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KIDNEY TRANSPLANT GRAFT OUTCOMES IN 379,257 RECIPIENTS ON THREE CONTINENTS

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Abbreviations: ANZDATA = Australia and New Zealand Dialysis and Transplant; NHSBT = National Health Service Blood and Transplant for the United Kingdom; SRTR = Scientific Registry of Transplant Recipients

Abstract

Kidney transplant outcomes that vary by program or geopolitical unit may result from variability in practice patterns or health care delivery systems. In this collaborative study, we compared kidney graft outcomes among four countries (United States, United Kingdom, Australia and New Zealand) on three continents. We analyzed transplant and follow-up registry data from 1988-2014 for 379,257 recipients of first kidney-only transplants using Cox regression. Compared to the United States, one-year adjusted graft failure risk was significantly higher in the United Kingdom (HR 1.22, 95% CI 1.18-1.26, p<0.001) and New Zealand (HR 1.29, 95% CI 1.14-1.46, p<0.001), but lower in Australia (HR 0.90, 95% CI 0.84-0.96, p=0.001). In contrast, long-term adjusted graft failure risk (conditional on one-year function) was significantly higher in the United States compared to Australia, New Zealand, and the United Kingdom (HR 0.74, 0.75, and 0.74, respectively; each p<0.001). Thus, long-term kidney graft outcomes are approximately 25% worse in the United States than in three other countries with well-developed kidney transplant systems. Case mix differences and residual confounding from unmeasured factors were found to be unlikely explanations. These findings suggest that identification of potentially modifiable country-specific differences in care delivery and/or practice patterns should be sought.

Introduction

Kidney transplantation is the preferred modality of renal replacement therapy for patients with end-stage renal disease and is performed in nearly 100 countries. Despite its broad application, long-term graft failure remains an important limitation. Meier-Kriesche et al. have reported that kidney transplant half-life has increased only modestly in recent years in the United States.[1]

The regular reporting of post-transplant outcomes to a centralized registry in some countries offers a unique opportunity to explore country-level differences in outcome. Kim et al. showed a 49% higher risk of death beyond the first post-transplant year in an 8-year cohort of United States kidney transplant recipients compared to a cohort of Canadians transplanted in the same time period.[2] However, the absolute long-term risk of death after kidney transplant is low, and recipients more commonly face allograft failure. Gondos et al. reported that graft survival among

various subsets of European kidney transplant recipients was superior to corresponding subsets in United States patients using period analysis of data submitted voluntarily to the Collaborative Transplant Study.[3] Country outcomes within Europe were not analyzed.

The overall effectiveness of well-established kidney transplant systems, using graft failure as the outcome of interest, has not been studied at a country level. Rather than undertake an individual patient data meta-analysis, the opportunity to use detailed patient-level longitudinal data from transplants performed over the past quarter century in four countries on three continents and reported to registries with robust data tracking motivated us to perform a study with the overarching goal to determine the existence and magnitude of country-level differences in kidney graft outcome.

Materials and Methods

Patient-level data were combined from three transplant registries covering four countries on first single-organ kidney transplants from 1988 through 2014, with follow-up through 2014. We obtained data from the Scientific Registry of Transplant Recipients (SRTR) for the United States, the National Health Service Blood and Transplant for the United Kingdom (NHSBT), and the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry for Australia and New Zealand.

Baseline recipient, donor, and transplant variables were harmonized across the three data sources prior to analysis. Ascertainment of graft failure, defined as the earliest of death, retransplant, transplant nephrectomy, or initiation of or return to dialysis, was based upon transplant program reporting to the respective registries. Death ascertainment was supplemented by linkages to other national databases in the United States[4] and the United Kingdom. Details of ANZDATA auditing have been previously reported.[5]

Recipient race and primary renal diagnosis were missing for 33% and 38% of United Kingdom recipients, respectively. Ischemia time for deceased donor transplants was missing for 2.4%, 7.9%, 46.5%, and 26.8% of transplants in Australia, New Zealand, the United Kingdom, and the United States, respectively, and for living donor transplants for 1.5%, 0.5%, 20.7%, and 44.0%,

respectively. In the United Kingdom, recipient race and ischemia time were not collected until 1998 and 2000, respectively. Donor cause of death was missing for 2.7% and 6.2% of Australia and New Zealand cases, respectively. The number of HLA mismatches was missing for 4.7% and 1.8% of transplants in Australia and New Zealand, respectively. For the remaining country and variable combinations, values were missing for no more than 1% of subjects (full list of covariates given below).

As recommended by Little et al.[6,7], missing data were handled by multiple imputation using the sequential regression imputation method [8], implemented with the Impute module of the IVEware software package.[9] We performed 40 imputations for missing data. Model results from individual imputations were combined using SAS Proc MIAnalyze to calculate overall the effect estimates and significance levels presented in the paper.[7] Results of models fitted from complete case data (Table S1) were very similar to those that used imputed data.

Descriptive statistics are given as median (quartile 1 – quartile 3) for continuous variables and as percentages for categorical factors.

Cox regression models were used to compare risk adjusted graft failure among the study countries. Separate models were fitted for one year (short-term) and long-term graft failure. The short-term graft failure model examined the time from transplant to graft failure (as defined above), censored at the later of end of follow-up or one year post-transplant. The long-term graft failure model was conditional on the recipient being alive with graft function at one year. Time at risk for the long-term model began at one year post-transplant and continued to the earliest of graft failure (as defined above), censored at end of follow-up. In addition to the country indicators, covariates in the short-term and long-term models included recipient characteristics (age, sex, race, primary renal diagnosis), donor characteristics (age, sex), donation type (living, donation after brain death, donation after circulatory determination of death), cause of donor death, relationship to recipient, total ischemia time, HLA mismatch, and year of transplant. Figures illustrating graft survival over time by country were produced using models stratified by country and presented for each country at study average covariate values. The short-term model revealed some evidence of non-proportional hazards in the country effects; country parameter

estimates for this model should be interpreted as the average effects over the first post-transplant year. The long-term graft failure model showed no evidence of violation of the proportional hazards assumption.

To test the robustness of our long-term model within covariate sub-cohorts, we tested whether country-specific hazard ratios for the long-term risk of graft failure varied across study subcohorts defined by the levels or categories of each tested covariate. In each model, we examined the country-specific risk of graft failure restricted to a subcohort defined by a specific level or category of one covariate. This was repeated for each level of all covariates, with each model adjusted for all other covariates. Country-specific hazard ratio p-values were adjusted using the stepdown Bonferroni adjustment for multiple comparisons.[10]

We examined trends in country-specific hazard ratios over calendar time with graft failure models that included country, year of transplant (continuous), and country-by-year interaction terms.

We explored the sensitivity of our results to the effect of potential unmeasured confounders using the method of Lin et al.[11], depicted graphically according to Weintraub et al.[12] This method allowed us to assess whether significant differences in country-specific risks of long-term graft failure could be explained by an unmeasured patient-level confounder with disparate prevalence across countries.

Statistical analyses were carried out using SAS version 9.4 (SAS Institute; Cary, NC). Results with a two-sided p-value ≤ 0.05 were considered statistically significant.

Results

Descriptive statistics

There were 379,257 kidney transplants performed in the four countries from 1988 to 2014. Characteristics of the study cohort are shown in Table 1. Median recipient age at transplant was 48; 61% of recipients were male. Median recipient age and sex were consistent across countries, as were donor age and sex. The distribution of recipient race varied considerably by country, as

did other donor variables. Living donor organs were used for 36%, 33%, and 40% of transplants in the United States, Australia, and New Zealand, respectively, and for 25% in the United Kingdom. The proportion of zero HLA-mismatched transplants was higher in the United States (8.8%) and the United Kingdom (9.4%) than in Australia (5.2%) and New Zealand (5.4%).

One year and conditional long-term graft failure models

Compared to the United States, the one year adjusted risk of kidney graft failure was 22% and 29% higher in the United Kingdom and New Zealand, respectively (HR 1.22 and 1.29; each $p<0.001$) (Figure 1A). The one year risk of graft failure in Australia was lower than in the United States (HR 0.90, $p=0.001$).

In contrast to the one year results, the risk of long-term graft failure (conditional on function at one year) was significantly lower in Australia, New Zealand, and the United Kingdom compared to the United States, by 26%, 25%, and 26%, respectively (adjusted HR 0.74, 0.75, and 0.74; each $p<0.001$) (Figure 1B). Median graft survival times at the overall average covariate values were 11.2 years for the United States, compared to more than 14.7 years for Australia, New Zealand, and the United Kingdom.

Long-term country-specific graft failure risk by covariate subcohorts

Subcohort models showed that the lower overall country-specific adjusted risks of long-term graft failure in Australia and the United Kingdom were mirrored by consistent results across individual covariate levels for most recipient, donor, and transplant factors (Table 2). For example, separate models for each primary renal diagnosis category showed that the risks of long-term graft failure in Australia and the United Kingdom were lower than the United States within each category (diabetes: HR=0.84 Australia vs United States, HR=0.60 United Kingdom vs United States; glomerulonephritis: HR=0.79 Australia vs United States, HR=0.83 United Kingdom vs United States; other diagnosis HR=0.74 Australia vs United States, HR=0.76 United Kingdom vs United States). These results suggest that important effect heterogeneity in individual covariates by country was unlikely to have been responsible for the large overall differences in long-term graft failure rates. In one notable exception, the subcohort of recipients in the United States whose race was other than white or Asian (principally but not exclusively

African-Americans) had significantly better long-term outcomes than their counterpart (principally but not exclusively Aboriginal recipients) in Australia. Subcohort models comparing New Zealand and the United States had limited statistical power due to small sample size, but followed the same patterns as Australia and the United Kingdom.

To examine whether the type of health care insurance (for United States recipients) disproportionately accounted for adverse United States outcomes, we ran two additional models comparing all recipients in the Australia, New Zealand, and United Kingdom countries to 1) the subset of United States recipients with private health care insurance and 2) those whose primary health care insurance was government-funded (Medicare/Medicaid). The risk of long-term graft failure for the recipient subsets in the United States in both cases was significantly higher (United States private insurance: [HR=0.86, p<0.001 Australia vs United States; HR=0.86, p<0.001 New Zealand vs United States; HR=0.90, p<0.001 United Kingdom vs United States]; United States Medicare/Medicaid: [HR=0.63, p<0.001 Australia vs United States; HR=0.66, p<0.001 New Zealand vs United States; HR=0.65, p<0.001 United Kingdom vs United States]).

Time trend in country-specific graft failure risk

The risk of short-term graft failure decreased significantly over the 27-year cohort time period (each within-country slope p<0.001) (Figure 2A). In 1988, one year risk was significantly higher in New Zealand and the United Kingdom than in the United States (p<0.001). Thereafter, a larger decrease in one year graft failure risk occurred over time in those countries than in the United States (United States HR=0.94 per year, New Zealand HR=0.92 per year; p=0.08), such that the one year risk became equal to the United States by 2014. The rate of improvement in one-year graft failure risk was not significantly different between the United States and Australia. The improvement in one year risk of graft failure was smaller in the United Kingdom compared to the United States although the effect size was modest (United States HR=0.94 per year, United Kingdom HR=0.95 per year, p<0.001).

Long-term graft failure risk, conditional on function at one year, also improved in all four countries over time (each p<0.001) (Figure 2B). The reduction in risk over time, compared to the United States, was slightly more marked in Australia (Australia HR=0.961 per year, United

States HR=0.967 per year; p=0.03) (Figure 2B). Long-term outcome remained worse in the United States throughout the period of study.

Possibility of an unmeasured confounder

We examined whether the significantly higher risk of long-term graft failure after kidney transplant in the United States could be explained by residual confounding by unmeasured factors. To negate the observed country-specific differences, there would need to be a strong enough association between the unmeasured factor, and sufficiently disparate prevalence of that confounder, to cause the upper 95% confidence limit of the country-specific hazard ratio to cross 1.0. Various combinations of effect sizes (hazard ratios) of a putative confounder and disparate prevalences in the recipients of comparator countries were tested. Figure 3 shows prevalence curves for Australia plotted across a range of United States prevalence and hazard ratios. These represent combinations where the upper 95% confidence limit of the hazard ratio for recipients in Australia versus the United States (0.77) would be elevated to 1.00 by inclusion of the unmeasured confounder. Given the existence of an unmeasured factor with a hazard ratio of 2.0, Figure 3 shows that the observed difference between the United States and Australia could only be explained by a factor that was at least 31 percentage points more prevalent in the United States than Australia, e.g., 36% vs 5% or lower, respectively. For the United Kingdom, the difference in prevalence compared to the United States would need to be at least 35 percentage points to explain the difference in long-term graft survival while the difference for New Zealand would need to be at least 26 percentage points. For unmeasured confounders with hazard ratios closer to 1.0, the corresponding required disparity in prevalence was even greater.

Discussion

Kidney transplantation is an effective treatment for end-stage renal disease, but a search for opportunities to improve long-term allograft function deserves attention. With the goal to learn from differences in outcomes, this collaborative study used detailed observational data reported to well-established transplant registries on three continents to assess differences in kidney graft outcomes across four countries using a uniform analytical methodology. We found that recipients in the United States had a lower risk of graft failure in the first post-transplant year compared to patients transplanted in the United Kingdom and New Zealand (but not significantly

different than Australians). While one year is the traditional short-term milepost for assessing outcome in kidney transplant, long-term outcome is a more relevant patient-centered metric. We found that the risk of long-term graft failure, among those whose grafts were functioning at one year, was approximately 25% lower in Australia, New Zealand, and the United Kingdom than in the United States. In patient-centered terms, this represents three years of forfeited kidney graft function time for the average recipient in the United States.

To evaluate the possibility that the striking differences in overall graft failure risk – despite extensive statistical adjustment for confounding covariates – were driven by heterogeneity of effects, we leveraged the large size of our cohort to focus on subcohorts. Compared to the United States, lower long-term risk was consistently demonstrated in Australia, New Zealand, and the United Kingdom across almost all tested subcohorts of recipient and donor demographics, donor source, and transplant characteristics (e.g., HLA mismatch). The result for the heterogeneous subcohort of recipient race other than white or Asian was an exception. Non-white, non-Asian recipients in Australia (principally Aboriginal) had significantly worse outcome than their non-white, non-Asian counterpart (overwhelmingly African-American) in the United States. While it is well established that Australian Aboriginal kidney transplant recipients have worse outcomes than non-indigenous Australians[13,14] and that African-Americans have worse outcomes than whites in the United States[15], we were not able to directly compare results between Native Americans in the United States and indigenous Australians due to small sample sizes and insufficient specificity of the underlying data, respectively. Interpretation of this finding is challenging, as there are many potential differences between indigenous Australians and African-Americans (e.g., socioeconomics, pharmacogenomics, social systems, access to care) that may explain the disparate outcomes.

It was not surprising that both one year and long-term outcomes significantly improved in each country over the quarter century encompassed by this study. This is consistent with improvements in kidney transplantation results worldwide. One-year outcomes, which were significantly better in the United States compared to the United Kingdom and New Zealand in the early years of the study, were similar in all four countries by 2014. For long-term outcomes,

the average reduction in graft failure risk ranged from 2.7% to 3.9% per year across the four countries.

The rates of improvement over time in long-term outcome in the United Kingdom and New Zealand were not significantly different from that in the United States, while the rate of improvement in Australia was significantly higher. Consequently, country-specific disparities in long-term outcome were sustained over time, even in the most recent years of the study; long-term outcome in the United States remains worse than in the United Kingdom, Australia, and New Zealand.

We had access to rich clinical data sets from all four countries; the three registries selected for this study had comparable data collection methods, analytical conventions, and longitudinal follow-up. Nonetheless, unmeasured confounders could have accounted for the observed differences in outcomes. It has been postulated that kidney transplant recipients in the United States may have more comorbid conditions that contribute to graft failure than recipients elsewhere.[16] If such data were available, and if their inclusion as adjustment covariates negated the observed excess long-term graft failure risk in the United States patients, it would explain why results were worse in the United States. We did not have uniform data on panel reactive antibody levels, but the majority of first-time kidney transplant recipients are unsensitized. In the current study, we adjusted for the presence or absence of diabetes mellitus, but we did not have access to patient-level data on cardiovascular disease, peripheral vascular disease, or other conditions. Conceptually, however, one or more variables important enough to negate our findings would have required, in aggregate, a very large effect size, combined with highly disparate prevalence in United States and non-United States recipients. This seems unlikely from a clinical standpoint, given the relative stringency of kidney transplant recipient eligibility assessment. As a further step, our study included a specific quantification of the possibility of unmeasured confounding using a method reported in other observational studies;[12] the results cast doubt on unmeasured confounding as the explanation for country-specific differences in outcome.

Limitations of the present study include the possibility of under-ascertainment of graft failure or death. However, each of the registries used supplemental data sources to capture dialysis or death. Race was based on registry files and may not be patient reported, a common problem in most clinical studies. Data on race were not available for early years in the United Kingdom; however, sensitivity analyses using complete case data were consistent with the main analyses performed using multiple imputation.

International studies of chronic diseases have the potential to reveal differences in outcomes that result from country-specific medical practice patterns or health care delivery systems that are exogenous to patient characteristics. In the Dialysis Outcomes and Practice Patterns Study, an international prospective observational study of hemodialysis patients, detailed adjustment for multiple comorbid conditions failed to explain excess mortality among United States dialysis patients, whereas more than half of the excess was accounted for by country-specific differences in vascular access practices.[17] In kidney transplantation, time-limited insurance coverage for immunosuppressive medication may mediate impaired long-term outcome in low-income recipients in the United States[18] and income-based outcome disparities were ameliorated after a three-year coverage limitation ended.[19] In each of the countries other than the United States studied here, health insurance coverage and medication availability are universal. Our sub-analysis showed that recipients in the United States with private health care insurance and government-funded health care insurance (Medicare/Medicaid) each had significantly higher risks of long-term graft failure than recipients in Australia, New Zealand and the United Kingdom.

Aside from health care insurance, there are other differences in health care systems and potentially identifiable differences in post-transplant care practice patterns that would be candidates to study as factors leading to disparate kidney transplant outcomes around the world. Focused studies of transplant center practices (e.g., the extent to which uniform patient care guidelines are used; the timing and extent of return of care responsibility from the transplant center to local physicians; differences in immunosuppression practices) are needed to better understand the differences in outcome we observed and to suggest interventions in post-transplant care to test as best practices.

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Data in the ANZDATA Registry are contributed by renal units through Australia and New Zealand; the Registry is funded by the Australian Organ and Tissue Authority, the New Zealand Ministry of Health, and Kidney Health Australia. The interpretation of data is that of the authors, not the ANZDATA Registry.

Data for the UK are reported by transplant and renal centres to the UK Transplant Registry held by National Health Service Blood and Transplant (NHSBT). The interpretation of the data is that of the authors.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Figure Legends

Figure 1. Adjusted graft survival by country for (A) one year follow-up (n=379,257, graft failures=33,981) and (B) long-term follow-up conditional on being alive with a functioning graft at one year (n=318,048, graft failures=119,322). Survival curves for each country were generated using average covariate values of the entire study cohort. Note that in panel (A) the y-axis has a

break that zooms in on the upper part of the range to make the differences in short-term graft survival more easily visible.

Figure 2. Trend in risk of graft failure over calendar time 1988-2014 by country (A) hazard ratio (HR) of graft failure within the first year and (B) long-term HR of graft failure conditional on being alive with a functioning graft at one year. The reference (HR=1.0) is the risk of graft failure in 1988 in the United States.

Figure 3. Effect of potential unmeasured confounder. The graph shows how large an effect and/or disparity in prevalence of a single confounder would need to be to explain the superior long-term graft outcome in Australia compared to the United States. For a given prevalence in Australia (each line represents a given prevalence) and in the United States (depicted on the x-axis), the values on the y-axis represent the hazard ratios for graft failure that would be required to account for the difference in the observed risk of graft failure. The dot in the figure represents the example of an unmeasured confounder with a hazard ratio of 2.0. A prevalence of 36% in the United States and 5% or fewer in Australia would be necessary to negate the observed difference in long-term outcome. Adapted from Weintraub et al.[12]

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. Complete case analysis of adjusted risk of long-term graft failure versus the United States by covariate subgroups. Bold face indicates statistically significant results. Each row below represents a separate Cox regression using complete case analysis.

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Table 1. Characteristics of the study cohort.

Characteristic Median (Q1,Q3) or n(%)	Australia (n=13,582)	New Zealand (n=2,471)	United Kingdom (n=44,781)	United States (n=318,423)	Total (n=379,257)
Recipient age (years)	48 (35,57)	46 (32,57)	46 (33,57)	48 (36,59)	48 (35,58)

Recipient sex: male	8,318 (61.2%)	1,540 (62.3%)	27,746 (62.0%)	192,297 (60.4%)	229,901 (60.6%)
Recipient race					
Asian	1,088 (8.0%)	165 (6.7%)	3,563 (8.0%)	14,939 (4.7%)	19,755 (5.2%)
White	11,343 (83.5%)	1,748 (70.7%)	24,462 (54.6%)	179,142 (56.3%)	216,695 (57.1%)
Other	1,111 (8.2%)	555 (22.5%)	2,087 (4.7%)	124,314 (39.0%)	128,067 (33.8%)
Missing	40 (0.3%)	3 (0.1%)	14,669 (32.8%)	28 (<0.1%)	14,740 (3.9%)
Recipient diagnosis					
Diabetes	1,172 (8.6%)	262 (10.6%)	2,878 (6.4%)	75,446 (23.7%)	79,758 (21.0%)
Glomerulonephritis	6,231 (45.9%)	1,105 (44.7%)	7,104 (15.9%)	86,588 (27.2%)	101,028 (26.6%)
Other	6,179 (45.5%)	1,104 (44.7%)	18,003 (40.2%)	156,154 (49.0%)	181,440 (47.8%)
Missing	0 (0.0%)	0 (0.0%)	16,796 (37.5%)	235 (0.1%)	17,031 (4.5%)
Donor age (years)	46 (33,56)	41 (28,51)	46 (33,56)	38 (26,49)	40 (26,50)
Donor sex: male	7,254 (53.4%)	1,255 (50.8%)	23,489 (52.5%)	169,534 (53.2%)	201,532 (53.1%)
Donor type					
Living	4,540 (33.4%)	994 (40.2%)	11,060 (24.7%)	115,642 (36.3%)	132,236 (34.9%)
Deceased (brain death)	8,224 (60.6%)	1,455 (58.9%)	28,325 (63.3%)	188,502 (59.2%)	226,506 (59.7%)
Deceased (circulatory death)	818 (6.0%)	22 (0.9%)	5,396 (12.0%)	14,279 (4.5%)	20,515 (5.4%)
Donor cause of death					
Trauma	2,910 (21.4%)	537 (21.7%)	7,242 (16.2%)	90,852 (28.5%)	101,541 (26.8%)
Non-trauma	5,765 (42.4%)	787 (31.8%)	26,327 (58.8%)	111,765 (35.1%)	144,644 (38.1%)
N/A (living donor)	4,540 (33.4%)	994 (40.2%)	11,060 (24.7%)	115,642 (36.3%)	132,236 (34.9%)
Missing	367 (2.7%)	153 (6.2%)	152 (0.3%)	164 (0.1%)	836 (0.2%)
Relationship to recipient					
Sibling	1,110 (8.2%)	271 (11.0%)	3,019 (6.7%)	35,949 (11.3%)	40,349 (10.6%)

Biologically related non-sibling	1,901 (14.0%)	392 (15.9%)	4,581 (10.2%)	42,954 (13.5%)	49,828 (13.1%)
Biologically unrelated	1,529 (11.3%)	331 (13.4%)	3,455 (7.7%)	35,857 (11.3%)	41,172 (10.9%)
N/A (deceased donor)	9,042 (66.6%)	1,477 (59.8%)	33,721 (75.3%)	202,781 (63.7%)	247,021 (65.1%)
Missing	0 (0.0%)	0 (0.0%)	5 (<0.1%)	882 (0.3%)	887 (0.2%)
Total ischemia time					
Living donor	2 (1,3)	3 (1,4)	3 (2,4)	2 (1,2)	2 (1,3)
Deceased donor	14 (11,18)	16 (12,19)	16 (13,20)	19 (13,25)	18 (13,25)
Number of HLA mismatches					
0	700 (5.2%)	134 (5.4%)	4,191 (9.4%)	28,037 (8.8%)	33,062 (8.7%)
1	1,307 (9.6%)	240 (9.7%)	4,926 (11.0%)	14,750 (4.6%)	21,223 (5.6%)
2	2,990 (22.0%)	572 (23.1%)	11,901 (26.6%)	35,416 (11.1%)	50,879 (13.4%)
3	2,893 (21.3%)	620 (25.1%)	13,289 (29.7%)	66,119 (20.8%)	82,921 (21.9%)
4	1,963 (14.5%)	466 (18.9%)	6,479 (14.5%)	66,991 (21.0%)	75,899 (20.0%)
5	2,053 (15.1%)	305 (12.3%)	2,729 (6.1%)	69,719 (21.9%)	74,806 (19.7%)
6	1,044 (7.7%)	90 (3.6%)	921 (2.1%)	34,644 (10.9%)	36,699 (9.7%)
Missing	632 (4.7%)	44 (1.8%)	345 (0.8%)	2,747 (0.9%)	3,768 (1.0%)
Era of transplant					
1988-1994	2,697 (19.9%)	522 (21.1%)	10,032 (22.4%)	59,765 (18.8%)	73,016 (19.3%)
1995-1998	1,605 (11.8%)	365 (14.8%)	5,624 (12.6%)	40,653 (12.8%)	48,247 (12.7%)
1999-2002	1,809 (13.3%)	381 (15.4%)	5,475 (12.2%)	47,986 (15.1%)	55,651 (14.7%)
2003-2006	2,023 (14.9%)	342 (13.8%)	6,071 (13.6%)	55,511 (17.4%)	63,947 (16.9%)
2007-2010	2,521 (18.6%)	426 (17.2%)	7,950 (17.8%)	57,429 (18.0%)	68,326 (18.0%)
2011-2014	2,927 (21.6%)	435 (17.6%)	9,629 (21.5%)	57,079 (17.9%)	70,070 (18.5%)

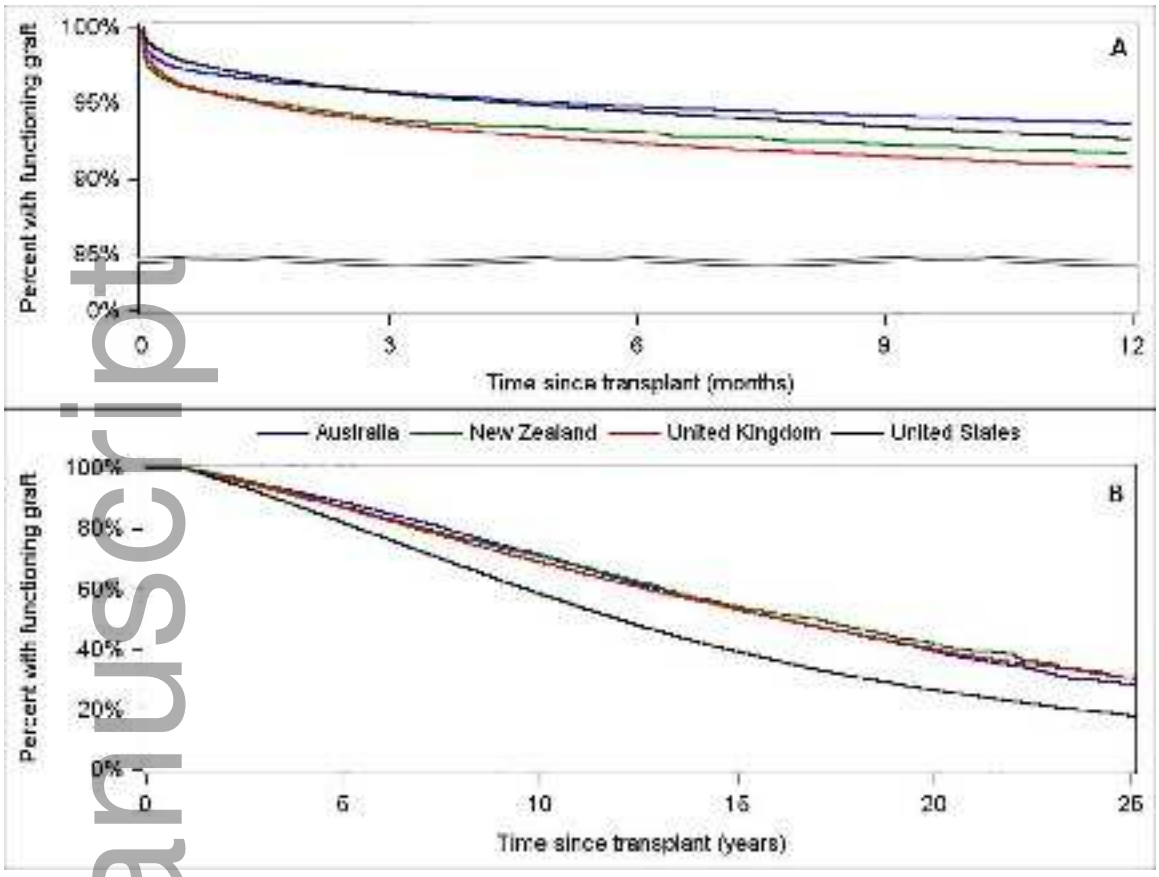
Table 2. Adjusted risk of long-term graft failure versus the United States by covariate subcohorts. Bold face indicates statistically significant results. Each row below represents a separate Cox regression.

Characteristic	Subcohort count (n)	Hazard ratio				p-value* vs United States		
		United States	Australia	New Zealand	United Kingdom	Australia	New Zealand	United Kingdom
Overall	322,624	1.00	**0.74**	**0.75**	**0.74**	**<0.001**	**<0.001**	**<0.001**
Recipient age at transplant: <12	8,449	1.00	0.73	1.25	**0.79**	0.087	1.000	**0.029**
Recipient age at transplant: 12 to 17	9,882	1.00	0.92	1.14	**0.75**	1.000	1.000	**<0.001**
Recipient age at transplant: 18 to 29	35,560	1.00	**0.71**	**0.68**	**0.69**	**<0.001**	**<0.001**	**<0.001**
Recipient age at transplant: 30 to 39	51,608	1.00	**0.70**	0.80	**0.68**	**<0.001**	0.236	**<0.001**
Recipient age at transplant: 40 to 49	70,690	1.00	**0.75**	**0.62**	**0.74**	**<0.001**	**<0.001**	**<0.001**
Recipient age at transplant: 50 to 59	78,217	1.00	**0.80**	0.84	**0.76**	**<0.001**	0.275	**<0.001**
Recipient age at transplant: 60 and over	68,218	1.00	**0.76**	**0.76**	**0.84**	**<0.001**	**0.035**	**<0.001**
Recipient sex: Female	127,274	1.00	**0.76**	**0.70**	**0.74**	**<0.001**	**<0.001**	**<0.001**
Recipient sex: Male	195,350	1.00	**0.73**	**0.79**	**0.74**	**<0.001**	**<0.001**	**<0.001**
Recipient race: Asian	18,439	1.00	0.82	0.94	0.96	0.117	1.000	1.000
Recipient race: White	196,372	1.00	**0.73**	**0.73**	**0.74**	**<0.001**	**<0.001**	**<0.001**
Recipient race: Other	107,813	1.00	**1.40**	1.12	**0.56**	**<0.001**	1.000	**<0.001**
Recipient diagnosis: Diabetes	69,376	1.00	**0.84**	**0.69**	**0.60**	**0.014**	**0.006**	**<0.001**
Recipient diagnosis: Glomerulonephritis	91,244	1.00	**0.79**	**0.82**	**0.83**	**<0.001**	**0.009**	**<0.001**
Recipient diagnosis: Other	162,004	1.00	**0.74**	**0.75**	**0.76**	**<0.001**	**<0.001**	**<0.001**

Characteristic	Subcohort count (n)	Hazard ratio				p-value* vs United States		
		United States	Australia	New Zealand	United Kingdom	Australia	New Zealand	United Kingdom
Donor age: <18	29,822	1.00	**0.79**	0.74	**0.75**	**<0.001**	0.159	**<0.001**
Donor age: 18 to 29	68,956	1.00	**0.74**	**0.75**	**0.74**	**<0.001**	**0.004**	**<0.001**
Donor age : 30 to 39	63,698	1.00	**0.74**	0.83	**0.71**	**<0.001**	0.519	**<0.001**
Donor age : 40 to 49	75,487	1.00	**0.74**	**0.71**	**0.75**	**<0.001**	**<0.001**	**<0.001**
Donor age : 50 to 59	58,519	1.00	**0.76**	**0.73**	**0.71**	**<0.001**	**0.001**	**<0.001**
Donor age : 60 and over	26,142	1.00	**0.74**	0.81	**0.76**	**<0.001**	1.000	**<0.001**
Donor sex: Female	150,971	1.00	**0.73**	**0.74**	**0.73**	**<0.001**	**<0.001**	**<0.001**
Donor sex : Male	171,653	1.00	**0.75**	**0.76**	**0.74**	**<0.001**	**<0.001**	**<0.001**
Donor type: Living	117,489	1.00	**0.76**	0.87	**0.71**	**<0.001**	0.613	**<0.001**
Donor type : Deceased (brain death)	188,654	1.00	**0.74**	**0.71**	**0.74**	**<0.001**	**<0.001**	**<0.001**
Donor type : Deceased (circulatory death)	16,481	1.00	0.70	1.18	**0.69**	0.077	1.000	**<0.001**
Donor cause of death (deceased donor): Trauma	86,576	1.00	**0.74**	**0.75**	**0.74**	**<0.001**	**<0.001**	**<0.001**
Donor cause of death (deceased donor): Other	118,559	1.00	**0.74**	**0.68**	**0.74**	**<0.001**	**<0.001**	**<0.001**
Donor relationship to recipient (living donor): Sibling	36,653	1.00	**0.82**	0.87	**0.78**	**0.044**	1.000	**<0.001**
Donor relationship to recipient (living donor): Biologic non-Sibling	44,694	1.00	**0.72**	0.81	**0.68**	**<0.001**	0.519	**<0.001**
Donor relationship to recipient (living donor): Biologically unrelated	36,142	1.00	**0.79**	1.04	**0.73**	**0.008**	1.000	**<0.001**

Characteristic	Subcohort count (n)	Hazard ratio				p-value* vs United States		
		United States	Australia	New Zealand	United Kingdom	Australia	New Zealand	United Kingdom
Total ischemia time: Living donor < 2 hrs.	49,838	1.00	**0.78**	0.95	**0.68**	**<0.001**	1.000	**<0.001**
Total ischemia time: Living donor ≥ 2 hrs.	67,651	1.00	**0.73**	0.81	**0.72**	**<0.001**	0.341	**<0.001**
Total ischemia time: Deceased donor < 20 hrs.	115,945	1.00	**0.73**	**0.72**	**0.74**	**<0.001**	**<0.001**	**<0.001**
Total ischemia time: Deceased donor ≥ 20 hrs.	89,190	1.00	**0.78**	**0.68**	**0.75**	**<0.001**	**<0.001**	**<0.001**
HLA mismatch: 0	29,611	1.00	**0.72**	0.88	**0.77**	**<0.001**	1.000	**<0.001**
HLA mismatch: 1	18,923	1.00	**0.76**	0.84	**0.80**	**<0.001**	1.000	**<0.001**
HLA mismatch: 2	44,988	1.00	**0.73**	**0.73**	**0.75**	**<0.001**	**<0.001**	**<0.001**
HLA mismatch: 3	72,290	1.00	**0.70**	**0.69**	**0.71**	**<0.001**	**<0.001**	**<0.001**
HLA mismatch: 4	63,922	1.00	**0.79**	**0.71**	**0.71**	**<0.001**	**0.002**	**<0.001**
HLA mismatch: 5	62,448	1.00	**0.77**	0.92	**0.72**	**<0.001**	1.000	**<0.001**
HLA mismatch: 6	30,442	1.00	**0.73**	0.86	**0.69**	**<0.001**	1.000	**<0.001**
Year of transplant: 1988-1994	60,257	1.00	**0.83**	**0.75**	**0.78**	**<0.001**	**<0.001**	**<0.001**
Year of transplant: 1995-1998	42,023	1.00	**0.73**	**0.78**	**0.74**	**<0.001**	**0.019**	**<0.001**
Year of transplant: 1999-2002	49,174	1.00	**0.66**	**0.75**	**0.68**	**<0.001**	**0.013**	**<0.001**
Year of transplant: 2003-2006	57,689	1.00	**0.71**	**0.66**	**0.65**	**<0.001**	**0.005**	**<0.001**
Year of transplant: 2007-2010	62,971	1.00	**0.70**	0.85	**0.73**	**<0.001**	1.000	**<0.001**
Year of transplant: 2011-2014	50,510	1.00	**0.67**	1.05	0.90	**0.033**	1.000	1.000

*P-values were adjusted for multiple comparisons using stepdown Bonferroni method.



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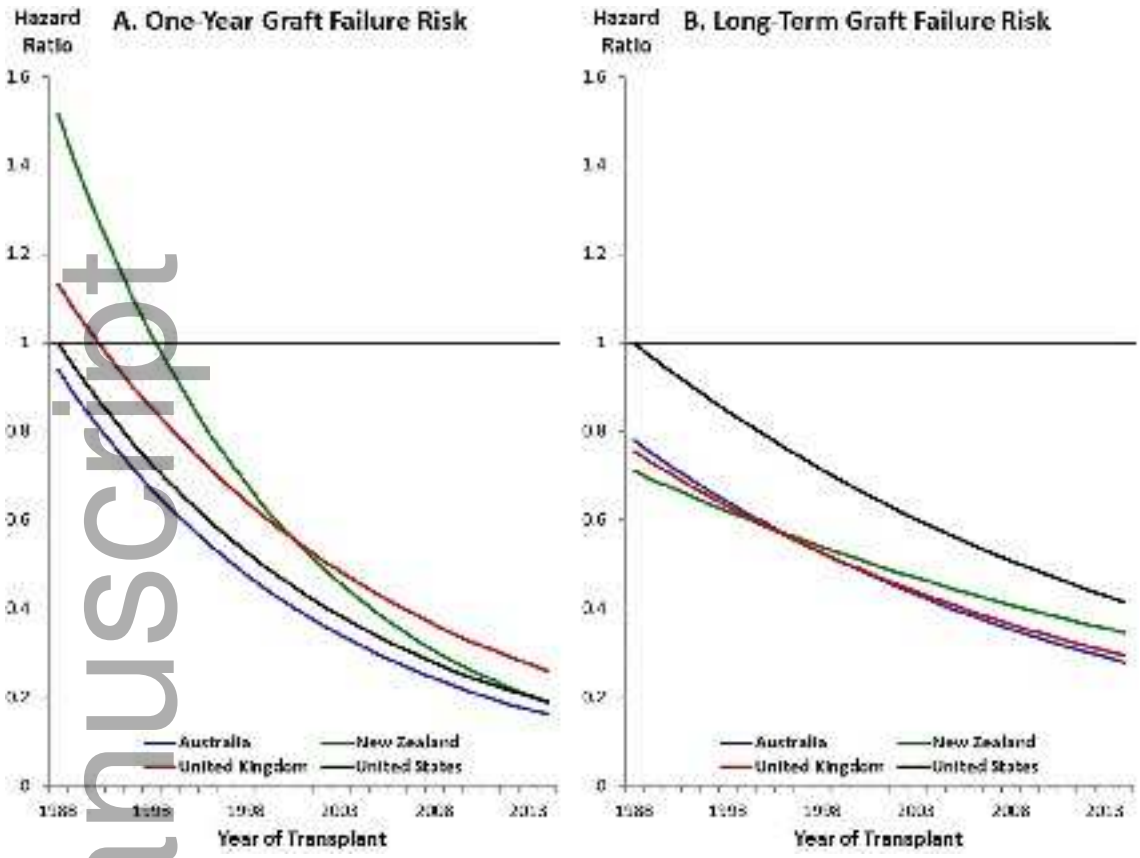

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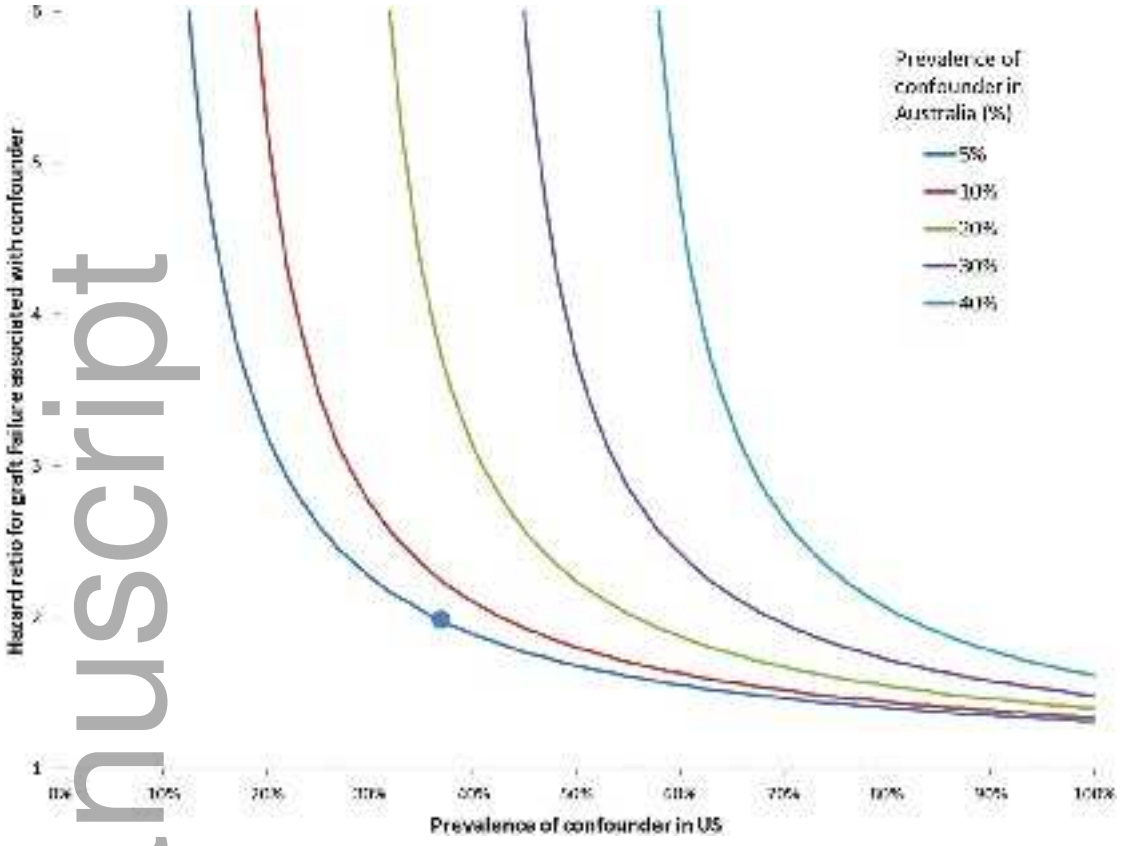

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