys are offered via a National Allocation System and DCD kidneys from donors younger than 50 years of age are offered regionally with one kidney being offered locally, and if the donor is over 50 years old both kidneys are offered locally.[11] This allocation policy is not altered when ECD kidneys, or kidneys with AKI are offered.

AKI, defined as an abrupt reduction in kidney function [12], occurs in many hospitalised patients, including up to 25% of critically unwell patients.[10] The kidney has an intrinsic capacity to repair itself and recover from an ischaemic or toxic insult [13], and the majority of patients with AKI may fully recover their renal function.[14,15] Therefore, the use of kidneys from donors with an AKI could be considered to help reduce unnecessary discard and expand the donor pool.

To date, several classifications for AKI have been identified and validated. In 2004, the Acute Dialysis Quality Initiative group developed the "RIFLE" criteria, referring to Risk, Injury and Failure with the two outcome classes, Loss and End-Stage Renal Disease (ESRD).[16] In 2007, a multidisciplinary collaborative network, the Acute Kidney Injury Network (AKIN), endorsed the RIFLE criteria with a small modification to include small changes in Serum Creatinine (SCr) (≥0.3 mg/dL or ≥26.4μmol/L) when they occur within a 48-hour period (**Table 1**) [12], and this classification was confirmed in 2011 by Kidney Disease: Improving Global Outcomes in its Clinical Practice Guideline for AKI.[17]

As it has been suggested that kidneys from donors with AKI may recover, it raises the question of whether discard of these kidneys is justified against the background of the persistent organ shortage. In this study we have investigated the effect of donor AKI on outcomes following kidney transplantation in a large UK cohort using the robust NHS Blood and Transplant (NHSBT) UK Transplant Registry.

Table 1. AKIN Criteria

AKI Stage	Serum Creatinine	Urine Output
Stage 1	Increase of ≥0.3 mg/dL (26.4 μmol/L) or increase to ≥150%-200% (1.5- to 2.0-fold) from baseline	<0.5 mL/kg/hr for 6-12 hours
Stage 2	Increase to >200%-300% (2.0- to 3.0-fold) from baseline	<0.5 mL/kg/hr for ≥12 hours
Stage 3	Increase of ≥4.0 mg/dL (≥354 μmol/L) or increase to >300% (3.0-fold) from baseline	<0.3 mL/kg/hr for ≥24 hours or anuria for ≥12 hours

Patients and Methods

The study population consisted of all UK adult deceased donors where at least one kidney was offered for transplantation between January 1, 2003 and December 31, 2013. Change in serum creatinine between admission and retrieval, and urine output were used to classify each donor as AKI stage 1, 2 or 3.[17] Donors who did not meet the AKIN criteria were classified as "no AKI". Donors without sufficient data to allow classification were excluded from all analyses. Offered kidneys used in first adult kidney-only transplants were included in posttransplant analyses.

Posttransplant endpoints

Transplant survival at 90 days and 1 year was used to measure short- and long-term outcome. This was defined as time from transplant to graft failure or patient death, censoring for patients who were alive with a functioning graft at the endpoint of the analysis.

Initial graft function was categorised as immediate function, delayed graft function (DGF) or primary non-function (PNF). DGF was defined as at least one dialysis treatment required in the first week after transplantation. Kidney function post transplantation was measured using four categories of estimated glomerular filtration rate (eGFR) (≥60, 45-60, 30-45 and <30 mL/min/1.73m^2). This was calculated using the four-variable MDRD equation from serum creatinine values reported at approximately 90 days and 1-year post transplantation. In order to reduce bias in the distribution of eGFR posttransplant, recipients whose graft had failed by each endpoint were included in an additional category: "returned to dialysis".

Statistical analysis

Donor demographic characteristics (cause of death, age, BMI, ethnicity, sex, and DBD or DCD) were summarised by offering outcome for No AKI versus AKI. For kidneys that were not transplanted, the reason for non-use was summarised by offering outcome and AKI stage. For kidneys that were transplanted, recipient demographic characteristics (age, time on transplant list, primary renal disease, HLA mismatch level, ethnicity and sensitisation) were summarised for No AKI versus AKI. Differences in donor and recipient characteristics for No AKI versus AKI were tested using the likelihood ratio test for a logistic regression model. For donor characteristics, additional adjustments were made for offering outcome or within each offering stage if there was significant evidence of an interaction. Differences in the proportion of kidneys not used due to poor function versus any other reason, across AKI stages, adjusted for offering outcome as before, were tested using the likelihood ratio test for a logistic regression model. Evidence of underestimation of variance due to correlation between kidneys from the same donor was identified using the deviance statistic. If estimated deviance was significantly greater than 1, confidence intervals (CIs) for odds ratios (ORs) were adjusted using the methods described by Collett.[18]

Kaplan-Meier estimates of transplant survival were compared across AKI stages using the log-rank test. Regression analyses were used to investigate the relationship between AKI stage and short- and long-term kidney transplant outcome (Cox model); initial graft function (logistic model); and short- and long-term kidney function posttransplant (eGFR as a categorical variable: ordinal logistic model; eGFR as a continuous variable: normal model).

Analyses were adjusted for risk factors pertinent to kidney transplantation.[7,19] Donor risk factors included age, history of hypertension, BMI, length of hospital stay, use of adrenaline, donor type (DBD or DCD), sex, ethnicity, blood group, and cause of death. Transplant and recipient risk factors included cold ischaemic time (CIT), age, time on transplant list, primary renal disease, HLA mismatch level, ethnicity, sensitisation, and DGF. Subgroup analyses were considered in each model by including interactions between donor AKI stage and donor age, type, BMI, sex, history of hypertension, cause of death, CIT, and recipient age. Interaction terms were only retained in each model if the likelihood ratio test was significant at the 5% level.

Analyses were undertaken using SAS/STAT, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The study cohort between 2003 and 2013 consisted of 11,649 donors. Most donors (79%) could be categorised by AKI stage based on both serum creatinine and urine output. Six hundred eighty-six (5.9%) donors were excluded for insufficient data.

Demographic characteristics of all 11,649 donors, by offering outcome and No AKI versus AKI are shown in **Table 2**. The proportion of donors with AKI was different across the three offering outcomes ($p < 0.005$). Transplanted donors are more likely to be classified as no AKI than donors whose kidneys are offered but not accepted. There was a difference in the proportion of donors with AKI for all donor characteristics ($p < 0.005$ in each case) except donor age ($p = 0.34$) and ethnicity ($p = 0.31$).

There was no evidence that the relationship between each donor characteristic and AKI was different for each offering outcome, except for donor type. Of donors whose kidneys were offered but not accepted, DBD donors are more likely to be classified as AKI than DCD donors, whereas of donors whose kidneys were transplanted, DCD donors are more likely to be classified as AKI than DBD donors.

Table 2. Donor characteristics by offering outcome and AKI stage, where at least one kidney per donor was offered for transplantation in the United Kingdom between January 1, 2003 and December 31, 2013 (N = 11,649)

Factor (p-value)	Level	Offered, not accepted			Accepted, not transplanted			Transplanted		
		Total	AKI Stage		Total	AKI Stage		Total	AKI Stage	
			No AKI	AKI		No AKI	AKI		No AKI	AKI
TOTAL		**2,361 (100)**	**1,627 (69)**	**510 (22)**	**571 (100)**	**389 (68)**	**139 (24)**	**8,717 (100)**	**6937 (80)**	**1,361 (16)**
Cause of death (<0.005)	Intracr. Injury	**1,154 (49)**	843 (52)	177 (35)	**326 (57)**	238 (61)	62 (45)	**5,522 (63)**	4,548 (66)	716 (53)
	Trauma	**21 (1)**	14 (1)	2 (0)	**3 (1)**	0 (0)	2 (1)	**339 (4)**	266 (4)	45 (3)
	Other	**1,186 (50)**	770 (47)	331 (65)	**242 (42)**	151 (39)	75 (54)	**2,856 (33)**	2,123 (31)	600 (44)
Age (0.32)	18 to 29	**98 (4)**	69 (4)	19 (4)	**13 (2)**	7 (2)	5 (4)	**1,108 (13)**	872 (13)	177 (13)
	30 to 39	**170 (7)**	118 (7)	35 (7)	**35 (6)**	25 (6)	8 (6)	**1,178 (14)**	958 (14)	169 (12)
	40 to 49	**345 (15)**	229 (14)	91 (18)	**81 (14)**	58 (15)	14 (10)	**2,009 (23)**	1,588 (23)	329 (24)

Factor (p-value)	Level	Offered, not accepted			Accepted, not transplanted			Transplanted		
		Total	AKI Stage		Total	AKI Stage		Total	AKI Stage	
			No AKI	AKI		No AKI	AKI		No AKI	AKI
	50 to 59	**535**	370	114	**129**	87	30	**2,280**	1,832	346
		(23)	(23)	(22)	**(23)**	(22)	(22)	**(26)**	(26)	(25)
	60 or older	**1,213**	841	251	**313**	212	82	**2,142**	1,687	340
		(51)	(52)	(49)	**(55)**	(54)	(59)	**(25)**	(24)	(25)
BMI (<0.005)	<18.5	**67 (3)**	50 (3)	8 (2)	**6 (1)**	4 (1)	1 (1)	**179 (2)**	150 (2)	24 (2)
	18.5 to <25	**730**	552	119	**155**	116	31	**3,462**	2,880	463
		(33)	(35)	((24)	**(28)**	(30)	(23)	**(41)**	(42)	(35)
	25 to <30	**841**	602	172	**228**	161	53	**3,237**	2,579	522
		(37)	(38)	(35)	**(42)**	(42)	(40)	**(38)**	(38)	(39)
	≥30	**608**	384	190	**155**	100	49	**1,616**	1,222	332
		(27)	(24)	(39)	**(28)**	(26)	(37)	**(19)**	(18)	(25)
Ethnicity (0.34)	White	**2,268**	1,560	488	**543**	370	132	**8,298**	6,608	1,282
		(96)	(96)	(96)	**(95)**	(95)	(95)	**(95)**	(95)	(94)
	Asian	**40 (2)**	28 (2)	11 (2)	**11 (2)**	7 (2)	3 (2)	**135 (2)**	107 (2)	27 (2)
	Black	**19 (1)**	15 (1)	3 (1)	**7 (1)**	4 (1)	2 (1)	**89 (1)**	69 (1)	17 (1)
	Other	**34 1)**	24 (1)	8 (2)	**10 (2)**	8 (2)	2 (1)	**195 (2)**	153 (2)	35 (3)
Sex (<0.005)	Male	**1,421**	947	339	**357**	242	89	**4,571**	3,456	870
		(60)	(58)	(66)	**(63)**	(62)	(64)	**(52)**	(50)	(64)
	Female	**940**	680	171	**214**	147	50	**4,142**	3,477	491
		(40)	(42)	(34)	**(37)**	(38)	(36)	**(48)**	(50)	(36)
Type (<0.005)	DBD	**384**	237	138	**199**	143	52	**6,209**	5,190	936
		(16)	(15)	(27)	**(35)**	(37)	(37)	**(71)**	(75)	(69)
	DCD	**1,977**	1,390	272	**372**	246	87	**2,508**	1,747	425
		(84)	(85)	(73)	**(65)**	(63)	(63)	**(29)**	(25)	(31)

Data are reported as N (%). Row percentage reported for total row; column percentage reported otherwise. Ordinal logistic regression used to test for differences in each donor characteristic across AKI Stage, adjusted for offering outcome, or within each offering outcome if significant evidence of interaction (donor type only).

Offering Outcomes

Overall, 16,735 (72%) of 23,204 offered kidneys from the 11,649 donors were transplanted and 6,469 (28%) kidneys from 3,563 donors were not used (**Figure 1**). For all 11,649 donors, where both kidneys were offered, the offering outcome was different for each kidney in the pair in 653 (6%) of cases. In the majority (631, 97%) of these 653 cases, at least one kidney was transplanted. The proportion of kidneys not used due to poor function was significantly different for donors at the different AKI stages, and this association was different at each stage of offer ($p < 0.005$) (**Table 3**).

There was no evidence of underestimation of variance due to correlation between kidneys from the same donor (p > 0.995). For kidneys that were not accepted, the odds of non-use due to poor function were 4 to 5 times as great for donors at AKIN stages 1 or 2, and more than 20 times as great for donors at stage 3, compared with donors with no AKI (OR: 5.01 [3.71-6.77]; OR: 4.36 [3.19-5.97]; OR: 20.53 [15.43-27.33] for stages 1, 2 and 3, respectively). For kidneys that were accepted but not transplanted, the odds of non-use due to poor function were about the same for donors at stage 1 (OR: 1.42 [0.70-2.86]) and about 2.5 times as great for donors at stages 2 or 3, compared with donors with no AKI (OR: 2.46 [1.29-4.68]; OR: 2.52 [1.19-5.33], for stages 2 and 3, respectively).

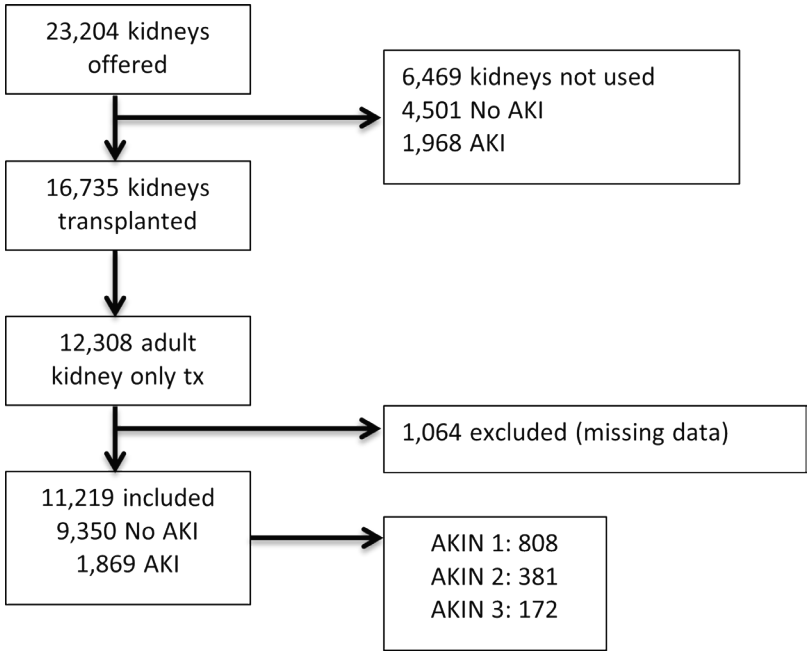

Figure 1. Flowchart of offering outcomes

Transplanted kidneys

Of the 16,735 transplanted kidneys, 12,540 (75%) were used in 12,308 first adult kidney-only transplants (12,076 single and 232 dual kidney transplants). Of these 12,308 transplants, 1146 (9%) were pre-emptive transplants. Characteristics of the recipients of all 12,308 transplants are shown in **Table 4**. We found no difference in recipient groups with and without AKI with respect to age (p = 0.39), time on the transplant list (p = 0.14), primary renal disease (p = 0.72), ethnicity (p = 0.34) and sensitisation (p = 0.12), although level of HLA mismatch was higher for recipients of AKI donor transplants (p < 0.005).

Table 3. Reasons for non-use of kidney, by offering outcome and AKI stage where at least one kidney per donor was offered for transplantation in the United Kingdom between January 1, 2003 and December 31, 2013 (N = 6,469)

Reason (p-value)	Offered, not accepted					Accepted, not transplanted				
	Total	AKI Stage				Total	AKI Stage			
		No AKI	1	2	3		No AKI	1	2	3
Poor function (<0.005)	456 (9)	152 (4)	74 (19)	64 (17)	135 (49)	92 (6)	50 (5)	10 (7)	13 (11)	9 (11)
Donor unsuitable – medical	576 (12)	384 (11)	74 (19)	47 (12)	23 (8)	283 (19)	185 (18)	34 (23)	31 (26)	21 (26)
Organ unsuitable – clinical	762 (15)	436 (13)	87 (22)	76 (20)	68 (24)	461 (31)	330 (32)	42 (28)	40 (34)	24 (30)
Donor unsuitable – non medical	2,743 (55)	2,198 (64)	125 (32)	168 (44)	33 (12)	95 (6)	88 (8)	0 (0)	3 (3)	0 (0)
Donor age	90 (2)	57 (2)	9 (2)	6 (2)	6 (2)	10 (1)	2 (0)	4 (3)	2 (2)	2 (3)
Other	83 (2)	45 (1)	2 (1)	4 (1)	2 (1)	381 (26)	279 (27)	40 (27)	25 (21)	16 (20)
Not reported	287 (6)	186 (5)	24 (6)	18 (5)	11 (4)	150 (10)	109 (10)	20 (13)	4 (3)	8 (10)

Data are reported as N (%), where % are column percentages. Logistic regression used to test for differences in proportion not used due to poor function versus any other reason across AKI Stage, within each offering outcome.

Of these 12,308 transplants, 1,064 (8.6%) were excluded from further analyses due to missing data, 25 (0.2%) due to inadequate follow-up data. Therefore, 11,219 transplants were considered for inclusion in the analyses of posttransplant outcome and kidney function. Eight hundred ninety-seven (8%) had no initial graft function data and were excluded from the DGF/PNF analysis and 985 and 692 had no serum creatinine reported at 90 days and 1 year posttransplant and were excluded from kidney function analyses.

Transplant survival

Kaplan-Meier estimates of transplant survival after first adult kidney-only transplant by donor AKI stage suggests some evidence that the chance of graft failure/recipient death after first adult kidney-only transplant differs across AKI stage (p = 0.05) (*data not shown*). Due to the small numbers of events (< 30) for some AKI stages, we then compared donors with and without AKI, which found that the chance of graft failure/recipient death after first adult kidney-only transplant is greater for donors with AKI than for those with no AKI (p = 0.02) (**Figure 2**).

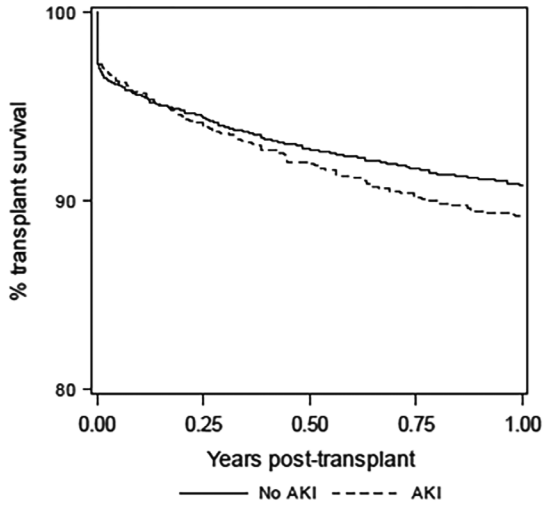

Figure 2. Transplant survival after first adult kidney-only transplant, compared for donors with and without AKI (N = 1,869 and 9,350, respectively). Log-rank test p = 0.02.

Table 4. Recipient characteristics for kidneys with and without AKI

Factor	Level	AKI Stage		p-value
		No AKI	AKI	
Age	18 to 29	721 (7)	135 (7)	0.39
	30 to 39	1,330 (14)	250 (13)	
	40 to 49	2,294 (24)	443 (23)	
	50 to 59	2,586 (27)	530 (27)	
	≥60	2,773 (29)	593 (30)	
Wait Time	<6 months	1,301 (13)	235 (12)	0.14
	6m - <2yr	3,068 (32)	602 (31)	
	≥2yr	5,335 (55)	1,114 (57)	
Ethnicity	White	7,591 (78)	1,496 (77)	0.34
	Asian	1,202 (12)	255 (13)	
	Black	656 (7)	151 (8)	
	Other	255 (3)	49 (3)	
HLA mm	1	1,231 (13)	203 (10)	0.003
	2	3,150 (32)	600 (31)	
	3	4,191 (43)	893 (46)	
	4	1,132 (12)	255 (13)	
Sensitisation	0 – 9	7,829 (81)	1,587 (81)	0.12
	10 – 39	669 (7)	149 (8)	
	40 – 84	872 (9)	146 (7)	
	≥85	334 (3)	69 (4)	

Data are reported as N (%).

Table 5. Cox Regression model for chance of graft failure/recipient death within 90 days and 1 year after first adult kidney-only transplant

Model	Hazard ratio (95% CI)	p-value
90 days posttransplant (events/transplants: No AKI – 521/9,350; AKI – 113/1,869)		
Donor with/without AKI		0.24
AKI by donor type		0.76
AKI by donor age		0.58
AKI by donor BMI		0.58
AKI by recipient age		0.84
AKI by CIT		0.18
AKI by donor sex		0.20
AKI by donor history of hypertension		0.92
AKI by donor cause of death		0.59
1 year posttransplant (events/transplants: No AKI – 848/9,350; AKI – 202/1,869)		
Donor with/without AKI		0.02
No AKI	1.00 (-)	
AKI stage 1, 2 or 3	1.20 (1.03-1.41)	
AKI by donor type		0.42
AKI by donor age		0.20
AKI by donor BMI		0.11
AKI by recipient age		0.64
AKI by CIT		0.38
AKI by donor sex		0.54
AKI by donor history of hypertension		0.58
AKI by donor cause of death		0.71

Hazard ratio reported for models where effect/interaction significantly associated with outcome. Interaction models also include main effects. All models adjusted for the following risk factors:
Recipient – age, time on transplant list, primary renal disease, HLA mismatch, ethnicity, sensitisation, CIT, DGF
Donor – age, type, BMI, sex, history of hypertension, length of stay in hospital, use of adrenaline, ethnicity, blood group, cause of death

After risk-adjustment, there was no evidence of an association between transplant survival and donor AKI within 90 days posttransplant (p = 0.24), but there was an association within 1 year posttransplant (p = 0.02) (**Table 5**). Estimated chance of graft failure/recipient death within 1 year is 20% greater (95% CI: 1.03-1.41) where the donor is classified as AKI stage 1, 2 or 3, compared with donors with no AKI. There are no significant interaction terms.

Longer-term graft survival was also investigated, and although long-term follow-up is only available for about half the cohort, there is a significant difference in long-term survival for AKI versus no AKI (3 years transplant survival no AKI: 85%; AKI:

83% p = 0.02, and 5 years transplant survival, no AKI: 78%; AKI: 76% [73%-78%] p = 0.009).

Initial graft function

Risk of DGF and PNF increase with donor AKI stage (p < 0.005 and 0.04, respectively) (**Table 6**). Odds of DGF are similar whether the donor is classified as AKI stage 1 or 2 (OR: 1.33 [95% CI: 1.15 – 1.54] and 1.67 [95% CI: 1.37 – 2.03], respectively), compared with donors with no AKI. However, where the donor is classified as AKI stage 3, odds of DGF are about three times greater, compared with donors with no AKI (OR: 2.98 [95% CI: 2.25 – 3.96]). Although there is no evidence of increased odds of PNF for donors classified as stage 1 or 2, odds of PNF are about three times greater for donors classified as stage 3, compared with donors with no AKI (OR: 3.09 [95% CI: 1.54 – 6.16]). There are no significant interaction terms.

Table 6. Logistic regression models for chance of DGF/PNF after first adult kidney-only transplant

Factor	Odds ratio (95% CI)		p-value
DGF versus immediate function			
Donor AKI stage	% DGF		<0.005
No AKI	28	1.00(-)	
Stage 1	35	1.33 (1.15 – 1.54)	
Stage 2	43	1.67 (1.37 – 2.03)	
Stage 3	55	2.98 (2.25 – 3.96)	
AKI stage by donor type			0.52
AKI stage by donor age			0.32
AKI stage by donor BMI			0.30
AKI stage by recipient age			0.73
AKI stage by CIT			0.57
AKI by donor sex			0.29
AKI by donor history of hypertension			0.36
AKI by donor cause of death			0.70
PNF versus immediate function			
Donor AKI stage	% PNF		0.04
No AKI	4	1.00 (-)	
Stage 1	4	0.92 (0.59 – 1.42)	
Stage 2	3	0.90 (0.46 – 1.73)	
Stage 3	9	3.09 (1.54 – 6.16)	

Odds ratio reported for models where effect/interaction significantly associated with outcome. Interaction models also include main effects. No interaction models for PNF outcome due to small number of cases of PNF in AKI donor group. All models adjusted for the following risk factors:
Recipient – age, time on transplant list, primary renal disease, HLA mismatch, ethnicity, sensitisation, CIT
Donor – age, type, BMI, sex, history of hypertension, length of stay in hospital, use of adrenaline, ethnicity, blood group, cause of death

Kidney Function

Risk of being in a lower eGFR category are between 20% and 30% greater where the donor is classified as AKI stage 1, 2 or 3, although odds ratios are not significantly greater than 1 for all of the AKI stages 1,2 and 3. This may be due to the small numbers of transplants in the worse eGFR categories for some AKI stages. Therefore, we compared donors with and without AKI and found the odds of being in a worse eGFR category are 19% (95% CI: 1.08 – 1.31) and 25% (95% CI: 1.14 – 1.38) greater at 90 days and 1-year posttransplant, respectively for donors with AKI compared with donors with no AKI ($p < 0.005$ in each case) (**Table 7** and **8**). There are no significant interaction terms. Similar results were obtained when eGFR was treated as a continuous variable. Donors classified as AKI stage 1, 2 and 3 have significantly lower eGFR at 90 days and 1 year than donors with no AKI ($p = 0.01$ and $p < 0.005$ at 90 days and 1 year, respectively), although the absolute reduction in eGFR is small (reduction of 1.1 mL/min/1.73m^2 [95% CI: 0.2-2.0] and 1.6 mL/min/1.73m^2 [95% CI: 0.7-2.5] at 90 days and 1 year, respectively).

Table 7. Recipient kidney function at 90 days and 1 year post first adult kidney-only transplant

	eGFR mL/min/1.73m^2					
End point	**>60**	**45-60**	**30-45**	**<30**	**Return to Dialysis**	**p-value**
90 days						<0.005
No AKI	1,953 (23%)	2,465 (29%)	2,542 (30%)	1,171 (14%)	425 (5%)	
AKI	363 (21%)	447 (26%)	530 (31%)	279 (16%)	84 (5%)	
1 year						<0.005
No AKI	1,951 (22%)	2,447 (28%)	2,915 (33%)	879 (10%)	618 (7%)	
AKI	342 (20%)	445 (26%)	614 (35%)	210 (12%)	131 (8%)	

Table 8. Linear regression model for recipient kidney function at 90 days and 1 year after first adult kidney-only transplant

Factor	Odds ratio (95% CI)	p-value
90 days posttransplant (eGFR ≥60, 45-<60, 30-<45, <30, returned to dialysis)		
Donor with/without AKI		<0.005
No AKI	1.00 (-)	
AKI stage 1, 2 or 3	1.19 (1.08 – 1.31)	
AKI by donor type		0.31
AKI by donor age		0.88
AKI by donor BMI		0.77
AKI by recipient age		0.90
AKI by CIT		0.17
AKI by donor sex		0.64
AKI by donor history of hypertension		0.53
AKI by donor cause of death		0.46
1 year posttransplant (eGFR ≥60, 45-<60, 30-<45, <30, returned to dialysis)		
Donor with/without AKI		<0.005
No AKI	1.00 (-)	
AKI stage 1, 2 or 3	1.25 (1.14 – 1.38)	
AKI by donor type		0.28
AKI by donor age		0.57
AKI by donor BMI		0.41
AKI by recipient age		0.25
AKI by CIT		0.47
AKI by donor sex		0.72
AKI by donor history of hypertension		0.34
AKI by donor cause of death		0.59

eGFR: estimated glomerular filtration rate calculated using the 4-variable MDRD equation, in mL/min/1.73m^2.
Odds ratio reported for models where effect/interaction significantly associated with outcome. Interaction models also include main effects. All models adjusted for the following risk factors:
Recipient – age, time on transplant list, primary renal disease, HLA mismatch, ethnicity, sensitisation, CIT, DGF
Donor – age, type, BMI, sex, history of hypertension, length of stay in hospital, use of adrenaline, ethnicity, blood group, cause of death

Discussion

The aim of this analysis was to assess the impact of donor AKI, as classified by the AKIN criteria, on outcomes in kidney transplantation. The question was whether discard of scarce donor kidneys is justified, if kidneys from donors with AKI are likely to result in a high percentage of graft failure and need for re-transplantation. We have found that 17% of potential kidney donors have AKI (9% AKIN stage 1, 5% AKIN stage 2 and 3% AKIN stage 3), and so could contribute significantly to the donor pool.

Despite the expanding discrepancy between the number of patients waiting for a kidney transplant and the number of kidney donors, 28% of kidneys in this study are not used. As expected, kidneys are more likely to be declined due to higher AKIN stage, and kidneys with AKI stage 3 are 20 times more likely to be discarded than those with no AKI.

However, this analysis has shown that 1-, 3- and 5-year graft survival is only 2% lower when using kidneys from donors with AKI. Although this difference is statistically significant, we question whether this reduction in graft survival is clinically relevant. This reduced graft survival needs to be taken in the context of remaining on the transplant waiting list with an annual death rate of 8.2%.[8] The 20% increased risk of graft failure due to AKI in the donor is similar to the 17% increased risk of graft failure associated with dialysis vintage of 6 months when compared to pre-emptive transplantation, and is significantly lower than the 37% and 55% increased risk of graft failure when dialysing for longer than one or two years prior to kidney transplantation.[20]

As would be expected, the rates of DGF increase as the AKI stage rises, and more importantly, the risk of PNF significantly increases when kidneys from donors with AKI stage 3 are transplanted (9% versus 4% with no AKI). This is not necessarily an unexpected finding as Ali et al. found that patients with severe AKI were less likely to recover their renal function.[15]

Although there is a risk of an inferior eGFR at 1 year when using kidneys with AKI, this absolute reduction is only 1.6 mL/min/1.73m^2 and is unlikely to be of clinical significance.

To investigate whether there was a cumulative effect of AKI with many other risk factors known to be pertinent in kidney transplantation, we performed a Cox-regression analysis to examine the interaction of AKI with many of these risk factors, and surprisingly did not find any interactions. This was especially surprising for age, as previous studies have found that increasing age is a risk for the development of chronic kidney disease (CKD) in patients following AKI.[21,22]

Our findings in the United Kingdom, are consistent with Kayler's analysis of the Scientific Registry of Transplant Recipients (SRTR) in the United States between January 1995 and July 2007 (82,262 kidney transplant recipients). This study found that kidneys from SCDs with a terminal creatinine of over 2 mg/dL had a graft survival that is as good as those from donors with a terminal serum creatinine of ≤ 1.5 mg/dL. If the donor was classed as an ECD, then the survival was worse if they had renal dysfunction, but equivalent to ECD donors with no AKI.[23]

More recently, Hall, in New Haven, analysed the outcomes of 886 kidneys with AKI, comparing them to 2,378 kidneys without AKI, using the AKIN criteria to define the severity of AKI. This study found that rates of DGF increased as the AKI stage increased, as we have also shown, and this did not lead to worse survival, since there was no significant difference in 1-year graft survival between the groups.[24] In this analysis the 6-month eGFR was no different between the groups, but the 1-year data was not complete, and so we are unable to compare with our findings. Heilman et al. compared kidneys with no AKI to those with AKI, defined as a terminal creatinine of ≥2.0 mg/dL. They also used the AKIN criteria to define the severity of AKI. As their control group includes many AKIN stage 1 kidneys, it is difficult to draw comparisons between their findings and ours. They found no significant difference in 1-year graft survival between the AKI and control groups, and no difference in 1-year eGFR, which may be because the control group included kidneys that had a mild form of AKI.[25]

Transplantation continues to be the treatment of choice for patients with end stage renal disease, and as an increasing number of patients are listed, the need to expand the donor pool has inevitably led to the acceptance of organs that are deemed to be 'marginal'. In many European national or international organ-sharing systems, it is current practice to not accept donor kidneys with AKI due to a perceived bad outcome after transplantation and need to return to dialysis. Our data demonstrate that these policies appear to be unjustified.

As pointed out in a recent review by a collaboration of barristers and clinicians, the perceived risk should be discussed with the potential recipients of these organs so that they can make an informed decision.[26] Despite many achievements in transplantation, uncertainty whether to accept donor organs for a particular recipient persists. Thus, to support better clinical decision making but also to prevent unnecessary discard, more evidence is needed. In this study we have looked at the outcomes of a large cohort of marginal kidneys in the United Kingdom, in an attempt to give clinicians as much information as possible to make an informed decision as to whether to use these kidneys, which they can then share with their patients to try to quantify this risk.

From these results, it would seem that in the United Kingdom, transplant clinicians are correctly identifying kidneys to be used for transplantation, and that we are appropriately cautious with kidneys with AKIN stage 3. This caution comes from evidence that as the severity of AKI increases, so does the risk of developing CKD [22,27,28], with Chawla et al. demonstrating that as the RIFLE score increased, the odds of developing CKD stage 4 increased significantly.[22] The hypothesis behind this could be that the tubular injury, inflammation, endothelial cell dysfunction, and vascular

injury seen in AKI are exacerbated by the ischaemia reperfusion injury during transplantation, leading to renal fibrosis and impaired longer-term function.[29,30]

This study has its limitations. As a retrospective registry review, there has already been a selection bias with clinicians selecting the donors that are perceived to be at lower risk. Although we can review the number of kidneys with AKI that were discarded and the reasons they were, we are unable to predict their outcome to see whether they were appropriately rejected. Unfortunately, we are unable to analyse whether the results seen are due to an effect of differences in immunosuppression, as the information about the immunosuppression used for each patient is poorly captured on the registry. Most UK centres will have individual immunosuppression protocols that will include a calcineurin inhibitor and an anti-proliferative, and most centres will not alter this for kidneys with an AKI. We have adjusted our results according to centre and we hope that this minimises some of the uncertainty with this.

Other studies that have shown good outcomes with AKI kidneys, and have had a high proportion of kidneys with "severe" injury being preserved using hypothermic machine preservation.[24] Unfortunately, this is one area of the UK registry that is not well populated, and we were unable to examine whether the kidneys in this study were preserved in this manner. As machine preservation is becoming more frequently used, this could be an important novel technology to assess and condition injured kidneys, allowing them to be transplanted.

In conclusion, this large UK study has demonstrated that although a fair number of kidneys with AKI are still discarded, the ones that are actually transplanted give good outcomes. Over the 10-year period observed, in the United Kingdom over 1,600 recipients received a kidney from a donor with AKI and still had a functioning graft at 1-year. We suggest that kidneys from donors with AKI stage 1 and 2 should not be discarded as they give comparable outcomes to kidneys from donors with no AKI. Discard of these viable donor kidneys is not justified, and transplantation will increase utilisation in many countries, significantly reducing waiting lists once the current "decline policy" has been amended. Due to the size of the cohort in this study we add that caution is advised for AKI stage 3 kidneys.

Acknowledgements

The authors would like to thank Ms L Bradbury from NHS Blood and Transplant for her help with the revisions.

References

1. Transplant NBa. Annual Report on Kidney Transplantation for 2014/2015 found at http://www.odt.nhs.uk/pdf/organ_specific_report_kidney_2015.pdf2015.
2. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LYC, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. New Englan Journal of Medicine. 1999;341(23):1725-30.
3. Summers DM, Johnson RJ, Allen J, Fuggle SV, Collett D, Watson CJ, et al. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. Lancet. 2010;376(9749):1303-11.
4. Aubert O, Kamar N, Vernerey D, Viglietti D, Martinez F, Duong-Van-Huyen JP, et al. Long term outcomes of transplantation using kidneys from expanded criteria donors: prospective, population based cohort study. Bmj. 2015;351:h3557.
5. Metzger RA, Delmonico FL, Feng S, Port FK, Wynn JJ, Merion RM. Expanded criteria donors for kidney transplantation. Am J Transplant. 2003;3 Suppl 4:114-25.
6. Port FK, Bragg-Gresham JL, Metzger RA, Dykstra DM, Gillespie BW, Young EW, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. Transplantation. 2002;74(9):1281-6.
7. Watson CJ, Johnson RJ, Birch R, Collett D, Bradley JA. A simplified donor risk index for predicting outcome after deceased donor kidney transplantation. Transplantation. 2012;93(3):314-8.
8. Merion RM, Ashby VB, Wolfe RA, Distant DA, Hulbert-Shearon TE, Metzger RA, et al. Deceased-donor characteristics and the survival benefit of kidney transplantation. Jama. 2005;294(21):2726-33.
9. Ojo AO, Leichtman AB, Punch JD, Hanson JA, Dickinson DM, Wolfe RA, et al. Impact of pre-existing donor hypertension and diabetes mellitus on cadaveric renal transplant outcomes. Am J Kidney Dis. 2000;36(1):153-9.
10. de Mendonca A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med. 2000;26(7):915-21.
11. Transplant NBa. Responsibilities of clinicians for the acceptance of organs from deceased donors 2015 [Available from: http://www.odt.nhs.uk/pdf/nhsbt_responsibilities_acceptance_organs_deceased_donors.pdf.
12. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
13. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest. 2011;121(11):4210-21.
14. 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. 2005;46(6):1038-48.
15. Ali T, Khan I, Simpson W, Prescott G, Townend J, Smith W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol. 2007;18(4):1292-8.
16. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204-12.

17. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, 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):1692-702.
18. Collett D. Modelling survival data in medical research. 2 ed. Florida: Chapman & Hall/CRC; 2003.
19. Johnson RJF, S V; O'Neill, J; Start, S; Bradley, J A; Forsythe, J L R; Rudge, C J. . Factors influencing outcome after deceased heart beating donor kidney transplantation in the United Kingdom: an evidence base for a new national kidney allocation policy. Transplantation. 2010;89(4):379-86.
20. Meier-Kriesche HU, Schold JD. The impact of pretransplant dialysis on outcomes in renal transplantation. Semin Dial. 2005;18(6):499-504.
21. Schmitt R, Coca S, Kanbay M, Tinetti ME, Cantley LG, Parikh CR. Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis. Am J Kidney Dis. 2008;52(2):262-71.
22. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney international. 2011;79(12):1361-9.
23. Kayler LK, Garzon P, Magliocca J, Fujita S, Kim RD, Hemming AW, et al. Outcomes and utilization of kidneys from deceased donors with acute kidney injury. Am J Transplant. 2009;9(2):367-73.
24. Hall IE, Schroppel B, Doshi MD, Ficek J, Weng FL, Hasz RD, et al. Associations of deceased donor kidney injury with kidney discard and function after transplantation. Am J Transplant. 2015;15(6):1623-31.
25. Heilman RL, Smith ML, Kurian SM, Huskey J, Batra RK, Chakkera HA, et al. Transplanting Kidneys from Deceased Donors With Severe Acute Kidney Injury. Am J Transplant. 2015;15(8):2143-51.
26. Dyson M, Watson CJ, Liddell K, Padfield N, Bradley A, Saeb-Parsey K. Transplanting suboptimal organs: medico-legal implications. Lancet. 2015;386:719-21.
27. Belayev LY, Palevsky PM. The link between acute kidney injury and chronic kidney disease. Curr Opin Nephrol Hypertens. 2014;23(2):149-54.
28. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney international. 2012;81(5):442-8.
29. Brodsky SV, Yamamoto T, Tada T, Kim B, Chen J, Kajiya F, et al. Endothelial dysfunction in ischemic acute renal failure: rescue by transplanted endothelial cells. Am J Physiol Renal Physiol. 2002;282(6):F1140-9.
30. Khairoun M, van der Pol P, de Vries DK, Lievers E, Schlagwein N, de Boer HC, et al. Renal ischemia-reperfusion induces a dysbalance of angiopoietins, accompanied by proliferation of pericytes and fibrosis. Am J Physiol Renal Physiol. 2013;305(6):F901-10.