Geographic Variation in Cold Ischemia Time: Kidney Versus Liver Transplantation in the United States, 2003 to 2011

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Background. Regional variations in kidney and liver transplant outcomes have been reported, but their causes remain largely unknown. This study investigated variations in kidney and liver cold ischemia times (CITs) across organ procurement organizations (OPOs) as potential causes of variations in transplant outcomes. Methods. This retrospective study analyzed the Standard Transplant Analysis and Research data of deceased donor kidney (n = 61,335) and liver (n = 39,285) transplants performed between 2003 and 2011. The CIT variations between the 2 types of organs were examined and compared. Factors associated with CIT were explored using multivariable regressions. Spearman rank tests were used to associate CIT with graft failure at the OPO level. Results. Significant CIT variations were found across OPOs for both organs (P < 0.05). The variation was particularly large for kidney CIT. Those OPOs with longer average kidney CIT were likely to have a lower graft survival rate (P = 0.01). For liver, this association was insignificant (P = 0.23). The regression analysis revealed sharp contrasts between the factors associated with kidney and liver CITs. High-risk kidney transplant recipients and marginal kidneys were associated with longer average CIT. The reverse was true for liver transplants. Conclusions. Large variations in kidney CIT compared to liver CIT may indicate that there is a room to reduce kidney CIT. Reducing kidney CIT through managerial improvements could be a cost-effective way to improve the current transplant system.

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A report by the Institutes of Medicine in 1998 was the first to identify geographic disparities in access to and outcomes of both liver and kidney transplants as a vital issue within the United States transplant system.1 For outcome disparity, it found that liver recipients living in smaller volume organ procurement organization (OPO) areas had a higher risk of posttransplant mortality. Other studies quickly followed to further investigate disparity issues. A smaller scale study in the same time period compared kidney graft survival rates across OPOs and found that 14 OPOs with the lowest graft survival rates recovered a significantly higher percentage of kidneys from older, hypertensive donors.2 Another study in 1998 did not evaluate outcome differences by OPO, but reported that transplant center effect was particularly significant in explaining the first year graft survival for both kidney and liver transplants.3 More recent studies reported that kidney and liver transplant recipients living in lower median income areas were more likely to have lower graft survival rates.4,5 A higher graft failure rate among kidney and liver recipients who lived further from the closest transplant center has also been reported.6,7

Despite this literature revealing geographic disparities in transplant outcomes, research investigating potential causes of the disparities is scant. The present study focused on cold ischemia time (CIT) as a risk factor for graft failure and examined variations in mean kidney and liver CITs across OPOs. Cold ischemia time is one of a few risk factors that participated in research, data analysis, and writing of the article. T.E.S. provided guidance to analysis, contributed to the writing of the article. J.D.M. contributed to the interpretation of the overall results and writing of the article. C.O.C. contributed to the interpretation of the overall results. J.K.M. developed research design, contributed to the interpretation of the results, and writing of the article. Correspondence: Naoru Koizumi, PhD, George Mason University, 3351 N. Fairfax Dr., Arlington, VA 22201. (nkoizumi@gmu.edu). Copyright © 2015 The Authors. Transplantation Direct. Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially. ISSN: 2373-8731 DOI: 10.1097/TXD.0000000000000529

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could vary by OPO depending on regional factors such as organ supply level, average proximity to donor hospitals, and how procuring OPO manages organ sharing. However, there is only 1 previous study that examined regional variation in CIT in transplantation. This study focused on liver CIT and aggregated the 56 OPOs into 4 groups (in terms of model for end-stage liver disease score quartiles) to compare the mean CIT. At this aggregate level, the study found no significant difference in mean CIT. The present study examined both kidney and liver CIT variations across OPOs in a more explicit fashion. Using multiple regression, we identified those characteristics of donors, recipients, and OPOs that influence CIT of each type of organ. The comparison of the 2 regression results revealed certain significant differences in the ways that OPOs handle procurements and placements of kidneys versus livers, which yielded important policy implications.

MATERIALS AND METHODS

Data Sources

The study used the Standard Transplant Analysis and Research data compiled and distributed by the Organ Procurement and Transplantation Network (OPTN). The kidney data recorded the clinical, administrative, demographic and locational information of 62,144 adult deceased-donor kidney transplant recipients who appeared on the waitlist and received a transplant(s) between January 1, 2003, and December 31, 2011. The liver data contained the analogous information of 39,686 adult liver transplant recipients for the same period. Basic demographic and clinical data on donors and donated organs were available for all recorded transplants. Locational variables in the dataset included 5-digit ZIP codes of: (a) transplant centers at which recipients were registered; (b) donor hospitals that recovered organs; and (c) the residences of transplant recipients at the time of registration and transplantation. The Standard Transplant Analysis and Research data was merged with two additional datasets, including: (i) county level demographic data available from the United States Census website and (ii) the list of counties that belong to each OPO. The latter list was made available by the Scientific Registry of Transplant Recipients upon request. Our analyses excluded transplant recipient data from Alaska, Puerto Rico, and Hawaii because our interest was to investigate geographic trends in CITs over the contiguous United States. After deleting these observations and the recipients with inaccurate or missing ZIP code information, the final data sets included the information for 61,335 kidney and 39,285 liver transplants.

Analytical Approaches and Methods

To visually inspect geographic variations in CITs, we created maps showing CIT variations over the contiguous US using Geographic Information System. Transplant centers and donor hospitals were mapped using their ZIP code centroids. All transplant recipients along with key transplant characteristics, together with OPO fixed effects. The variable, GTD, was available in the database and represents the distance (in miles) between donor hospital and transplant center. Various sets of independent variables, with and without OPO fixed effects (i.e., transplant center dummy variables), were tested to examine the size and sign consistencies of the coefficients across regressions.

### Table 1.

**Patient and OPO Characteristics Included in the Regressions Variables for Multivariable Linear Regressions: Kidney and Liver**

| Variable | Kidney (N = 61,335) | Liver (N = 39,285) |
|----------|---------------------|--------------------|
| Transplant Recipient Characteristics | | |
| Age at transplant, mean (SD) | 51.58 (12.89) | 52.95 (10.38) |
| Race, n (%) | | |
| Caucasian (reference) | 32,388 (53) | 26,520 (66) |
| AA | 17,553 (29) | 6,395 (16) |
| Hispanic | 7,437 (12) | 5,088 (13) |
| Asian | 2,929 (5) | 854 (2) |
| Days waited for a transplant, mean (SD) | 576 (509) | 160 (280) |
| Multiracial, % (SD) | 16 (37) | 7 (23) |
| Status 1 patient, % (SD) | n/a | 2,231 (6) |
| MELD score > 15 at transplant, % (SD) | n/a | 35,124 (89) |
| Deceased Donor and Organ Characteristics | | |
| Age: mean (SD), y | 37.59 (16.64) | 41.16 (17.19) |
| ECD donor, n (%) | 10,095 (16) | 9,924 (25) |
| BMI, mean (SD) | 26.69 (6.88) | 26.80 (5.60) |
| Creatinine, mean (SD) | 1.12 (0.84) | 1.47 (1.54) |
| Bilirubin, mean (SD) | 1.04 (1.46) | 0.96 (1.25) |
| Cold ischemic time in hours, mean (SD) | 17.64 (9.58) | 7.30 (3.51) |
| Graft travel distance or GTD in miles, mean (SD) | 237.88 (435.03) | 148.21 (251.74) |
| Organ sharing status, n (%) | | |
| Local organ | 43,914 (72) | 27,811 (71) |
| Regional organ | 6,006 (10) | 9,044 (23) |
| National organ | 11,408 (19) | 2,421 (6) |
| OPO Characteristics | | |
| Single transplant center OPO, n (%) | 7 (13) | 19 (34) |
| No. transplants, mean (SD) | 1,095 (702) | 702 (480) |
| Proximal L/K Ratio, ratio (SD) | 0.62 (0.10) | 0.62 (0.10) |
| Median income in U.S. dollars, median (SD) | 51,221 (8,218) | 51,221 (8,218) |
| Percentage of African Americans, % mean (SD) | 18 (12) | 18 (12) |

*Dependent and statistically significant (P < 0.1) independent variables.*

*Organ that was procured and transplanted within the same OPO.*

*Organ that was transported from outside the OPO’s donation service area but within the United Network of Organ Sharing region.*

*Organ that was transported from outside the United Network of Organ Sharing region.*

n/a indicates not applicable; (−), not significant; MELD, model for end-stage liver disease; L, liver; K, kidney.
Table 1 summarizes the dependent variable (i.e., CIT) and the final sets of significant predictors of kidney and liver CITs. For convenience, the predictors were classified into groups, including those variables related to (i) patient characteristics, (ii) donor/organ characteristics, and (iii) OPO characteristics. To construct the OPO level variables, we aggregated recipient, transplant center, donor hospital, and county level demographic information to the OPO level. All other variables measure individual characteristics. A hierarchical linear model was also tested because of the hierarchical nature of the data. The results are not shown because it produced comparable results to those produced by the ordinary least square regressions with significant fixed effects.

To investigate the relationship between mean CIT and graft failure rate across OPOs, Spearman rank tests were used. The negative effect of CIT on transplant outcome for organs in general is well known. However, the hypothesis that OPOs with longer mean CIT tend to have higher graft failure rates has not been tested. In data not shown, we also performed survival analysis to estimate the impacts of common risk factors, including CIT on graft survivals. The risk factors and covariates used in the analyses include length of dialysis, expanded criteria donors (ECD), number of previous transplants, donor and patient race and age, patient history of vascular disease and diabetes, donor history of hypertension, pumped kidneys, and donation after cardiac death (DCD) status. Here, we used a Weibull distribution, which yielded the best fit (Akaike Information Criterion: 59172.57) among all parametric models (Exponential, Gompertz, Weibull, Lognormal, and Gamma) tested. The Weibull survival regression model was chosen over Cox regression model to allow estimation of a survival function yielding probabilities of surviving beyond any given time t. In the present paper, we only showed and discussed the (significant with a P value less than or equal to 0.05) coefficients of liver and kidney CITs and their impacts on transplant outcomes.

RESULTS

Spatial Variation of Kidney and Liver CITs

Figures 1 and 2 present the spatial patterns of kidney and liver CITs. In both figures, OPO boundaries were drawn in blue, and transplant center locations were denoted by black triangles. In Figure 1, red to orange areas denote regions with longer kidney CITs, whereas green to blue areas denote shorter kidney CITs. In Figure 2, brown areas denote regions with longer liver CITs, whereas yellow areas denote shorter liver CITs. Overall spatial trends in kidney and liver CITs exhibited considerable differences. As expected, both the mean and the variance of CITs were considerably smaller for liver than kidney. The maps revealed that OPO boundaries often coincide with these CIT differences, especially for kidneys. We also prepared CIT maps in state boundaries, and visually confirmed that differences were far less dramatic at the state level.

Analysis of variance tests exposed that CITs varied significantly by OPO (kidney: F = 236.26, P < 0.001; liver: F = 35.95, P < 0.001). The post hoc HSD tests indicated that, among the mutually exclusive 1540 pairs of OPOs, CITs were significantly different (P < 0.05) for 948 OPO pairs in kidney and for 650 pairs in liver transplants.

OPO Effects of CIT on Graft Failure

Spearman rank test revealed that, for kidneys, those OPOs ranking high in mean CIT are likely to rank high in graft failure rates (N = 56, Spearman ρ = 0.35, P = 0.01). For livers, however, statistical independence between mean CITs and graft failure ranks could not be rejected (N = 56, Spearman ρ = 0.16, P = 0.23).

Factors Influencing CIT

Table 2 summarizes the results of the CIT regressions (N = 55,895 kidney transplants, N = 35,908 liver transplants). For all regressions in which multicollinearity was not an issue (VIF < 10), the coefficients of nonfixed-effect explanatory
variables exhibited reasonable consistency both in their signs and sizes. Coefficients on the 56 OPO fixed effects are not reported in Table 2. Although some of these fixed effects were quite significant ($P < 0.001$), their use here was primarily to control for unobserved spatial variations. On average, about 40 OPO fixed effects were found to be significant ($P < 0.05$) predictors of CIT for both organ types even after adjusting for other confounding factors. Even with these additional fixed effects, the adjusted R$^2$ for these kidney and liver regressions remained relatively low (0.34 and 0.11, respectively), indicating that there are a host of unexplained factors influencing CITs, especially in the case of livers. The following subsections summarize the findings related to each type of explanatory variables.

**Patient Characteristics**

Patients who had priority on the waitlist had shorter average CIT because they tend to receive first offers. For kidneys, multiorgan recipients had significantly shorter average CIT ($\beta = -4.14, P < 0.001$) because they are likely to receive priority, and their kidneys are typically dealt together with other organs that have a shorter maximum CIT. For livers, status 1 and higher model for end-stage liver disease recipients had shorter average CITs ($\beta = -1.44, P < 0.001$) because they tend to receive priority. The number of days spent on dialysis (kidney) or on the waitlist (liver) was positively associated with CITs ($\beta = 0.31$ per 1000 days, $P < 0.001$ for kidney, and $\beta = 0.24, P < 0.001$ for liver). Some coefficients exhibited sharp contrasts between kidney and liver recipients. Kidney recipients who were African American ($\beta = 0.92, P < 0.001$), Hispanic ($\beta = 1.03, P < 0.001$) or older ($\beta = 0.02, P < 0.001$) had longer average CITs, whereas liver recipients in the same demographic groups had shorter average CITs ($\beta = -0.16, P = 0.001$ for AA; $\beta = -0.14, P = 0.01$ for Hispanic, and $\beta = -0.01, P < 0.001$ for age).

**Donor/Organ Characteristics**

A comparison of the kidney and liver regression results revealed 1 striking difference. Although GTD coefficients were relatively similar between the 2 regressions ($\beta$: 3.06 vs 2.34 hours for kidney vs liver, $P < 0.001$), average CITs of shared organs, after adjusting for distance, differed dramatically between kidneys and livers. Specifically, average CITs of those kidneys transferred outside the procuring OPO area were substantially larger than those livers transferred outside the procuring OPO area ($\beta$: 4.80 vs 0.70 hours for regionally shared kidney vs liver, and 6.49 vs 1.15 hours for nationally shared kidney vs liver, $P < 0.001$).

The variables related to lower quality of organ or marginal organs also exhibited contrasting results between liver and kidney regressions. Although there is no universal definition of marginal organs, their characteristics frequently include those from (i) DCD, (ii) older donors, (iii) ECD, (iv) donors with a history of hypertension, or a higher level of (v) creatinine, (vi) bilirubin, or (vii) body mass index (BMI).41,42 For kidneys, marginal organs were consistently associated with longer average CITs ($\beta = 0.01$, $P < 0.001$ for age, $\beta = 0.01$, $P = 0.59$ for BMI, $\beta = 0.65, P < 0.001$ for creatinine, $\beta = 0.08, P = 0.003$ for bilirubin, $\beta = 0.11, P < 0.001$ for DCD, $\beta = 2.43, P < 0.001$ for history of hypertension, and $\beta = 1.20, P < 0.001$ for ECD). For livers, the relationship was almost reversed. Specifically, 3 of 4 coefficients ($\beta = -0.16, P = 0.001$ for age, $\beta = -0.03, P = 0.001$ for creatinine, $\beta = -0.24, P = 0.004$ and $\beta = -0.24, P = 0.004$ for DCD) indicated that marginal livers were transplanted with shorter average CITs.

**OPO Characteristics**

Coefficients of 3 OPO characteristics were significant for both organ types: OPOs with a single transplant center had

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**FIGURE 2.** Spatial trend of liver CIT and locations of liver transplant centers across OPO service areas.
shorter average CITs ($\beta = -1.43, P < 0.001$ for kidney; $\beta = -0.14, P = 0.001$ for liver), OPOs transplanting a higher than average volume of kidneys (or livers) had longer average kidney (or liver) CITs ($\beta = 0.49, P < 0.001$ for kidney and $\beta = 0.29, P < 0.001$ for liver), OPOs recovering more (transplanted) livers than kidneys had longer average kidney CITs ($\beta = 2.20, P < 0.001$) and shorter average liver CITs ($\beta = -1.25, P < 0.001$). The OPOs with higher proportions of shared organs had longer average CITs ($\beta = 3.79, P < 0.001$ for regionally shared and $\beta = 8.99, P < 0.001$ for nationally shared kidney; $\beta = 3.69, P < 0.001$ for nationally shared liver). Kidney recipients living in higher income OPOs had shorter average CITs ($\beta = -0.12$ in '000, $P < 0.001$), whereas those living in the OPOs with higher percentages of African Americans had longer average CITs ($\beta = 1.98, P < 0.001$). Conversely, liver recipients in OPOs with a higher percentage of African Americans had shorter average CITs ($\beta = -1.83, P < 0.001$).

**Impact of CIT on Transplant Outcomes**

Our survival analyses estimated the effect of reducing kidney CIT on graft survival along with other commonly known risk factors and covariates including length of dialysis, number of previous transplants, donor and patient race and age, patient history of vascular disease and diabetes, pumped kidneys, donor history of hypertension, and ECD, DCD status. The survival function for the Weibull model (evaluated at average levels of all explanatory variables) indicated that the probability of surviving at least 1 year would be increased by about 1% if kidney CIT is reduced from the current average of 17 hours to 7 hours (the mean liver CIT).

**DISCUSSION AND CONCLUSIONS**

The study revealed that average CIT varied significantly by OPO for both organs, but particularly for kidneys. Further, for kidneys, OPOs with a higher mean CIT were more likely to have a higher graft failure rate. These findings indicate that previously reported regional variations in kidney transplant outcomes are at least partially attributable to the regional variation in CIT. The regression results provided several OPO factors associated with CIT. The OPOs with only 1 transplant center were, on average, placing organs more quickly. This may suggest that coordination becomes increasingly difficult when OPOs must deal with multiple transplant centers receiving organs simultaneously. Or it is possible that OPOs with 1 transplant center may be more resource abundant
on average. Those OPOs performing more transplants had longer average CITs, possibly indicating that OPOs with aggressive local transplant center(s) tend to use as many organs as possible, even those with higher CITs. Alternatively, this may mean that OPOs performing more transplants are more comfortable transplanting organs with longer CIT or have more schedule conflicts, which, in turn, prolongs CIT. Those OPOs recovering and transplanting more livers than kidneys had longer average kidney CIT and shorter average liver CIT. This may reflect a general tendency among OPOs and transplant centers to prioritize livers over kidneys because of their shorter medically accepted CIT and relative scarcity, as well as the lack of alternative treatment methods for end-stage liver disease patients. Finally, those OPOs transplanting more shared organs had longer average CITs after adjusting for GTD, possibly reflecting inevitable increase in administrative burden as organs are transported to outside the original OPO area.

Sharp contrasts were seen between the kidney and liver analysis results. In particular, average CITs of regionally and nationally shared kidneys were substantially longer than those of shared livers after adjusting for GTD. The result may indicate OPOs’ general inclination to prioritize liver over kidney placement, especially when these organs are exported outside the OPO. A previous case study reports significant differences in the procurement and handling of kidneys as compared to other organs. This study reported that 38% of kidneys were recovered by the physicians who procured liver and/or pancreas and that the recipients of these kidneys were not yet identified at the time of procurement. Kidneys and livers may also be handled differently in terms of transportation mode arranged for organ transfer, degree of commitment to resolve surgery scheduling conflicts.

Marginal kidneys had longer average CIT than standard quality kidneys, perhaps because of the general difficulty in placing these organs. Previous studies on ECD kidneys suggest that repeated declines of ECD organ offers and biopsies undertaken on those kidneys could prolong ECD kidneys’ CITs. Kidneys from donors who are older, with higher levels of BMI, creatinine or bilirubin may be treated likewise. In contrast, marginal livers overall had shorter average CIT. The result may indicate that physicians and transplant centers utilize marginal livers only when their CITs are short and that marginal livers with prolonged CITs tend to be discarded to avoid potential graft failure. As to the patients’ characteristics, higher-risk patients were receiving livers with shorter average CIT. Higher liver graft failure rates have consistently been reported among African American and Hispanic recipients. Our results may reflect the effort among transplant centers and physicians to minimize graft failure among high-risk patients by transplanting livers with short CITs into that group of patients. In contrast, those kidney transplant recipients with greater risk of graft failure including African Americans and those who were on dialysis longer were receiving kidneys with longer average CIT. The positive association may reflect a physicians’ view that even marginal kidney grafts when successfully transplanted have the benefit of prolonged patient survival compared to remaining dialysis dependent. These findings together suggest that differences in kidney and liver handling and perception by OPOs, physicians, and transplant centers are partially attributable to the gap between kidney and liver CITs. Using a survival analysis, we evaluated a possible positive impact of reducing kidney CIT on graft survival. The result indicated that the probability of surviving 1 year or longer will increase by 1% if kidney CIT is reduced from the current average of 17 hours to 7 hours (the average of liver CIT). Thus, given that about 10,000 deceased donor kidneys are transplanted annually, it can be expected that an additional 100 of these patients (10,000 × 0.01) would survive beyond 1 year. Here it is important to note that when organs fail for kidney recipients, these patients often return to the transplant waitlist while on dialysis. Thus, eliminating 100 graft failures could in principle allow 100 additional candidates to receive transplants. This reduction in graft failures would also avoid the need for Medicare coverage on dialysis, as well as the increased costs associated with relisting and retransplanting a more complicated patient population. Although a detailed cost effectiveness analysis of reduced CIT is beyond the scope of this study, such savings could be even larger given the reported long-run negative effects of kidney CIT on graft failure.

Several limitations should be noted. First, we were unable to investigate the effects of different transportation modes on CIT. This is because the information is currently not collected at the federal level. Second, as indicated by the relatively low coefficients of determination of the CIT regressions, large variations in CITs remain to be explained. Third, some of our results suggest existence of transplant center effects in determining CIT. A future study may explore CIT variations across transplant centers. Lastly, the spatial trend of organ sharing changes as organ allocation rules are revised. Thus, the results presented here may be affected by the recent change in the kidney allocation system.

Despite these caveats, we believe that the results highlighted above strongly promote further investigations of operation logistics and efficiencies of OPOs and transplant centers in kidney procurement and placement. Further, given that average kidney CIT is longer for higher risk donor/recipient combinations, we propose that these high-risk combinations receive special consideration when undergoing renal transplantation with an additional effort undertaken to minimize CIT. Finally, reducing kidney CIT through managerial shifts in how organs are currently allocated, transported, and transplanted would necessitate additional resource allocation directed to this purpose. However, the number of candidates waiting and deaths while waiting are largest for kidney transplant candidates, among all organs. Reducing kidney CIT and thus graft failures could be the most effective way to improve the current transplant system.

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