Survival Benefit of Kidney Transplantation in HIV-infected Patients

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Objective: To determine the survival benefit of kidney transplantation in human immunodeficiency virus (HIV)-infected patients with end-stage renal disease (ESRD).

Summary Background Data: Although kidney transplantation (KT) has emerged as a viable option for select HIV-infected patients, concerns have been raised that risks of KT in HIV-infected patients are higher than those in their HIV-negative counterparts. Despite these increased risks, KT may provide survival benefit for the HIV-infected patient with ESRD, yet this important clinical question remains unanswered.

Methods: Data from the Scientific Registry of Transplant Recipients were linked to IMS pharmacy fills (January 1, 2001 to October 1, 2012) to identify and study 1431 HIV-infected KT candidates from the first point of active status on the waiting list. Time-dependent Cox regression was used to establish a counterfactual framework for estimating survival benefit of KT.

Results: Adjusted relative risk (aRR) of mortality at 5 years was 79% lower after KT compared with dialysis (aRR 0.21; 95% CI 0.10–0.42; P < 0.001), and statistically significant survival benefit was achieved by 194 days of KT. Among patients coinfected with hepatitis C, aRR of mortality at 5 years was 91% lower after KT compared with dialysis (aRR 0.09; 95% CI 0.02–0.46; P = 0.004); however, statistically significant survival benefit was not achieved until 392 days after KT.

Conclusions: Evidence suggests that for HIV-infected ESRD patients, KT is associated with a significant survival benefit compared with remaining on dialysis.

Keywords: human immunodeficiency virus, kidney transplantation, survival benefit


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METHODS

Data Source

The study used data from the Scientific Registry of Transplant Recipients, which includes data submitted by members of the Organ Procurement and Transplantation Network (OPTN) on all donors, waitlisted candidates, and transplant recipients in the United States. The Health Resources and Services Administration of the US Department of Health and Human Services provides the oversight to the activities of the OPTN and SRTR contractors. Since HIV status is not collected when a patient registers for the waiting list, a novel linkage with pharmacy fill data from IMS Health was used to identify HIV-infected patients. IMS Health collects medication fills through

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participating pharmacies. Fifty-six percent of incident kidney waitlist candidates from 2001 to 2012 had pharmacy fills in the linked IMS database that overlapped with the candidate time on the waitlist.

Study Population

Adult KT candidates who filled at least 1 HIV-specific medication while on the waitlist between January 1, 2001 and October 1, 2012 were identified through IMS pharmacy fills. Patients listed inactive who never changed to active status were excluded, as they were not an appropriate counterfactual. However, patients listed inactive who eventually changed to active were included, but only at the first active date (n = 1431). The candidate’s first listing while HIV+ was kept.

Exploratory Data Analyses

Candidate characteristics were compared by transplant status and donor type (living vs. deceased donor). Donor characteristics were compared by donor type. Continuous variables were analyzed using Wilcoxon rank-sum tests, and categorical variables were examined using chi-square tests of independence.

Outcome Ascertainment

The primary outcome was mortality. Death dates were supplemented from the Centers for Medicare and Medicaid Services and the Limited Access Death Master File available from the National Technical Information Service. Multiple simultaneous listings were collapsed. Exposure time began at the later of waitlisting or first HIV medication fill to the earlier of patient death or administrative end of study (October 1, 2012).

Survival Analyses

Survival analyses were performed using the Cox Proportional Hazards model with time-dependent variables for transplantation. Transplant recipients contributed time-at-risk to the waitlist group until receiving their transplant, at which point they began contributing time-at-risk to the transplant group. If the first antiretroviral medication fill was after listing date, the person was left-truncated until the time of first fill to ensure time on the waitlist was only captured once a candidate was known to be HIV infected. To quantify the mortality risk associated with receiving a transplant versus remaining on the waitlist, we allowed the hazard associated with transplantation to vary as a function of the number of days posttransplant. For every day postlisting, a new record was created for each person to capture whether the person had been transplanted as of that day, as well as the number of days posttransplant (if applicable) at that event time. If the person had not yet been transplanted, both variables were coded as 0. This allowed the reference level for the effect to be a person still on the waitlist; furthermore, a comparison could be made at any time point posttransplant versus the counterfactual of remaining on the waitlist.

To model the hazard, we used the pspline function in R, which fit a series of penalized basis splines to a continuous variable. A major benefit of pspline is the ability to fit an effect without assuming a particular shape to the hazard. While research exists describing the mortality hazard posttransplant for some populations, we did not want to assume that the effect of transplantation on HIV-infected individuals would mirror that previously described for uninfected individuals. Pspline also avoids the pitfalls of user-specified spline knots, where a single misspecified knot can adversely affect the fit of a variable for its entire range. An indicator for transplantation was included; this controlled for the transition between the untransplanted and transplanted states while allowing the effect of days posttransplant to be as extreme as necessary.

Adjusted analyses included all of the covariates from the most recent SRTR PSR kidney waitlist mortality models, which were run on a national cohort of kidney waitlist candidates from 2012 to 2013. Covariates were chosen using the LASSO procedure as described by Snyder et al.14 Covariates significant at P<0.10 are presented. An additional model separated the effect of transplantation in the HIV-infected cohort by donor type. All statistical analyses were performed using R version 9.4 (Vienna, Austria).

RESULTS

Patient and Donor Characteristics

Waitlist candidate and transplant recipient characteristics are shown in Table 1. Between January 1, 2001 and October 1, 2012, 1431 HIV-infected waitlist candidates were identified who at some point were active status; of these, 113 achieved living donor transplantation, 426 achieved deceased donor transplantation, and 892 remained on the waitlist. HIV-infected waitlist candidates and transplant recipients were commonly men, African American, and between the ages of 35 to 49 years. Waitlist candidates who were older or blood group B were less likely to achieve transplantation.

Characteristics of living and deceased donors received by HIV-infected candidates are shown in Table 2. Compared with deceased donors, living donors were more often <50-year old, less likely to have hypertension, and more likely to be woman and African American. Among deceased donor kidney transplants, 12% were extended criteria donors, 10.6% were donors after cardiac death, and the median cold ischemia time was 16.4 hours (range, 11.9–23.4).

Unadjusted Death Rates

There were 310 (21.7%) deaths among all HIV-infected patients in the study. Among those who never achieved transplantation, 223 (25.0%) died before study end. There were 9 deaths among 113 living donor transplant recipients (8.0%) and 78 deaths among 426 deceased donor transplant recipients (18.3%). Unadjusted death rates for HIV-infected transplant candidates and recipients were 8.7 per 100 PY (223 per 2555.9 PY) and 3.1 per 100 PY (87 per 2819.6 PY) respectively; furthermore, by donor type, death rates were 1.6 per 100 PY (9 per 578.7 PY) for living donors and 3.5 per 100 PY (78 per 2240.8 PY) for deceased donors.

Adjusted Risk of Death for Transplant Recipients Versus Candidates Without Transplant

The adjusted relative mortality risk at 5 years was 79% lower among transplant recipients compared with remaining on dialysis [adjusted relative risk (aRR) 0.21; 95% confidence interval (CI) 0.10–0.42; P < 0.001] (Table 3 and Fig. 1). More specifically, among living donor recipients the risk was 82% lower (aRR 0.18; CI 0.10–0.30; P < 0.001) and among deceased donor transplantation recipients the risk was 77% lower (aRR 0.23; CI 0.10–0.50; P < 0.001) (Table 4 and Fig. 2). Adjusted patient survival at 5 years was 80.1% among waitlist candidates compared with 90.6% among transplant recipients, conditional on survival to the median time to transplant in the cohort (1.7 yrs postlisting).

Mortality risk was not statistically different between waitlist candidates and transplant recipients during the first 7 months posttransplant. Mortality risk steadily declined among HIV-infected transplant recipients thereafter, with transplantation providing a statistically significant survival benefit by 194 days posttransplant.
HIV-infected Patients Coinfected With HCV

One hundred thirty-four HIV-infected patients (9.4%) were willing to accept a kidney from a HCV+ donor and were presumed to be coinfected with HCV. Fifty-seven (42.5%) coinfected patients died during the study period, and 35 (61.4%) of those deaths occurred posttransplant. The adjusted relative mortality risk at 5 years was 91% lower among transplant recipients compared with remaining on dialysis (aRR 0.09; 95% CI 0.02–0.46; \( P = 0.004 \)). Among coinfected patients, mortality risk was not statistically different between waitlist candidates and transplant recipients during the first-year posttransplant. Mortality risk, however, steadily declined among coinfected transplant recipients thereafter, with transplantation providing a statistically significant survival benefit 392 days posttransplant (Fig. 3).

DISCUSSION

In this national study of HIV-infected kidney waitlist candidates, we found that KT was associated with a statistically significant survival benefit by 194 days posttransplant. Older age, longer time on dialysis, and coinfection with HCV were each associated with increased risk of death postlisting, regardless of transplant status. Our finding of an 8.7% yearly death rate among HIV-infected waitlist candidates is significantly higher than the 4.9% annual death rate reported among the uninfected general waitlist population. This almost 2-fold increase rate of death among HIV-infected waitlist candidates is consistent with previous published reports indicating significantly higher mortality rates among HIV-infected dialysis patients compared with their uninfected counterparts. Reasons for higher rates of death among HIV-infected dialysis patients remain elusive, but may in part be explained by the increased cardiovascular risk associated with antiretroviral therapies. Importantly, however, annual death rates among HIV-infected KT recipients (3.1%) are similar to their uninfected counterparts (3.3%), and emphasize the benefit of KT in this unique population.

HCV status is not currently captured at the time of waitlisting, and as such, willingness to accept an HCV+ kidney was used as a surrogate marker for HCV status. We identified 134 HIV-infected patients coinfected with HCV. Despite the small sample size, among the identified coinfected subset, we found that KT was associated...
with a 91% lower risk of mortality compared with dialysis. However, statistically significant benefit was not achieved until 392 days posttransplant, which was 198 days longer than their HIV mono-infected counterparts, and suggests that coinfection with HCV portends more severe morbidity and mortality. Poor outcomes associated with HCV are not limited to HIV-infected KT recipients. Further study will be needed to determine whether HIV-infected ESRD patients achieve the same survival benefit with kidneys from HIV-coinfected patients with the plan for eradication of HCV in the immediate posttransplant period, and as such, decrease the time from coinfection with HCV independent of HIV infection has been associated with HCV are not limited to HIV-infected KT recipients and as such, may shorten waiting times for HIV-infected candidates.

Importantly, these findings demonstrate that HIV-infected ESRD patients achieve a significant survival benefit with transplantation compared with remaining on dialysis, promoting the continued practice of offering KT to this vulnerable population. Recently, the HIV Organ Policy Equity Act [42 U.S.C. § 274f-5(b)] was signed into law, which has provisions for the recovery of organs from HIV-infected individuals. Implementation of the HIV Organ Policy Equity Act will afford HIV-infected ESRD patients the opportunity to achieve transplant using kidneys from HIV-infected donors, and as such, may shorten waiting times for HIV-infected candidates. Further study will be needed to determine whether HIV-infected ESRD patients achieve the same survival benefit with kidneys from HIV-infected donors.

TABLE 2. Donor Characteristics for HIV+ Recipients of Living Donor and Deceased Donor Transplants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Living Donor</th>
<th>Deceased Donor</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>113 (46.2)</td>
<td>426</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0–17</td>
<td>0 (8.7)</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>18–34</td>
<td>32 (28.3)</td>
<td>141 (33.1)</td>
<td></td>
</tr>
<tr>
<td>35–49</td>
<td>57 (50.4)</td>
<td>138 (32.4)</td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>24 (21.2)</td>
<td>110 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male 51 (41.5)</td>
<td>257 (60.3)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Female 62 (54.9)</td>
<td>169 (39.7)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>White 54 (47.6)</td>
<td>285 (66.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Black 46 (40.7)</td>
<td>65 (15.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hispanic 11 (9.7)</td>
<td>64 (15.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other 2 (1.8)</td>
<td>12 (2.8)</td>
<td></td>
</tr>
<tr>
<td>ECD (deceased donor only)</td>
<td>2 (1.8)</td>
<td>99 (23.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DCD (deceased donor only)</td>
<td>51 (12.0)</td>
<td>145 (33.6)</td>
<td></td>
</tr>
<tr>
<td>HCV+ (deceased donor only)</td>
<td>59 (13.8)</td>
<td>191 (44.2)</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>2 (1.8)</td>
<td>99 (23.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>22 (5.2)</td>
<td>110 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Cause of death</td>
<td>Anoxia 119 (27.9)</td>
<td>143 (33.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular/stroke 143 (33.6)</td>
<td>150 (35.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Head trauma 150 (35.2)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other 13 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold ischemia time in hours (median)</td>
<td>1 (0.5–1.3)</td>
<td>16.4 (11.9–23.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DCD indicates donor after cardiac death; ECD, expanded criteria donor.

registry. The OPTN does not collect data on CD4 count, viral loads, or infections, and collects limited data on acute rejection and malignancies, all of which are factors thought to influence long-term outcomes among HIV-infected dialysis patients and transplant recipients. However, the National Institutes of Health multicenter protocol, which has been adopted widely across the US, uses relatively restricted criteria for waitlisting and transplantation of HIV-infected ESRD patients, requiring undetectable viral loads and CD4 counts >200, and it is unlikely that there would be major deviations from this protocol within national data. Moreover, the sample size for subgroup analyses among coinfected patients was small and may limit the accuracy of the time-to-event analyses. Further, IMS Health only captures medication fills for 56% of the incident kidney waitlist, and as such, it is likely that our study underestimated the number of kidney waitlist candidates infected

FIGURE 1. Adjusted relative mortality risk among HIV+ kidney transplant recipients compared with remaining on dialysis.
with HIV. Finally, use of IMS data to identify HIV-infected waitlist candidates may have introduced misascertainment bias. However, the data from this unique cohort represent the HIV-infected transplant candidate and recipient population in the real world, and as such, contribute new and important information about the survival benefits of kidney transplantation in this vulnerable population.

To date, this is the first national study examining the survival benefit of KT over dialysis among HIV-infected ESRD patients. Our results suggest that KT is associated with 79% lower risk of death compared with dialysis among HIV-infected ESRD patients. Moreover, HIV-infected ESRD patients achieve this benefit within 7 months posttransplant. These results are encouraging and support the continued use of KT as a lifesaving modality for HIV-infected ESRD patients.

REFERENCES


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