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Brief Communication

Centers for Disease Control 'High-Risk' Donors and Kidney Utilization

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The aims of this study were to determine whether Centers for Disease Control high risk (CDCHR) status of organ donors affects kidney utilization and recipient survival. Data from the Scientific Registry of Transplant Recipients were used to examine utilization rates of 45 112 standard criteria donor (SCD) deceased donor kidneys from January 1, 2005, and February 2, 2009. Utilization rates for transplantation were compared between CDCHR and non-CDCHR kidneys, using logistic regression to control for possible confounders. Cox regression was used to determine whether CDCHR status independently affected posttransplant survival among 25 158 recipients of SCD deceased donor kidneys between January 1, 2005, and February 1, 2008. CDCHR kidneys were 8.2% (95% CI 6.9–9.5) less likely to be used for transplantation than non-CDCHR kidneys; after adjusting for other factors, CDCHR was associated with an odds ratio of utilization of 0.67 (95% CI 0.61–0.74). After a median 2 years follow-up, recipients of CDCHR kidneys had similar posttransplant survival compared to recipients of non-CDCHR kidneys (hazard ratio 1.06, 95% CI 0.89–1.26). These findings suggest that labeling donor organs as 'high risk' may result in wastage of approximately 41 otherwise standard kidneys per year.

Key words: Disease transmission, extended criteria donors, kidney transplantation, organ donation, organ utilization

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Introduction

Developed in 1994 by the Centers for Disease Control (CDC), the Public Health Service guidelines shown in Table 1 designate organ donors as 'high risk' if they meet any of the criteria for high-risk behaviors that present an increased chance of human immunodeficiency virus (HIV) transmission (1). This designation is intended to alert and protect transplant candidates from the risks of infection, because even negative antibody testing of potential donors does not entirely eliminate the possibility of disease transmission due to the window period between infection and seroconversion (2). Nevertheless, the actual risk of false negative disease transmission is likely very low. Although limited by a voluntary reporting system, current estimates suggest the combined risk of transmission of HIV, hepatitis B or hepatitis C from a seronegative donor is less than 1% (3). For example, until recently a case of HIV transmission from solid organ transplantation had not been reported in the United States in more than 20 years (4). Furthermore, studies have shown that utilizing nucleic acid amplification testing during the screening process can further reduce the risk of disease transmission, though the cost-benefit remains uncertain.

Despite the low risk of transmission, disclosure of CDCHR donor status and informed consent of transplant recipients is recommended by ethicists and required by Organ Procurement and Transplantation Network (OPTN) policy (5,6). Specific mechanisms of disclosure and informed consent are left up to each transplant center, and a study on this matter has demonstrated that significant within- and between-center variation exists in disclosure practices (2). We hypothesized that the CDCHR label might result in potential recipients and transplant physicians turning down organs that would be otherwise suitable for transplantation. We chose to focus on the utilization of kidney allografts because kidney transplantation is not as immediately lifesaving as transplantation of many other solid organs, and thus risks of disease transmission may be given stronger consideration.

Therefore, the aims of this study were (1) to determine whether CDCHR labeling affects deceased donor kidney utilization after controlling for other factors and (2) to determine whether use of CDCHR kidneys from deceased donors negatively impacts patients' posttransplant survival.

Methods

The data source was the Scientific Registry of Transplant Recipients (SRTR) Standard Analysis File as of February 2, 2009. To analyze utilization rate, we

Table 1: Public Health Service criteria for High Risk Behavior (1, 2)

Category	Description
MSM	Men who have had sex with another man in the preceding 5 years
IDU	Persons who report nonmedical intravenous, intramuscular or subcutaneous injection of drugs in the preceding 5 years
Hemophiliac	Persons with hemophilia or related clotting disorders who have received human derived clotting factor concentrates
Prostitution	Men and women who have engaged in sex in exchange for money or drugs in the preceding 5 years
High-risk sex	Persons who have had sex in the preceding 12 months with any person described in items 1–4 above or with a person known or suspected to have HIV infection
Exposed to HIV	Persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or through contact with an open wound, non-intact skin, or mucous membrane
Jail	Inmates of correctional systems (This exclusion is to address issues such as difficulties with informed consent and increased prevalence of HIV in this population.)

chose deceased kidney donors who were standard criteria other than their behavioral risk profile, and donated between January 1, 2005, and February 2, 2009 (n = 45 128 kidneys). Standard criteria donors (SCD) from whom at least one organ was used for the purpose of transplantation were chosen in order to analyze kidneys that would otherwise have a reasonable chance of being used. This particular time period was chosen to begin when the CDCHR label started being routinely recorded in the SRTR file. To analyze posttransplant survival, the sample consisted of individuals who underwent deceased-donor single kidney transplantation from SCD donors during the time period between January 1, 2005, and February 1, 2008 (n = 25 868 patients). Transplants within the last year of data (February 2, 2008, to February 2, 2009) were excluded to allow a minimum follow-up time of 1 year. Time at-risk was censured at the last expected follow-up.

Certain variables had greater than 1% missing values. These variables were donor creatinine (1.3% missing), cold ischemia time (11.3% missing) and peak panel reactive antibody (peak PRA) (1.1% missing). To avoid bias associated with listwise deletion of large numbers of observations, we used standard methods of imputation for these variables with significant missing data (7). An imputation flag was created and included in all subsequent analyses to protect against bias from the imputation process. In the case of the cold ischemia time and peak PRA, the imputation flag demonstrated that data was missing in a statistically significant manner. Therefore we generated a missing data variable and included it in the analysis to adjust for bias from these potential confounders. This prevented the observations with missing data from being excluded during further statistical analysis. Small amounts of missing data from other variables resulted in a final sample size of 45 112 kidneys for the multivariable utilization analysis and a sample size of 25 858 patients for the multivariable survival analysis.

Utilization rate was defined as kidneys transplanted as a percentage of the total available kidneys from deceased donors, with a donor defined as anyone from whom at least one organ was recovered for the purpose of transplantation. The proportion of available kidneys that were subsequently transplanted was calculated for both CDCHR and non-CDCHR donors, and the chi-square test was used to determine the statistical significance of the difference.

Next, multivariable logistic regression was used to adjust for other donor characteristics, which might confound utilization comparisons between CDCHR versus non-CDCHR organs. Variables for donor characteristics included in the analysis were CDCHR status, donation after cardiac death, age, race, cause of death, height, serum creatinine, gender, blood type O, HBV positive, HCV positive, history of hypertension and history of diabetes (8,9). Donor age, race and cause of death were each stratified into several subcategories. Because organ utilization may have been affected by other variables not present in the database, we performed sensitivity analysis by adjusting for number of organs transplanted per donor (OTPD). We also analyzed utilization rates over time to determine the effect of enactment of the OPTN policy in December 2007 requiring notification of recipients about CDCHR status. Then, predicted probabilities were calculated to determine expected utilization rates during this time period if the CDCHR label did not exist. This method involves using the regression model to predict utilization of all SCD kidneys at baseline and then with CDCHR set to zero, and was used to calculate the number of otherwise usable kidneys that are potentially 'wasted' per year because of the CDCHR appellation.

Finally, Cox proportional hazards regression was used to determine if transplantation of CDCHR kidneys is associated with decreased posttransplant survival after controlling for potential confounders. Variables included the same donor characteristics from the analysis above, in addition to the following recipient characteristics: age, race, gender, history of diabetes, previous transplants, previous dialysis and peak PRA, as well as the following transplant characteristics: cold ischemia time, and whether the kidney was nationally or locally recovered (9). Death status and death date for the Cox analysis were drawn from the Social Security Master Death File data in the SRTR data set.

Results

Over the studied time period (January 2005–February 2009), there were 45 128 donated kidneys, of which 4482 (9.9%) were from CDCHR donors and 40 646 (90.1%) were from non-CDCHR donors. As shown in Table 2, CDCHR donors tended to have more characteristics associated with favorable graft function such as young age and lower serum creatinine. In total, 37 924 of the donated kidneys were transplanted (utilization rate 84.1%). Of the 4482 CDCHR kidneys, 3437 were used for transplantation (utilization rate 76.7%, 95% CI 75.4–77.9), while of the 40 646 non-CDCHR kidneys, 34 505 were used for transplantation (utilization rate 84.9%, 95% CI 84.5–85.2). Thus, the utilization rate of CDCHR kidneys was 8.2% (95% CI 6.9–9.5) lower than that of non-CDCHR kidneys. When analyzed by donor, utilization rates of both kidneys versus one kidney were 67.4 and 9.2% for CDCHR donors, respectively, compared to 70.6 and 7.5% for non-CDCHR donors ($p < 0.001$).

In the multivariable logistic regression shown in Table 3, donor characteristics significantly associated with lower utilization were older age, donation after cardiac death, Hispanic or Other, non-Caucasian race, cause of death other

Table 2: Donor characteristics

	CDC high risk (n = 2241 donors)	Non-CDC high risk (n = 20 323 donors)	p-Value
Median age (years)	34	35	0.02
Gender (% male)	71.2%	61.5%	<0.001
Race			
Black	18.1%	14.4%	<0.001
Hispanic/Latino	12.7%	15.1%	0.003
Caucasian	67.4%	67.5%	0.93
Non-Caucasian other	1.8%	3.0%	0.001
Median height (cm)	175.3	172.7	<0.001
Cardiac death	8.6%	10.7%	0.002
Blood type O	49.3%	47.3%	0.07
HBV positive	11.3%	3.7%	<0.001
HCV positive	17.2%	2.7%	<0.001
History of hypertension	18.6%	18.4%	0.87
History of diabetes	5.3%	6.0%	0.18
Serum creatinine (mg/dL)	1.0	1.1	<0.001
Cause of death			
Anoxia	28.3%	19.7%	<0.001
Cerebrovascular accident	23.1%	28.9%	<0.001
Head trauma	45.3%	46.5%	0.05
Other	3.2%	3.9%	0.12

Table 3: Logistic regression of kidney transplantation for non-ECD deceased donors

Variable (donor characteristics)	Odds ratio	95% C.I.	p-Value
CDC high risk	0.67	0.61–0.74	<0.001
Donation after cardiac death	0.52	0.47–0.57	<0.001
Age (ref = 35–49)			
0–10	2.14	1.67–2.74	<0.001
11–17	2.19	1.86–2.58	<0.001
18–34	1.57	1.44–1.71	<0.001
50–64	0.62	0.56–0.67	<0.001
65+	[1]		
Race (ref = Caucasian)			
Black	1.03	0.94–1.12	0.531
Hispanic/Latino	1.31	1.19–1.44	<0.001
Non-Caucasian other	1.56	1.29–1.90	<0.001
Cause of death (ref = head trauma)			
Anoxia	0.87	0.80–0.94	0.001
Cerebrovascular accident	0.73	0.67–0.79	<0.001
Other	0.50	0.43–0.57	<0.001
Height (per 10 cm)	1.04	1.45–1.54	<0.001
Serum Creatinine	0.40	0.39–0.42	<0.001
Male	0.87	0.81–0.93	<0.001
Blood type O	1.06	1.00–1.13	0.058
HBV positive	0.59	0.52–0.67	<0.001
HCV positive	0.11	0.10–0.12	<0.001
History of hypertension	0.53	0.49–0.57	<0.001
History of diabetes	0.46	0.42–0.52	<0.001

CI, confidence interval.
[1] Dropped from model due to colinearity.

than head trauma, height, serum creatinine, male gender, positive serologic tests for hepatitis B or C, and a history of diabetes or hypertension. After controlling for all of these potential confounders, kidneys from CDCHR donors were even less likely to be used for transplantation than those from non-CDCHR donors (odds ratio 0.67, 95% CI 0.61–0.74, $p < 0.001$). In sensitivity analysis, after adjusting for OTPD the odds ratio for CDCHR status remained significant at 0.75 (95% CI 0.65–0.86, $p < 0.001$), suggesting the absence of substantial unmeasured confounders. Utilization rates of CDCHR kidneys did not change over time despite implementation of the OPTN policy in December 2007 mandating recipient notification (data not shown).

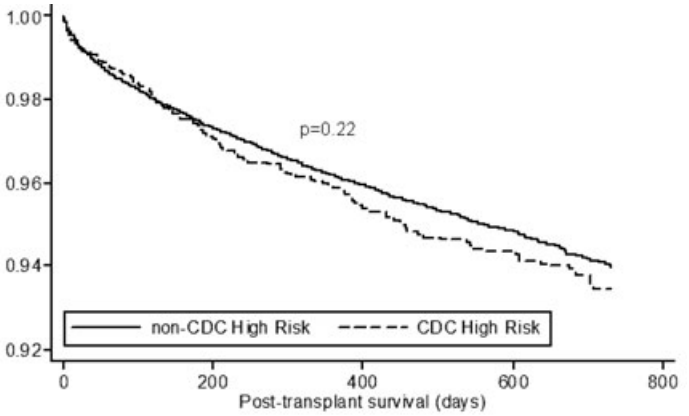
This regression model had an area under the receiver-operating characteristic curve (AUROC) of 0.84, indicating excellent performance for predicting utilization. Based on this model, the predicted utilization rate for all non-ECD kidneys during this time period would increase by 0.37% if the CDCHR label did NOT exist. This suggests that 165 kidneys from January 2005 to February 2009, or approximately 41 kidneys per year are potentially being wasted as a result of the CDC-high risk appellation.

Although CDCHR kidneys appear to be turned down more often than non-CDCHR ones, receiving a CDCHR kidney does not appear to negatively affect survival. At a median follow-up time of 731 days, patients who received a CDCHR kidney had similar survival to those who received a non-CDCHR kidney, as shown in Figure 1. Despite controlling for multiple potential confounders using Cox regression, receiving a kidney with CDCHR status was not associated with worse posttransplant survival (hazard ratio 1.06, 95% CI 0.89–1.26, $p = 0.54$).

Discussion

This study has demonstrated that kidney allografts bearing a CDCHR label are approximately one-third less likely to be used for transplantation than would otherwise be the case if this label did not exist. Furthermore, we demonstrate that CDCHR donor status has no significant impact on median 2-year recipient posttransplant survival. This lack of impact on short-term posttransplant survival was also demonstrated in a recent study by Reese et al. (10). Therefore, we estimate that approximately 41 otherwise standard kidneys per year are potentially being wasted due to being labeled as 'high risk'.

Despite the reassuring survival outcomes for these organs as a group, we do not propose that stratification of donors by disease transmission risk or recipient notification should be abandoned. Instead, updated criteria need to be developed which reflect the continuous nature of transmission risk. A continuous measure may be more accurate in predicting risk associated with individual organs, and could also help avoid the psychological bias associated with a dichotomous 'high risk' label (11). Additionally, although we had hypothesized that underutilization of CDCHR organs



Number at risk					
Non-CDC High Risk	23482	20989	13245	13096	5608
CDC High Risk	2376	2146	1390	1375	625

[1]Includes only recipients of standard criteria donor (SCD) kidneys.

Figure 1: Survival curves for kidney transplant patients receiving organs from CDC high risk donors versus non-CDC high risk donors. Includes only recipients of standard criteria donor (SCD) kidneys.

would be caused in part by recipient notification requirements, we found no change in utilization of these organs after implementation of the OPTN recipient notification policy in December 2007. This could be due to the limited time since implementation of the policy, or it could suggest that utilization of CDCHR organs depends mainly upon the individual physicians and/or transplant centers rather than the recipient. Indeed, an earlier study demonstrated that centers with formal protocols and procedures for consenting recipients actually have higher utilization rates of CDCHR organs (2). Therefore, utilization of these organs may depend not so much on *whether* recipients are notified but rather *how* this notification is done. We propose that standardized mechanisms need to be developed for educating patients about the risks associated with all organs, not just those designated as CDCHR. These methods should build upon work which has demonstrated that risk communication is best done (1) using graphs, (2) using absolute rather than relative risks and (3) providing contextual information to account for innumeracy (12–14). Such methods could then be applied to all risks associated with transplantation of any solid organ. Finally, standardized protocols may also reduce fear of litigation, another potential reason for underutilization of CDCHR kidneys. Such fear is indeed justifiable, since a recent case of HIV transmission has generated lawsuits alleging failure to adequately inform the candidate of this potential risk (6).

The primary limitation of this study is the observational nature. While the results demonstrate a strong association between the CDCHR label and lower kidney utilization rates, we cannot be certain the relationship was causal. Furthermore, this data cannot determine whether decreased utilization of CDCHR kidneys is occurring due to turn-down by the physician or patient. This limitation is particularly important because it will be difficult to fix the problem without understanding its root location. Another limitation is the duration of the follow-up time in our survival analysis. While the median follow-up time is approximately 2 years, we were limited by when the CDCHR status started to be consistently recorded in the SRTR data set. Ideally, our survival analysis would examine a longer posttransplant time scale. Finally, we were unable to measure actual rates of disease transmission. At present the only mechanism for measuring transmission rates relies on voluntary reporting by transplant centers, and is not reported in the SRTR database (3).

In conclusion, we found that the label 'CDCHR' is independently associated with lower utilization of deceased donor kidneys. Yet these kidneys on average tend to have characteristics associated with favorable graft function, and individuals that do receive CDCHR kidney transplants do not experience worse posttransplant survival at 2 years. These findings suggest that a dichotomous label is inadequate for expressing risk of disease transmission, and may actually be causing harm. Future research should focus on developing continuous models to predict disease transmission risk associated with individual organs, and on formalizing mechanisms for recipient education and notification about organ-specific risks.

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