Interstate Transplant Recipients Exhibit Improved Kidney Allograft Survival Compared to Natives of that State

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Abstract

**Objectives:** Regional disparity in access to organs for kidney transplantation has led to inter-state “transplant tourism.” Our objective is to examine demographic and outcome differences between “transplant tourists” and regional residents.

**Materials and Methods:** The Scientific Registry of Transplant Recipients was analyzed to examine deceased donor kidney transplants performed from 03/2006 to 05/2015 at a single institution (n=581). The recipients numbered 329 from Ohio and 252 from Michigan.

**Results:** The Ohio group exhibited higher incidence of diabetes mellitus (DM; 45.9% vs. 36.7%, p=0.044), lower educational attainment beyond high school (43.2% vs. 72.5%, p<0.001), and greater likelihood of receiving an extended criteria kidney (16.1% vs. 8%, p=0.008). No other demographic differences were noted.

Incidence of delayed graft functions or of rejection at 90 days or 1, 3, or 5 years was equivalent between the two groups. Michigan patients exhibited better death censored graft survival overall (81.6% vs 89%, p=0.022) and at 1-year post transplantation (92.5% vs. 97.3%, p=0.022). The Michigan group also exhibited improved patient survival overall (80.8% vs. 88.6%, p=0.018). Graft loss among Ohioans was associated with elderly (>65 years) status (19.3% vs. 5%, p=0.037), prior renal transplantation (33.3% vs. 17.5%, p=0.045) or high (>20%) panel reactive antibody (PRA; 36.2% vs. 16.3%, p=0.036). Ohio recipients also exhibited decreased patient survival with high panel reactive antibody (23.4% vs. 2.0%, p=0.002), diabetes mellitus, (30.8% vs 16.1%, p=0.021), or with a donation after cardiac death kidney (20.8% vs. 17.4%, p=0.017).

**Conclusions:** In this single center study, patients traveling from outside the state of transplantation exhibited similar donor and recipient demographics to Ohioans yet experienced superior allograft outcomes and were less affected by risk factors. These benefits may be tied to socioeconomic factors as evidenced by the discrepancy in education levels.

**Keywords:** Renal, Transplant, Demographics

Introduction

Chronic Kidney Disease (CKD) and End Stage Renal Disease (ESRD) are major health problems in the United States. The incidence of CKD in the United States was estimated at 13.6% in 2012 and the estimated cost to Medicare exceeded 87 billion dollars [1]. In that same year there were 636,905 patients treated for ESRD. The incidence continues to rise [2]. Furthermore, the number of kidney transplants has increased 78% since 2000 [3].

Equitable access to donor organs regardless of location continues to be a major goal of the transplant community. Despite this, less than 20% of patients on the transplant waitlist will receive a kidney within their first year on the waitlist [4]. Extended wait time contributes to negative transplant outcomes. Therefore, many patients list at multiple transplant centers in an effort to decrease personal wait time.

The wait time for renal transplantation in Michigan averages between 4-6 years versus 19 months in Ohio [5]. Given this disparity in wait time many patients from Michigan travel across the state line to list at Michigan and Ohio transplantation programs. Patients who have a longer wait time in their original donation service area (DSA), like our Michigan population, are more likely to seek multiple listings in another DSA with a shorter average wait time [6].
It may be expected that patients who travel greater distances, have poorer follow-up post-transplantation and therefore may have worse outcomes. However, patients who multiple-list have been shown to have higher educational and socioeconomic status than patients who list at only one transplant program which may correlate with improved graft survival [7]. The aim of our study was to compare the patients' and graft survival of patients transplanted at the University of Toledo Medical center that were native to Ohio with those patients who travelled from Michigan.

Materials and Methods

We analyzed the Scientific Registry of Transplant Recipients to examine all deceased donor kidney transplants performed from March 2006 to May 2015 at The University of Toledo Medical center (n=581). The patients were divided into those who resided in Ohio (n=329) and Michigan (n=252). Approval was obtained from the Institutional Review Board. We excluded recipients of living donor renal transplantation from this analysis. We reviewed patient data using Trans Chart electronic medical record software (TransChart LLC, Dublin, Ohio).

Preoperative immunosuppression included: Alentuzumab - 30mg IV, or 0.5mg/kg if less than 60kg. Diphenhydramine - 25mg IV, Methylprednisolone - 500mg IV, Mycophenolate sodium - 720 by mouth (PO). The majority of recipients were steroid free. The post-operative steroid taper consisted of: methylprednisolone 250mg IV on post-operative day 1, methylprednisolone 125mg IV on post-operative day 2, prednisone 60 mg PO on post-operative day 3, prednisone 40 mg PO on post-operative day 4, and, finally, prednisone 20 mg PO on post-operative day 5. Prednisone at 5-10 mg PO was continued indefinitely for patients with a high risk of rejection; African American patients, patients receiving a repeat transplant or patients with a high panel reactive antibody (PRA) or who experienced delayed graft function.

Starting on post-operative day 1, Tacrolimus 1.5 mg PO (Prograf, Astellas Pharma, Tokyo, Japan) and mycophenolate sodium (Myfortic, Novartis Nutley NJ) 540 mg PO twice per day were given. Tacrolimus levels were measured and titrated to the correct dose of 4-11 ng/dL. If a patient developed an abnormal white blood cell count, Mycophenolate sodium was administered at 2/3 dose until the white blood cell count returned to normal.

Antimicrobial prophylaxis was started post-operatively with sulfamethoxazole (800 mg)-trimethoprim (160 mg) 1 tab PO (Bactrim DS, AR Scientific, Philadelphia, PA) 3 times per week and clotrimazole troche 10 mg dissolved in the mouth 4 times per day following oral care. In the event of a cytomegalovirus mismatch, daily valgancyclovir (Valcyte, Hoffman-La Roche, Basel, Switzerland) was prescribed.

Our follow up regimen is as follows: At 30 days' post-transplantation, monitor for acute rejection, post-operative complications, and adverse effects due to immunosuppressive medications every 1 to 3 weeks. Screen for adherence and the same complications listed previously every 1 to 3 weeks for months 1 to 3, then every 4 to 8 weeks for months 4 to 12 after the transplant. After one year, monitor for graft dysfunction every 2 to 4 months. Monitor for graft dysfunction and cardiovascular disease risk, cancer, adverse effects of immunosuppressive medications, general health maintenance, and adherence every 3 to 6 months. We also carry out screenings based on recommendations from the Kidney Disease: Improving Global Outcomes Organization (Table 4).

Deceased donor and recipient data were collected from the SRTR database and analyzed. Standard definitions for standard criteria donors (SCD), extended criteria donors (ECD), and CDC high risk donors were used (8, 9). Donor Kidney Donor Profile Index (KDPI) was calculated retrospectively on greater than 90% of patients on whom all necessary data elements were available. Patients who actually received a kidney transplant were analyzed, not all patients on the deceased donor waiting list.

Statistical Methods

Student's t-test or Mann-Whitney U test were used for continuous variables and Pearson’s Chi-squared Test or Fisher’s Exact Test for categorical variables were used for the data. Patient and graft survival were assessed using the life method. Factors associated with survival were identified using univariate Cox Proportional Hazards regression, with final multivariate models selected from the results as well as factors of interest. For multivariate models, univariate variables with p < 0.1 were used initially and those with p > 0.05 were removed at each iteration. All tests were performed at a 95% confidence interval, and a significant level of p < 0.05 was used. Survival curves were generated using the life table method, with statistical comparisons computed with the log-rank method. All statistical analyses were conducted using IBM SPSS ver23. (IBM Corp., Armonk, NY).

Results

Donor demographics

Both sets of recipients received demographically similar donor allografts (p<0.05). However, the Ohio group received more ECD kidneys (16.1% vs 8.0%, p=0.008).

Recipient demographics

There were more Asians (0.8% vs 4.2%, p=0.017) and fewer Hispanics (8.6% vs. 2.2%, p=0.006) in the Michigan group. The incidence of Diabetes Mellitus (45.9% vs 36.7%, p=0.044) in the Ohio group exceeded the incidence in the Michigan group. More patients from Michigan obtained an education beyond high school (43.2% vs 72.5%, p<0.001), obtained a college degree (10.9% vs 22%, p<0.05) and obtained a graduate degree (2.9% vs 16.2%, p<0.05) (Table 1).

Outcomes

Delayed Graft Function did not differ significantly (12.1% vs 11%, p=0.777) and the number of patients who lost allografts at 90 days, 1 year, 3 years, and 5 years were not statistically significant. The long-term death censored graft survival was not different among the two groups at 5 years (Figure 1) however the Michigan group exhibited better death censored graft survival overall (81.6% vs 89%, p=0.022) and at 1-year post transplantation (92.5% vs. 97.3%, p=0.022). Improved patient survival overall (80.8% vs 88.6%, p=0.018) was noted in the Michigan group, though this difference was not apparent at the 1, 3, and 5 year marks (Figure 2). Rejection rates did not differ significantly due to nonadherence of immunosuppressive therapy (68.4% vs 70%, p=0.854) (Table 2).
worse outcomes in both graft loss and death than the Michigan recipients. Ohio patients experienced increased graft loss if they were elderly (19.3% vs 5%, p=0.037) were receiving their second transplant (23.4% vs 20.0%, p=0.002), were diabetic (30.8% vs 16.1%, p=0.021), or were receiving kidneys from a donor after cardiac death (20.8% vs 17.4%, p=0.017) (Table 3). Ohio recipients showed longer median follow-up time when compared to Michigan patients (1567+/− 998.7 days vs 1315+/− 915.8 days, p=0.037).
Discussion

The US Department of Health and Human Services issued the "Final Rule" in 1998 stating, "Organs and tissues ought to be distributed on the basis of objective priority criteria and not on the basis of accidents of geography" [10]. Unfortunately, the goal of this statement has not been met. Since its institution, there has been no significant reduction in disparity based on waiting times, transplant rates, pre-transplant mortality, and organ quality [11]. Organs from a given DSA, of which there are 58 in the nation, are allocated first to the patients within that DSA. If there are no matches, the allocation expands to surrounding DSAs and eventually to the entire country to find an appropriate recipient. The problem with this system, however, is that the boundaries of the DSA are gerrymandered to fit the needs of individual transplant hospitals and therefore inhibit equal access to organs. Certain DSAs have sicker populations and therefore have a higher need for organ transplants without an increase in donors, leading to longer wait times [11]. This is particularly evident at our institution because of its close proximity to the Michigan border and another DSA. Patients in Michigan with a 4-6 year wait time may live less than a half hour away from Northwestern Ohio, where the average wait is 19 months [5]. The substantial difference in wait time between Ohio and Michigan has led to Michigan residents becoming a significant portion of the transplanted population at our center. Our goal was to determine if these patients fared better than their local Ohio counterparts and why.

Our baseline data show that both the donors and recipients exhibit relatively similar characteristics. The data does show a difference in education levels, with more Michigan recipients receiving college education. The superior outcomes noted in our study may be a function of such socioeconomic factors. There is a positive correlation between socioeconomic status and the concept of health literacy: A patient’s “ability to access, understand, interpret, and use health-related information to manage and improve health” [12]. Poor health literacy is a nationwide problem, with 36% of Americans found to be health illiterate [13, 14]. The correlation between higher socioeconomic status and health literacy could explain why socioeconomic was increased in the Michigan group. Furthermore, poor health literacy correlates with a higher rate of nonadherence to post-transplant immunosuppressant therapy [2]. Nonadherence is very common with renal transplant recipients. Some studies report that as many as one-third of kidney recipients are non-adherent [13]. Nonadherence is an independent risk factor for the development of antibody-mediated rejection, the most common mechanism leading to graft failure. Furthermore, graft loss can be contributed to nonadherence of immunosuppressive drugs 47% of the time [15]. In our case, 70% of our non-compliant patients were from Ohio (42 vs 18). Therefore, one could extrapolate that the Michigan patients, because of their higher education and socioeconomic status, also have higher health literacy and therefore may have better outcomes due to better adherence post-transplant.

Multiple listing does provide a solution to the long wait times in DSAs, but it also creates many issues post-transplantation. Receiving a transplant at a different institution proves very strenuous, time consuming and expensive for patients. We required patients to stay in Toledo for an extended period of time immediately following the procedure. One could assume this would deter many patients in need of a transplant from listing in DSAs that are not near their home. Further extrapolation leads to the conclusions that the Michigan patients are of higher socioeconomic status because they are the only group that can afford to take the time off from work and continually travel to their follow-up appointments. A study by Davis et al.

<table>
<thead>
<tr>
<th>Rejection</th>
<th>Graft Loss</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>Ohio</td>
<td>Michigan</td>
</tr>
<tr>
<td>Elderly</td>
<td>17 (26.3%)</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Delayed Graft Function</td>
<td>17 (56.7%)</td>
<td>11 (42.3%)</td>
</tr>
<tr>
<td>Retransplant</td>
<td>26 (39.8%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Panel Reactive Antigen&gt;20%</td>
<td>20 (42.6%)</td>
<td>14 (28.6%)</td>
</tr>
<tr>
<td>Expanded Criteria Donor</td>
<td>12 (30%)</td>
<td>6 (31.6%)</td>
</tr>
<tr>
<td>Donor After Cardiac Death</td>
<td>9 (37.5%)</td>
<td>7 (30.4%)</td>
</tr>
<tr>
<td>High school education or less</td>
<td>38 (28.4%)</td>
<td>14 (23.3%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>30(25.6%)</td>
<td>19 (21.8%)</td>
</tr>
<tr>
<td>Black</td>
<td>17 (23.6%)</td>
<td>19 (38.5%)</td>
</tr>
</tbody>
</table>

Table 3: Select Risk Factors for Negative Outcomes by State.

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Rejection</th>
<th>Graft Loss</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Cr</td>
<td>1 wk</td>
<td>1 mo</td>
<td>2-3 mo</td>
</tr>
<tr>
<td>Complete Blood Count</td>
<td>Daily</td>
<td>2-3 per wk</td>
<td>Weekly</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Weekly</td>
<td>Monthly</td>
<td>Monthly</td>
</tr>
<tr>
<td>Lipid Profile</td>
<td>Monthly</td>
<td>Monthly</td>
<td>Monthly</td>
</tr>
<tr>
<td>BKV NAT</td>
<td>Monthly</td>
<td>Monthly</td>
<td>Monthly</td>
</tr>
<tr>
<td>EBV NAT (seronegative)</td>
<td>Once</td>
<td>Monthly</td>
<td>Monthly</td>
</tr>
<tr>
<td>BP, pulse, Ht/wt.</td>
<td>Done at every clinic visit</td>
<td>Done at every clinic visit</td>
<td>Done at every clinic visit</td>
</tr>
</tbody>
</table>

Table 4: KDIGO Recommendations for Post-Transplant Screening.
determined that patients with lower socioeconomic status are more likely to have a longer wait time, be listed later in their disease progression, and are unlikely to list outside of their local DSA [16]. While some Michigan patients may only have to drive relatively short distances because of Toledo’s close proximity to the Michigan border, some patients may have to travel significant distances. This is a problem faced all over the country. Steve Jobs, a high profile and public example of transplant tourism, traveled across the country for a liver transplant, demonstrating how personal resources can significantly affect a person’s ability to obtain an organ [17]. Liver transplant recipients travelled an average distance of 580 miles outside of their original DSA. To add further significance to the distance traveled for a liver, 67% of patients who were on multiple transplant lists received their organ from the second DSA on which they were listed [7]. A significant number of patients who are listed in multiple DSAs end up receiving their organ from a site outside of their DSA and are required to travel a significant distance to receive their care.

This reiterates the question of equal access relative to geography, and both personal and national resources. Multiple studies have shown that geography plays a role in access, despite the Final Rule [18-20]. The disparity in access can be demonstrated by comparing DSA wait times. Between the 58 DSAs in the country, the median time to transplantation varied from 0.61 to 4.57 years [16]. The Final Rule attempted to even out the distribution of organs and decrease the disparities in time spent on the wait list between regions. However, the Final Rule has not accomplished this goal. Furthermore, DSAs with longer wait times use more kidneys with a higher KDPI, extended criteria donors, and donors with hepatitis C [16]. These areas are forced to use lower quality kidneys due to the higher demand and insufficient supply, leading to worse outcomes for transplant recipients. Patients in DSAs with long wait times and lower transplant rates have lower graft and patient survival [16,19].

Race also plays a role in time spent on the wait list, with the median wait times of minorities nearly twice those of whites. Vranic, et al. hypothesized that minorities are more likely to live in an Organ Procurement Organization (OPO) area with a longer wait, indicating that geography is a bigger obstacle relative to race [20]. The data from this study demonstrates that when other variables are corrected for, geographic location of waitlisted candidates plays the most important role in racial disparities in wait times for deceased donor kidney transplantation [20]. The average wait time between minority and Caucasian candidates within an OPO differed only by 38.4 days compared to a national average wait time between minority and Caucasian candidates plays the most important role in racial disparities in wait times for deceased donor kidney transplantation [20]. The average wait time between minority and Caucasian candidates within an OPO differed only by 38.4 days compared to a national average wait time between minority and Caucasian candidates plays the most important role in racial disparities in wait times for deceased donor kidney transplantation [20].

The strengths of our study include its comprehensive, single-center nature, including data from every patient transplanted with a deceased donor kidney at our center for ten years, with long term follow up. We examined a large number of variables and identified those which were significantly different between groups, most notably education.

Limitations of our study are that it was a retrospective study. We only examined patients who received a transplant, and did not look at survival of all listed patients, or all those on chronic dialysis. We did not examine the difference between Michigan patients who received a transplant at our center versus those who remained on the list in Michigan, though this could be an area of future study.

Our assumption would be that the Michigan patients who traveled outside of their DSA would have better outcomes than those who stayed in Michigan due to shorter wait list times. There would also likely be differences in baseline patient characteristics among those who sought multiple listing. We recognize that this information remained outside of the scope of our current study but see it as an area for future research.

Patients travelling across a state line to receive a kidney transplant have graft survival equal to or better than local recipients and are less effected by common renal transplant risk
factors. Socioeconomic factors including education most likely play a role in this outcome.

References


