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## Is Delayed Graft Function Causally Associated with Long-Term Outcomes after Kidney Transplantation? Instrumental Variable Analysis<sup>1</sup>

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### Abstract

**Background**—While some studies have found an association between delayed graft function (DGF) after kidney transplantation and worse long-term outcomes, a causal relationship remains controversial. We investigated this relationship using an instrumental variables model (IVM), a quasi-randomization technique for drawing causal inferences.

**Methods**—We identified 80,690 adult, deceased-donor, kidney-only transplant recipients from the Scientific Registry of Transplant Recipients between 1997 and 2010. We used cold ischemia

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### Statement of Competing Interests

The authors of this study declare no competing interests.

time (CIT) as an instrument to test the hypothesis that DGF causes death-censored graft loss and mortality at 1 and 5 years post-transplant, controlling for an array of characteristics known to affect patient and graft survival. We compared our IVM results to a multivariable linear probability model (LPM).

**Results**—DGF occurred in 27% of our sample. Graft loss rates at 1 and 5 years were 6% and 22%, respectively, and 1-year and 5-year mortality rates were 5% and 20%, respectively. In the LPM, DGF was associated with increased risk of both graft loss and mortality at 1 and 5 years ( $p < 0.001$ ). In the IVM, we found evidence suggesting a causal relationship between DGF and death-censored graft loss at both 1 year (13.5% increase;  $p < 0.001$ ) and 5 years (16.2% increase;  $p < 0.001$ ), and between DGF and mortality at both 1 year (7.1% increase;  $p < 0.001$ ) and 5 years (11.0% increase;  $p < 0.01$ ). Results were robust to exclusion of lower-quality as well as pumped kidneys and use of a creatinine-based definition for DGF.

**Conclusion**—Instrumental variables analysis supports a causal relationship between DGF and both graft loss and mortality.

### Keywords

delayed graft function; kidney transplantation; outcomes; cold ischemia time; allograft failure

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### Introduction

Delayed graft function (DGF) is an early complication of kidney transplantation that may reflect acute allograft injury and suboptimal early allograft function. DGF results in increased hospital length of stay and costs in the short term (1), but it is unclear if DGF is associated with poor long-term kidney transplant recipient outcomes. Some studies have found that DGF is associated with increased risk of graft loss (2–6) or mortality (7, 8) while others have not found a significant effect (9–13). Determining whether DGF causes worse long-term outcomes would have important implications for the use of DGF as a valid surrogate outcome in transplant clinical trials and for development of therapies to treat DGF.

Plausible biological mechanisms have been described to explain how DGF leads to allograft failure or worse allograft function. Ischemic injury may cause increased HLA expression (14), precipitating rejection and subsequent graft loss. Additionally, maladaptive repair of parenchymal and tubular cells after allograft injury may promote fibrosis and permanent loss of filtration function (15). Alternatively, a relationship between DGF and poor allograft survival might not be causal, since DGF is reversible (16); this relationship could instead be confounded by unobservable characteristics, such as lower intrinsic kidney quality, that cause both DGF and allograft loss.

The use of instrumental variables in multivariable analyses allows one to draw causal inferences with observational data. This technique was developed in economics and has been widely applied in medical and epidemiological literature (17–22), although rarely in transplantation studies. In traditional linear regression, unobserved variables affecting both exposure and outcomes can confound relationships between these variables (Figure 1). The use of an instrumental variables model (IVM) can overcome this problem by isolating only the variation in the exposure that is not otherwise associated with the outcome. In an IVM, an exogenous instrumental variable is used to predict variation in the exposure variable. These predicted values of the exposure are then used in a regression to determine whether there is a relationship with the outcome of interest. In order for an instrumental variable to be valid, it must be both relevant and exogenous: a relevant instrument is strongly associated with the exposure, and an exogenous instrument is not associated with the outcome except through the pathway of the exposure (23).

This study investigated the relationship between DGF and recipient outcomes using cold ischemia time (CIT) as an instrument. DGF stems from ischemic injury to an organ during procurement and transport as well as reperfusion injury in the peri-operative period (24). CIT, a measure of the transport and storage time of an organ, is a relevant instrument for predicting DGF since it has been shown to be an independent risk factor for DGF (25). Additionally, CIT should function as an exogenous instrument, given that CIT is primarily dependent on transport and procurement practices which are unlikely to be related to graft failure or mortality other than through the pathway of DGF. The aim of this study was therefore to determine whether the use of CIT as an instrumental variable supported a causal association between DGF and the outcomes of allograft failure and mortality.

## Results

Descriptive summary statistics classified by median CIT are detailed in Tables 1–3. CIT in our sample ranged widely and had a median of 17.55 hours (interquartile range 12, 24). Many donor and recipient variables which affect DGF were relatively balanced across median CIT.

DGF occurred in 20,185 participants, which was 27% of the cohort. Death-censored graft loss occurred in 4,382 (6%) individuals by 1 year and 9,252 (22%) individuals by 5 years. The mortality rates in our sample were 5% at 1 year (n=3,853) and 20% at 5 years (n=9,444).

We assessed the strength of our instruments using the F-test, which examines whether the inclusion of the instrument in the first-stage regression model is relevant. An F-statistic  $> 10$  is suggested as a general rule to classify an instrument as relevant (26). The F-statistics for exclusion of the instrumental variable were 63.56 and 156.80 in the 1-year and 5-year graft loss models, respectively, and 62.48 and 147.02 in the 1-year and 5-year mortality models, respectively. These are all greater than 10, indicating that the instrument was relevant in our models.

### DGF and Graft Loss (Table 4)

DGF was associated with a 10.07% increase in probability of 1-year graft loss ( $p < 0.001$ ) in the linear probability model (LPM), which corresponds to an approximate relative risk of 3.98. The magnitude of this effect was larger in the IVM, where DGF was associated with a 13.55% increase in probability of 1-year graft loss ( $p < 0.001$ ), corresponding to an approximate relative risk of 5.01. DGF was associated with a 12.48% increase in probability of 5-year graft loss ( $p < 0.001$ ) in the LPM, corresponding to an approximate relative risk of 1.69. The magnitude of this effect was larger in the IVM, where DGF was associated with a 16.18% increase in probability of 5-year graft loss ( $p < 0.001$ ), corresponding to an approximate relative risk of 1.89.

### DGF and Mortality (Table 4)

In the IVM, DGF was associated with a 7.11% increase in probability of 1-year mortality ( $p < 0.001$ ), corresponding to an approximate relative risk of 2.72. Additionally, DGF was associated with an 11.03% increase in probability of 5-year mortality ( $p = 0.002$ ) in the IVM, corresponding to an approximate relative risk of 1.64.

### Supplemental Results

The rate of DGF as defined by lack of reduction in serum creatinine by 25% in a week was 50.37% (n=28,998) in our sample. Upon repeating our IVM with this alternate specification, we continued to find evidence suggesting a causal relationship between DGF and graft loss

at both 1 year (12.00% increase,  $p < 0.001$ ) and 5 years (12.90% increase,  $p = 0.007$ ) and between DGF and mortality at both 1 year (7.68% increase,  $p < 0.001$ ) and 5 years (8.56% increase,  $p = 0.014$ ). These were similar in magnitude and statistical significance to results using the original specification of DGF, indicating our analysis is robust to this alternate specification.

Upon regressing our outcomes on CIT using only observations without DGF, we found no association between cold ischemia time and 5-year graft loss ( $p = 0.221$ ). While we did find a statistically significant association between CIT and 1-year graft loss ( $b = 0.00022$ ,  $p = 0.036$ ) and mortality at 1 year ( $b = 0.00038$ ,  $p < 0.001$ ) and 5 years ( $b = 0.00061$ ,  $p = 0.035$ ), the magnitude of these coefficients were clinically insignificant suggesting these associations were likely a function of our large sample size only and do not refute our assertion that CIT was exogenous.

Upon repeating our original IVM after exclusion of the 20,479 individuals who had a Kidney Donor Risk Index (KDRI) greater than 1.155, the 75<sup>th</sup> percentile in our sample, we continued to find evidence suggesting a causal relationship between DGF and graft loss at 1 year (10.52% increase,  $p < 0.001$ ) and 5 years (10.64% increase,  $p = 0.007$ ) and between DGF and mortality at 1 year (5.94% increase,  $p = 0.001$ ) and 5 years (9.90% increase,  $p = 0.002$ ). These were all similar in magnitude and statistical significance to our original results, indicating our analysis is robust to exclusion of individuals receiving lower quality kidneys.

Approximately 22.16% of our sample ( $n = 16,333$ ) received kidneys that were pumped. Upon repeating our IVM analyses stratifying by whether individuals had received pumped kidneys, we continued to find evidence of a causal relationship between DGF and graft loss at 1 year (11.63% increase,  $p < 0.001$ ) and 5 years (16.01% increase,  $p < 0.001$ ) as well as between DGF and mortality at 1 year (5.41% increase,  $p = 0.001$ ) and 5 years (12.94% increase,  $p = 0.001$ ) among non-pumped kidney recipients. Among pumped kidney recipients, we continued to find evidence of a causal relationship between DGF and both graft loss (24.87% increase,  $p = 0.007$ ) and mortality (14.47% increase,  $p = 0.006$ ) at 1 year, though we did not find evidence of a causal relationship between DGF and graft loss (6.07% increase;  $p = 0.569$ ) or mortality (9.57% decrease;  $p = 0.369$ ) at 5 years. Our analysis among non-pumped kidney recipients is concordant with our primary results, but among pumped kidney recipients, a causal effect only persists for 1 year outcomes, likely due to loss of statistical power from excluding the majority of our sample (only 6466 of 41138 observations remain in 5-year graft loss and only 7545 of 47604 observations remain in 5-year mortality models).

## Discussion

This study uses instrumental variables analysis, a quasi-randomization technique for drawing causal inferences. We used CIT as an instrument for DGF to find evidence suggesting a causal relationship between DGF and both graft loss and mortality at 1 year and 5 years. These effects were robust to exclusion of individuals with high KDRI and pumped kidneys and use of an alternate specification of DGF.

In our study, evidence suggesting a causal relationship between DGF and graft loss was present at both 1 and 5 years in the IVM. These findings are consonant with a 2009 meta-analysis by Yarlagadda et al., which found that patients with DGF had a significantly higher risk of graft loss (RR 1.41, 95% CI: 1.27–1.56) at a mean of 3.2 years of follow-up (27). However, a more recent study by Kayler et al. that used a paired-kidney analysis to examine the impact of CIT-induced DGF on graft failure did not find a difference in graft survival between paired donor transplants with and without DGF when CIT differences were less than 15 hours (28). Of note, in our study, the magnitude of the increase in probability of

graft loss at 1 and 5 years as a result of DGF was greater in our IVM analyses (13.55% and 16.18% at 1 and 5 years, respectively) compared to the LPM analyses (10.07% and 12.48%, at 1 and 5 years, respectively) suggesting that other, unaccounted-for variables may be masking the magnitude of the true effect of DGF on graft loss in non-IVM analyses. For instance, kidney transplant recipients who are sicker at baseline may be more likely to get DGF, yet their risk of graft loss may be somewhat mitigated if they receive closer supervision in their post-transplant care than less sick individuals. Such a mechanism could explain the lack of a statistically detectable effect in kidneys with shorter CIT in Kayler et al. While paired kidney analysis controls for unobserved donor characteristics, it does not adjust for unobserved recipient factors confounding the relationship between DGF and graft loss that may have biased this relationship downwards. IVM analysis may offer advantages over a paired kidney analysis in accounting for the effects of confounders.

Evidence suggesting a causal relationship between DGF and death was also present at both 1 and 5 years in the IVM in our study. The meta-analysis by Yarlagadda et al. pooled data from 8 studies and found no significant increase in risk of mortality among those with DGF (27), though one study included in this review by Fontan et al. in 1996 found a relationship between DGF lasting greater than 3 weeks and an excess in mortality (7). A study by Patel et al. published since this review examined 231 high risk deceased-donor kidney transplant recipients who received routine induction therapy with anti-thymoglobulin and found that DGF was associated with a lower 1 year survival rate (99% non-DGF vs. 91% DGF;  $p=0.001$ ) (29). Additionally, a more recent study by Tapiawala et al. used observations the US Renal Data system between years 1998 and 2004 to examine the relationship between DGF and mortality among those who died with a functioning graft and found that patients with DGF were significantly more likely to die (adjusted HR: 1.53, 95% CI: 1.45–1.63) (8).

Our evidence suggesting that DGF causes a long-term effect in kidneys has important implications for the prognosis of many individuals, given that DGF is the most common immediate post-transplant complication (30). Our results support that increased attention should be given to individuals with DGF post-transplant to prevent future graft loss. These patients may benefit from modifications in their induction and maintenance immunosuppression regimens and close monitoring of graft function for several years after discharge (31). The potentially causal association of DGF with graft failure should not suggest an increased rate of refusal of marginal quality organs that may benefit transplant candidates on the waiting list out of fear of DGF, but rather should stimulate development of agents for alleviating effects of ischemia-reperfusion injury and graft failure. Trials evaluating such agents could target DGF as an efficient surrogate outcome for early drug development clinical trials, given the ease and immediacy of measurement relative to following kidney transplants for several years in order to accumulate graft loss events. Alternatively, patients with DGF could be randomized in treatment trials for testing of clinical management strategies to prevent progression of graft loss. Furthermore, a potential causal effect of DGF on graft loss has important implications for the long-term effects of other types of AKI, given that histological findings on biopsy in kidneys with DGF mimic those found in acute tubular necrosis in native kidneys (32). If the findings concerning the relationship between DGF and graft loss generalize to other types of kidney injury, the results from our study suggest that AKI can potentially cause future chronic kidney disease and add to the growing literature on the long-term effects of AKI (33, 34).

Nevertheless, our findings need to be interpreted in light of our limitations. The DGF specification we used is specific, but not sensitive, and may thus bias our analysis towards an effect (35). However, some patients may require dialysis after transplant for other indications, despite good allograft function, which would bias our analysis towards the null. Our results were also robust to an alternate, more sensitive specification of DGF.

Additionally, the two-stage least squares specification for IVM results in artificially large standard errors in settings where binary outcome variables are congregated near 0 or 1, resulting a higher likelihood of rejecting our alternative hypotheses in favor of the null. [22] However, we overcome this conservative approach to hypothesis testing with our large sample size, and we find a statistically significant effect in all our IVM analyses. Finally, CIT may not have been a completely exogenous instrument. It is possible that CIT relates to outcomes through a non-DGF mechanism, such that worse kidneys may be turned down from more centers and take longer to place. Therefore, poor kidney quality could both prolong CIT and associate with allograft failure. However, we adjust for variables that may reflect kidney quality in our model, which would be expected to lessen the impact of such a mechanism on our results. Additionally, the robustness of our results to exclusion of individuals with a high KDRI, which reflects lower allograft quality, suggests that this mechanism is unlikely. Furthermore, the lack of a clinically significant association between CIT and our outcomes in absence of DGF suggests that the only meaningful relationship between CIT and our outcomes is through DGF. Finally, DGF may have different biological implications among those with pumped kidneys compared to those without pumped kidneys, which may not be completely addressed by simple inclusion of this variable in our primary IVM analyses. However upon stratifying our analyses by whether kidneys were pumped, our findings persisted in all models with the exception of the 5-year outcomes among those with pumped kidneys; this non-significant finding with 5-year mortality outcomes may be due to the exclusion of the majority of our sample in these models.

In conclusion, this paper uses a novel technique for analyzing the relationship between DGF and long-term outcomes. Using IVM analyses, we find highly suggestive evidence of a causal effect of DGF on both graft loss and mortality at 1 and 5 years. In addition to the clinical implications of our results on patient prognosis, the results of this study open up new avenues for research using DGF as a surrogate outcome and improving long-term outcomes by testing therapies to prevent progressive loss in graft function among recipients with DGF.

## Materials and Methods

### Participants and study design

This study used data from the Scientific Registry of Transplant Recipients (SRTR). We included all 101,565 adult deceased-donor single primary kidney-only transplant recipients from January 1997 to December 2010 without primary graft failure. We excluded 8,870 recipients with missing CIT, 6,976 recipients who were not on dialysis prior to transplant, and 12,005 recipients with 0 HLA mismatches, given the systematically altered allocation practices of such kidneys that affect both CIT and outcomes. Our final sample was 73,714 observations.

### Variables

The primary exposure examined was DGF, defined as dialysis in the 1<sup>st</sup> week post-transplant. The primary outcomes were death-censored graft loss and mortality. Graft loss at 1 and 5 years from transplant was calculated as time to recorded graft failure or to start of chronic maintenance dialysis, whichever was shorter. Mortality at 1 and 5 years was calculated as time to death as reported in the Social Security Master Death File, with inclusion of additional death dates reported by centers to the Organ Procurement Transplantation Network. For analyses of 5-year mortality and graft loss, we only included the sub-cohort of kidney transplant recipients from January 1997 to December 2006, so that all individuals would have opportunity for 5 years of follow-up. The instrumental variable was CIT, in hours.

We also included recipient, donor, and allograft characteristics known to affect outcomes as covariates. Recipient characteristics included transplant year, organ procurement organization (OPO), age, sex, education, race, insurance, diabetes type, days on waiting list, and peak panel reactive antibodies (PRA). Donor characteristics included age, sex, race, history of diabetes, history of hypertension, terminal serum creatinine, cause of death, and whether the kidney was a donation after circulatory determination of death (DCDD). Allograft characteristics included number of HLA mismatches and whether the allograft was pumped.

### Statistical analysis

To perform IVM analysis, we used a two-stage least squares regression specification: in the first stage, we used CIT as an instrument to predict DGF independent of outcomes; in the second stage, we examined the relationship between predicted DGF values and outcomes. Given that DGF, graft loss, and mortality are all binary variables and that we have included a large number of covariates, the two-stage least squares regression specification was most appropriate for our IVM because it produces estimates that are very similar to nonlinear specifications, such as logistic or bivariate probit (36), yet these estimates are more robust to potential misspecification of the distribution of error terms (37). For additional information on IVM analysis, please refer to the digital supplemental content (SDC, Detailed Methods). We compared these IVM results to those from a simple linear probability model (LPM) of the relationship between DGF and outcomes. This LPM was calculated using simple least-squares regression with a binary outcome variable regressed on DGF and all of the covariates included in the IVM.

To assess strength of the IVM, we used the F-test, which examines whether the inclusion of the instrument in the first-stage regression model is relevant. All models adjusted for the recipient, donor and allograft characteristics listed above. Missing data in categorical variables was treated as a separate category using a dummy variable. Observations with missing data in quantitative variables were dropped from the regression model, though this accounted for less than 0.5% of the total sample. All standard errors were heteroskedasticity-robust and clustered around OPO. For ease of interpretation, relative graft loss and mortality rates were approximated from absolute risk differences in the IVM and LPM analyses as  $1 + \frac{\text{absolute risk difference}}{\text{graft loss or mortality rates among those without DGF}}$  in a manner similar to Stukel et al. (21). All analyses were conducted using STATA 11.0 IC (StataCorp, College Station, TX).

We also conducted several supplemental analyses. In order to remove concerns about the sensitivity of our specification of DGF, we repeated our original analyses using an alternate specification of DGF defined as either dialysis in the 1<sup>st</sup> week post-transplant or a failure for a recipient's creatinine to decline by 25% or more in the first 24 hours. In order to remove concerns about an alternate pathway between CIT and outcomes, we examined the association between CIT and outcomes among those without DGF in a multivariate linear probability regression using our fully adjusted model. Additionally, we repeated analyses excluding individuals with the top 25% KDRI (38) and stratified our analyses by whether a kidney was pumped.

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere. 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. The data reported here have been supplied by the Minneapolis Medical Research Foundation as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation by the SRTR or the U.S. Government.

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## Abbreviations

<b>AKI</b>	acute kidney injury
<b>CIT</b>	cold ischemia time
<b>DCDD</b>	donation after circulatory determination of death
<b>DGF</b>	delayed graft function
<b>ECD</b>	expanded criteria donor
<b>IVM</b>	instrumental variables model
<b>KDRI</b>	kidney donor risk index
<b>LPM</b>	linear probability model
<b>OPO</b>	organ procurement organization
<b>PRA</b>	panel reactive antibody
<b>SRTR</b>	Scientific Registry of Transplant Recipients

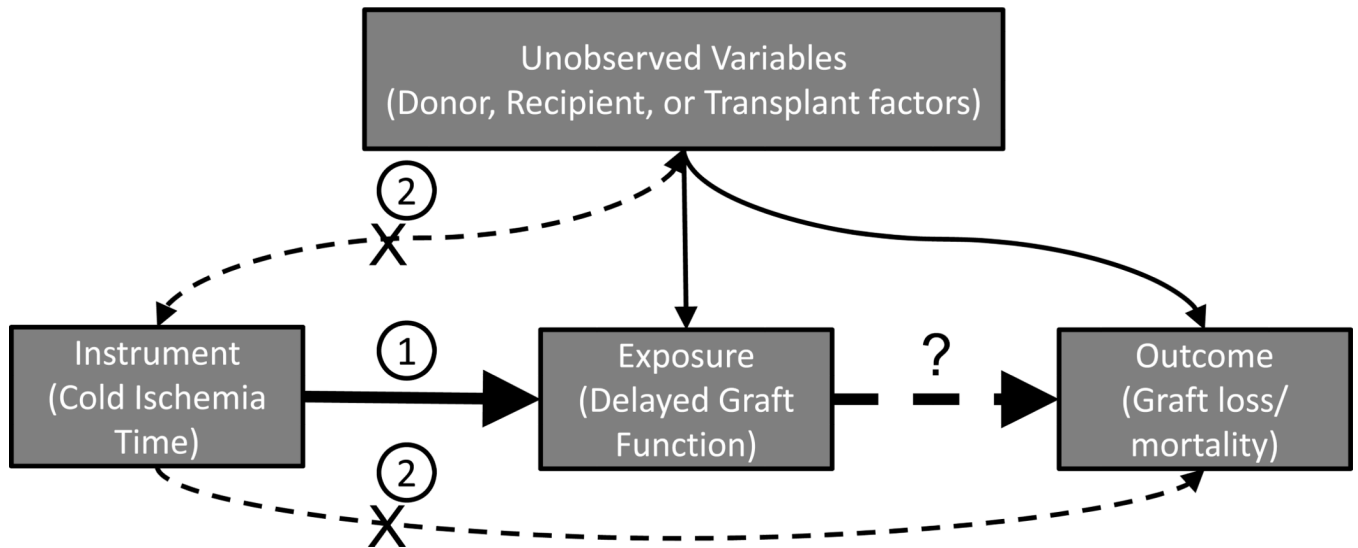
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**Figure 1. Instrumental variables analysis**

1. There must be a relevant association between the instrument and the exposure. This bold line indicates that the instrument is relevant.
2. There must not be a relationship between the instrument and the dependent variable either directly or through association with unobserved variables. The “X” through the thin dotted lines indicates that the instrument is exogenous. Any relationship between the instrument and the dependent variable may only exist through the independent variable.

**Table 1**

Recipient and donor characteristics (categorical variables), stratified by median cold ischemia time

Variable	n (% of total)	n CIT<17.55 hrs (%)	n CIT≥17.55 hrs (%)
<b>Total sample</b>	73714 (100%)	36854 (50%)	36860 (50%)
<i>Recipient characteristics</i>			
<b>Gender</b>			
Female	27942 (38%)	13951 (50%)	13991 (50%)
Male	45772 (62%)	22903 (50%)	22869 (50%)
<b>Education</b>			
None	504 (1%)	267 (53%)	237 (47%)
Grade school (0–8)	4628 (6%)	2335 (50%)	2293 (50%)
High school (9–12) or GED	29829 (40%)	15177 (51%)	14652 (49%)
Attended college/technical school	14124 (19%)	7312 (52%)	6812 (48%)
Associate/bachelor degree	7981 (11%)	4117 (52%)	3864 (48%)
Post-college graduate degree	3082 (4%)	1579 (51%)	1503 (49%)
Unknown	12337 (17%)	5629 (46%)	6708 (54%)
Missing	1229 (2%)	438 (36%)	791 (64%)
<b>Race</b>			
Other	1486 (2%)	864 (58%)	622 (42%)
White	31583 (43%)	16065 (51%)	15518 (49%)
Black	26289 (36%)	12734 (48%)	13555 (52%)
Asian	4489 (6%)	2466 (55%)	2023 (45%)
Hispanic	9867 (13%)	4725 (48%)	5142 (52%)
<b>Insurance</b>			
Other	566 (1%)	223 (39%)	343 (61%)
Private	19179 (26%)	9742 (51%)	9437 (49%)
Public	53969 (73%)	26889 (50%)	27080 (50%)
<b>Diabetes Type</b>			
No	47930 (65%)	24114 (50%)	23816 (50%)
Type I	1485 (2%)	827 (56%)	658 (44%)
Type II	8650 (12%)	4683 (54%)	3967 (46%)
Other Type	106 (0%)	58 (55%)	48 (45%)
Unknown Type	13743 (19%)	6491 (47%)	7252 (53%)
Unknown	665 (1%)	281 (42%)	384 (58%)
Missing	1135 (2%)	400 (35%)	735 (65%)
<i>Donor characteristics</i>			
<b>Gender</b>			
Female	30233 (41%)	15053 (50%)	15180 (50%)
Male	43481 (59%)	21801 (50%)	21680 (50%)
<b>Race</b>			
Other	725 (1%)	365 (50%)	360 (50%)
White	51888 (70%)	26254 (51%)	25634 (49%)

Variable	n (% of total)	n CIT<17.55 hrs (%)	n CIT≥17.55 hrs (%)
Black	9927 (13%)	4776 (48%)	5151 (52%)
Asian	1728 (2%)	921 (53%)	807 (47%)
Hispanic	9446 (13%)	4538 (48%)	4908 (52%)
<b>History of Hypertension</b>			
None	53549 (73%)	27217 (51%)	26332 (49%)
Yes, 0–5 years	9439 (13%)	4682 (50%)	4757 (50%)
Yes, 6–10 years	3227 (4%)	1530 (47%)	1697 (53%)
Yes, >10 years	3587 (5%)	1629 (45%)	1958 (55%)
Yes, Unknown duration	3189 (4%)	1459 (46%)	1730 (54%)
Unknown	643 (1%)	308 (48%)	335 (52%)
Missing	80 (0%)	29 (36%)	51 (64%)
<b>History of Diabetes</b>			
None	68822 (93%)	34548 (50%)	34274 (50%)
Yes, 0–5 years	2304 (3%)	1136 (49%)	1168 (51%)
Yes, 6–10 years	776 (1%)	330 (43%)	446 (57%)
Yes, >10 years	804 (1%)	373 (46%)	431 (54%)
Yes, Unknown duration	556 (1%)	269 (48%)	287 (52%)
Unknown	368 (0%)	168 (46%)	200 (54%)
Missing	84 (0%)	30 (36%)	54 (64%)
<b>Kidney pumped</b>			
Not pumped	57111 (77%)	29709 (52%)	27402 (48%)
Pumped	16333 (22%)	7024 (43%)	9309 (57%)
Missing	270 (0%)	121 (45%)	149 (55%)
<b>Cause of Death</b>			
Anoxia	11330 (15%)	5718 (50%)	5612 (50%)
Stroke	30358 (41%)	14999 (49%)	15359 (51%)
Head trauma	29691 (40%)	15075 (51%)	14616 (49%)
CNS tumor	541 (1%)	264 (49%)	277 (51%)
Other	1730 (2%)	776 (45%)	954 (55%)
Missing	64 (0%)	22 (34%)	42 (66%)
<b>Non-Heart Beating Donor</b>			
Missing	106 (0%)	34 (32%)	72 (68%)
No	67702 (92%)	34070 (50%)	33632 (50%)
Yes	5906 (8%)	2750 (47%)	3156 (53%)

CIT = cold ischemia time

**Table 2**

Recipient and donor characteristics (continuous variables), stratified by median cold ischemia time

Variable	Mean (SD)	Mean if CIT <17.55 hrs (SD)	Mean if CIT ≥17.55 hrs (SD)
Recipient age	51.21 (12.99)	51.06 (13.16)	51.36 (12.84)
Days on waiting list	818.78 (651.89)	829.31 (652.77)	808.26 (650.86)
Peak PRA <sup>a</sup>	2 (15)	2 (15)	2 (15)
HLA mismatches	4.22 (1.21)	4.27 (1.19)	4.18 (1.23)
Donor age	39.32 (16.69)	38.93 (16.35)	39.71 (17.02)
Donor serum creatinine	1.15 (1.11)	1.10 (1.03)	1.20 (1.18)

SD = standard deviation; CIT = cold ischemia time; PRA = panel reactive antibody

<sup>a</sup>Peak PRA reported as median (IQR)

**Table 3**

Exposure and outcome variables, stratified by median cold ischemia time

Variable	n (% of total)	n CIT ≤17.5 hrs (%)	n CIT >17.5 hrs (%)
<b>DGF</b>			
No	53423 (73%)	28508 (53%)	24915 (47%)
Yes	20185 (27%)	8293 (41%)	11892 (59%)
<b>One year graft loss</b>			
Graft functional	66329 (94%)	33562 (51%)	32767 (49%)
Graft lost	4382 (6%)	1893 (43%)	2489 (57%)
<b>Five year graft loss</b>			
Graft functional	32461 (78%)	15733 (48%)	16728 (52%)
Graft lost	9252 (22%)	4098 (44%)	5154 (56%)
<b>One year mortality</b>			
Alive	69861 (95%)	35093 (50%)	34768 (50%)
Deceased	3853 (5%)	1761 (46%)	2092 (54%)
<b>Five year mortality</b>			
Alive	38837 (80%)	18604 (48%)	20233 (52%)
Deceased	9444 (20%)	4234 (45%)	5210 (55%)

CIT = cold ischemia time

**Table 4**  
Effect of DGF on graft loss and mortality at 1 and 5 years using a conventional linear probability model regression versus an instrumental variable analysis

Dependent variable	One year graft loss (N=69,922)		Five year graft loss (N=41,138)		One year mortality (N=72,879)		Five year mortality (N=47,604)	
	LPM	IVM	LPM	IVM	LPM	IVM	LPM	IVM
Coefficient on DGF	0.10072	0.13546	0.12475	0.16183	0.03312	0.07112	0.05986	0.11032
(standard error)	(0.00375)	(0.02224)	(0.00465)	(0.03805)	(0.00233)	(0.01493)	(0.00466)	(0.03529)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002

LPM = Linear Probability Model; IVM = Instrumental Variables Model

All standard errors are heteroskedasticity robust and clustered by region

Multiply coefficient by 100 to derive the probability of dependent variable on outcome.

All models control for the following covariates: transplant year, organ procurement organization, age, sex, educational level, race, insurance status, diabetes type, days on waiting list, peak panel reactive antibodies, and number of HLA mismatches at transplant, donor age, donor sex, donor race, donor diabetes, donor hypertension, whether the kidney was pumped, terminal serum creatinine, donor cause of death, and whether the kidney was a donation after circulatory determination of death.