ORIGINAL ARTICLE

Outcomes of kidney transplant from deceased donors with acute kidney injury and prolonged cold ischemia time – a retrospective cohort study

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SUMMARY

While deceased donor renal transplants (DDRT) from donors with either acute kidney injury (AKI) or long cold ischemia time (CIT) are associated with increased risk of delayed graft function (DGF), recipients of these kidneys have good patient and allograft survival. There are limited data on whether kidneys with both AKI and long CIT have outcomes similar to kidneys with only one of these insults. Using data from the Scientific Registry of Transplant Recipients, we analyzed transplant outcomes in patients (2005–2015) receiving kidneys with AKI (terminal creatinine ≥2.0 mg/dl) and CIT 24–30 h ($n = 1289$), 30–36 h ($n = 734$), and >36 h ($n = 614$), using kidneys with AKI and CIT <24 h ($n = 5434$) as a reference. DGF was more common with increasing CIT up to 36 h, then decreased slightly (41.2% vs. 46.8% vs. 52.5% vs. 50.2%, $P < 0.001$). Death-censored graft survival (DCGS) at 3 years was better with CIT <24 h compared with other groups (92.5% vs. 90.8% vs. 92% vs. 89.2%, $P = 0.018$). On multivariable analysis, donor creatinine was predictive of DCGS, whereas only CIT >36 h was predictive of DCGS (aHR 1.27, $P = 0.03$). Recipients transplanted with kidneys with both AKI and long CIT have excellent intermediate-term outcomes.

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Key words
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Introduction

Kidney transplantation is the optimal treatment for end-stage renal disease, with decreased mortality and improved quality of life compared with dialysis [1,2]. However, the increase in the supply of organs available for transplantation has not matched the increase in the number of patients in need of transplant, leading to prolonged waiting times for transplant [3]. In an attempt to increase the supply of organs for transplant, kidneys considered "suboptimal" or "marginal" are often used for transplantation, including kidneys from donors who had acute kidney injury (AKI) at the time of death. Multiple single-center studies have demonstrated that kidneys transplanted from donors with AKI, typically defined as a terminal creatinine ≥2.0 mg/dl, have an increased risk of delayed graft function (DGF), with greater risk of DGF seen with more severe AKI [4–7]. Despite the increased risk of early complications, these kidneys are associated with excellent allograft survival

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and allograft function in the short term, even with increasing severity of AKI in the donor [4,5,8–10.] However, the majority of kidney transplants included in these studies had cold ischemia time (CIT) <24 h.

Similar to donor AKI, prolonged CIT has also been associated with an increased risk of DGF [11]. Several studies have reported that prolonged CIT is also associated with an increased risk of allograft failure [11,12]. However, other studies have suggested that prolonged CIT may not increase the risk of allograft failure after controlling for other risk factors [13,14]. While both donor AKI and prolonged CIT are associated with an increased risk of DGF, there are limited data on how the combination of these two factors impacts allograft survival after kidney transplant. A single-center study found similar graft survival in kidneys with AKI and CIT 20–30 h vs. >30 h, although there were only 39 transplants with >30 h CIT [15]. Analysis of paired kidneys from donors with AKI suggested that greater CIT differences between kidneys were not associated with any reduction in long-term patient or allograft survival [16]. However, as higher terminal creatinine is associated with an increased risk of unilateral kidney discard, this study may have excluded a significant number of kidneys with both AKI and prolonged CIT [17]. We performed a registry analysis to address further the impact of donor AKI and prolonged CIT on outcomes.

Methods

Study design and participants

This study used data from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) file. We conducted a retrospective cohort study to analyze all DDRTs from 2005 through 2015 that had CIT >24 h and AKI as defined by a terminal serum creatinine ≥2 mg/dl. The reference group was all DDRTs from the same period with AKI and <24 h of CIT. Over that 11-year period, we identified 113 923 total deceased donor kidneys that were transplanted alone. After excluding kidneys from donors with a terminal creatinine <2 mg/dl and pediatric recipients, we identified a final cohort of 8071 kidneys (Fig. S1).

Definition of organ quality and transplant characteristics

Organ quality was estimated by calculating the Kidney Donor Risk Index (KDRI) and Kidney Donor Profile Index (KDPI), which are currently used as part of the Kidney Allocation System (KAS) for deceased donor kidneys in the United States (U.S.) [18]. We calculated the KDRI, as described by the Organ Procurement and Transplantation Network (OPTN), and mapped the calculated values onto a cumulative percentage scale to generate the KDPI. Because our analysis identified kidneys recovered from 2005 to 2015, as recommended by the OPTN, we used a scaling factor of 1.2175005163 – the median KDRI value among all deceased donor kidneys procured in 2015 [19]. Large volume transplant centers were defined as those performing ≥1700 kidney transplant from 2000 to 2016. Complete machine perfusion was defined as perfusion performed by both organ procurement organizations (OPO) and the transplant center. Partial machine perfusion was defined as perfusion by either the OPO or the transplant center, but not both. Academic transplant center was defined as the one affiliated with a university medical center.

Outcomes

All-cause graft failure was defined as loss of graft or recipient death. DGF was defined as the need for dialysis within the first week post-transplant. Death with a functioning graft was defined as a recipient having: (i) a reported death date but no graft failure date; or (ii) death and graft failure dates share the same date. Death-censored graft survival (DCGS) was also evaluated.

Statistical analysis

Pearson's chi-square tests and the nonparametric Wilcoxon or Kruskal–Wallis tests were performed for categorical and continuous variables, respectively. All continuous values are expressed as means and standard deviation (SD). Logistic regression models were used to predict the odds of DGF. Kaplan–Meier survival curves were generated and compared using the log-rank test of equality. Cox proportional hazard models were used to evaluate the risk of recipient mortality and graft failure (death-censored and all-cause). We confirmed that the proportionality for the Cox model was met using both Schonfeld residuals and visual inspection. Time-to-event was calculated as the number of days from the date of transplantation to the date of reported graft failure or death, date of censoring (e.g. loss of follow-up), or the end of the study period. Multivariable models were developed using variables that were significant on univariate analysis and informed by clinical experience.

Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and STATA 15 (Stata Corp, College Station, TX, USA). Statistical significance was determined at $P < 0.05$.

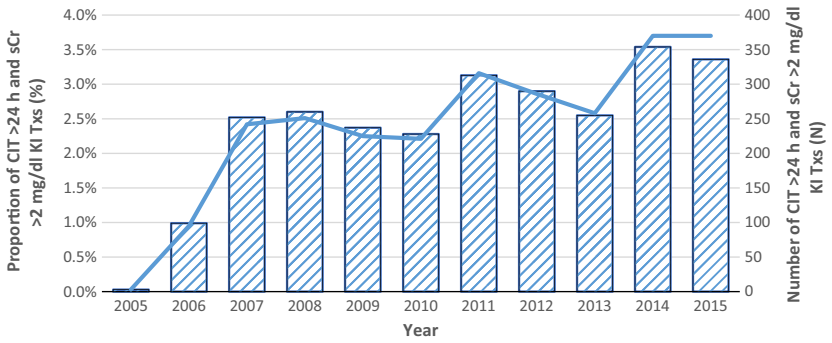
Results

The study cohort consisted of 8071 adult recipients of a DDRT alone between January 1, 2005 and December 31, 2015 who received a kidney from a donor with AKI (Fig. S1). Two thousand six hundred thirty-seven (32.7%) of these kidneys had CIT >24 h. During this time, the number of kidneys from donors with both AKI and prolonged CIT increased substantially, from three cases in 2005 to 370 in 2015, representing 2.4% of all adult DDRTs during this time period. The percentage of DDRTs from donors with AKI and prolonged CIT increased from 0.03% in 2005 to 3.4% in 2015 (Fig. 1).

While the total number of kidney transplants from these donors increased substantially over the study period, the vast majority of these kidneys were transplanted at a small number of transplant centers restricted to certain geographic areas (Fig. 2). Forty-five transplant centers, located in just 10 OPO, transplanted 1963 (74.5%) of all the kidneys with AKI and prolonged CIT during the study period, and nearly one-quarter of these kidneys (613, 23.3%) were transplanted in a single OPO (Table S1). This clustering of utilization of kidneys with AKI and prolonged CIT was present despite the widespread procurement of AKI organs across regions (Fig. 3).

Donor, recipient, and transplant characteristics

Organs and recipients were divided into four groups for analysis based on the duration of CIT: kidneys with CIT <24 h (n = 5434, 67.3% of cohort), kidneys with 24–30 h of CIT (n = 1289, 16.0%), kidneys with 30–36 h of CIT (n = 734, 9.1%), and kidneys with >36 h of CIT (n = 614, 7.6%). Donor characteristics are shown in Table 1. Kidneys with shorter CIT tended to come from younger donors and were less likely to come from donors with a history of diabetes or hypertension. The median KDPI was slightly lower in the group with <24 h of CIT. As our study period included years before and after the introduction of the new Kidney Allocation System in 2014, we looked at utilization of marginal quality kidneys by examining both the number of extended-criteria donor (ECD) kidneys and the number of high KDPI (KDPI >85%) kidneys in each group. The proportion of ECD and high KDPI kidneys was slightly lower among donors with <24 h of CIT. There was no significant difference in donor age or gender, hepatitis C seropositivity, or Public Health Service Increased Risk designation between groups.



Year	Number of CIT >24 h and sCr ≥2 mg/dl KI Txs (N)	Proportion of CIT >24 h and sCr ≥2 mg/dl KI Txs (%)
2005	3	0.03%
2006	95	1.0%
2007	242	2.5%
2008	251	2.6%
2009	225	2.4%
2010	221	2.3%
2011	316	3.1%
2012	286	2.9%
2013	258	2.6%
2014	370	3.5%
2015	370	3.4%

Figure 1 The proportion and frequency of all adult transplanted deceased donor kidneys with >24 h of cold ischemia time and serum creatinine ≥ 2 mg/dl in the U.S. stratified by year (n = 2637).

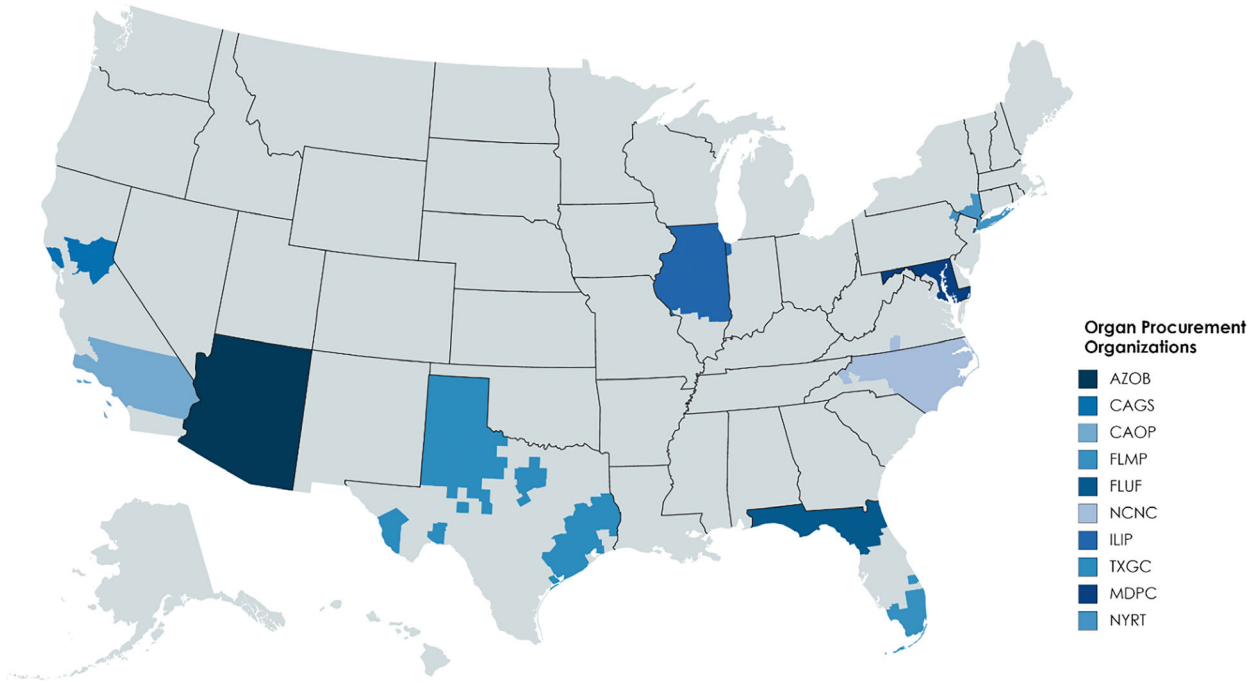


Figure 2 Map of the U.S. showing the 10 organ procurement organizations donor service areas where 74.5% (n = 1963) of all adult deceased donor kidneys with >24 h of cold ischemia time and serum creatinine ≥ 2 mg/dl were transplanted from 2005 to 2015.

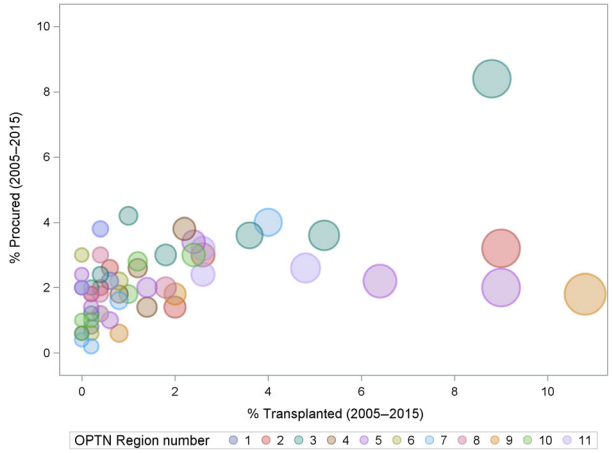


Figure 3 Bubble plot representing the proportion of adult deceased donor kidneys with acute kidney injury (AKI) and cold ischemia time >24 h transplanted within each Organ Procurement and Transplantation Network (OPTN) region by the proportion of adult deceased donor kidneys with AKI procured within each OPTN region, 2005–2015.

Overall, 61.7% of kidneys received some hypothermic machine perfusion. Lack of use of any machine perfusion was progressively less common as CIT increased (44.83% group 1, 31.96% group 2, 23.02% group 3, and 12.54% group 4, $P < 0.001$), while use of complete machine perfusion was more common with increasing CIT (22.96% group 1, 23.97% group 2, 29.43% group 3, 45.11% group 4, $P < 0.001$). Kidneys with CIT >24 h were also more likely to be transplanted in large volume transplant centers compared with kidneys with CIT <24 h.

Recipient characteristics stratified by group are shown in Table 2. There were no significant differences in recipient age, gender, body mass index, history of diabetes, or prior solid organ transplant among the four groups. Kidneys with longer CIT were more likely to be transplanted into Hispanic patients and patients who were pre-emptive. Mean waiting time for recipients decreased with increasing CIT, with a similar trend seen in the pre-KAS and post-KAS eras. There was no significant difference in median estimated post-transplant survival (EPTS) among groups.

Transplant characteristics are shown in Table 2. Zero-HLA mismatch transplants were less common with increasing CIT. With increasing CIT, patients were less likely to receive an IL-2 receptor blocker for induction (16.08% group 1, 16.14% group 2, 13.08% group 3, 10.1% group 4; $P < 0.001$).

Delayed graft function

Delayed graft function was a common clinical outcome, affecting 43.8% of the total cohort. DGF occurred more frequently with longer CIT. The rate of DGF increased from 41.15% in group 1 to 50.16% in group 4. Surprisingly, the DGF rate was highest in group 3 (52.45%)

Table 1. Donor and transplant center-level characteristics of the study cohort stratified by CIT time grouping (n = 8071), 2005–2015.

	CIT (h)				
	<24	24–30	30–36	>36	*P*-value
N (row %)	5434 (67.3)	1289 (16.0)	734 (9.1)	614 (7.6)	
Col %, max, mean ± SD					
Donor characteristics					
Age at recovery (years)	35.54 ± 13.45	37.18 ± 13.75	37.03 ± 14.07	37.39 ± 13.26	**<0.001**
Male	3947 (72.6)	932 (72.3)	511 (69.62)	438 (71.34)	0.364
African-American/black	1098 (20.21)	289 (22.42)	157 (21.39)	123 (20.03)	0.320
Blood type AB	185 (3.4)	45 (3.49)	18 (2.45)	16 (2.61)	0.405
Death due to stroke	1240 (22.82)	327 (25.37)	194 (26.43)	147 (23.94)	0.061
History of diabetes	380 (7.03)	116 (9.06)	75 (10.26)	74 (12.13)	**<0.001**
History of hypertension	1466 (27.17)	405 (31.67)	237 (32.38)	198 (32.46)	**<0.001**
PHS-IR kidney	885 (16.31)	241 (18.73)	136 (18.53)	103 (16.78)	0.124
HCV positivity	46 (0.85)	14 (1.09)	3 (0.41)	2 (0.33)	0.203
KDPI	49.46 ± 23.49	53.09 ± 24.21	53.26 ± 24.16	53.14 ± 22.92	**<0.001**
KDPI >85%	470 (8.65)	148 (11.48)	96 (13.08)	59 (9.64)	**<0.001**
DCD	477 (8.78)	98 (7.6)	34 (4.63)	48 (7.82)	**0.001**
ECD	711 (13.08)	225 (17.46)	118 (16.08)	95 (15.47)	**<0.001**
Terminal sCr	3.04 ± 1.57	3.17 ± 1.42	3.27 ± 1.38	3.24 ± 1.32	**<0.001**
Initial sCr	1.54 ± 0.93	1.61 ± 0.94	1.60 ± 0.87	1.53 ± 0.74	0.155
Machine perfusion					
None	2435 (44.83)	412 (31.96)	169 (23.02)	77 (12.54)	**<0.001**
Partial	1750 (32.22)	568 (44.07)	349 (47.55)	260 (42.35)	**<0.001**
Complete	1247 (22.96)	309 (23.97)	216 (29.43)	277 (45.11)	**<0.001**
CIT (h; median (IQR)	16 (9.45)	26.03 (2.90)	32.3 (3)	41.83 (8.4)	**<0.001**
Organ share type					
Local	4371 (80.44)	547 (42.44)	168 (22.89)	138 (22.48)	**<0.001**
Regional	641 (12.79)	328 (25.45)	145 (19.75)	70 (11.40)	**<0.001**
National	422 (8.8)	414 (32.12)	421 (57.36)	406 (66.12)	**<0.001**
TX center-level characteristics					
Academically affiliated TX center	3406 (62.68)	903 (70.05)	626 (85.29)	583 (94.95)	**<0.001**
TX center associated with a for-profit governing hospital	295 (5.43)	52 (4.03)	17 (2.32)	8 (1.3)	**<0.001**
Large volume TX center	2940 (54.1)	858 (66.56)	593 (80.79)	540 (87.95)	**<0.001**

AKI, acute kidney injury; BMI, body mass index; CIT, cold ischemia time; DCD, donation after cardiac death; ECD, expanded criteria donor; EPTS, estimated post-transplant survival; ESRD, end-stage renal disease; HCV, hepatitis C virus; IQR, interquartile range; KDPI, kidney donor profile index; PHS-IR, Public Health Services-Increased Risk; sCr, serum creatinine; SOT, solid organ transplant. Statistically significant values are highlighted in bold.

(Table 2). We analyzed the risk factors for DGF in this cohort (Table 3). On multivariate analysis, DCD kidneys had an adjusted odds ratio (aOR) of 2.34 for DGF, while use of a nationally shared kidney had an aOR of 1.46 and donor terminal creatinine had an aOR of 1.3 for each 1 mg/dl increase in terminal creatinine. Compared with kidneys with CIT <24 h, kidneys with CIT 24–30 h had an aOR of 1.24, kidneys with 30–36 h CIT had an aOR of 1.6, and kidneys with >36 h CIT had an aOR of 1.57. DGF was less common in younger patients. Use of machine perfusion was not associated with a lower rate of DGF in our cohort. Because use of terminal creatinine to define AKI may capture some kidneys in which the injury was chronic, we performed a sensitivity analysis restricted to those kidneys in which the terminal creatinine was >0.3 mg/dl higher than the initial creatinine (Table S2). The findings were similar to those seen in the total cohort.

Allograft and patient survival

There was no difference in 1-year allograft survival between groups (Table 2). A small but statistically significant difference in DCGS among groups emerged with increasing duration of follow up (Fig. 4). Actuarial graft survival at 6 years was 87.9% in kidneys with

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Table 2. Recipient characteristics and transplant outcomes of the study cohort stratified by CIT time (n = 8071), 2005–2015.

	CIT (h)				
	<24	24–30	30–36	>36	*P*
N (row %)	5434 (67.3)	1289 (16.0)	734 (9.1)	614 (7.6)	
Col %, max, mean ± SD					
Recipient characteristics					
Age at TX	53.46 ± 12.88	53.94 ± 12.69	54.35 ± 12.92	54.24 ± 12.53	0.202
African-American/black	1816 (33.42)	444 (34.45)	241 (32.83)	225 (36.64)	0.374
Male	3319 (61.08)	784 (60.82)	467 (63.62)	385 (62.7)	0.498
Hispanic	929 (17.1)	226 (17.53)	143 (19.48)	138 (22.48)	**0.007**
History of hypertension	4085 (89.58)	977 (88.1)	557 (87.99)	497 (90.69)	0.229
History of diabetes	2011 (37.23)	492 (38.44)	265 (36.5)	223 (36.68)	0.799
BMI	28.31 ± 5.4	28.31 ± 5.47	28.85 ± 7.82	28.72 ± 5.62	0.361
Pre-emptive TX	415 (7.64)	118 (9.15)	68 (9.26)	62 (10.1)	**0.046**
High PRA (>80%)	550 (10.12)	129 (10.01)	65 (8.86)	41 (6.68)	**0.035**
History of vascular disease	3284 (17.94)	148 (15.27)	80 (13.82)	79 (15.55)	**0.024**
Previous SOT	616 (11.34)	150 (11.64)	86 (11.72)	68 (11.07)	0.970
Wait time (years)					
Pre-KAS	2.67 ± 2.08	2.38 ± 1.84	2.34 ± 1.87	2.21 ± 1.48	**<0.001**
Post-KAS	5.21 ± 3.66	4.67 ± 3.47	4.6 ± 3.27	3.88 ± 3.3	**<0.001**
Median ESRD time (years; IQR)	3.67 (3.5)	3.17 (4.1)	3.15 (3.8)	3.23 (3.5)	**<0.001**
Zero-HLA mismatches	316 (5.82)	90 (6.98)	36 (4.9)	9 (1.47)	**<0.001**
HLA mismatches (#)	4.18 ± 1.5	4.1 ± 1.56	4.21 ± 1.45	4.32 ± 1.18	**0.008**
Median EPTS (IQR)	35 (44.0)	35 (46.0)	36 (46.0)	36 (47.0)	0.955
Induction agent classification					
Polyclonal anti-T cell	2878 (52.96)	619 (48.02)	390 (53.13)	310 (50.49)	**0.014**
IL-2 receptor blockers	874 (16.08)	208 (16.14)	96 (13.08)	62 (10.1)	**<0.001**
Polyclonal anti-T cell & IL-2 receptor blockers	159 (2.93)	74 (5.74)	58 (7.9)	114 (18.57)	**<0.001**
Monoclonal antibody	706 (12.99)	207 (16.06)	104 (14.17)	83 (13.52)	**0.039**
None/other	817 (15.03)	181 (14.04)	86 (11.72)	45 (7.33)	**<0.001**
Outcomes					
Follow-up time (years)	4.7 ± 2.7	4.8 ± 2.7	4.6 ± 2.7	4.5 ± 2.8	**0.026**
Patient mortality					
1-year	202 (3.72)	43 (3.34)	38 (5.18)	27 (4.4)	0.161
3-year	396 (7.29)	90 (6.98)	74 (10.08)	51 (8.31)	**0.045**
All-cause graft failure					
1-year	408 (7.51)	103 (7.99)	66 (8.99)	54 (8.79)	0.370
3-year	721 (13.27)	192 (14.9)	122 (16.62)	105 (17.1)	**0.007**
Death-censored graft failure					
1-year	242 (4.45)	68 (5.28)	33 (4.5)	32 (5.21)	0.533
3-year	410 (7.55)	119 (9.23)	59 (8.04)	66 (10.75)	**0.018**
DGF	2236 (41.15)	603 (46.78)	385 (52.45)	308 (50.16)	**<0.001**

BMI, body mass index; DGF, delayed graft function; EPTS, estimated post-transplant survival; ESRD, end-stage renal disease; HLA, human leukocyte antigen; IQR, interquartile range; KAS, Kidney Allocation System (implemented Dec. 4, 2014); PRA, panel reactive antibody; SOT, solid organ transplant; TX, transplant. Statistically significant values are highlighted in bold.

<24 h CIT, 85.1% in kidneys with 24–30 h CIT, 87.5% in kidneys with 30–36 h CIT, and 84.0% in kidneys with >36 h CIT (Table S5). We performed a multivariate analysis of risk factors for allograft failure (Table 4). Death-censored graft failure was more common in recipients who had a prior transplant (adjusted hazard ratio (aHR) 1.31, $P = 0.003$), had greater degrees of HLA mismatching (aHR 1.08 per each increase in mismatch, $P < 0.001$), or were African-American (aHR 1.47, $P < 0.001$). Higher KDPI was associated with an increased risk of graft failure (aHR 1.12 for each 1% increase in KDPI, $P < 0.001$). Compared with kidneys

Table 3. Bivariable and multivariable logistic regression models predicting the odds of delayed graft function.

Parameters	OR (95% CI)	*P*	aOR* (95% CI)	*P*
Age at TX (years)	1.00 (1.00–1.00)	0.829	0.98 (0.97–0.98)	**<0.001**
Hispanic	1.34 (1.20–1.50)	**0.024**	1.22 (1.09–1.38)	**0.001**
High PRA (>80%)	0.90 (0.78–1.05)	0.185	–	–
Zero-HLA mismatches	0.53 (0.43–0.65)	**0.001**	0.46 (0.37–0.57)	**<0.001**
EPTS	1.00 (1.00–1.00)	**0.009**	1.01 (1.01–1.01)	**<0.001**
DCD	1.72 (1.46–2.02)	**<0.001**	2.34 (1.97–2.78)	**<0.001**
KDPI	1.00 (1.00–1.01)	**0.002**	–	–
Donor age (years)	1.00 (1.00–1.00)	0.829	1.01 (1.01–1.01)	**0.007**
Donor terminal sCr	1.29 (1.24–1.33)	**<0.001**	1.30 (1.25–1.35)	**<0.001**
CIT [h; median (IQR)]	1.01 (1.01–1.02)	**<0.001**	–	–
CIT groups			–	–
<24 h	Ref	–	Ref	–
24–30 h	1.26 (1.11–1.42)	0.508	1.24 (1.07–1.44)	**0.005**
30–36 h	1.58 (1.35–1.84)	**0.002**	1.60 (1.26–2.02)	**<0.001**
>36 h	1.44 (1.22–1.70)	0.117	1.57 (1.13–2.20)	**0.008**
Machine perfusion			–	–
None	Ref	–	Ref	–
Partial	0.98 (0.89–1.09)	0.717	0.89 (0.78–1.03)	0.121
Complete	0.79 (0.70–0.88)	**<0.001**	0.82 (0.65–1.05)	0.117
Organ share type				
Local	Ref	–	Ref	–
Regional	1.27 (1.02–1.58)	**0.032**	1.01 (0.88–1.16)	0.857
National	1.94 (1.63–2.32)	**<0.001**	1.46 (1.26–1.70)	**<0.001**
Large volume TX center	1.17 (1.02–1.223)	**0.017**	–	–
Academically affiliated TX center	1.01 (0.92–1.11)	0.876	0.97 (0.88–1.08)	0.594
TX center associated with a for-profit governing hospital	1.12 (0.91–1.39)	0.272	–	–
Transplantation year	1.05 (1.03–1.07)	**<0.001**	1.03 (1.01–1.04)	**0.005**
Interaction: machine perfusion & CIT (h)	0.98 (0.97–99)	**<0.001**	–	–
Interaction: machine perfusion * CIT groups	0.85 (0.74–0.97)	**0.013**	0.93 (0.86–0.99)	**0.03**
Interaction: CIT groups * donor terminal sCr	1.00 (0.92–1.08)	0.908	–	–

*Adjusted for age at transplant (years), Hispanic ethnicity, zero human leukocyte antigen mismatches, estimated post-transplant survival, donation after cardiac death, donor age (years), donor terminal serum creatinine, cold ischemia time (CIT) group, machine perfusion, organ share type, academic center, transplantation year, and the interaction between machine perfusion and CIT group. Statistically significant values are highlighted in bold.

with <24 h CIT, only kidneys with CIT >36 h had an increased risk of graft failure (aHR 1.27, $P = 0.033$). We performed a sensitivity analysis using only those kidneys in which the terminal creatinine was >0.3 mg/dl above the initial creatinine (Table S3). aHRs were similar to those seen in the primary analysis.

Patient survival is shown in Table 2 and Fig. S3. Patients were followed for a mean of at least 4.5 years in each group, with total follow up being slightly but significantly shorter with longer CIT ($P = 0.026$ for trend). There was no difference in short-term patient survival at 1 year (Table 2). There was a small but statistically significant decrease in patient survival over the long term. Actuarial patient survival at 6 years was 83.9% in kidneys with <24 h CIT, 82.7% in kidneys with 24–30 h CIT, 79.7% in kidneys with 30–36 h CIT, and 82.7% in kidneys with >36 h CIT (Table S5). We performed a multivariate analysis of risk factors for mortality (Table S4). The adjusted hazard ratio for mortality was higher with increasing age (aHR 1.03 per year, $P < 0.001$), in diabetics (aHR 1.36, $P < 0.001$), and was lower in Hispanics (aHR 0.67, $P = 0.005$) and African-Americans (aHR 0.84, $P = 0.006$). Compared with CIT <24 h, CIT 30–36 h was associated with a significant increase in the risk of mortality (aHR 1.31, $P = 0.003$), while CIT 24–30 h and CIT >36 h were not associated with a significant increase in the risk of death.

Discussion

The increase in the number of patients awaiting kidney transplant has not been matched by an increase in the number of organs transplanted. In an effort to reduce

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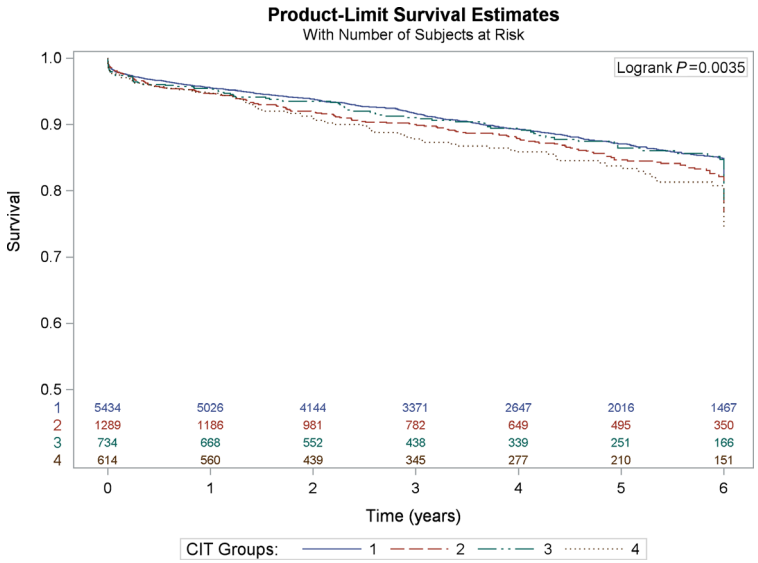

Figure 4 Kaplan–Meier curves illustrating the probability of death-censored graft survival stratified by cold ischemia time groupings.

waiting times, transplant centers have utilized kidneys considered "suboptimal" based on donor characteristics. AKI tends to be reversible, yet donor AKI prior to procurement is associated with an increased risk of discard. In an analysis of SRTR data from 1995 to 2007, Kayler *et al.* [20] found that a terminal creatinine of 1.6–2.0 mg/dl or ≥2.0 mg/dl was associated with a 2.71 and 7.04 increase in the odds of discard, respectively. Marrero *et al.* [21], using data from a more recent era (2000–2012), similarly found that a terminal creatinine >1.5 mg/dl was associated with an increase in the risk of discard (OR 4.31). During the period studied in our analysis, 2399 donors with AKI had both kidneys procured but discarded and 699 donors with AKI had one kidney transplanted and one kidney discarded.

Although kidneys from donors with AKI are more likely to be discarded, multiple centers have reported excellent transplant outcomes from donors with a terminal creatinine ≥2.0 mg/dl. Ugarte *et al.* [5] reported 90% 1-year and 69% 6-year graft survival in 65 patients who received kidneys from donors with AKI, compared with 90% and 74% in recipients of kidneys from donors with a creatinine <1.5. Farney *et al.* [22] reported 78% 5-year actuarial graft survival in 84 recipients of kidneys from donors with AKI, compared with 71% in recipients of kidneys from donors without AKI. Kayler *et al.* [20], analyzing registry data, found that kidneys from donors with a terminal creatinine ≥2.0 mg/dl were associated with an increased risk of allograft failure only for ECD kidneys, with an aHR of 1.17.

Single-center studies and registry analyses have found that kidneys from donors with AKI were associated with an increased risk of developing DGF [6,20]. These studies analyzed all donors with AKI, including those with shorter CIT. Prolonged CIT also is associated with an increased risk of DGF. Several studies have also found that longer CIT is associated with reduced long-term allograft survival [11,23]. There are limited data on how the combination of longer CIT and donor AKI impacts long-term outcomes. Xia *et al.* found no effect on patient or allograft survival in a paired kidney analysis. However, there were relatively few cases with very long CIT, and due to study design cases in which only one kidney was transplanted were excluded from analysis [16].

Our analysis of DDRTs from donors with AKI and CIT >24 h performed from 2005 to 2015 shows several key findings. First, over this period there was a significant increase in the overall number of transplants from donors with AKI and long CIT, as well as a significant increase in the percentage of these kidneys as a proportion of the total annual DDRT volume. In the most recent year studied, approximately one of every 30 DDRTs in the US came from a donor with AKI and CIT greater than 24 h. The increased utilization of kidneys from these donors likely represents a response to the worsening organ shortage. Our study period included patients transplanted in the first full year of the new KAS implemented in December 2014. Although the data are preliminary, the number of transplants from these donors in 2015 was similar to the year prior, suggesting that the new allocation system may not impact the number of transplants from donors with both AKI and long CIT. Further study is needed to confirm this finding.

Second, although the number of transplants with these kidneys increased significantly over the study period, there was significant geographic disparity in utilization of

Table 4. Bivariable and multivariable cox proportional hazard model predicting the risk of death-censored graft failure.

Parameters	HR (95% CI)	*P*	aHR* (95% CI)	*P*
Recipient				
Age at TX (year)	0.98 (0.98–0.99)	**<0.001**	0.98 (0.97–0.98)	**<0.001**
African-American/black	1.67 (1.48–1.89)	**<0.001**	1.47 (1.30–1.68)	**<0.001**
Male	1.12 (0.99–1.28)	0.069	–	–
Hispanic	0.74 (0.62–0.88)	**<0.001**	–	–
History of hypertension	0.81 (0.67–0.99)	**0.036**	–	–
History of diabetes	0.87 (0.77–0.99)	**0.041**	–	–
ESRD years	1.02 (1.00–1.04)	**0.026**	1.01 (0.99–1.03)	0.342
EPTS (unit = 1%)	1.00 (0.99–1.00)	**0.003**	–	–
High PRA (>80%)	1.02 (0.84–1.25)	0.811	–	–
HLA mismatches (unit = 1)	0.58 (0.42–0.79)	**<0.001**	1.08 (1.03–1.13)	**<0.001**
Previous TX	1.35 (1.13–1.61)	**<0.001**	1.31 (1.10–1.57)	**0.003**
Donor			–	–
Age at recovery (year)	1.02 (1.02–1.03)	**<0.001**	–	–
Male	0.81 (0.71–0.93)	**0.002**	0.91 (0.80–1.04)	0.180
African-American/black	1.71 (1.50–1.95)	**<0.001**	–	–
Blood type AB	0.83 (0.58–1.19)	0.305	–	–
Death due to stroke	1.70 (1.50–1.94)	**<0.001**	–	–
History of diabetes	1.92 (1.60–2.30)	**<0.001**	–	–
History of hypertension	1.72 (1.52–1.95)	**<0.001**	–	–
PHS-IR kidney	0.72 (0.60–0.88)	**0.001**	0.92 (0.75–1.12)	0.390
HCV positivity	2.07 (1.24–3.44)	**0.005**	–	–
KDPI >85%	2.61 (2.24–3.04)	**<0.001**	–	–
KDPI (unit = 1%)	1.02 (1.02–1.02)	**<0.001**	1.12 (1.02–1.02)	**<0.001**
CIT (h)	1.01 (1.00–1.01)	**<0.001**	–	–
CIT groups			–	–
<24 h	Ref	–	Ref	–
24–30 h	1.23 (1.04–1.44)	**0.013**	1.12 (0.95–1.32)	0.175
30–36 h	1.08 (0.86–1.34)	0.517	0.97 (0.78–1.21)	0.772
>36 h	1.38 (1.11–1.70)	**0.003**	1.27 (1.02–1.58)	**0.033**
Terminal sCr (mg/dl)	0.94 (0.89–0.98)	**0.009**	1.00 (0.96–1.05)	0.907
DCD	1.21 (0.98–1.50)	0.075	–	–
ECD	1.75 (1.51–2.03)	**<0.001**	–	–
Procedure type			–	–
Left KI	Ref	–	–	–
Right KI	1.00 (0.82–1.23)	0.989	–	–
Enbloc/sequential	0.78 (0.45–1.37)	0.392	–	–
Machine perfusion			–	–
None	Ref	–	Ref	–
Partial	1.28 (1.11–1.47)	**<0.001**	1.12 (0.96–1.05)	0.129
Complete	1.12 (0.96–1.32)	0.152	1.02 (0.86–1.20)	**0.014**
Organ share type			–	–
Local	Ref	–	–	–
Regional	0.84 (0.62–1.13)	0.252	–	–
National	1.02 (0.81–1.27)	0.884	–	–
Large volume TX center	0.92 (0.81–1.04)	0.183		
Academically affiliated TX center	1.20 (1.05–1.38)	**0.007**	–	–
TX center associated with a for-profit governing hospital	1.49 (1.18–1.90)	**0.001**	–	–
TX year	0.92 (0.89–0.94)	**<0.001**	0.93 (0.91–0.96)	**<0.001**
Interaction: machine perfusion & CIT (h)	1.00 (0.98–1.01)	0.514	–	–
Interaction: machine perfusion * CIT groups	0.94 (0.79–1.11)	0.441	–	–

*Adjusted for age at transplant (years), African-American/black race, end-stage renal disease years, number of human leukocyte antigen mismatches, previous transplant, donor sex, PHS-IR kidney, Kidney Donor Profile Index, cold ischemia time group, machine perfusion, terminal serum creatinine, and transplant year. Statistically significant values are highlighted in bold.

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these kidneys. Nearly three-quarters of these kidneys were transplanted in centers located in just 10 OPOs, and centers in a single OPO accounted for nearly one-quarter of transplants from these donors. The majority of these transplants were performed at large volume centers. We hypothesize that transplant centers in regions with shorter average waiting times may be less willing to utilize organs from donors who are perceived as higher risk because of factors such as premorbid AKI or anticipated long CIT. Centers may also be concerned about the increased risk of DGF in these patients, with the attendant impact on resource utilization and length of stay. Small volume centers may be less willing to transplant organs perceived as high risk because of the potential impact on graft outcomes and the possibility that these organs could lead to flagging for poor performance.

Third, we confirmed the high rate of DGF in kidneys from donors with AKI. Nearly one-half of kidneys with >24 h CIT had DGF, which is roughly twice as high as the rate of DGF among all DDRTs in the United States [24]. This incidence of DGF is similar to that reported in previous single-center studies of transplants from donors with AKI, although somewhat higher than the rate reported in a previous UNOS analysis which examined patients transplanted in an earlier era [5,8,20]. Compared with CIT of <24 h, CIT 24–30, 30–36, and >36 h were associated with an increased risk of DGF. However, the rate of DGF was higher in the 30–36 h group than in the >36 h group. We hypothesize that this finding is due to unmeasured donor and/or recipient factors that may have influenced a center's decision to utilize a particular organ for a particular patient.

Finally, we found a small but significant difference in patient and allograft survival when AKI kidneys with <24 h of CIT were compared with kidneys with longer CIT, although these small differences in outcomes must be weighed against the annual mortality on the waiting list. There were some differences in patient and allograft survival in certain subgroups of patients. Overall survival was reduced in patients with 30–36 h of CIT compared with patients with more or less CIT. It is likely that unmeasured recipient factors contributed to this finding, so that patients who were perceived as being at higher risk for mortality were less likely to be offered organs that would have CIT beyond 36 h. Mortality was lower in Hispanic recipients, a finding which has been reported previously [25]. The biggest risk factors for death-censored graft failure were receipt of a prior transplant and African-American race. Outcomes with retransplant in general are inferior to outcomes with primary transplants, in part because of recipient sensitization [26]. We did not have data on the presence of preformed donor-specific antibodies to determine whether sensitization contributed to the inferior outcomes among retransplant recipients. Allograft survival in African-American recipients has been found to be inferior in prior studies, and this finding has been attributed to varied factors including socioeconomic status, reduced access to care and differences in antirejection medication metabolism [27]. Our data also demonstrated that allograft survival was better in kidneys that received machine perfusion, confirming a finding which has been reported previously [28].

Our study has several limitations, including those seen with retrospective registry data analyses. There may be donor, recipient, and transplant center-level factors that are not captured in the UNOS registry that may contribute to outcomes with kidneys from donors with AKI and long CIT. For example, recipients of these kidneys may have had a lower burden of comorbidities or may have been perceived as better able to tolerate the anticipated DGF compared with patients who were not offered these kidneys. Similarly, procurement injuries to the ureter or renal vasculature were not captured but may have an impact on the rate of DGF and allograft survival, and may have contributed to the accumulation of significant CIT before a recipient could be identified. We used the UNOS definition of DGF. However, our data do not allow us to comment on the duration of DGF, the rate of renal function recovery once DGF resolves, or the rate of renal recovery in those patients who did not experience DGF. We do not have data on long-term renal function. Prior studies have suggested that renal function is similar at 1 year in kidneys from donors with and without AKI [6,8]. However, renal function may be slightly lower in recipients of AKI kidneys who experience DGF [7]. Our definition of AKI was based on terminal creatinine, rather than admission or peak creatinine, limiting our ability comment on how the etiology of AKI, which cannot be discerned from the data reported to UNOS, may influence outcomes. However, previous analysis of UNOS data found no impact on transplant outcomes when comparing admission creatinine to terminal creatinine [29]. While defining AKI can be challenging, the definition of AKI used in this study is consistent with the majority of studies analyzing this type of kidney, allowing for comparison with previously published outcomes [4–6,8,16]. Additionally, when we restricted our analysis only to those kidneys in which the terminal creatinine was >0.3 mg/dl higher than the initial creatinine the results were similar. We were unable to analyze histologic findings on procurement biopsies that were associated with utilization of kidneys from donors with AKI and

prolonged CIT. It is possible that there was significant selection bias, whereby only those AKI kidneys thought to be successfully transplanted were in fact used. Finally, we did not have data on dosing of induction and maintenance immunosuppression medications. It is possible that certain strategies that may have an impact on rates of DGF, patient survival, and allograft survival, such as longer duration of use of induction agents combined with delayed introduction of calcineurin inhibitors (CNI), CNI minimization, or CNI avoidance with use of belatacept, may have been used in some recipients.

In conclusion, the prevalence of kidney transplants from donors with AKI and prolonged CIT is increasing, and transplants from these donors result in excellent long-term clinical outcomes, with 3-year graft survival rates similar to those reported among all DDRT recipients in the U.S [30]. Although these kidneys had a high rate of DGF, patient and allograft survival were similar to that seen in prior studies of AKI kidneys with shorter mean durations of CIT. Given these findings, anticipation of a longer duration of CIT should not be used alone as a reason to discard or decline an organ offer for an otherwise transplantable kidney from a donor with AKI.

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Conflicts of interest

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Inclusion/exclusion flow chart of study cohort.

Figure S2. Delayed graft function prevalence and median cold ischemia time (CIT) trends from 2005 to 2015 among kidneys with terminal creatinine ≥2.0 mg/dl and CIT >24 h (n = 2637).

Figure S3. Kaplan–Meier curves illustrating the probability of recipient survival stratified by cold ischemia time groupings.

Table S1. Forty-five transplant centers located within 10 organ procurement organizations donor service areas are responsible for transplanting ~74.5% (n = 1963) of all adult deceased donor kidneys with a cold ischemia time >24 h and serum creatinine ≥2 mg/dl, 2005–2015.

Table S2. Sensitivity analysis: multivariable logistic regression model predicting the odds of delayed graft function among recipients of acute kidney injury (confirmed) kidneys.

Table S3. Sensitivity analysis: multivariable cox model predicting the risk of death-censored graph failure among acute kidney injury (confirmed) kidneys.

Table S4. Bivariable and multivariable cox proportional hazard model predicting the risk of recipient mortality.

Table S5. Percentage patient mortality and death-censored graft failure at 6 years.

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