

Cold Ischemia Time and Allograft Outcomes in Live Donor Renal Transplantation: Is Live Donor Organ Transport Feasible?

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One of the greatest obstacles to the implementation of regional or national kidney paired donation programs (KPD) is the need for the donor to travel to their matched recipient's hospital. While transport of the kidney is an attractive alternative, there is concern that prolonged cold ischemia time (CIT) would diminish the benefits of live donor transplantation (LDTx). To examine the impact of increased CIT in LDTx, 1-year serum creatinine (SCr), delayed graft function (DGF), acute rejection (AR) and allograft survival (AS) were analyzed in 38 467 patients by 2 h CIT groups (0–2, 2–4, 4–6 and 6–8 h) using data from the United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN). Adjusted probabilities of DGF and AR were estimated in multivariate logistic regression models and AS was examined in multivariate Cox proportional hazards models. Although some increase in DGF was observed between the 0–2 h (4.7%) and 4–6 h (8.3%) groups, prolonged CIT did not result in inferior SCr, increased AR or compromised AS in any group with >2 h CIT compared with the 0–2 h group. Comparable long-term outcomes for these grafts suggests that transport of live donor organs may be a feasible alternative to donor travel in KPD regions where CIT can be limited to 8 h.

Key words: Donor exchange, live donor renal transplantation, organ shipping, paired donation, paired kidney exchange

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Introduction

The association between prolonged cold ischemia time (CIT) and inferior renal allograft outcomes has been established in deceased donor transplantation. Between July 2004 and June 2005, nearly one-third of deceased donor organs were transported either regionally or nationally in the United States (1). Inevitably, this practice increases the duration of CIT. Prolonged preservation time of deceased donor organs has been shown to result in an increased incidence of delayed graft function (DGF), with consequences that include increased length of hospital stay, increased rates of acute rejection (AR), poor long-term outcomes and higher health care expenditures (2–15). These data, however, cannot be directly extrapolated to the effect of CIT on live donor kidneys because deceased donor organs are exposed to additional injury associated with brain death and, in the case of donors after cardiac death (DCD), prolonged warm ischemia time.

A significant graft survival advantage has been demonstrated for live donor organs compared with deceased donor organs over the last decade (based on Organ Procurement and Transplantation Network [OPTN] data as of May 26, 2006). However, an estimated 2500–4000 patients each year are unable to take advantage of this benefit because they have a blood type incompatibility or a positive crossmatch with their only willing live donor (16). Some of these patients may be candidates for preconditioning protocols that reduce donor-specific antibody to permit successful transplantation across this immunologic barrier. The downside to this approach is that these protocols are associated with additional costs (17) and an increased risk of antibody mediated rejection (18,19) compared with transplantation in compatible live donor recipients. For many recipients with incompatible live donors, kidney paired donation (KPD) is the best transplantation option because it circumvents the incompatibility altogether (20–22).

We have previously demonstrated that recipients of grafts that were allocated using a local KPD program experienced clinical outcomes that were comparable to compatible live donor recipients (20). Because these procedures took place within the same center, the duration of CIT was limited to less than 2 h. To scale KPD to the regional or

national level and optimize the opportunities for transplantation in difficult-to-match patients, either donors or kidneys will need to travel long distances in some circumstances (17). The conundrum of donor travel versus graft transport is perceived as a major barrier to wider acceptance of KPD. On the one hand, donor travel involves unreimbursed costs which may favor those with the financial means necessary to support this alternative. In addition, it separates families at a critical time when their support may be necessary. Alternatively, the transport of kidneys to recipient centers after simultaneous donor nephrectomies has been challenged on the grounds of a perceived reduction in the benefit that is attributed to the short CIT which occurs in live donation. This argument is based on the assumption that increased CIT has the same impact on kidneys from both deceased and live donors.

In order to better understand the effect of prolonged CIT on live donor organs, we performed a study of over 38 000 adult, live donor renal transplant recipients with up to 8 h of CIT using national United Network for Organ Sharing (UNOS)/OPTN data. Our hypothesis was that CIT in the range that might be expected with the regional transport of live donor kidneys is not associated with a measurable difference in long-term outcomes. We demonstrate a small increase in the rate of DGF in patients with prolonged CIT, however, we observed no association between increased duration of CIT and decline in renal function, increased rates of AR, or decline in allograft survival (AS) in recipients of live donor kidneys. We feel that these findings support the transport of live donor kidneys across geographic regions that produce CIT of 8 h or less.

Materials and Methods

Study design

This was a retrospective cohort study in adult primary live donor renal transplant recipients that evaluated the association between the duration of CIT and four outcome measures: DGF, renal function at 1 year following transplantation, AR within 1 year following transplantation and AS.

Study population

The study population included patients who were available for analysis in the UNOS Kidney/Pancreas Standard Transplant Analysis and Research (STAR) Files. We evaluated 231 565 recipients who underwent renal transplantation between January 1990 and September 2005. Adult (≥ 18 years of age) recipients of live donor kidneys over this interval were included in this analysis. All pediatric recipients ($n = 12\,450$) and deceased donor renal transplant recipients ($n = 138\,254$) were excluded from analysis. Live donor recipients with a history of a prior renal transplant procedure were not considered in this analysis ($n = 6198$).

The 56 341 identified recipients were stratified by the duration of CIT exposure. These strata included: 0–2, 2–4, 4–6, 6–8 and over 8 h. Because of the extremely broad distribution of CIT's in recipients in the CIT >8 h group (median: 30 h, IQR: 20–40 h), as well as the high likelihood of technical complications or data entry errors for these grafts, these observations were excluded from analysis ($n = 813$, 1.4%). In addition, all recipients who had no reported CIT ($n = 17\,061$, 30.3%) were excluded from further analy-

sis. The patients who were excluded for missing CIT values were compared with those who were included in this analysis and found to be similar with respect to all model covariates used in the multivariate modeling steps and the four outcome measures that were used in this study (as detailed below). Based upon these findings, we believe that these data are missing at random and are noninformative for the purposes of our analysis.

Statistical analyses

Regression modeling techniques: All multiple logistic and Cox proportional hazards regression models were developed through a series of steps. The first phase of modeling consisted of the unadjusted analysis of donor, recipient and immunologic match covariates. The appropriate functional form of model covariates was determined by exploratory data analysis in unadjusted models. The primary group variable was the duration of CIT which was examined in strata of 0–2, 2–4, 4–6 and 6–8 h. The recipient covariates that were examined included: age, gender, race/ethnicity, ABO blood group, history of diabetes mellitus, history of hypertension, history of pretransplant blood transfusion, history of previous pregnancy, peak panel-reactive antibody (PRA) level and history of pretransplant dialysis. The donor covariates included: age, gender, race/ethnicity and ABO blood group. Immunologic match was examined using separate covariates for the number of HLA-A, HLA-B and HLA-DR mismatches that were present between the donor and recipient.

Those variables that were found to be statistically significant predictors of the outcome measure in unadjusted models were included in a preliminary multivariate model. In order to adjust for the most important potential confounders of the association between CIT and the outcome measures, parsimonious models were developed by testing nested models for a reduction in the Akaike's Information Criterion (AIC). Model covariates were excluded if they met the following two criteria: (1) exclusion of the covariate from the model led to either no change or a reduction in the AIC value (2); testing of all covariates that were under consideration for exclusion together by the likelihood ratio test did not demonstrate a statistically significant ($p < 0.05$) finding suggesting that the combination of the covariates contributed to the explanatory power of the model. The absence of multi-collinearity was confirmed by examination of covariate variance inflation factors in all models. Furthermore, in the Cox proportional hazards regression models, proportional hazards assumptions were examined in complementary log-log plots by CIT group and tested by examination of Schoenfeld residuals in both univariate and multivariate models. We refer to the final model that resulted from this series of steps as the parsimonious model for each analysis. Notably, each model was empirically designed using the above steps and without predetermined assumptions of the necessary adjustment variables. For this reason, there were differences in the covariates that were included for adjustment in the final parsimonious models for each of the outcome measures.

Renal function

Renal function was measured using serum creatinine (SCr) level in mg/dL. SCr levels at 1 year following transplantation were defined as those values that were recorded between 11 and 13 months following the date of transplantation. The number of patients with functioning allografts who did not have recorded SCr values during this period ranged from 28.9% to 30.1% in the CIT groups.

Delayed graft function

DGF was defined as need for dialysis within the first week following transplantation. The level of missing data for DGF by CIT group ranged from 0.3% to 1.5%. The association of DGF with duration of CIT was evaluated in a parsimonious multiple logistic regression model. The covariates that were identified through parsimonious modeling steps to be necessary for inclusion in the adjusted model included recipient race/ethnicity (reference

group: white recipient), recipient history of diabetes mellitus (reference group: absence of diabetes mellitus), recipient history of pretransplant transfusion (reference group: absence of pretransplant transfusion), peak PRA level categories (groups: 0, 1–20, 21–80, 81–100, reference group: 0), HLA-A mismatch (reference group: 0 mm), HLA-DR mismatch (reference group: 0 mm), donor race/ethnicity (reference group: white donor). The fit of the logistic regression model to the observed data was confirmed by the Hosmer-Lemeshow goodness-of-fit test grouped into deciles of risk (C statistic: 6.2, p-value: 0.63). Adjusted probabilities of DGF that accounted for potential confounders in the parsimonious model were calculated from the logistic regression model by algebraic transformation of the odds of the event.

AR within the first year following transplantation

A subgroup analysis was performed on recipients with at least 365 days of follow-up to evaluate the association between the development of AR and duration of cold ischemic time. Patients were excluded from this analysis if they had <365 days of follow-up as determined by subtracting the date of transplant from the date that the data were captured for our dataset. A total of 2774 patients (7.2%) were excluded with follow-up of <365 days. The field TRTRESJ1Y_KI was used to define rejection events. The level of missing data on AR by CIT group ranged from 26.0% to 30.1%. The parsimonious multiple logistic regression model that was used to evaluate the association between CIT and AR included the following adjustment covariates: recipient age (reference group: ≥ 55 years), recipient race/ethnicity (reference group: white recipient), recipient history of pretransplant transfusion (reference group: absence of pretransplant transfusion), recipient history of dialysis prior to transplantation (reference group: no history of dialysis), peak PRA level categories (groups: 0, 1–20, 21–80, 81–100, reference group: 0), HLA-A mismatch (reference group: 0 mm), HLA-B mismatch (reference group: 0 mm), HLA-DR mismatch (reference group: 0 mm), donor age (groups: <40 years, 40–55 years, >55 years, reference group: <40 years) and donor race/ethnicity (reference group: white donor). The Hosmer-Lemeshow goodness-of-fit test statistic in this model was 6.74 ($p = 0.56$) indicating adequate overall fit of the observed and predicted measures when analyzed by deciles of risk. Adjusted probabilities of AR that accounted for the potential confounders in the parsimonious model were calculated from the logistic regression model by algebraic transformation of the odds of the event.

Survival analyses

Unadjusted overall AS and death-censored AS rates were estimated using Kaplan-Meier methodology. The graft survival time for recipients who had a recorded allograft loss time of 0 ($n = 184$, 0.5%) was adjusted to 0.001 months in order to include these patients in the survival analysis. There was no difference in the proportion of patients who required this adjustment by CIT group ($p = 0.91$). Comparison of unadjusted survival experience between CIT groups and between groups stratified on both DGF and CIT, was performed with the log-rank test. For death-censored analysis of survival, graft loss observations were censored for patients who had a date of death that was equivalent to the date of allograft loss.

Death-censored AS was further analyzed in Cox proportional hazards regression models. Based upon our parsimonious modeling steps, the following covariates were found to be necessary in the adjusted Cox proportional hazards model: recipient age (as a continuous measure), peak PRA level (reference group: <20%), level of HLA mismatch (reference group: 0 mm), donor age (reference group: <50 years).

Statistical significance

Unless otherwise specified, all tests were two-sided with statistical significance set at the $\alpha = 0.05$ level. All analyses were performed using Stata 9.1 for Linux (StataCorp, College Station, TX).

Results

Demographics

A total of 38467 adult, live donor renal transplant recipients were identified who met criteria for inclusion in this analysis. These patients were stratified by the duration of CIT into the following groups: 0–2, 2–4, 4–6 and 6–8 h. CIT duration of less than 2 h was considered the 'ideal' CIT group and was used as the reference group for comparisons. The characteristics of these subjects are presented in Table 1. A large majority of live donor recipients in the United States (85.1%) received grafts with less than 2 h of CIT. The CIT duration was 2–4 h for 12.1%, 4–6 h for 1.8% and 6–8 h for 1.0% of the recipients, respectively.

Delayed graft function

The rate of DGF was low across all CIT groups. The baseline unadjusted probability of DGF was 4.9% in the 0–2 h CIT group. With increased duration of CIT, there was a small absolute increase in the unadjusted probability of DGF. Patients with 2–4, 4–6 and 6–8 h of CIT had DGF rates of 5.8%, 8.4% and 7.5%, respectively. Using a parsimonious multivariate logistic regression model, adjusted probabilities of DGF were estimated for each of the CIT groups in order to account for potential confounders (Figure 1). The adjusted probability of DGF in the 0–2 h group was 4.7% (95% CI: 4.4–5.0%). The adjusted probabilities of DGF in the 2–4, 4–6 and 6–8 h CIT groups were 4.9% (95% CI: 4.3–5.8%), 8.3% (95% CI: 6.1–11.2%) and 9.2% (95% CI: 4.1–19.1%), respectively. Compared with the 0–2 h group, only the 4–6 h CIT group was observed to differ in a statistically significant fashion ($p < 0.001$).

Renal function

Renal function at 1 year following transplantation was analyzed in patients with functioning allografts (Figure 2). There were no statistically significant differences in 1-year SCr level between recipients in any of the groups with CIT >2 h and the reference group ($p > 0.05$ for all comparisons). The 1-year SCr values in the 0–2, 2–4, 4–6 and 6–8 h groups were 1.4 (IQR: 1.1–1.7), 1.4 (IQR: 1.1–1.7), 1.4 (IQR: 1.2–1.7) and 1.5 (IQR: 1.2–1.8) mg/dL, respectively.

AR within 1 year Following transplantation

AR episodes that occurred within the first year following transplantation were examined in a subgroup of the cohort with at least 1 year of follow-up. Unadjusted rates of AR were 27.0%, 21.4%, 19.7% and 41.6% in the 0–2, 2–4, 4–6 and 6–8 h groups, respectively. Multivariate adjustment of the probability of AR within the first year following transplantation was performed in order to account for potential confounders using a parsimonious multiple logistic regression model. The results of this analysis are presented in Figure 3A. The adjusted probabilities of AR in the 0–2, 2–4, 4–6 and 6–8 h groups were 26.5% (95% CI: 25.7–27.2%), 20.5% (95% CI: 18.9–22.1%), 18.9% (15.2–23.1%) and

Table 1: Characteristics of live donor kidney recipients in the United States (1990–2005) by the duration of cold ischemic time

	Duration of Cold Ischemic Time				Overall
	0–2 h	2–4 h	4–6 h	6–8 h	
N	32 719	4663	692	393	38 467
(% Total)	(85.1%)	(12.1%)	(1.8%)	(1.0%)	
Age (IQR)	43 (32–53)	45 ¹ (34–55)	46 ¹ (35–54)	40 ¹ (29–49)	43 (32–54)
Gender ² (% male)	58.3%	57.9%	61.7%	58.8%	58.3%
Race ² (%)					
White	69.6%	68.7%	70.5%	71.1%	69.5%
Black	14.5%	14.0%	14.0%	12.5%	14.4%
Hispanic	11.1%	12.0%	11.3%	12.8%	11.2%
Asian	2.9%	3.2%	3.5%	2.3%	3.0%
AI/AN	0.9%	1.0%	0.6%	0.5%	0.9%
NH/PI	0.5%	0.6%	0.3%	0.3%	0.5%
Other	0.5%	0.4%	0.0%	0.5%	0.5%
ABO Blood Group ² (%)					
O	45.6%	44.7%	47.4%	46.1%	45.6%
A	38.2%	38.4%	37.6%	37.7%	38.2%
B	12.6%	13.2%	10.3%	13.7%	12.7%
AB	3.5%	3.7%	4.8%	2.5%	3.5%
HLA Mismatch					
HLA mismatches (IQR)	3 (2–4)	3 ¹ (2–4)	3 ¹ (2–4)	2 ¹ (1–3)	3 (2–4)
0 Ag mismatch ³	14.7%	11.7%	13.4%	16.3%	14.3%
6 Ag mismatch ⁴	5.4%	6.1%	7.5%	4.6%	5.5%
Comorbid disease					
Diabetes mellitus ⁵	27.3%	28.5%	27.6%	20.0%	27.4%
Medically managed HTN ³	80.0%	86.0%	83.5%	82.1%	80.9%

AI/AN = American Indian/Alaskan Native; NH/PI = Native Hawaiian/Pacific Islander; IQR = inter-quartile range

¹p < 0.001 compared with 0–2 h group by Wilcoxon ranksum test.

²p > 0.05 by Pearson chi square test.

³p < 0.001 by Pearson chi square test.

⁴p = 0.02 by Pearson chi square test.

⁵p = 0.17 by Pearson chi square test.

27.9% (95% CI: 20.7–36.4%), respectively. The decrease in AR rates in the 2–4 and 4–6 h groups compared with the 0–2 h group were found to be statistically significant ($p < 0.05$). Notably, there was no evidence of an increase in the probability of AR for any of the groups with CIT >2 h compared with the 0–2 h reference group.

Recognizing that AR rates have declined over the period of study, we also analyzed a dataset that was limited to the current era of immunosuppression (year of transplantation: 2002–2005, $n = 8566$). This subgroup analysis did not reveal any statistically significant differences in the adjusted probability of AR within the first year following transplantation for groups with >2 h CIT compared with the 0–2 h group (Figure 3B, $p > 0.05$ for all comparisons). The adjusted probabilities of AR within the first year following transplantation for recipients in the 0–2, 2–4, 4–6 and 6–8 h groups in the current era were 11.1% (95% CI: 10.1–12.2%), 12.9% (95% CI: 10.9–15.2%), 8.5% (95% CI: 5.0–14.2%) and 12.8% (95% CI: 3.9–34.8%).

Allograft survival

Unadjusted Kaplan-Meier estimates of overall AS and death-censored AS are presented in Figure 4 and Table 2. We did not observe a statistically significant difference

in the survival experiences between CIT groups when all causes of graft loss were considered ($p = 0.15$). Examination of the Kaplan-Meier curves for overall AS (Figure 4A) reveals a similar pattern of allograft loss for all groups over the initial 10 years following transplantation. There is no evidence of either early or late divergence between the survival curves. The 10-year AS estimates for the 0–2, 2–4, 4–6 and 6–8 h groups were 56.4%, 55.5%, 53.7% and 55.6%, respectively. The median durations of AS when all causes of graft loss were considered were 136, 133, 134 and 136 months, respectively.

A death-censored analysis of AS was undertaken in order to eliminate death with a functioning allograft from consideration as a graft loss event in the survival statistics. When death was censored as an etiology of graft loss, there were no statistically significant differences in AS across the CIT groups ($p = 0.45$). At 10 years following transplantation, the difference between the minimum and maximum death-censored AS estimates across CIT groups was 1.8% (0–2 h group: 69.2%, 4–6 h group: 67.4%, Table 2). Examination of the Kaplan-Meier curves presented in Figure 4B again reveals very similar patterns of allograft loss across the 10-year posttransplantation period. There is no indication of increased rate of loss in the early posttransplant period or

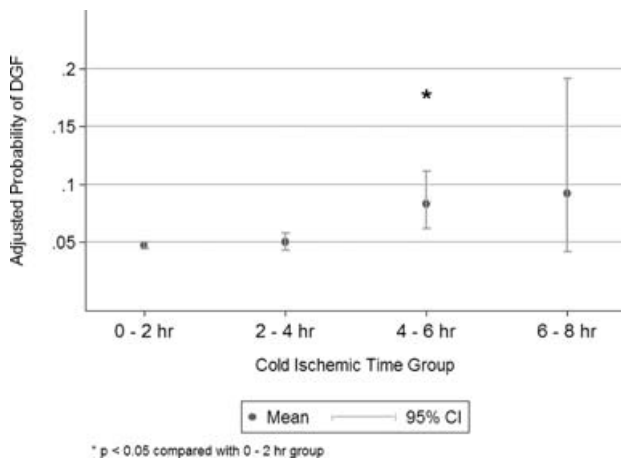


Figure 1: Adjusted probability of delayed graft function following live donor renal transplantation, by duration of cold ischemic time. Delayed graft function was defined as the need for dialysis during the first week following transplantation. A parsimonious multivariate logistic regression model was used to estimate the adjusted probability of delayed graft function associated with the duration of cold ischemic time. Covariates used for adjustment in the parsimonious model included recipient race/ethnicity, recipient history of diabetes mellitus, recipient history of pretransplant transfusion, peak panel-reactive antibody level, HLA-A mismatch, HLA-DR mismatch and donor race/ethnicity.

acceleration of long-term losses in the groups of patients who experienced prolonged CIT. Median death-censored AS estimates for the 0–2, 2–4, 4–6 and 6–8 h groups were 174, 161, >177 and 171 months, respectively.

Death-censored AS was further examined by Cox proportional hazards modeling to investigate the relationship between CIT and allograft loss accounting for potential con-

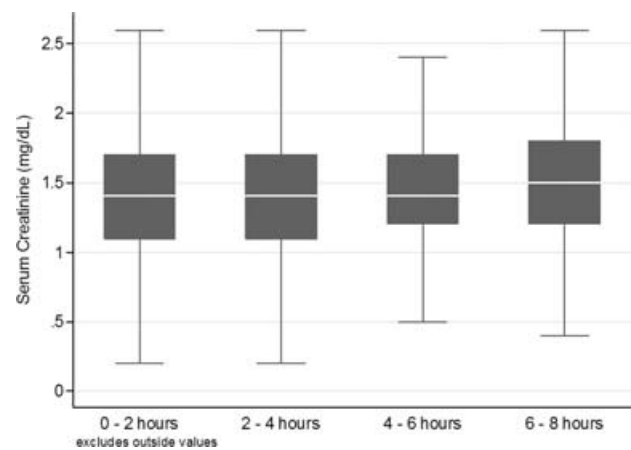


Figure 2: Analysis of renal function at 1 year following transplantation, by duration of cold ischemic time. One-year serum creatinine levels in recipients of live donor renal allografts are presented by cold ischemic time group. Statistical comparisons were performed between groups with >2 h cold ischemic time and the 0–2 h cold ischemic time reference group. There were no statistically significant differences between any of the >2 h cold ischemic time groups and the reference group (<2 h cold ischemic time) at 1 year following transplantation (p > 0.05).

founders (Table 3). The 0–2 h group was used as the reference group for these models. No statistically significant association was found between the duration of CIT and death-censored AS in either unadjusted or adjusted Cox proportional hazards models.

Discussion

Despite a nearly 2-fold expansion in the rate of live donor renal transplantation over the past decade, a wide

Table 2: Unadjusted Kaplan-Meier estimates of overall and death-censored allograft survival by duration of cold ischemic time following live donor renal transplantation.

	CIT duration (h)	1-year (95% CI)	5-year (95% CI)	10-year (95% CI)	Median survival (mos)
Allograft Survival¹	0–2	94.4% (94.1–94.6)	79.4% (78.9–79.9)	56.4% (55.5–57.3)	136
	2–4	93.4% (92.6–94.1)	77.9% (76.3–79.5)	55.5% (52.1–58.8)	133
	4–6	91.3% (88.9–93.2)	77.1% (72.6–81.0)	53.7% (45.3–61.4)	134
	6–8	91.5% (88.2–93.9)	76.7% (71.9–80.9)	55.6% (49.5–61.2)	136
Death-censored allograft survival²	0–2	96.2% (96.0–96.4)	86.3% (85.8–86.7)	69.2% (68.3–70.1)	174
	2–4	95.7% (95.0–96.2)	85.6% (84.2–86.9)	67.9% (64.3–71.1)	161
	4–6	94.5% (92.4–96.0)	86.6% (82.7–89.6)	67.4% (57.8–75.3)	>177
	6–8	94.0% (91.1–96.0)	83.0% (78.5–86.7)	67.8% (61.7–73.2)	171

CIT = cold ischemia time

¹p > 0.05 for comparison of overall AS experience between cold ischemic time groups.

²p > 0.05 for comparison of death-censored AS experience between cold ischemic time groups.

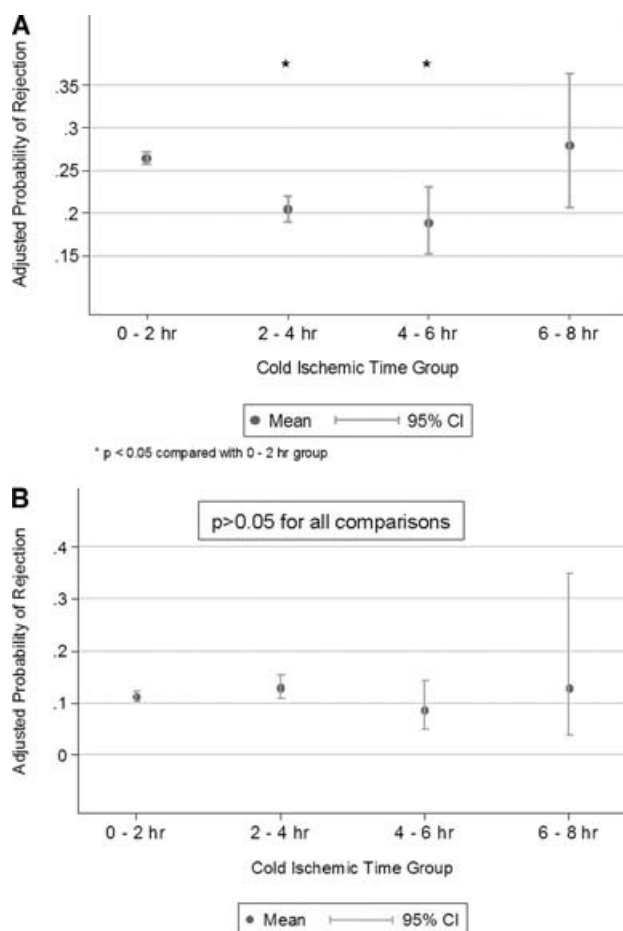


Figure 3: Adjusted probability of acute rejection within the first year following live donor transplantation, by duration of cold ischemic time. Acute rejection within the first year following transplantation was analyzed by multiple logistic regression modeling. This analysis was performed in a subgroup of recipients with at least 1 year of follow-up between 1990 and 2004 (A) and in the current era of immunosuppression between 2002 and 2004 (B). The following covariates were included for adjustment in the final multiple logistic regression model: recipient age, recipient race/ethnicity, recipient history of pretransplant transfusion, recipient history of dialysis prior to transplantation, peak PRA level, HLA-A mismatch, HLA-B mismatch, HLA-DR mismatch, donor age and donor race/ethnicity. Comparisons were between each group with CIT > 2 h and the 0–2 h reference group.

disparity between organ availability and need persists. HLA and blood type incompatibility remain two of the most significant barriers to increasing live donation. Through simulation modeling we have estimated that between 2500 and 4000 patients who enter the system each year have an antibody-mediated incompatibility with their only willing live donor (16). Using optimized matching algorithms nearly 50% of these patients could potentially be paired with an ABO compatible, negative crossmatch donor in a 2-way KPD (i.e. an exchange that involves two donors and two recipients) (17). However, there remain signifi-

cant logistical challenges to the creation of a regional or national KPD program. Principal among these is the question of how to deal with the matching of pairs across large geographic areas. Forcing donors to travel to the hospital of their matched recipient for the transplant procedure involves significant unreimbursed expenses and the separation of these patients from their loved ones. For example, a maternal donor might be separated from her child for a prolonged period of time after donation. An alternative is to perform the donor operations simultaneously and transport the kidneys to the recipient centers, allowing families to remain together. This approach has been criticized because of the perception that the increased CIT would eliminate, or greatly reduce, the benefits of live donation. However, this assumption is derived from the extrapolation of studies that investigated the impact of CIT on deceased donor organs that were transported through regional and national sharing programs. These organs are subjected to injury associated with brain death and, in some circumstances, prolonged warm ischemia (DCD kidneys) and, therefore, the effect of CIT cannot be directly compared to live donor transplantation (LDTx). In addition, the vast majority of live donor kidneys are exposed to CIT durations that are much shorter than those which are encountered in deceased donor transplantation. As a result, little is known about the consequences of increased CIT on live donor kidneys.

In this analysis, we show that patients who receive live donor allografts with CIT durations as long as 8 h have a slight increase in the rate of DGF but were unable to demonstrate differences in renal function, AR or long-term AS. It is notable that the prolongation of CIT up to 8 h during these live donor procedures was likely unintended in many cases and may have resulted from complications associated with organ procurement, the recipient operation, or both. It is, therefore, possible that the DGF association observed with prolongation of CIT is in part due to these untoward technical complications.

In the deceased donor recipient population, Ojo and colleagues observed an increased rate of AR, prolonged length of hospital stay and reduced graft survival associated with the development of DGF (2). In their analysis of over 38000 recipients from the U.S. Renal Data System database, they found CIT to be one of the strongest predictors of DGF development. DGF is much more common among deceased donor recipients than it is in the live donor recipient population. According to UNOS data, the incidence of DGF among adult, primary deceased donor recipients has remained consistent at a rate of approximately 24% over the last decade (based on OPTN data as of September 14, 2005).

In contrast to the incidence of DGF that is encountered in the deceased donor recipient population, the rates that were observed for live donor recipients in this study were significantly lower across all CIT groups. In an analysis that

Table 3: Cox proportional hazards models of death-censored renal allograft survival stratified by duration of cold ischemic time

Cold ischemia time	Unadjusted model			Adjusted model		
	Unadjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
0–2 h	1.00	Ref	Ref	1.00	Ref	Ref
2–4 h	1.05	0.97–1.15	0.24	1.09	0.98–1.20	0.12
4–6 h	1.07	0.86–1.32	0.54	1.13	0.88–1.46	0.33
6–8 h	1.10	0.91–1.34	0.32	1.05	0.82–1.35	0.69

HR = hazard ratio.

Cox proportional hazards regression modeling was performed to determine the association between cold ischemic time and death-censored allograft survival. The model was adjusted for recipient age, peak panel-reactive antibody level, total HLA mismatch level and donor age.

accounted for a number of potential confounding variables in the relationship between CIT and DGF, the adjusted rates of DGF were 4.7%, 4.9%, 8.3% and 9.2% in recipients who received kidneys with 0–2, 2–4, 4–6 and 6–8 h of CIT, respectively. Notably, this small increase in DGF that occurred with increased CIT was not associated with compromised renal function at 1 year or an increased rate of AR during the first year following transplantation. In addition, renal AS was not found to differ between the CIT groups over posttransplant follow-up of up to 10 years.

Eight hours is not a sufficient duration of time to permit transport of organs across all possible distances that would be expected between donor and recipient transplant centers in a national KPD program. However, our previous work has shown that fewer than 3% of pairs would need to travel outside of their UNOS-defined region in order to optimize the number of matches in a national KPD program (17). Most of these donors and recipients will be from hard-to-match pairs and there may be donors who would be willing to travel or recipients who would consider a live donor graft with longer CIT in order to gain the benefits of a national match in such circumstances.

Based upon estimates of 3 h of storage between cold perfusion of the organ and departure from the airport at the donor location and three additional hours of transport between the destination airport and the start of implantation, a total in-air travel time of approximately 2 h would maintain CIT at 8 h. With these assumptions, donors in Baltimore would be able to provide organs for recipients in locations that include Atlanta, Birmingham, St. Louis, Nashville, Chicago, Albany and Boston based upon standard passenger airline travel times. We acknowledge that these are very rough estimates because of the numerous logistic issues that would be encountered in paired donation. Additional factors that might prolong CIT which must be considered include distance and traffic congestion that exists between transplant centers and airports, air traffic delays, availability of recipient operating rooms in the latter half of the day, and difficulties encountered during the preimplantation phase of the recipient procedure. Donors and recipients will need to be well informed of the poten-

tial known and unknown complications resulting from the practice of live donor organ transport.

During the period of analysis, a dramatic shift in the approach to live donor nephrectomy occurred. Most studies comparing laparoscopic and open techniques have not shown a difference in DGF, slow graft function, AR, or graft loss rates. Between 1990 and 1999, there are limited data in the UNOS registry on the type of donor procedure that was performed (46–99% of all donors missing data on nephrectomy procedure type). Among 16 822 procedures that were performed between 2000 and 2005 (43.7% of the study population), the overall rate of laparoscopic donor nephrectomy was 70.0%. A total of 70.6%, 69.6%, 56.4% and 38.6% of donors in the 0–2, 2–4, 4–6 and 6–8 h CIT groups were recorded as having laparoscopic procurement procedures ($p < 0.001$). Unfortunately, the registry does not specify whether some of these differences resulted from laparoscopic procedures that were converted to open operations. The lack of data preclude a valid subgroup analysis between those who received laparoscopic and open donor procedures.

We acknowledge several additional limitations in this study. As with many retrospective analyses of large national datasets, we encountered incomplete data for the grouping variables and outcome measures that were analyzed. We performed a comparison between patients who were missing information on their duration of CIT and those who were included in this analysis and found that these groups were similar across outcome measures and model covariates that were used in this study. We therefore feel that the study population was an appropriate sample of the overall cohort of live donor recipients who underwent transplantation during this period. Inferences from our findings on each outcome measure must be made based upon the assumption that there was no systematic bias in data reporting on DGF, SCr level, AR or graft loss that would impact one CIT group to a different degree than another CIT group, thereby altering the associations, or lack thereof, which were found in this study. As with all regression modeling studies, the analyses are limited to available data and we acknowledge that there may be additional important

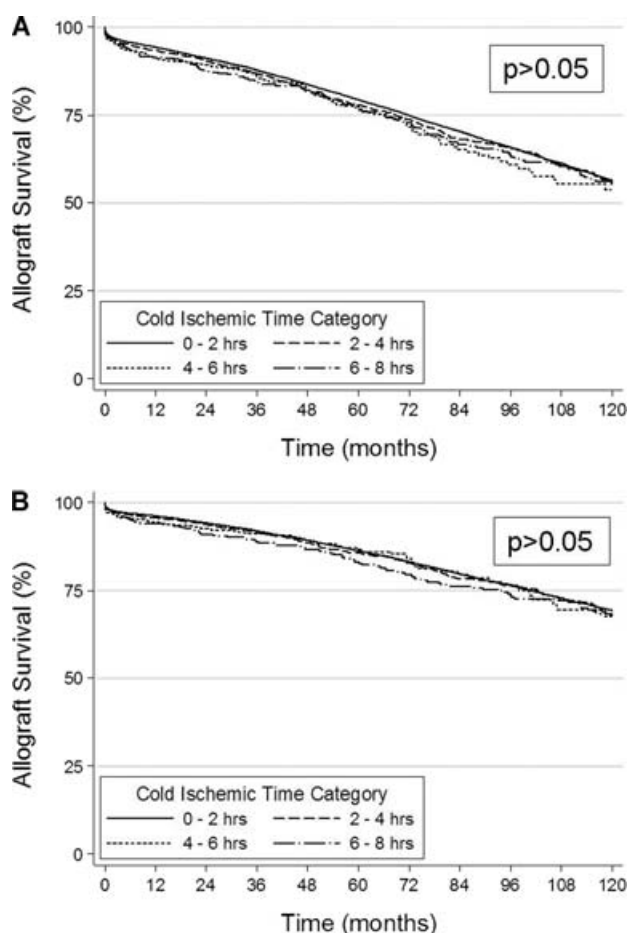


Figure 4: Unadjusted Kaplan-Meier estimates of death-censored allograft survival, by duration of cold ischemic time.

Allograft survival was estimated for each of the cold ischemic time categories using Kaplan-Meier methodology. There was no statistically significant difference in survival between the cold ischemic time groups by log-rank test on either the overall (A) or death-censored (B) analysis.

variables that influence the outcome measures that are presented in this study which were not included in our modeling strategy.

Conclusion

In summary, we present an analysis of the association between extended durations of CIT and renal allograft outcomes in live donor recipients from UNOS/OPTN registry data. While we identified a small increase in the rate of DGF with increased CIT of up to 8 h, this prolongation of preservation time did not compromise renal function, increase AR rates, or influence long-term AS. The data presented in this study suggest that the use of organ transport with CIT maintained at less than 8 h will not reduce the benefit of live donor kidney transplantation and should be consid-

ered in the national debate over the optimal approach to KPD. The impact of CIT durations that exceed 8 h will require prospective pilot studies of organs shared over wider geographic regions.

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