A Clinical Study on Deceased Kidney Donors in Puerto Rico and the Survival Outcome of the Grafts: A Retrospective Study of 187 Kidneys from 2009–2011

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Objective: In this study, we assessed the Kidney Donor Risk Index (KDRI) in Puerto Rican deceased kidney donors whose donations took place from 2009 to 2011 and evaluated short-term graft survival in the recipients of those kidneys. The results highlight differences between the distributions of KDRI values in the populations of the 48 contiguous states of the United States, Alaska, and Hawaii and that of Puerto Rico. Additionally, we evaluated the impacts of polyomavirus (BKV) infection and anti-donor HLA antibodies on the recipients.

Methods: Of the 377 kidneys obtained from deceased donors by LifeLink of Puerto Rico from 2009 to 2011, 187 were transplanted in Puerto Rico. Data was collected from the deceased donors of these 187 kidneys for calculating KDRI, as well as from the transplant recipients. KDRI values of the donors were calculated using the same formula as previously reported for the United States; death-censored graft survival, incidence of antibody-mediated rejection, and prevalence of polyoma virus infection (BKV) were examined in the recipients.

Results: The mean KDRI value was 1.19. However, the distribution of KDRI values in the Puerto Rican population deviates substantially from that of the United States (not including Puerto Rico). A 1-peak distribution pattern describes Puerto Rican KDRI values. Graft survival for the study period was 89.6%. The prevalence of BKV was 16.9%. Of the patients studied, 6.25% developed overt nephropathy, 46.2% developed de novo post-transplant donor-specific alloantibodies, and 19.5% had pre-existing alloantibodies.

Conclusion: Our study evidences the role of various characteristics in the distribution of KDRI values in the Puerto Rican population, suggesting that the identification of variables specific to a geographically distinct group may result in better donor categorization for predicting transplant outcomes. In addition, our graft-survival results, despite the elevated rates of BKV and anti-donor antibodies, highlight the increasing need to monitor the presence of antibodies in a prospective and an anticipatory manner to identify and manage patients at risk for antibody-mediated rejection. [*P R Health Sci J 2019;38:92-96*]

Key words: Kidney transplantation, Kidney donation, BKV, Kidney Donor Risk Index

The principal challenge that transplant clinicians face today is to ensure long-term allograft survival. Factors impacting short- and long-term outcomes include donor and recipient characteristics, cold ischemia time, donor–recipient match, immune-suppression regimes, and infection with polyoma virus.

Predictive tools have been developed to assess the donor-specific risk of graft failure. In 2009 Rao et al. proposed the Kidney Donor Risk Index (KDRI) as a new tool for evaluating the quality of a given donor's kidneys and estimating the intrinsic risk of their failure (1, 2). The authors' proposal is part of a trend in kidney allocation that is seeking to maximize life years from transplant by giving the kidneys with the lowest graft-failure risk to the recipients with the longest expected lifetimes. Rao et al. calculated the KDRI using the graft population of the United

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States, not including Puerto Rico, from 1995 to 2005. Rao and his team based their risk index on the following donor variables: weight, age, height, ethnicity, diabetes, hypertension, hepatitis C virus infection, serum creatinine, and donation after cardiac death. They analyzed their data set using a multivariable Cox proportional hazard regression model, and determined the relevant variables (mentioned above) using a stepwise variable deletion method. The resulting index, the KDRI, gave (and gives) an approximation of the relative risk of graft failure using a kidney from a particular donor compared to using one from a member of the general donor population. The median United States donor has a KDRI value of 1 (1, 3, 4, 5). Values higher than 1 imply a greater risk of failure. Values lower than 1 imply a lesser risk of failure.

Moreover, several different surgical techniques and immunosuppression management have together circumvented early surgical complications and early cellular rejection. However, there seems to be a wide range of protocols and differences as to how transplant programs deal with the long-term management of renal transplant recipients. Reviews have suggested that the development of alloantibodies and polyomavirus (BKV)–related allograft dysfunction are important mechanisms of late-onset graft loss (6, 7).

New light has been thrown on the importance of alloantibodies, with improved detection methods and a greater understanding of the pathophysiology of humoral rejection (6). It is not uncommon for transplant programs to routinely monitor pre- and post-transplant levels of alloantibodies, albeit with different protocols and management thresholds. Alloantibody monitoring can be done on high-immunologic-risk recipients, in intent-to-treat situations, and/or simply on every recipient along a given post-transplant timeline. Likewise, polyomavirus has garnered similar attention due to improved detection and its important role as a purveyor of allograft damage (7, 8). Transplant clinicians are faced with the dilemma of lowering immunosuppression, thereby increasing the risk of *de novo* alloantibodies and triggering an early or late humoral response to the allograft.

The Puerto Rico Kidney Transplant Program routinely gathers alloantibody and polyomavirus data on all transplant recipients. It is our belief that an aggressive post-transplant follow-up protocol yields acceptable graft survival and allows for the early management of high-risk recipients. Nearly 80% of patients receive their transplants from deceased local donors, for whom a KDRI has been calculated. This study reports the outcome of a cohort of deceased-kidney transplant recipients and looks for associations between outcomes and selected donor and recipient characteristics.

Methods

We performed a single-center retrospective study to obtain information about deceased kidney donors whose donations occurred from 2009 to 2011 in Puerto Rico and graft survival in the transplant recipients who received those kidneys. LifeLink of Puerto Rico is the organ procurement organization for Puerto Rico and the US Virgin Islands. The Auxilio Mutuo Transplant Center is the only kidney transplant center in Puerto Rico. The data obtained from donors included race, age, weight, height, history of hypertension and diabetes, serum creatinine, cause of death, hepatitis C status, and HLA-B and HLA-DR mismatches. These data were used to calculate the individual KDRI values, as well as to identify other factors related to transplant outcome. The data obtained from recipients included the most recent creatinine level (mg/dl), peak creatinine (mg/dl), viral load of polyomavirus (DNA copies/ml), and the quantization of alloantibodies, pre- and post-transplant. These data were collected in order to assess the renal function and predictive values of graft survival in the recipients. Information about the recipients was obtained via TransChart®LLC, Viracor-IBTTM, and record reviews at Auxilio Mutuo Hospital. The information about the donors was obtained using LifeLink of Puerto Rico's database. The use of the LifeLink database was approved by MSC IRB protocol #1250211, which is currently active. The information recorded was made anonymous by stripping patient names, addresses, social security numbers, and hospital record numbers off the protocol files. The protocol was approved by the institutional review boards of UPR-MSC and Auxilio Mutuo Hospital.

KDRI values were calculated using the method of computation developed and used for United States deceased donor kidneys, which is the one applicable to Puerto Rican donors, also, as part of the nationwide organ-sharing network (1).

The Kaplan–Meier method was used to calculate three-year allograft survival for the entire recipient population (death uncensored). Survival differences were compared in recipients without detectable alloantibodies and those with *de novo* and pre-existing alloantibodies and in those recipients with and those without detectable BKV.

The immunosuppressive therapy for the recipients included induction with thymoglobulin (5 mg/kg) and a triple-drug maintenance regimen consisting of prednisone, tacrolimus, and mycophenolic acid. Steroid avoidance was practiced in patients with panel-reactive antibodies of 0%. Biopsies are performed on an intent-to-treat basis at our institution. Treatment of biopsy-proven or suspected clinical cellular rejection consisted of pulse steroids with or without thymoglobulin, up to 7 mg/kg. Recipients with non-donor alloantibodies were observed clinically and no intervention was made unless allograft dysfunction was detected. Donor-specific antibody (DSA) monitoring was performed every 3 weeks, on average. The early detection of donor-specific alloantibodies with an identifiable upward trend in minimal fluorescence intensity (MFI) without proteinuria and/or rising creatinine was treated with intravenous immunoglobulin (IVIG), 1 to 2 gm/kg, in divided doses, depending upon patient tolerance. The presence of donor-specific alloantibodies with proteinuria, allograft dysfunction,

and biopsy-proven antibody-mediated rejection (AMR) including but not limited to glomerulitis, capillaritis, and c4d fixation was treated with plasmapheresis and IVIG (200 mg/kg) followed by rituximab.

The quantification of BKV viral load in urine and blood was performed using PCR. The presence of BKV in plasma was treated with immunosuppressive dose reduction. The discontinuation or dose reduction of mycophenolic acid was the first approach. If rapid viral reduction was not attained, the tacrolimus dose was reduced, followed by a reduction in prednisone.

Results

Of the 377 kidneys recovered from deceased donors in Puerto Rico from 2009 to 2011, 187 kidneys were transplanted locally. In terms of donor cause of death, 51.30% died from cerebro-vascular stroke, 38.30% from head trauma, 8.92% from anoxia, and 1.48% from other causes. The mean KDRI value for the Puerto Rican donors was found to be 1.19, in a 1-peak distribution curve (Fig. 1). The donor KDRI for kidneys with graft failure was 1.20, which is comparable to the KDRI for the entire cohort (Fig. 2). However, recipients with creatinine levels over 1.7 mg/dL were found to have a significantly higher donor KDRI, 1.36, in comparison to that of the cohort. The distribution of KDRI values in the Puerto Rican population deviates substantially from that of the United States population, with 46.5% of the Puerto Rican KDRIs ranging from 0.5 to 1.0; in the United States, just 21% of the KDRI values fall into the 0.5 to 1.0 range (1, 9).

Figure 3 shows the age distribution of the deceased Puerto Rican kidney donors, with 39% having been from 16 to 30 years of age.

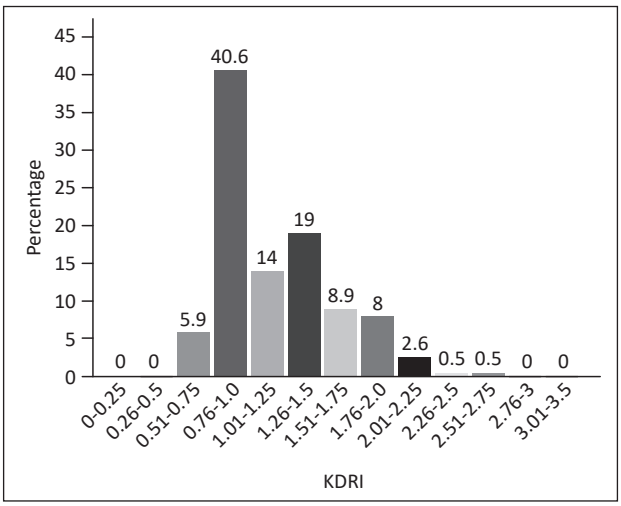

Figure 1. Puerto Rico's KDRI Distribution. The graph plots the KDRI score versus the percentage of donors within each range. The 1-peak distribution (with 46.5% of the KDRI ranging from 0.5 – 1) highlights the importance of analyzing the entire population's KDRI distribution and not just the mean KDRI value.

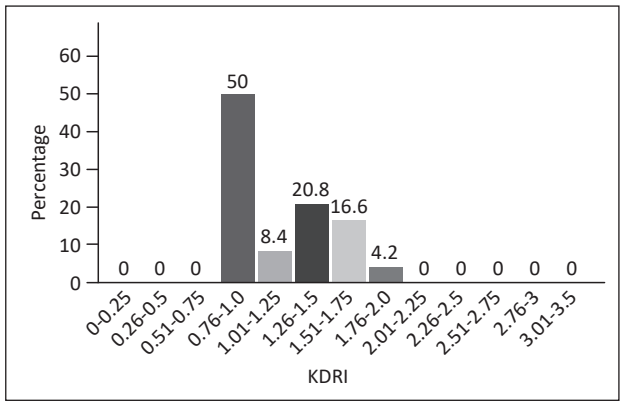

Figure 2. KDRI Distribution of Graft Failure/Death. The graph shows the percentage of recipients that experienced graft failure or death versus the donor KDRI. This graph accentuates the fact that the mean KDRI associated with graft failure is very similar to that of the entire cohort. Furthermore, it follows the same 1-peak distribution.

Of the 187 recipients in the study, 60.9% were male. The ages of the recipients ranged from 5 to 73 years. Of the 125 recipients for whom alloantibody data were available, 46.2% had developed *de novo* post-transplant donor-specific alloantibodies, and 19.5% had had pre-existing and post-transplant alloantibodies. Of the patients who developed de novo alloantibodies, 40.2% and 19.6% were found to have had only class I DSAs or class II DSAs, respectively; 31.4% had both class I and II DSAs, while 8.8% had non-donor alloantibodies. Of the allografts from patients with *de novo* antibodies, 6.9% were lost to AMR. Of the allografts from recipients with pre-existing and post-transplant alloantibodies, 4.7% were lost to rejection. Of the AMRs that resulted in graft failure, 75% were acute, while only 25% were chronic. Patients that had no pre- or post-transplant anti-HLA antibodies did not suffer from AMR episodes. For the cohort, the overall AMR that led to graft failure was 4.3%. The average

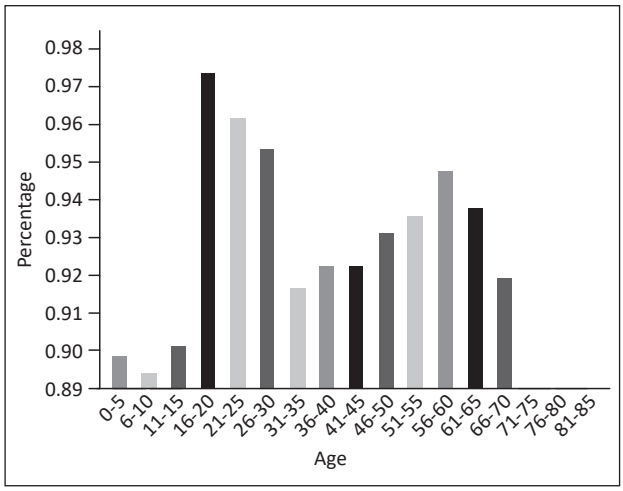

Figure 3. Age Distribution of Puerto Rican Deceased Kidney Donors. This figure highlights the age distribution of the Puerto Rican deceased kidney donors, of which 39% were from 16 to 30 years of age at the time of death.

time for graft failure due to AMR to occur was 15 months after the onset of rejection. Biopsy-proven AMR was treated with plasmapheresis and IVIG (200 mg/kg) followed by rituximab. No difference in survival was found between recipients without detectable alloantibodies and those with *de novo* and pre-existing alloantibodies ($p = 0.67$).

The rate of BKV detection for the entire 187-recipient cohort was 16.9%. Although 6.25% of the recipients lost their allografts to BKV nephropathy, no survival difference was found between those recipients with and those without detectable BKV ($p = 0.25$). The death-uncensored allograft survival for the study period, shown in Figure 4, was 89.6%, with other allograft loss occurring for other reasons, such as t-cell–mediated recalcitrant rejection, systemic infection with end-organ damage, or patient death.

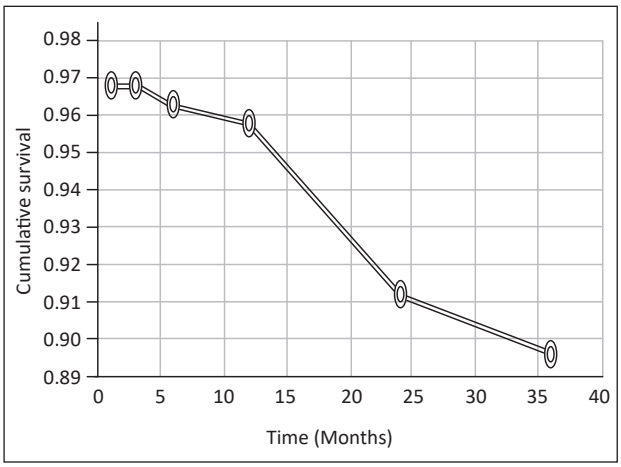

Figure 4. Allograft Survival (death uncensored). This graph shows the survival of recipients versus time after transplant. Graft survival for the 3-year study period was 89.6%. These results depict how excellent outcomes beyond the first year may be obtained in recipients of kidneys from high KDRI donors.

Discussion

This small, retrospective, single-center study highlights how distinct Puerto Rican characteristics affect the distribution of KDRI values in comparison to that distribution in the United States population. Moreover, the 1-peak distribution, seen in Figure 1, accentuates how a population's mean KDRI value fails to accurately describe the state of its donor kidneys and the importance of evaluating the entire population's KDRI distribution.

Figure 3 highlights the main differences in the KDRI distributions between these 2 populations: the percentage of Puerto Rican donors having KDRIs under 1 is 46.5%, while the percentage of United States donors with similar (low) KDRIs is only 21%. Additionally, the prevalence of KDRI values over 1.5 in Puerto Rican donors is 20.5%; in United States donors, that measure has a prevalence of 12% (9). The first difference might be a result of the high prevalence of young donors in the Puerto Rican population (39% of the donors were 16–30 years of age), most of whose records listed trauma as cause of death. The effect young donor age seems to have on our KDRI distribution may be a feature shared by other populations with high incidences of trauma and youth mortality. However, the higher prevalence of KDRI values over 1.5, compared to the prevalence of those values in the United States, might be explained by the higher incidences of diabetes and hypertension in the Puerto Rican population (10, 11).

The mean KDRI value for the Puerto Rican population was found to be 1.19, which is considerably higher than the median of the United States donors (KDRI value of 1). This implies that the relative risk of kidney graft failure for the Puerto Rican median donor population is expected to be 1.19 times higher than that of the median donor in the United States. The higher mean KDRI value is probably the result of the high prevalence of KDRI values over 1.5 in the Puerto Rican donor population. However, as depicted in Figure 2, an interesting finding is that the mean KDRI for graft failure is very similar to that of the entire cohort (1.20 and 1.19, respectively). Moreover, the KDRI for graft failure follows the same 1-peak distribution as that of the cohort.

At the same time, as depicted in Figure 4, our results show that excellent outcomes beyond the first year may be obtained in recipients of a kidney from a donor with a high KDRI. Graft survival for the 3-year study period was 89.6%, which is relatively similar to that found by international studies and in the continental US (12). Because Puerto Rico is a small island and is geographically distant from the United States mainland, most organs for transplant are acquired from local organ donors, thus reducing the cold ischemia time associated with organ transportation to a minimum. This finding supports a more liberal use of donor kidneys that have a higher KDRI, which would result in a larger donor pool available for patients on the waiting list for a kidney transplant in Puerto Rico. The 3-year transplant rate at our center is 38.6%, with only one fourth of those waiting being transplanted within 21.3 months. The mortality rate of individuals on the waiting list is 5.3% (13). An increase in the local donor pool should result in shorter waiting times and lower waitlist mortality.

In the past, the prevalence of graft failure due to BKV nephritis in the renal transplant population in the United States ranged from 30% to 60% (14). This high prevalence was partly due to the fact that BKV remains asymptomatic until recipients experience renal insufficiency (15). Currently, the new and more assertive method used for early detection (e.g. the quantification of viral load in the urine and blood using viral DNA) and prompt treatment have significantly reduced the case fatality rate. Potent immunosuppressive drugs in conjunction with tacrolimus and mycophenolate mofetil have been associated with an increased risk in the development of BKV (16). Thus, the objective of the treatment is to optimize the immunosuppressive dose in order to eradicate the virus while preventing allograft rejection; in some cases, antiviral therapies can be provided. We have a relatively low detection

rate of polyoma virus (16.9%) in comparison to that in the US, which is approximately 20% (17). This could be explained by our current immunosuppression protocol. Even though immunosuppression was appropriately decreased in these patients, 6.25% of them lost their grafts. However, when taken in the context of overall survival, transplant centers should not be discouraged from following these recipients aggressively, given the multiple therapeutic strategies available.

Previous studies in the United States have reported as many as 25% of recipients developing *de novo* post-transplant donor-specific alloantibodies (18, 19). However, of the 125 local recipients for whom alloantibody data was available, 46.2% developed *de novo* post-transplant donor-specific alloantibodies. Again, this can be partly explained by our current immunosuppression protocol. The management of alloantibodies poses many challenges to clinicians. Although results concerning alloantibody+ recipients are biased since all the transplants performed were done with a negative flow-cytometric crossmatch and we have no established desensitization protocol, the association between the presence of alloantibodies and graft loss is well documented. Therefore, we believe that aggressive solid-phase assay monitoring for donor-specific antibodies should be included in all post-transplant follow-up protocols.

Resumen

Objetivo: El propósito de este estudio es evaluar el índice de riesgo del riñón donado (KDRI, por sus siglas en inglés) en los riñones donados por puertorriqueños en los años 2009 al 2011. En adición, se busca estudiar la sobrevida del órgano a corto plazo. Los resultados obtenidos evidencian una diferencia sustancial en la distribución de los valores del KDRI entre las poblaciones puertorriqueña y estadounidense. Métodos: De los 377 riñones cadavéricos donados a través de LifeLink de Puerto Rico desde el 2009 al 2011, 187 riñones fueron trasplantados localmente. Se recogieron datos de los donantes de estos 187 riñones para calcular el KDRI. Los valores del KDRI fueron calculados usando el mismo método computacional utilizado en los Estados Unidos. La sobrevida del órgano, la incidencia de rechazo mediada por anticuerpos y la prevalencia de infección con el virus de polioma BK (VBK) fueron examinadas en los recipientes. Resultados: El valor promedio de KDRI fue de 1.19. La distribución de los valores de KDRI en la población puertorriqueña se desvía sustancialmente de la estadounidense. La sobrevida de la cohorte de órganos donados fue de 89.6% a los 3 años. La prevalencia de VBK en suero fue de 16.9%. De estos pacientes, 6.25% desarrollaron nefropatía, 46.2% desarrollaron anticuerpos específicos al donante de novo y 19.5% tenían estos anticuerpos anterior al trasplante. Conclusión: Nuestro estudio demuestra el papel que juegan las características de la población puertorriqueña en la distribución de los valores del KDRI. Esto puede sugerir que la identificación de variables específicas a distintos grupos geográficos podría resultar en mejor clasificación de donantes y predicción de resultados.

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