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Mortality After Kidney Transplantation: A Comparison Between the United States and Canada

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There is a paucity of comparative studies on country-specific outcomes in kidney transplantation. We compared post-transplant mortality among primary, adult, solitary kidney transplant recipients (KTR) from the United States (n = 70 708) and Canada (n = 5773), between January 1, 1991 and December 31, 1998, using data from the Scientific Registry of Transplant Recipients and the Canadian Organ Replacement Register. Multivariable Cox regression revealed higher adjusted post-transplant mortality among U.S. (vs. Canadian) KTR (HR = 1.35 [95% CI 1.24, 1.47; p < 0.005]). Mortality risk in the first post-transplant year was similar in both countries but higher in the United States beyond the first year (HR = 1.49–1.53; p < 0.005). There was no difference in mortality among patients transplanted within 1 year of starting dialysis, but mortality was increased in U.S. (vs. Canadian) patients after 1–2 and 4+ years on dialysis (HR = 1.36–1.66; p < 0.005). Greater mortality was also seen in U.S. patients with diabetes mellitus and/or graft failure. In conclusion, there are considerable differences in the survival of KTR in the United States and Canada. A detailed examination of factors contributing to this variation may yield important insights into improving outcomes for all KTR.

Key words: Canada, Kidney transplantation, post-transplant mortality, United States

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Introduction

Survival probability for kidney transplant recipients (KTR) has increased over the last 10–15 years, largely due to improvements in surgical technique, greater specificity of immunosuppressive therapies and better long-term medical management (1,2). Despite these advances, the mortality rate of KTR remains significantly elevated above the age-adjusted mortality rate of the general population (3). In fact, patient death is a leading cause of kidney transplant failure, accounting for about half of all failure events (4,5). Given the dominant role that patient death exerts on post-transplant outcomes, it is crucial to reduce the post-transplant mortality rate in order to improve the longevity of both KTR and their allografts.

Comparisons of hemodialysis outcomes across distinct geographic regions have helped to elucidate the determinants of these country-specific variations (6–8). The Dialysis Outcomes and Practice Patterns Study (DOPPS) revealed that differences in country-specific mortality rates persist after comprehensive adjustment for demographics, comorbid conditions and other case-mix variables (8). This suggests that other factors, such as variations in practice patterns, may account for the observed discrepancies in mortality. There is a paucity of similar comparative studies in the outcome of kidney transplantation. Therefore, we undertook the current study to compare the post-transplant mortality experience of patients undergoing kidney transplantation in the United States and Canada, using data from the national organ transplant registries of each country.

Methods

Data on U.S. patients were collected by the Organ Procurement and Transplant Network and obtained from the Scientific Registry of Transplant Recipients (SRTR). Canadian data were obtained from the Canadian Organ Replacement Register (CORR), which is administered by the Canadian Institute for Health Information. Both the SRTR and CORR are national, population-based, organ failure registries that track all solid-organ transplants and their associated outcomes. Patient-specific data are submitted directly to each registry by the transplant centers within each country.

The study population included patients ≥18 years of age at the time of transplantation, who received a primary, solitary, kidney transplant between January 1, 1991 and December 31, 1998. There were 70 708 such patients in the United States and 5773 patients in Canada. The patient cohorts were chosen to coincide with the CORR data most recently available to the

authors (DES, SSAF). Patients began follow-up at the time of transplantation and were followed until the earliest of death, loss to follow-up or the conclusion of the observation period (December 31, 1998). Patients who experienced graft failure (GF) were not censored at the time of GF. Mortality information is reported by the kidney transplant centers within each country. In the SRTR, death ascertainment is supplemented by the Social Security Death Master File (SSDMF). Since no such mechanism is employed by CORR, deaths among U.S. patients that were only ascertainable through linkage to the SSDMF were censored to minimize the potential for ascertainment bias. Analyses that incorporated the extra mortality ascertainment through SSDMF showed results that closely mimicked those reported here (data not shown).

Crude (unadjusted) mortality rates were computed for each country as the ratio of the number of deaths to patient-years (PY) of follow-up, and expressed as deaths per 1000 PY. Kaplan-Meier survival curves were also computed and assessed for equality based on the log-rank test. Covariate-adjusted hazard ratios (HR) were computed using Cox regression, with adjustment for age (in years), sex, race (African descent [both African American and African Canadian], Asian, white, other), cause of end-stage renal disease (ESRD), year of transplantation, donor source and pre-transplant time on dialysis (in months). Since age is a very strong risk factor for death, the Cox models were stratified by single-year intervals representing the age of recipients at the time of transplantation. As a result, each model includes a separate baseline hazard for each year of age.

The models also contained age-by-diabetes and time on dialysis-by-diabetes interaction terms. Using the first Cox model, the covariate-adjusted HR (United States relative to Canada) was estimated. Subsequent models examined interactions, i.e., the degree to which the United States/Canada HR differed by each of the adjustment covariates. In addition, we fitted a non-proportional hazards model that estimated the HR by post-transplant follow-up year. We also fitted a model with GF as a time-dependent covariate, in order to examine whether the United States/Canada HR was modified by the occurrence of GF.

All statistical analyses were performed using SAS 8.2 (SAS Institute; Cary, NC). A two-sided p-value of 0.05 was considered statistically significant.

Table 1: Characteristics of the study population

Characteristic	Canada (%)	United States (%)
Age group (years)**		
18–29	13.5	14.8
30–49	49.4	48.1
50–59	21.6	22.8
60+	15.5	14.2
Sex**		
Male	63.8	60.0
Female	36.2	40.0
Race**		
White	81.8	71.2
African descent	2.6	23.2
Asian	5.4	3.4
Other minority	10.2	2.2
Cause of ESRD**		
Diabetes	17.6	22.7
Glomerulonephritis	23.2	15.6
Polycystic kidney disease	11.3	9.2
Vascular diseases	8.0	4.0
Other	40.0	48.5
Donor source**		
Deceased	76.4	69.6
Living	23.6	30.4
Pre-transplant time on dialysis**		
Preemptive	4.2	11.3
>0 to <1 years	25.9	29.2
1 to <2 years	16.0	13.3
2+ years	53.9	50.1
Transplant era*		
1991–1993	35.2	33.8
1994—1996	38.2	38.1
1997—1998	26.6	28.1

Significantly different pattern by country using Chi-square test for homogeneity: *$p < 0.05$; **$p < 0.005$; percentages may not add to 100 due to rounding.

Results

Characteristics of the study population are provided in Table 1. There was close similarity between the United States and Canada with respect to the distribution of recipient age at transplant. For both countries, just under half of the primary kidney transplants were performed in the 30–49 year age group. The male to female ratio was greater in Canada (64:36) compared with the United States (60:40). The most noteworthy discrepancy was seen in the recipient racial distributions of the two countries. In Canada, approximately 82% of patients were white, while the corresponding figure in the United States was 71%. Recipients of African descent comprised 23% of U.S. patients, but only 3% of the Canadian cohort. A greater percentage of U.S. patients had diabetes mellitus as the cause of ESRD (23%) and received living donor kidney transplants (30%) compared with their Canadian counterparts (18% and 24%, respectively). For each characteristic, the difference in the distribution between Canada and the United States was statistically significant ($p < 0.05$), mostly owing to the large sample size, as opposed to the magnitude of the discrepancies in the country-specific distributions.

The unadjusted post-transplant mortality rate was 29.8 deaths per 1000 PY in Canada and 40.9 per 1000 PY in the United States (Table 2). The covariate-adjusted HR (United States relative to Canada) was 1.35 (95% CI, 1.24–1.47) indicating that the covariate-adjusted mortality was 35% greater in the United States compared with Canada ($p < 0.005$). Kaplan-Meier survival curves for U.S. and Canadian KTR are displayed in Figure 1. The log-rank test revealed a highly significant difference between the two curves ($p < 0.005$). Covariate-adjusted Breslow-Aalen survival curves for KTR age 50–59 years showed very similar results to the unadjusted Kaplan-Meier curves (data not shown).

Results based on various subgroups are listed in Table 3. The United States/Canada mortality HR was quite consistent across all age categories. The effect was accentuated among patients of African descent ($HR = 3.23$; $p < 0.005$).

Table 2: Crude post-kidney transplant mortality rate and covariate-adjusted and hazard ratios (United States/Canada)

Country	Deaths	Patient-years (PY)	Rate: Deaths per 1000 PY	HR (un-adjusted) (95% CI)	HR (covariate-adjusted) (95% CI)
Canada	613	20 540	29.8	1.00	1.00
United States	9854	240 695	40.9	1.36* (1.26, 1.46)	1.35* (1.24, 1.47)

*$p < 0.005$ compared with Canada.

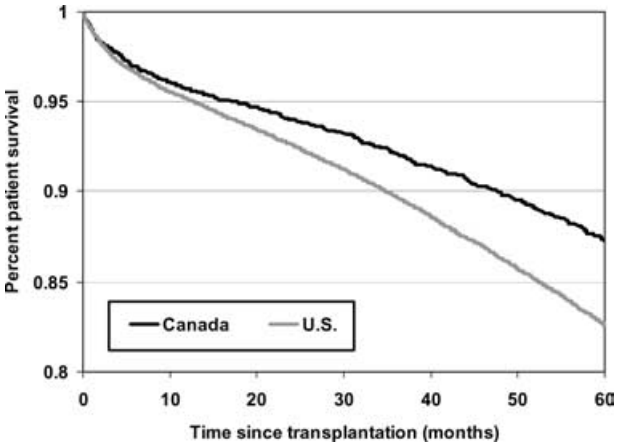

Figure 1: Unadjusted Kaplan-Meier post-transplant survival curves for Canada and the United States. Patients include all recipients of a kidney transplant between January 1, 1991 and December 31, 1998, with follow-up until December 31, 1998. The Kaplan-Meier curves are significantly different based on the log-rank test ($p < 0.005$).

However, the mortality increase for the United States was less pronounced among diabetic patients (HR = 1.22; $p = 0.01$) compared with non-diabetics (HR = 1.41; $p < 0.005$). A dose-response gradient in mortality risk was observed in relation to pre-transplant time on dialysis (Figure 2). Among patients who waited less than 1 year on dialysis prior to transplantation, there was virtually no post-transplant mortality difference between Canada and the United States (HR = 1.04; $p = 0.41$). However, the longer patients waited for a transplant, the greater the difference in mortality between U.S. and Canadian patients, with a HR ranging from 1.36 ($p < 0.005$) to 1.66 ($p < 0.005$) for patients who waited 1–2 and 4+ years on dialysis, respectively. The effect of country was also accentuated by graft failure. Relative to Canadian patients, U.S. KTR had a 36% higher mortality hazard prior to GF (HR = 1.36; $p < 0.005$) and a 69% higher mortality after GF (HR = 1.69; $p < 0.005$). Based on the likelihood ratio test, interactions with race, pre-transplant time on dialysis and graft failure attained statistical significance ($p < 0.05$).

Figure 3 displays the United States/Canada HR by post-transplant follow-up interval. In the first year following kidney transplantation, covariate-adjusted mortality was comparable between U.S. and Canadian KTR (HR = 1.09; $p = 0.30$). For post-transplant years 2 through 8, however, the mortality risk was consistently elevated for KTR in the United States (relative to Canada), with HR = 1.53, HR = 1.49, and HR = 1.51 for the 1–2, 2–3 and 3–8 year intervals, respectively ($p < 0.005$ in each case). Similarly, the HR for death beyond the first year in KTR who were alive at 1-year post-transplant was 1.51 (95% CI, 1.36–1.66; $p < 0.005$).

Discussion

This comparative analysis, based on the SRTR and CORR databases, revealed that the covariate-adjusted mortality

Table 3: Post-kidney transplant mortality hazard ratios (United States/Canada) by subgroups

Characteristic	HR (95% CI)	p-value
Overall	1.35 (1.24, 1.47)	<0.005
Age at transplant (years)		
18–39	1.33 (1.10, 1.59)	<0.005
40–59	1.29 (1.15, 1.46)	<0.005
60+	1.34 (1.16, 1.56)	<0.005
Sex		
Male	1.28 (1.16, 1.42)	<0.005
Female	1.50 (1.30, 1.73)	<0.005
Race*		
White	1.33 (1.22, 1.45)	<0.005
African descent	3.23 (1.61, 6.48)	<0.005
Asian	1.51 (1.05, 2.15)	0.03
Other minority	1.09 (0.78, 1.53)	0.61
Cause of ESRD		
Non-diabetic	1.41 (1.27, 1.55)	<0.005
Diabetic	1.22 (1.05, 1.42)	0.01
Donor source		
Deceased	1.33 (1.22, 1.46)	<0.005
Living	1.50 (1.16, 1.92)	<0.005
Pre-transplant time on dialysis (years)*		
0–1.0	1.04 (0.95, 1.14)	0.41
1.1–2.0	1.36 (1.24, 1.48)	<0.005
2.1–3.0	1.46 (1.33, 1.60)	<0.005
3.1–4.0	1.53 (1.38, 1.70)	<0.005
> 4.0	1.66 (1.48, 1.86)	<0.005
Primary graft failure*		
No	1.36 (1.23, 1.50)	<0.005
Yes	1.69 (1.46, 1.96)	<0.005
Transplant era		
1991–1993	1.36 (1.22, 1.51)	<0.005
1994–1996	1.29 (1.11, 1.49)	<0.005
1997–1998	1.55 (1.13, 2.14)	0.007

*Significant interaction by likelihood ratio test: $p < 0.05$.

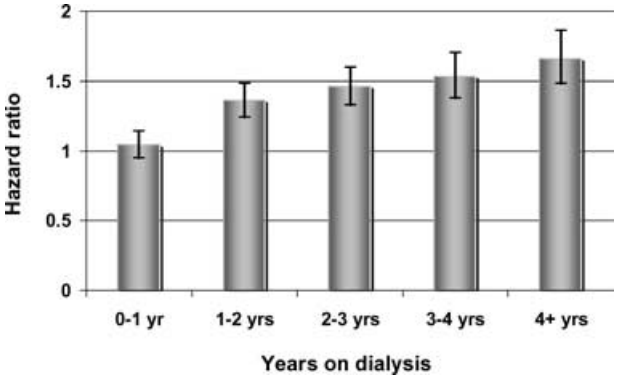

Figure 2: Post-transplant mortality hazard ratios (United States/Canada) by pre-transplant years on dialysis. Hazard ratios are adjusted for age, sex, race, cause of ESRD, year of transplant and donor source. Bars represent hazard ratios, while the range denotes the 95% confidence interval. All hazard ratios are significantly different from 1.00 ($p < 0.005$) except for U.S. and Canadian patients with less than 1 year of pre-transplant time on dialysis ($p = 0.41$).

risk after kidney transplantation is significantly higher in the United States relative to Canada. The risk of post-transplant mortality in the United States and Canada was equal in the first year following transplantation, but was significantly higher among U.S. patients thereafter. No mortality difference was observed among KTR who were on dialysis for less than 1 year prior to transplantation. However, among patients transplanted after at least 1 year on dialysis, the elevation in mortality risk among U.S. patients increased steadily with increasing pre-transplant time on dialysis. The mortality increase among U.S. patients was observed in

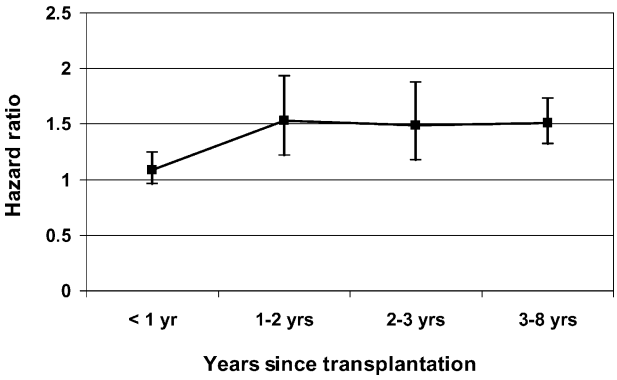

Figure 3: Post-transplant mortality hazard ratios (United States/Canada) by post-transplant follow-up interval. Hazard ratios are adjusted for age, sex, race, cause of ESRD, year of transplant, donor source and pre-transplant time-on-dialysis. Points represent hazard ratios, while the range denotes the 95% confidence interval. All hazard ratios are significantly different from 1.00 ($p < 0.005$) except in the first post-transplant follow-up year ($p = 0.30$).

every tested demographic subgroup, including each age category, both sexes and all racial groups. The effect was observed for both deceased and living donor KTR.

An important difference in the patient characteristics of the two countries is the proportion of recipients of African descent. The proportion of U.S. KTR of African descent is approximately 10-fold that of Canada. Interestingly, the hazard of death in recipients of African descent is higher than any other racial group when transplanted in the United States compared to Canada ($HR = 3.23$, $p < 0.005$). This may be a function of the biologic differences between African-American versus African-Canadian patients and/or issues related to differential access to long-term health care before or after transplantation.

Other potential explanations for the study results deserve mention. The diminished difference in the risk of mortality in KTR with diabetes mellitus (vs. those without diabetes mellitus) may be the result of more intense medical surveillance of this patient group in both countries (due to their high prevalence of comorbid conditions). This would provide a mechanism by which post-transplant complications, such as infections or cardiovascular disease, can be detected and treated at an earlier stage. Alternatively, the high mortality for diabetic KTR in both countries might blunt the ratio of death rates between them. Similar patterns of mortality have been documented in international comparisons of ESRD patients with and without diabetes mellitus (6) and specifically for hemodialysis patients (8).

The elevated U.S. post-transplant HR suggests that a longer duration of pre-transplant dialysis has a more detrimental effect on post-transplant patient survival in the United States compared with Canada. There also appears to be a dose-response effect such that the risk in the United States (compared with Canada) increases monotonically with increasing pre-transplant time on dialysis. The reason for this is unclear but may reflect the downstream effects of factors that contribute to the comparatively lower mortality rate seen in Canadian dialysis patients (9,10). It is possible that country-specific differences in pre-dialysis care and/or specific dialysis practice patterns (e.g., rates of arteriovenous fistula use, duration of hemodialysis sessions, management of calcium-phosphorus metabolism, etc.) may have implications for the risk of post-transplant mortality.

The increased risk of mortality when returning to dialysis after GF has been highlighted by a number of investigators (11,12). Our study suggests that the hazard of death is significantly elevated in patients who return to dialysis after graft loss and that this risk is greater in U.S. versus Canadian patients. Interestingly, the relative increase in the risk of death after GF in U.S. patients is greater than what would have been expected if the pattern of mortality post-GF reflected the pre-GF experience. Kaplan et al. noted that one of the strongest predictors of death after graft

loss is the duration of dialysis prior to transplantation, with a longer duration portending a worse outcome (12). Therefore, the greater adverse impact of time on dialysis for post-transplant mortality in U.S. KTR, relative to their Canadian counterparts, may also accentuate the differences seen in the relative hazard of death after GF. Moreover, differences in dialysis practice patterns post-GF may also partially explain the disparity in country-specific post-GF mortality rates.

To our knowledge, this study represents the first attempt to systematically compare the outcomes of kidney transplantation across two countries using multivariable modeling techniques. Rabbat et al. have shown that the benefits of deceased donor kidney transplantation are consistent in certain regions of the United States and Canada, despite differing wait-listed mortality rates and a wide-ranging prevalence of diabetes mellitus among transplanted patients (13). However, a direct comparison of kidney transplant outcomes was not undertaken. International comparisons of outcomes of cardiac and cancer patients have revealed important discrepancies in mortality rates between countries (14–17). Some of these studies have proposed that differences in the structure of the health care system and approaches to clinical practice may account for the observed variations in outcome (14–16). Whether similar factors are driving the differences seen in U.S. and Canadian kidney transplant survival is speculative at this time and requires further study.

The present study employed a retrospective cohort design, allowing us to identify and track individual KTR over time through national registries and determine their vital status in follow-up. The large numbers of patients provided reasonably precise estimates of mortality risk in various subgroups of KTR. The follow-up information from both registries (especially for vital status) is known to be quite complete; thus biases related to differential loss-to-follow-up are likely minimal.

Despite these strengths, there are several study limitations that should be noted. First, differences in the detail and breadth of data collection likely exist between the two registries. An example of this phenomenon is the lack of detailed donor data in CORR during the study period. Akin to the discrepancies seen in recipient characteristics, there may be variations in donor characteristics that may contribute to the differences in post-transplant mortality. In particular, donor age, the use of expanded criteria donor kidneys and donors of African descent may be quite variable in the two countries. Whether such systematic variation in donor characteristics exist and to what degree they account for the differences in post-transplant mortality remain open questions at this time.

Second, the lack of information on clinical practice patterns (such as immunosuppressive protocols, frequency of follow-up and management of post-transplant complications) limited our ability to investigate whether these factors might in part explain the observed differences in post-transplant mortality. However, even if pertinent data were available, adjustment for practice patterns may not be appropriate in this study. For example, if the two countries differed with respect to the management of comorbid conditions, and if such differences lead to increased mortality, adjustment for this aspect of clinical practice would attenuate the very contrast of interest. However, adjustment for practice patterns would be useful in attempting to account for potential factors contributing to the mortality difference. In order to further explore these and other potential determinants of post-transplant mortality, a more extensive and richer dataset will be necessary.

Third, adjustment for comorbid conditions could not be accomplished due to limitations of both registries. Comorbidity data (based on present/absent disease indicators) were available for about 90% of CORR patients starting from January 1, 1988, but only at the time of initiation of dialysis. Limited information on comorbid conditions in the SRTR was collected at the time of wait-listing but these data were available for only two - thirds of the patients. Given the differences in the timing and completeness of data collection, it was not desirable to adjust for comorbidity in the main analysis. However, when we fitted a model adjusting for comorbidity using the subset for whom comorbidity data were available, the mortality hazard ratio was virtually unchanged from that reported in Table 2 (HR = 1.33; 95% CI 1.22, 1.44).

Fourth, discrepancies in the coding of data elements in each registry may make direct comparisons of country-specific outcomes problematic. However, the data elements from each registry used in this report are reasonably similar with respect to the information they capture, and it is unlikely that any coding errors would occur at a systematically higher rate in one country versus the other. Furthermore, after imposing the use of comparable methods of death ascertainment, errors in the assessment of mortality were unlikely to be significantly biased between the two countries.

Finally, the study period spans the years 1991–1998. Whether the relative mortality experience of U.S. and Canadian KTR has changed in the more recent era cannot be assessed using the current dataset. It should be noted, however, that United States/Canada hazard ratios specific to that period offer no evidence that the relative hazards have decreased over time. Even in 1997–1998, the adjusted mortality hazard was 50% higher in the United States than in Canada ($p < 0.01$).

In summary, significant differences in mortality were observed in patients transplanted in the United States and Canada over the years 1991–1998. The relative increase in mortality among U.S. patients was observed in all major patient subgroups, was not significantly attenuated by

adjustments for potentially confounding variables and persisted in long-term follow-up. Given the limitations of registry data, comparisons of country-specific mortality rates must be interpreted with caution. Future international comparative studies will require more detailed, prospective data collection. A thorough examination of the factors contributing to variations in country-specific post-transplant mortality rates may provide important insights into improving the survival of KTR and their allografts.

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