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Shipping living donor kidneys and transplant recipient outcomes

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Kidney paired donation (KPD) is an important tool to facilitate living donor kidney transplantation (LDKT). Concerns remain over prolonged cold ischemia times (CIT) associated with shipping kidneys long distances through KPD. We examined the association between CIT and delayed graft function (DGF), allograft survival, and patient survival for 1267 shipped and 205 nonshipped/internal KPD LDKTs facilitated by the National Kidney Registry in the United States from 2008 to 2015, compared to 4800 unrelated, nonshipped, non-KPD LDKTs. Shipped KPD recipients had a median CIT of 9.3 hours (range = 0.25-23.9 hours), compared to 1.0 hour for internal KPD transplants and 0.93 hours for non-KPD LDKTs. Each hour of CIT was associated with a 5% increased odds of DGF (adjusted odds ratio: 1.05, 95% confidence interval [CI], 1.02-1.09, $P < .01$). However, there was not a significant association between CIT and all-cause graft failure (adjusted hazard ratio [aHR]: 1.01, 95% CI: 0.98-1.04, $P = .4$), death-censored graft failure ([aHR]: 1.02, 95% CI, 0.98-1.06, $P = .4$), or mortality (aHR 1.00, 95% CI, 0.96-1.04, $P > .9$). This study of KPD-facilitated LDKTs found no evidence that long CIT is a concern for reduced graft or patient survival. Studies with longer follow-up are needed to refine our understanding of the safety of shipping donor kidneys through KPD.

Abbreviations: ACGF, all cause graft failure; CIT, cold ischemia time; DGF, delayed graft function; DM, diabetes mellitus; ESRD, end stage renal disease; KPD, kidney paired donation; LDKT, living donor kidney transplant; NKR, National Kidney Registry; PVD, peripheral vascular disease; RRT, renal replacement therapy; UNOS, United Network for Organ Sharing.

KEYWORDS
clinical research/practice, delayed graft function (DGF), donors and donation: paired exchange, graft survival, health services and outcomes research, kidney transplantation/nephrology

1 | BACKGROUND

The burden of end-stage renal disease (ESRD) is high in the United States, with approximately 98 000 patients waiting for a kidney transplant (Organ Procurement and Transport Network [OPTN] data as of May 22, 2017). Living donor kidney transplantation (LDKT) is a better alternative to waiting for a deceased donor organ when the recipient candidate has a willing and compatible donor. If the donor and candidate are incompatible, however, kidney paired donation (KPD) provides a means to exchange donors with another incompatible pair so that both candidates can undergo a compatible LDKT. Recent acceptance of the practice of KPD in the United States has given rise to national KPD registries that facilitate KPD exchanges between kidney donors and recipients separated by long distances.[1] Although these nationwide exchanges allow more incompatible pairs to participate in LDKT, the long distances between transplant centers result in prolonged cold ischemia time (CIT) for the shipped kidney.

The transplant community varies in whether they support shipping living donor kidneys long distances through KPD programs adding significant CIT. Some national programs, such as in Canada or The Netherlands, never ship extirpated living donor kidneys.[2,3] On the other hand, the National Kidney Registry (NKR) in the United States has routinely shipped living donor kidneys since inception in 2008.[4] Our ability to evaluate and compare these different policies on shipping kidneys and establish an evidence-based, standard approach is limited by a paucity of research. Initial preliminary studies of shipped LDKT in KPD programs have suggested minimal to no association between CIT and graft or patient outcomes; however, these studies were limited by small sample sizes and minimal follow-up times.[5,6] Additionally, none of these studies identified potential risk factors or predictors of poorer outcomes in shipped KPD kidneys with prolonged CIT. In a slightly different study population, a recent report of non-KPD LDKTs incurring longer CIT (maximum of 8 hours) in older donors (>50 years old) demonstrated poorer graft survival.[7] In larger studies of deceased donor organs, there has been conflicting evidence for the association between long CIT (upwards of 24 hours) and delayed graft function (DGF), poorer allograft survival, or poorer patient survival.[8,9]

In order to address the important clinical and programmatic questions about the benefits and risks of shipping KPD kidneys, this study compares a large cohort of KPD recipients facilitated by the NKR, a large national KPD exchange program, to a national cohort of unrelated LDKTs not shipped or facilitated in a KPD exchange, which was identified from the Scientific Registry of Transplant Recipients (SRTR). This study aims to identify associations between CIT and KPD recipient DGF, allograft failure, and patient death. Additionally, we sought to identify any associated risk factors for poorer outcomes. In comparison to data used in previous studies, the unique experience of the NKR offers a larger study population and longer CIT from transcontinental shipping.

2 | METHODS

2.1 | The National Kidney Registry

The NKR is a nonprofit, 501c organization comprising 76 transplant centers within the United States participating during this study period. Details of the NKR have been previously described.[5] NKR policies are available online at: http://www.kidneyregistry.org. Protocols for evaluating patients, performing the transplant procedures, and postoperative care are outlined by the NKR; however, these functions are ultimately carried out by the participating transplant centers abiding by, and in concordance with, the individual center protocols. The shipping of kidneys was performed utilizing existing organ procurement organizations methodologies in accordance with Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS) standards. Cold preservation solution without pumping was used for storage of the kidneys during transport. To date, the NKR has facilitated over 2000 KPD exchanges, >80% of which involve shipping the living donor organ across the United States.

2.2 | Study population

KPD transplants between February 1, 2008 and November 30, 2015 were identified from the NKR registry. The NKR registry was linked to the SRTR using the UNOS donor identifier to obtain demographic and clinical variables for the recipients and donors. Any transplant that could not be linked or validated on transplant center, transplant date, ABO, and gender was excluded from the study (5%, n = 78). Additionally, as a comparison group, we included the cohort of all living unrelated non-KPD transplants identified from the SRTR that had their transplant at an NKR-participating center, during the same time period, and with short CIT (<1.33 hours, the average CIT of in-center NKR exchanges). NKR exchanges where the kidney was shipped were termed "shipped exchange," NKR exchanges within the same center were termed "in-center exchanges," and the additional cohort of living unrelated non-KPD transplants from SRTR were termed "other nonexchange."

2.3 | Cold ischemia time

In this study, CIT was defined as the hours of cold ischemia time associated with facilitating the transplant. Three records of CIT >36 hours (exchange) and 2 records of CIT > 12 hours (in-center exchange) were

recoded as unknown CIT as the prolonged CIT in these cases was likely due to confounding recipient factors.

2.4 | Delayed graft function

Delayed graft function (DGF) was ascertained through SRTR and defined as requiring dialysis in the first week after transplantation. We studied whether longer CIT was associated with increased odds of DGF. We adjusted for recipient factors (sex, black race, BMI, diabetes mellitus [DM], primary diagnosis of congenital disease, panel reactive antibodies [PRA] at transplant, previous transplant, preemptive transplant, and years on renal replacement therapy [RRT]), donor factors (living kidney donor profile index [LD KDPI][10]), and transplant factors (HLA mismatch and year of transplant).

2.5 | All-cause graft failure

All-cause graft failure (ACGF) was ascertained through the SRTR. Recipients were followed until graft failure, death, or administrative censorship on November 30, 2015. We studied whether longer CIT was associated with an increased hazard of ACGF. Adjusted ACGF estimates were based on a SRTR risk-adjustment approach. Recipient factors included years of age at transplant, black race, peripheral vascular disease (PVD), DM, PRA at transplant, preemptive transplant, years of RRT, public insurance, highest education level, and year of transplant. Donor factors were adjusted for through LD KDPI.

2.6 | Death censored graft failure

Death censored graft failure (DCGF) was ascertained through SRTR. Recipients were followed until graft failure, censorship for death, or administrative censorship on November 30, 2015. We studied whether longer CIT was associated with an increased hazard of DCGF, adjusting for the same recipient and donor factors as ACGF.

2.7 | Mortality

Mortality was ascertained through SRTR. Recipients were followed until death, or administrative censorship on November 30, 2015. We studied whether longer CIT was associated with an increased hazard of mortality. Adjusted mortality estimates were based on SRTR risk-adjustments. Recipient factors included years of age at transplant, sex, black race, PVD, DM, previous transplant, preemptive transplant, years of RRT, highest education level of grade school or none, public insurance, and year of transplant. Donor factors were adjusted for through LD KDPI, and donor ABO O.

2.8 | Donors older than 50

We investigated whether CIT was associated differently with DGF, ACGF, DCGF, and mortality based on whether the donor was 50 years of age or older. This was accomplished using an interaction term in the regression models of CIT and donor age >50 years of age described in the Statistical Analysis section below.

2.9 | Data sources

This study was approved by the UCLA David Geffen School of Medicine Institutional Review Board (IRB protocol #11-003253-CR-00004) as well as the Johns Hopkins Medical Institutions Institutional Review Board (IRB-00048731). The NKR research committee granted access to the administrative NKR database to perform this study. Representatives and employees of the NKR provided data but did not directly participate in the design, analysis, or manuscript preparation for this study.

This study used data from the SRTR. The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the OPTN, and has been described elsewhere.[11] The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

2.10 | Statistical analysis

All analyses were conducted in Stata 14.2/MP for Linux (College Station, TX). For all analyses, $P < .05$ was considered statistically significant. Odds of DGF were estimated using a multilevel logistic regression that accounted for transplant center–level variation. Hazard of graft failure and mortality was estimated with Cox regression models with shared frailty to account for center-level variation. The shared frailty framework accounts for center-level variation in a manner similar to multilevel generalized linear regression models. We used the log-likelihood ratio (LLR) test to test whether models fit with random-effects parameters (multilevel models) were better fit than regression models without these parameters. In this case, since the LLR compares the multilevel model with random effects to the single-level model, a LLR $P < .05$ implies that the association between CIT and posttransplant outcomes varies by center. In addition to these models, the hazard of ACGF, DCGF, and patient mortality stratified by type of LDKT (shipped exchange vs in-center exchange vs other nonexchange) were examined with Kaplan-Meier methods. Multiple imputation by chained equations with 10 imputations over 100 iterations was used to handle missing covariates. Missing PRA categories were imputed as a nominal variable; missing CIT, BMI, and LD KDPI were linearly imputed. All methods of handling missing data were compared to case-wise deletion regression models.

3 | RESULTS

3.1 | Study population characteristics

From 2008 to 2015, the 76 transplant centers considered in this study performed 6272 total LDKTs. Of these, 1472 (24%) were NKR-facilitated transplants with validated linkages to SRTR data. (Note that this sample does not comprise the total number of NKR-facilitated transplants to date since only transplants conducted up to 2015 were

TABLE 1 Study sample characteristics

	Shipped exchange n = 1267	In-center exchange n = 205	*P* value[b]	Other nonexchange n = 4800	*P* value[b]
Cold ischemia time (h)[a]	9.3 (6.9-12.2)	1.0 (0.8-1.5)	<.001	0.9 (0.5-1.0)	<.001
Recipient					
Age, y[a]	50 (39-60)	50 (39-60)	>.9	50 (41-59)	.6
Female	599 (47%)	74 (36%)	<.01	1557 (32%)	<.001
Diabetic	307 (24%)	53 (26%)	.6	1349 (28%)	<.01
Primary diagnosis					
DM	232 (18%)	46 (23%)	.07	1078 (22%)	<.001
GN	412 (33%)	60 (29%)		1401 (29%)	
PKD	158 (12%)	30 (15%)		824 (17%)	
Congenital	48 (3.8%)	1 (0.5%)		108 (2.3%)	
Other	417 (33%)	68 (33%)		1389 (29%)	
Years on RRT[a]	1.4 (0.2-2.9)	1.8 (0.6-3.6)	.048	0.5 (0-1.6)	<.001
Previous transplant	358 (28%)	35 (17%)	.001	504 (11%)	<.001
Preemptive transplant	306 (24%)	40 (20%)	.1	1818 (38%)	<.001
Black (vs nonblack)	211 (17%)	50 (24%)	<.01	554 (12%)	<.001
PRA at transplant					
0	522 (41%)	119 (58%)	<.001	3291 (69%)	<.001
1-10	67 (5.3%)	14 (6.8%)		327 (6.8%)	
11-79	347 (27%)	39 (19%)		661 (14%)	
≥80	324 (26%)	26 (13%)		111 (2.3%)	
Missing	7 (0.6%)	7 (3.4%)		410 (8.5%)	
BMI[a]	27 (23-31)	26 (23-31)	.3	27 (24-31)	<.01
Donor					
Age, y[a]	45 (35-52)	48 (38-56)	<.01	45 (36-53)	.02
Female	789 (62%)	126 (62%)	.8	3217 (67%)	<.01
Black (vs nonblack)	137 (11%)	24 (12%)	.7	385 (8.0%)	<.01
LD KDPI[a]	12.2 (−0.84–25.0)	12.0 (−0.51–31.3)	.4	15.2 (1.86-30.1)	<.001
HLA mismatches					
0	9 (0.7%)	0	.08	17 (0.4%)	<.001
1	29 (2.3%)	3 (1.5%)		38 (0.8%)	
2	81 (6.4%)	10 (4.9%)		207 (4.3%)	
3	198 (16%)	38 (19%)		633 (13%)	
4	340 (27%)	44 (22%)		1348 (28%)	
5	404 (32%)	68 (33%)		1620 (34%)	
6	182 (14%)	41 (20%)		907 (19%)	
Missing	22 (1.7%)	0		30 (0.6%)	
Year of transplant[a]	2013 (2012-2014)	2012 (2010-2014)	<.001	2012 (2010-2014)	<.001

DM, diabetes mellitus; GN, Glomerulonephritis; LD KDPI, live-donor kidney donor profile index; PKD, paired kidney donation; PRA, panel reactive antibodies; RRT, renal replacement therapy.

[a]Median (interquartile range). Cold ischemia time missing in 30 (15%) in-center exchanges, 21 (1.7%) of shipped exchanges, and none of the other nonexchanges. Recipient BMI missing in 1 (0.5%) in-center exchange, 4 (0.3%) of shipped exchanges, and 150 (3.2%) of the other nonexchanges. LD KDPI missing in 3 in-center exchanges, 48 shipped exchanges, 242 of other nonexchanges.

[b]*P* values are compared to the Shipped Exchange group only.

sampled.) Among the total 6272 LDKTs, 1267 (20%) were shipped KPD LDKTs and 205 (3%) were nonshipped in-center KPDs arranged by NKR. The remaining 4800 (77%) were other unrelated, non-KPD LDKT recipients identified from the SRTR with CIT <1.33 hours. The study sample characteristics of each group are shown in Table 1. The median follow-up was 3.2 years. Of the shipped kidneys, 1046 (83%)

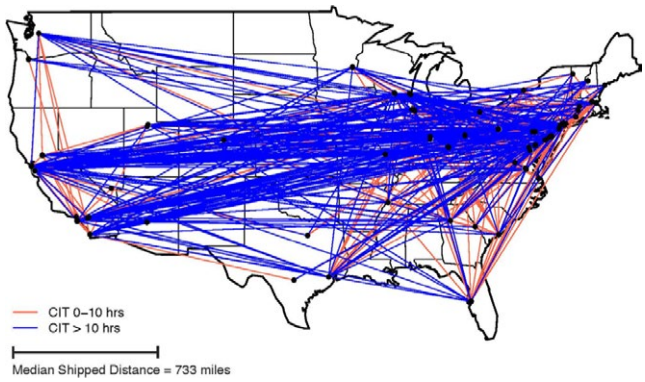


FIGURE 1 Geographic distribution of shipped kidneys. A total of 1267 KPD transplants were shipped. The median shipping distance was 733 miles (1.5-2717 mile range)

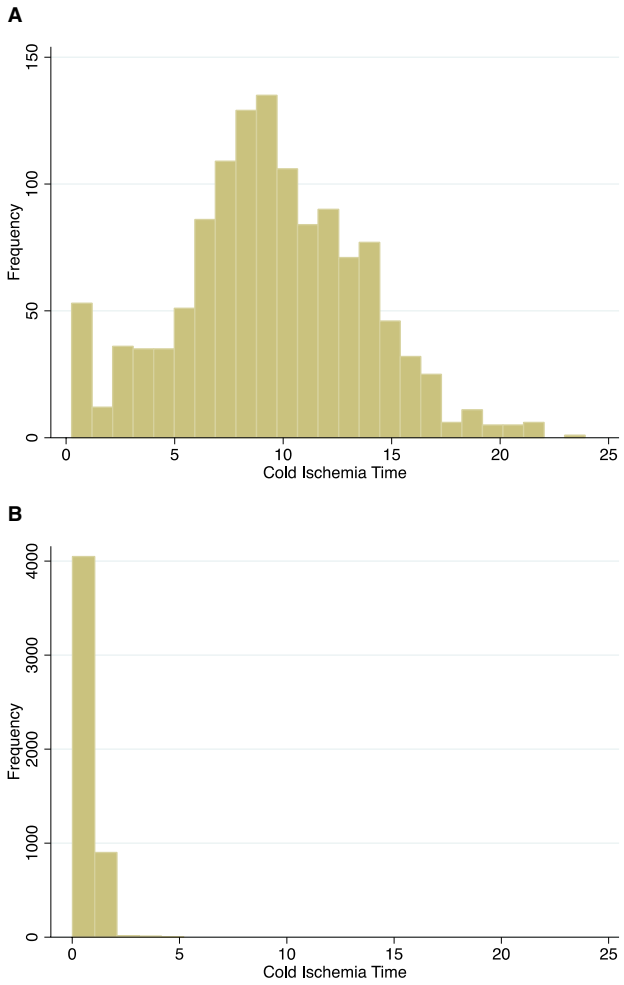


FIGURE 2 (A) Cold ischemia time of shipped kidney paired donation transplants. (B) Cold ischemia time of in-center kidney paired donation and other nonexchange transplants. Note: while there was no maximum cold ischemia time set for the In-Center KPD transplants, the maximum was for other non-change KPD transplants was set at 1.33 hours

were transported via air and 206 (16%) via ground transportation. The median shipping distance was 733 miles (1.5-2717-mile range). Figure 1 shows the geographic distribution of the 1267 shipped LDKTs in this sample, coded by shipped KPD with 0-10 (red) and >10 hours (blue) of CIT.

TABLE 2 Risk factors for delayed graft function among KPD and non-KPD living kidney donor transplant recipients

	aOR (95% CI)	*P* value
Cold ischemia time (/h)	1.05 (1.02-1.09)	<.01
Black recipient	2.37 (1.71-3.28)	<.001
Female recipient	0.74 (0.54-1.03)	.07
Recipient BMI (centered at 25)	1.00 (1.00-1.00)	.8
Diabetic recipient	1.39 (1.02-1.89)	.04
Primary diagnosis of congenital disease	2.30 (1.07-4.98)	.03
PRA at transplant		
0	REF	-
1-10	0.78	.4
11-79	1.00	>.9
80+	0.93	.8
Preemptive transplant	0.30 (0.19-0.49)	<.001
Previous transplant	1.08 (0.69-1.67)	.7
Years of RRT	1.10 (1.05-1.15)	<.001
LD KDPI	1.01 (1.00-1.02)	<.01
Year of transplant	0.92 (0.86-0.99)	.02

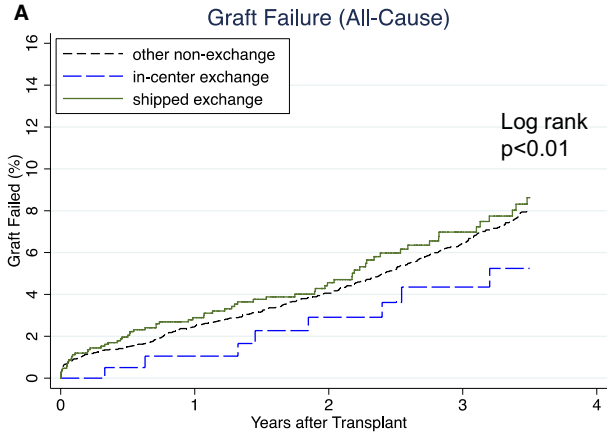
aOR, adjusted odds ratio; CI, confidence interval; DGF, delayed graft function; KPD, kidney paired donation; LD KDPI, live donor kidney donor profile index; PRA, panel reactive antibodies; RRT, renal replacement therapy.
DGF was modeled in a multilevel logistic regression to adjust for center variation (n = 6267). Five cases of DGF were unknown since the patient died in the first week before DGF could be ascertained. Missing data were handled through multivariate imputation.

3.2 | Cold ischemia time

Shipped KPD recipients had a median (interquartile range) CIT of 9.3 (6.9-12.2) hours that ranged from 0.25 to 23.9 hours, longer than in-center KPD recipients with 1.0 hour (0.8-1.5) of CIT that ranged from 0.22 to 5.2 hours, and other nonexchanges with 0.93 (0.5-1.0) hours of CIT that ranged from 0.01 to 1.33 hours (by study design) (Table 1). The distribution of CIT is shown in Figure 2 separately for shipped KPD (Figure 2A) and in-center KPD and other nonexchange transplant (Figure 2B). CIT that were missing from SRTR were imputed using CIT reported to NKR in 53 cases. CIT remained missing in 30 (15%) in-center exchanges, in 21 (1.7%) of shipped exchanges, and none of the other nonexchanges. These remaining 51 cases with missing CIT were imputed statistically in each model in subsequent analyses.

3.3 | Delayed graft function

Shipped KPD recipients experienced 64 (5.1%) cases of DGF, in-center KPD experienced 7 (3.4%), and other non-KPD LDKT



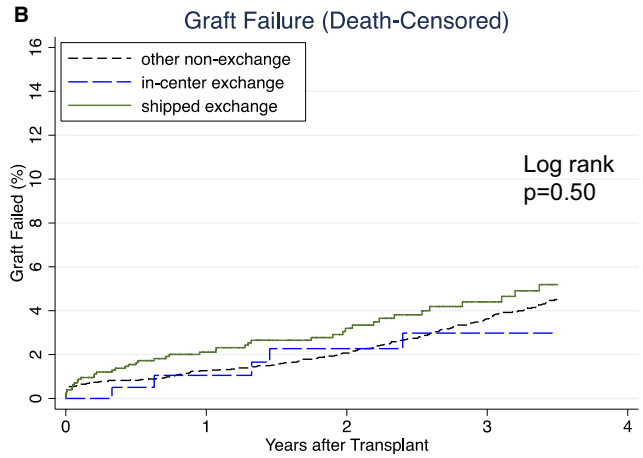


FIGURE 3 (A) Time to graft failure (all-cause) after transplant. (B) Time to graft failure (death-censored) after transplant. KPD, kidney paired donation; LDKT, living donor kidney transplant

experienced 137 (2.9%) cases of DGF (χ^2 test, P = .001). Five cases were excluded from analysis because the recipient died before DGF could be ascertained. The odds of DGF varied between transplant centers (P = .03). After accounting for heterogeneity between centers, recipient characteristics, and donor characteristics, each hour of CIT was associated with a 5% increased odds of DGF (adjusted odds ratio [aOR] 1.05, 95% CI, 1.02-1.09, P < .01). Black race, DM, primary diagnosis of congenital disease, years on RRT, and LD KDPI were also associated with increased odds of DGF. Preemptive transplant and more recent year of transplant were associated with decreased odds of DGF (Table 2). Multivariate imputations were used for missing CIT in 51 (0.8%) cases, missing BMI in 155 (2.5%) cases, missing LD KDPI in 293 (4.8%) cases, and missing PRA at transplant in 424 (7%) cases. In an identically adjusted model where cases with missing data were handled by case-wise deletion (n = 5522), CIT remained associated with increased DGF (aOR 1.06; 95% CI, 1.02-1.09, P < .01).

TABLE 3 Risk factors for all-cause graft failure among KPD and non-KPD living kidney donor transplant recipients

	aHR (95% CI)	*P* value
Cold ischemia time (/h)	1.01 (0.98-1.04)	.4
Recipient age at transplant (/y)	1.00 (0.98-1.02)	.8
Per y <40	0.96 (0.93-0.99)	.01
Per y >55	1.05 (1.01-1.09)	.01
Black recipient	1.04 (0.81-1.34)	.8
Peripheral vascular disease	1.23 (0.81-1.87)	.3
Diabetic recipient	1.47 (1.21-1.79)	<.001
PRA at transplant		
0	REF	-
1-10	0.95	.8
11-79	1.20	.1
80+	0.90	.6
Preemptive transplant	0.69 (0.55-0.86)	.001
Years of RRT	1.04 (1.00-1.08)	.049
Public insurance	1.24 (1.02-1.51)	.03
High school (or lower) education	1.05 (0.87-1.26)	.6
LD KDPI	1.01 (1.01-1.01)	<.001
Year of transplant	0.91 (0.86-0.96)	.001

All-cause graft failure was modeled in a Cox regression with shared frailties to adjust for center variation (n = 6272). Missing data were handled through multivariate imputation.
aHR, adjusted hazard ratio; CI, confidence interval; KPD, kidney paired donation; LD KDPI, live donor kidney donor profile index; PRA, panel reactive antibodies; RRT, renal replacement therapy.

3.4 | All-cause graft failure

One-year ACGF was 2.9% in shipped KPD, 1.1% in in-center KPD, and 2.5% in other non-KPD. Three-year ACGF was 7.0% in shipped KPD, 4.4% in in-center KPD, and 6.4% in other non-KPD (Figure 3A). After accounting for heterogeneity between centers, recipient characteristics, and donor characteristics, there was not a significant association between CIT and ACGF (adjusted hazard ratio [aHR] 1.01, 95% CI, 0.98-1.04, P = .4). Each year of recipient age <40 years was associated with a lower hazard of ACGF. Each year of recipient age >55 years was associated with an increased hazard of ACGF. Recipients with public insurance, DM, years of RRT, and LD KDPI were associated with an increased hazard of ACGF. Preemptive transplants and more recent year of transplant were associated with decreased hazard of ACGF (Table 3). In an identically adjusted model where cases with missing data were handled by case-wise deletion (n = 5506), CIT was not associated with increased ACGF (aHR 1.02; 95% CI, 0.98-1.07, P = .3).

3.5 | Death-censored graft failure

One-year graft survival was 97.9% in shipped KPD, 99.0% in in-center KPD, and 98.7% in other non-KPD. Three-year graft survival was

TABLE 4 Risk factors for death-censored graft failure among KPD and non-KPD living kidney donor transplant recipients

	aHR (95% CI)	*P* value
Cold ischemia time (/h)	1.02 (0.98-1.06)	.4
Recipient age at transplant (/y)	0.96 (0.95-0.97)	<.001
Per year >55	1.02 (0.98-1.06)	.3
Black recipient	1.28 (0.94-1.74)	.1
Peripheral vascular disease	0.68 (0.29-1.55)	.4
Diabetic recipient	1.07 (0.79-1.44)	.7
PRA at transplant		
0	REF	-
1-10	0.97	.9
11-79	1.46	.01
80+	1.08	.7
Preemptive transplant	0.65 (0.48-0.89)	<.01
Years of RRT	1.01 (0.96-1.07)	.7
Recipient public insurance	1.33 (1.02-1.73)	.04
High school (or lower) education	1.23 (0.96-1.57)	.1
LD KDPI	1.01 (1.00-1.02)	.001
Year of transplant	0.92 (0.85-0.99)	.03

Death-censored graft failure was modeled in a Cox regression with shared frailties to adjust for center variation (n = 6272). Missing data were handled through multivariate imputation.
aHR, adjusted hazard ratio; CI, confidence interval; KPD, kidney paired donation; LD KDPI, live donor kidney donor profile index; PRA, panel reactive antibodies; RRT, renal replacement therapy.

95.6% in shipped KPD, 97.0% in in-center KPD, and 96.4% in other non-KPD (Figure 3B). After accounting for heterogeneity between centers, recipient characteristics, and donor characteristics, there was no association found between CIT and death-censored graft failure (aHR 1.02, 95% CI, 0.98-1.06, *P* = .4). Recipient public health insurance, PRA 11-79, and LD KDPI were associated with increased hazard of DCGF. Recipient age, preemptive transplantation, and more recent year of transplant were associated with lower hazard of DCGF (Table 4). In an identically adjusted model where cases with missing data were handled by case-wise deletion (n = 5506), CIT was not associated with increased DCGF (aHR 1.03; 95% CI, 0.99-1.05, *P* = .1).

3.6 | Mortality

One-year patient survival was 99.0% for shipped KPD, 100% for in-center KPD, and 98.7% for other non-KPD. Three-year patient survival was 97.2% for shipped KPD, 98.6% for in-center KPD, and 96.8% for other non-KPD (Figure 4). After accounting for heterogeneity between centers, recipient, and donor factors, there was no association found between CIT and posttransplant mortality (aHR 1.00, 95% CI, 0.96-1.04, *P* > .9). Each year of recipient age at transplant >40, DM, PVD, years of RRT, previous transplant, and LD KDPI were associated with increased hazard of mortality. Preemptive transplant, black race, and more recent year of transplant were associated with lower hazard of mortality (Table 5). In an identically adjusted model where cases with missing data were handled by case-wise deletion (n = 5506), CIT was not associated with increased mortality (aHR 1.05, 95% CI, 0.99-1.11, *P* = .1).

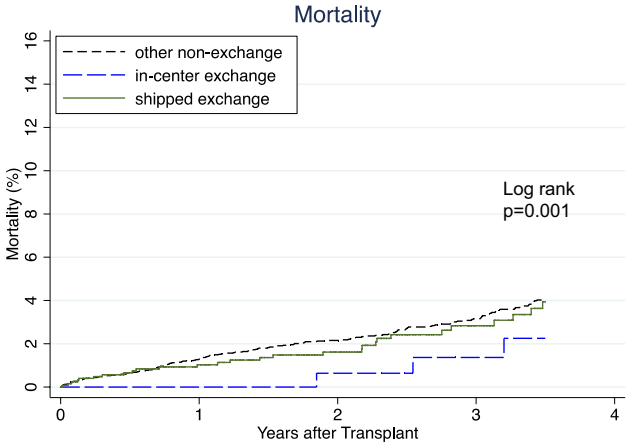


FIGURE 4 Time to mortality after transplant

TABLE 5 Risk factors for posttransplant mortality among KPD and non-KPD living kidney donor transplant recipients

	aHR (95% CI)	*P* value
Cold ischemia time (/h)	1.00 (0.96-1.04)	>.9
Recipient age at transplant (/y)	0.99 (0.95-1.03)	.6
Per year >40	1.07 (1.02-1.12)	<.01
Female recipient	0.79 (0.60-1.04)	.1
Black recipient	0.62 (0.40-0.98)	.04
Peripheral vascular disease	1.71 (1.09-2.66)	.02
Diabetic recipient	1.97 (1.53-2.54)	<.001
Recipient previous transplant	1.48 (1.04-2.11)	.03
Preemptive transplant	0.64 (0.47-0.87)	<.01
Years of RRT	1.06 (1.01-1.11)	.01
Grade school (or none) education	0.68 (0.32-1.46)	.3
Recipient public insurance	1.10 (0.85-1.41)	.5
LD KDPI	1.01 (1.00-1.01)	.02
Donor ABO O	0.97 (0.75-1.25)	.8
Year of transplant	0.91 (0.84-0.98)	.02

Mortality was modeled in a Cox regression with shared frailties to adjust for center variation (n = 6272). Missing data were handled through multivariate imputation.
aHR, adjusted hazard ratio; CI, confidence interval; KPD, kidney paired donation; LD KDPI, live donor kidney donor profile index; RRT, renal replacement therapy.

3.7 | Donors older than 50 years

There was no modified association between CIT and DGF among those with a donor aged >50 years (interaction $P = .06$). CIT remained associated with DGF among those with a donor aged 50 years or younger with aOR 1.07 (95% CI, 1.03-1.11, $P < .001$). There was no modified association between CIT and ACGF ($P = .4$), DCGF ($P = .3$), or mortality ($P = .8$) among those with older donors aged >50 years.

4 | DISCUSSION

The effect of shipping living donor kidneys on transplant recipient outcomes has been a major concern. In this retrospective cohort study of shipped live donor kidneys to KPD recipients in a large multicenter exchange program, each hour of CIT was associated with a 5% increased odds of DGF. As an example, a transplant recipient with a 3% chance of DGF might experience a 3.1% chance of DGF with 1 additional hour of CIT, a 3.6% chance of DGF with 4 additional hours of CIT, and a 5.3% chance of DGF with 12 additional hours of CIT. CIT was not found to be associated with graft failure or mortality. These results indicate only a minimal association between graft and patient outcomes and shipping living donor kidneys in a large multicenter KPD exchange program.

Similar to this study's observations with LDKT, in deceased donor kidney transplantation (DDKT) prolonged CIT has been identified as an independent risk factor for DGF.[12,13] The direct impact of CIT-induced DGF in the DDKT studies has not consistently predicted graft survival, implicating alternative or multifactorial etiological factors underlying DGF within deceased donor organs, such as cytokine release with brain death, or other factors, which lead to poorer outcomes.[9] Similar to deceased donor organs, prolonged cold storage in living donation appears to be associated with development of DGF; however, this small increase in DGF did not appear to be associated with graft or patient outcomes in this study. While this study was not specifically designed to investigate "CIT-induced DGF" as an etiology of allograft injury leading to poor graft and patient survival, our findings are comparable to those in the study published by Kayler et al, which was specifically designed to address "CIT-induced DGF" DDKT outcomes and attempted to control for other confounding factors surrounding the donor circumstance.[9] Other large observational studies have found no significant associations between CIT and deceased donor allograft function.[14] Finally, transplant centers should be aware of the small increase in risk for DGF that comes with increased shipping times demonstrated by this study, and incorporate that risk into their expectations for the transplant's performance along with other, more detrimental risk factors, such as additional time on RRT. An important line of research in this area includes additional investigation of the phenotype of the DGF (eg actual length of dialysis, and creatinine values shortly after transplant).[15] Further description of DGF phenotypes associated with shipping kidneys could help transplant centers determine whether or not the small risk of DGF associated with long shipping times is clinically meaningful to them.

Although recent studies reported poorer allograft outcomes with prolonged CIT in living donor recipients not participating in exchange programs, we observed no association between CIT and allograft or patient survival in our shipped KPD cohort. Krishnan et al found that among Australian recipients of kidneys from donors aged >50 years, CIT of 4-8 hours was associated with an increased odds of death-censored and all-cause graft failure.[7] We found no evidence that DGF, graft failure, or mortality differed by donors aged >50 years and those younger than age 50 years. These conflicting findings may be explained by differences in the study populations, study designs, and definitions of CIT used. In the Krishnan study, the kidneys were not shipped, and they excluded exchange transplants, transplants with CIT > 8 hours, and ABO-incompatible transplants. Although that study had longer follow-up (median 6.6 years), their maximum CIT was only 8 hours, less than the median CIT of 9 hours and a maximum of 23.9 hours in this study. Other previous studies of living donor exchange programs and shipping kidneys in the United States were limited by small sample sizes and shorter CIT, but report findings similar to what this study reports in regard to DGF and graft and patient outcomes.[5,6]

Aside from CIT, previous studies investigating outcomes of LDKT found risk factors that were similar to our results for DGF, allograft, and patient survival.[16-18] Routine use of older living donors is increasing in clinical practice, and organs from older donors have been repeatedly shown to have worse outcomes in LDKT but remain comparatively better than standard, young deceased donor organs.[19] In particular, DGF rates above 5% are seen with donors above the age of 60 years, which is well above the recent overall DGF rate of 2.75% for LDKT reported in the SRTR Annual Report.[20] On the other hand, higher donor age, which independently predicted poorer graft survival in this study, suggests that prolonged CIT may prove less harmful than other factors (such as age). Considering these and other acceptable risk factors for poorer outcomes in LDKT, distance between centers, shipping, and potentially prolonged cold storage can be a consideration in optimizing strategies for matching for exchange outcomes. However, this study does not suggest that long shipping times should prevent exchanges from occurring or contribute to the barriers to transplantation.

The results of this study need to be considered in the context of study design. The primary limitation of the study is its limited follow-up time, with a maximum of 7.8 years. Ultimately, long-term graft survival after shipped KPD entailing long CIT must be investigated, and continued follow-up of the participants in this study is an important next step. Next, retrospective studies like this one are limited by unmeasured confounding variables. While attempts were made to account for other transplant center, recipient, and donor factors that may be associated with post-transplant outcomes, there are other unique unmeasured/unrecognized variables in exchange programs that potentially alter graft and patient outcomes. These include variables such as improved HLA-matching, use of alternate, potentially less aggressive desensitization protocols, and garnering more "high profile" attention

as exchange cases in transplant centers. Unmeasured variations between shipping protocols and in-center exchanges also could contribute to the differences in outcomes. These would include differences in packing and handling the organs, variations in operative techniques (donor and recipient), and unfamiliar donor and recipient surgeons working together in out-of-center exchanges. Furthermore, recipients in exchange programs tend to be more complex immunologically (sensitized), have donor-specific antibodies, have undergone prior transplantation, or have other extenuating circumstances surrounding their operative procedure. Together, these unmeasured factors could be confounding the outcomes we studied in shipped KPDs. A third limitation of using large administrative databases is with missing data. Additionally, the impact of pumping the organ during transport could not be studied here. In this study, CIT was missing in 51 cases from both SRTR and NKR. Several other recipient and donor factors had small varying degrees of missingness. These missing values were imputed through multivariate imputation. Inferences remained consistent through case-wise deletion and multivariate imputation analysis.

Future studies on KPD exchange programs and the practice of shipping kidneys incurring long cold ischemia times could begin to focus on implementing enhanced matching algorithms for refining donor selection to minimize risk of poor outcomes balanced by patient willingness to assume risks through a thorough and informed consent process. Efforts are also needed that focus on issues and barriers with international exchanges between countries that abide by ethical and laboratory standards.[21] Further studies are needed, particularly in the context of increased acceptance and practice of compatible pair KPD.

The practice of shipping living donor kidneys in KPD exchange programs increases CIT in kidney allografts. This study demonstrated increased odds of DGF for KPD recipients of shipped kidneys, but no associations between CIT and graft or patient survival. These findings support the current practice of shipping living donor organs in efforts to increase overall living donor transplantation, but should be considered along with the caveat that the long-term outcomes of shipping kidneys are not yet known. This study will hopefully guide further research and contribute new evidence around the upper limits of cold time and shipping distance acceptable for KPD programs, allaying some of the fears of transporting living donor kidneys in the international transplant community.

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DISCLOSURE

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