Cold ischemia time up to 16 hours has little impact on living donor kidney transplant outcomes in the era of kidney paired donation

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In living donor transplantation, cold ischemia time is a concern in transplants involving kidney paired donation. The impact of cold ischemia time over eight hours is unknown. Here we examined the association of cold ischemia time with delayed graft function and allograft loss among 48,498 living recipients in the Scientific Registry of Transplant Recipients registry. The incidence of delayed graft function was low but significantly higher among patients with longer cold ischemia times (0-2.0 hours: 3.3%; 2.1-4.0 hours: 3.9%; 4.1-8.0 hours: 4.3%; 8.1-16.0 hours: 5.5%). In multivariate analyses, only those with cold ischemia times of 8.1-16.0 hours had increased odds of delayed graft function (odds ratio 1.47; 95% confidence interval 1.05-2.05) compared to patients with times of 0-2.0 hours. In multivariate time-to-event analyses, cold ischemia times of 16 hours or less were not associated with allograft loss from any cause including death or death-censored graft loss with hazard ratios for cold ischemia times between 8.0-16.0 hours of 0.97 (95% confidence interval 0.74-1.26) and 1.09 (0.81-1.48) compared to patients with times of 0-2.0 hours). The results were consistent in paired and non-kidney paired donation transplants and in those with living donors over 50 years of age. In subgroup analysis restricted to kidney paired donation recipients, there was no difference in the risk of delayed graft function with an odds ratio of 1.40 (0.88, 2.40) or all-cause graft loss with a hazard ratio of 0.89 (0.62, 1.30) in transplant recipients who received kidneys that were shipped versus not shipped. Thus, a cold ischemia time up to 16 hours has limited impact on living donor outcomes. These findings may help expand living donor transplantation through kidney paired donation.

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The impact of cold ischemia time (CIT) on outcomes after living donor kidney transplantation remains unclear. Simpkins *et al.*[1] reported an increased risk of delayed graft function (DGF) among patients who received a living donor transplant in the United States between 1990 and 2005 and had a CIT between 4 and 6 hours compared with patients with a CIT between 0 and 2 hours. There was no association between CIT as long as 8 hours and allograft loss. A recent ANZDATA (Australian and New Zealand Dialysis and Transplant Registry) analysis of patients who received a living donor transplant in Australia and New Zealand between 1997 and 2012 found that every hour of CIT was associated with a progressively higher risk of DGF and that patients who received kidneys from donors older than 50 years of age with a CIT between 4 and 8 hours had a higher risk of all-cause graft loss (ACGL) and death-censored graft loss (DCGL) compared with patients with a CIT of 1 to 2 hours.[2] Neither study was able to examine the impact of a CIT >8 hours or to specifically examine the impact of CIT in the context of kidney paired donation (KPD). The study of Simpkins *et al.* only included transplantations performed until 2005, before the proliferation of KPD programs in the United States, and there were too few KPD transplantations in Australia and New Zealand to draw meaningful insights. This is potentially important because the impact of CIT may vary in KPD transplantations (in which longer CITs are likely due to shipping) versus directed living donor transplantations (in which longer CIT may reflect other factors). Allen *et al.*[3] recently described the outcomes of 84 KPD transplant recipients in Australia for whom the kidneys were shipped and in 16 KPD transplant recipients for whom the kidneys were not shipped and found similarly favorable outcomes in both. Similarly, Treat *et al.*[4] compared the outcomes of recipients at the University of California, Los Angeles whose kidneys were shipped through the national kidney registry exchange program to a matched cohort of non-KPD living donor transplant recipients who underwent transplantation locally. However, the mean CIT of KPD transplants that were shipped was relatively short (only 6.8 hours in the Australian analysis), and there were too few transplants to draw meaningful conclusions.

Understanding the implications of prolonged CIT in living donor transplantation is increasingly important in the current era in which KPD transplants[5,6] and transplants from older

living donors are increasingly common.[6,7] Accordingly, we examined the association of CIT with living donor outcomes and specifically determined whether the impact of CIT varied between KPD and non-KPD transplants and among transplants from older aged living donors.

RESULTS

Among the 48,498 living donor transplant recipients included in the study, the median CIT was 1.0 hour (quartile [q]1 = 0.7, q3 = 2.0). CIT was longer in the KPD transplants ($N = 2839$) compared with the non-KPD transplants ($N = 45{,}659$) (Figure 1). The median CIT in KPD transplants was 2.0 hours (q1 = 1.0, q3 = 6.6) versus. 1.0 hour (q1 = 0.7, q3 = 2.0) in non-KPD transplants ($P < 0.001$). Table 1 shows the donor, recipient, and transplant characteristics by CIT group. The majority of transplants with a CIT of 8.1 to 16.0 hours were in the context of KPD and were performed after 2012. Recipients of transplants with a CIT of 8.1 to 16.0 hours were more frequently sensitized, had more human leukocyte antigen mismatches with their donors, and had longer pretransplantation dialysis exposure (all likely reflective of the high proportion of KPD transplants). Recipients of transplants with a CIT of 8.1 to 16.0 hours had older donors (30% older than 50 years of age), which may reflect the acceptance of older living donors in recent years.

Association of CIT with DGF

The incidence of DGF was low overall, but was statistically higher in groups with longer CITs (CIT 0–2.0 hours: 3.3%, CIT 2.1–4.0 hours: 3.9%, CIT 4.1–8.0 hours: 4.3%, CIT 8.1–16.0 hours: 5.5%; $P < 0.001$). When we excluded preemptive transplant recipients, the incidence of DGF was 4.4% in the CIT 0–2 hour group; 4.9% in the CIT 2.1–4.0 hour group, 5.7% in the CIT 4.1–8.0 hour group, and 6.5% in the CIT 8.1–16.0 hour group; $P < 0.001$).

After adjustment for potential confounders (Table 2), there was a trend toward an increased odds of DGF with increasing CIT, but only patients with a CIT of 8.1 to 16.0 hours had a statistically significant higher odds of DGF (odds ratio: 1.47; 95% confidence interval [CI] 1.05–2.05). When the analysis was restricted to recipients whose donor was older than 50 years age, patients with longer CITs had higher point estimates for the odds of DGF, but these associations were also not statistically significant. There was no significant interaction between CIT and donor age ($P = 0.31$). Similarly, there was no significant interaction between CIT and KPD transplantation ($P = 0.76$) for the outcome of DGF. Notably, there was no difference in the median duration of transplantation hospitalization between CIT groups: the median length of transplantation hospitalization (q1, q3) was 4 days (4, 6) for a CIT of 0 to 2.0 hours, 5 days (4, 6) for a CIT of 2.1 of 4.0 hours; 5 days (4, 7) for a CIT of 4.1 to 8.0 hours, and 4 days (4, 6) for a CIT of 8.1 to 16.0 hours ($P = 0.11$).

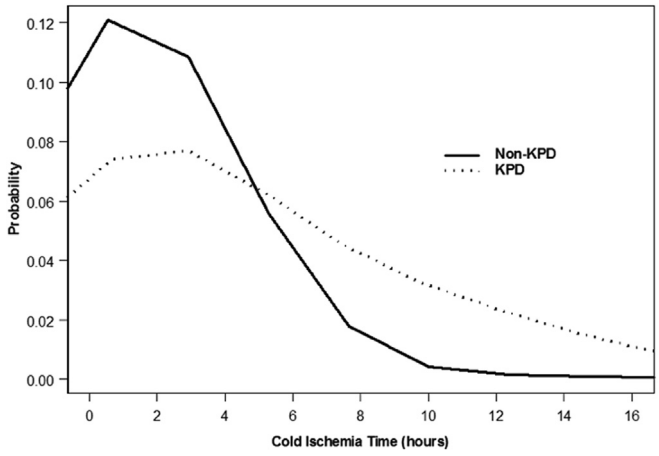

Figure 1 | Distribution of cold ischemic time in KPD (n = 2839) and non-KPD (n = 45,659) (living donor kidney transplants between 2005–2015).

Association of CIT with allograft survival

Figure 2 shows the Kaplan-Meier survival curves for the outcome of ACGL by CIT group for recipients of KPD and non-KPD living donor transplants including the subgroup of recipients who received a transplant from a living donor 50 years of age and older. There was no difference in the time to ACGL among non-KPD and KPD recipients with longer CITs (Figure 2a and b); these results were consistent among the subgroup of non-KPD recipients who received kidneys from living donors 50 years of age and older (Figure 2b) and KPD recipients (Figure 2c and d). These Kaplan-Meier analyses were also performed for the outcome of DCGL, and no differences were identified (results not shown). Table 3 shows the results of Cox multivariate analyses for the outcome of ACGL. There was no association between CIT groups and ACGL after adjustment for relevant confounders (Table 3). There was no significant interaction between CIT and donor age ($P = 0.76$) or CIT and KPD status ($P = 0.32$).

Cox multivariate models for the outcome of DCGL revealed no association between CIT and DCGL; hazard ratio (HR) and 95% CI 1.09 (0.81–1.48) for a CIT of 2.1 to 4.0 hours; 1.17 (0.97–1.40) for a CIT of 4.1–8.0 hours; and 1.01 (0.92–1.10) for a CIT of 8.1–16.0 hours compared with the reference group of patients with a CIT of 0–2.0 hours). There was no significant interaction between CIT and donor age ($P = 0.71$) or CIT and KPD status ($P = 0.31$) for the outcome of DCGL.

Association of shipping with DGF and allograft loss in KPD recipients

Supplementary Table S1 outlines the characteristics of transplant recipients for whom kidneys were shipped ($N = 772$) and those for whom kidneys were not shipped ($N = 1651$). The median CIT was 8 hours in shipped versus nonshipped KPD kidneys. The incidence of DGF was 4.5% in recipients for whom kidneys were shipped and 3.3% in recipients for whom kidneys were not shipped ($P = 0.14$). After adjustment for potential confounders, there was no significant difference in the odds of DGF in KPD recipients for whom the kidney was shipped or not (odds ratio [95% CI]: 1.40 [0.88–2.40]). Supplementary Figure S1 shows the Kaplan-Meier survival